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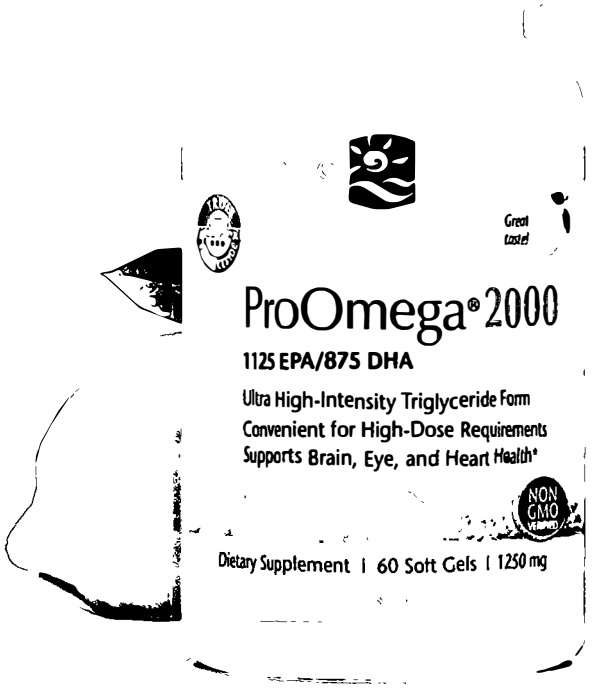

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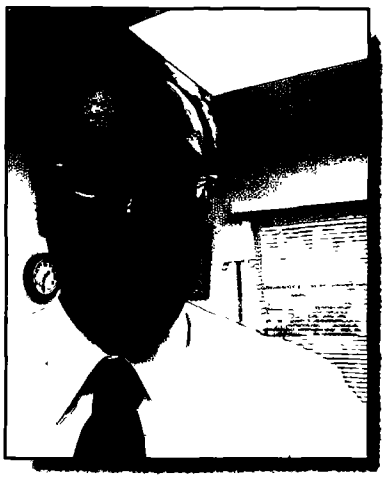

Off Into the Wild, Blue Yonder ... No ... ICD-10 Coding

Physician burnout has always been the bane of medical practice (or malpractice), what with physicians burning the midnight oil and awakening for rounds at ungodly hours. Moreover, EMR, insurance reports, quality-control reviews, and prescription preauthorization requests have mightily taxed physicians and their staff. Now ICD-10 coding, replacing long-used ICD-9 coding, is jeopardizing the little sleep that physicians manage to secure each night. The ICD-10 code seeks to precisely define each disease, condition, and injury into a quantifiable form that "Big Data" will be able to analyze epidemiologically and economically. From an orthopedic standpoint, the ICD-10 code contrasts a fracture of the right and left radius, open or closed, proximal or distal, epidemiology, and whether it is healing or not healing.

The number crunchers want the code to offer as exact a diagnosis as possible, so that appropriate medical and surgical costs can be determined.

ICD-10 is looking to do away with vague diagnostic fatigue (R53.83), arthralgia (M25.50), abdominal pain (R10.9), and anxiety (F41.9). Good luck on that – I intend to irk the bean counters by utilizing these nonspecific ICD-10 codes. Of course, when abdominal pain is due to diverticulitis (K57.32) or fatigue is secondary to iron-deficiency anemia (D50.9), then I will oblige by using the more specific diagnosis. And if it's iron-deficiency anemia, I shall comply with more accurate coding, if it is due to bleeding from colon cancer (C18.9 and D50.0).

Still, the ICD-10 is replete with 100,000 codes, and it will be difficult to offer the precision that the insurance carriers and Medicare demand. Expect that by 2018 there will be quality-control letters in the mail asking for an explanation of why there are so many patients being treated for nutritional deficiency (E63.9), hypothyroidism (E03.9), adrenal deficiency/fatigue (R53.83), and obesity (E66.9).

Expect that those quality-control letters may be shuttled to the state medical board for overview and audit.

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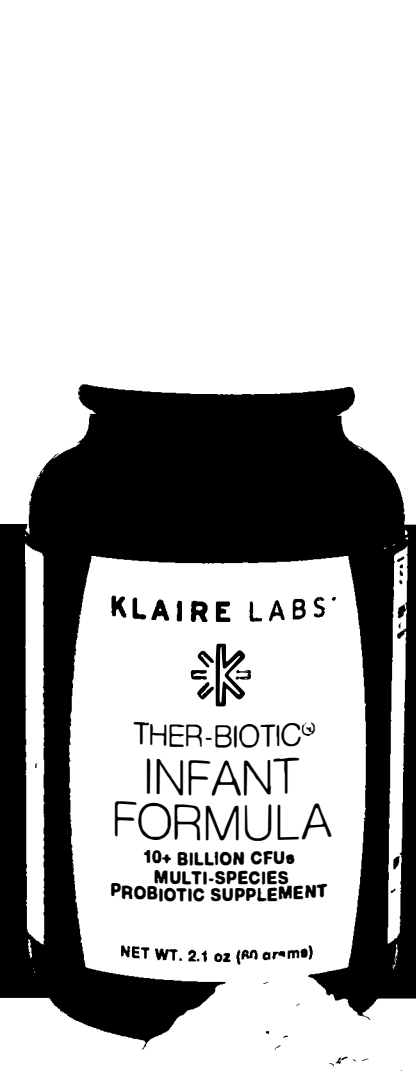

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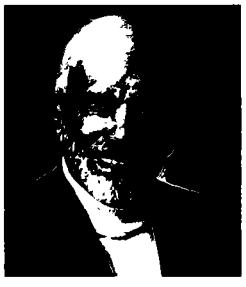

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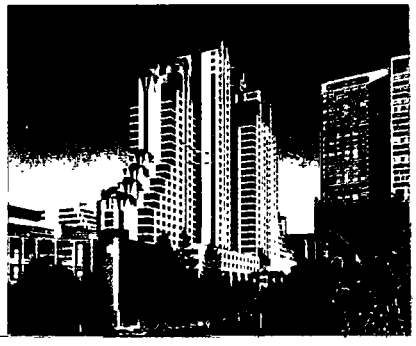

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Letter from the Publisher

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How Much Should A Drug Cost?

A few months back, a former hedge-fund manager, Martin Shkreli, shocked the world by raising the price of an antiparasitic drug, Daraprim, from $13.50 a tablet to $750. Shkreli is CEO of Turing Pharmaceuticals, the sole manufacturer of the antitoxoplasmosis drug. While parasitic infestation is relatively rare, it is a major concern for AIDS patients who acquire the disease; without Daraprim, most infected patients would die. Nevertheless, given the limited number of patients who develop toxoplasmosis, and the short period of time that is needed to treat it, there is minimal need for the drug. That would mean that Turing Pharmaceuticals only generates meager prescription sales for Daraprim, and that is the rub. It's the bottom line versus the cost for the cure. If there is such a paltry profit to be made manufacturing a drug, should the company be permitted to dramatically increase the price?

Shkreli, who was captured, in a photo that went viral, posing smugly like a Cheshire cat, relishing the financial windfall that his company would soon be enjoying, reversed his position after experiencing considerable backlash. Initially, he condescendingly quipped that it was his right to hike the price to ensure financial profit. Shkreli claimed that part of the profits would be used for R&D to develop a new antiparasitic drug. Later, he offered to reduce the price increase, and promised that the drug would be made available to indigent patients requiring it. He insisted, however, that medicine for rare diseases would need to be expensive to compensate for development costs and ensure profitability.

Turing is not alone among generic drug manufacturers seeking sharp increases in drug pricing. Doxycycline, a medication frequently prescribed by the Lyme disease-"literate" medical community, as well as by physicians treating nonspecific chronic illnesses, has recently increased greatly in price. Rodelis Therapeutics, a manufacturer of a pharmaceutical for tuberculosis, drastically increased its price. However, following complaints that the price increase was unreasonable and unfair, Rodelis reversed itself, restoring the drug manufacture and price control to its original owner, a university.

Valeant Pharmaceuticals quadrupled the price for Cuprimine, a drug required for treatment of Wilson's disease. For the patient with Medicare, the price for a month's supply jumped overnight from $9000 to $35,000, with the patient's out-of-pocket expense being $1800. J. Michael Pearson, CEO of Valeant, defends the eye-popping price increase, claiming a fiduciary need for his stockholders. When Valeant bought Salix Pharmaceuticals earlier this year, it immediately increased the price of Glumetza, a medication for diabetes, 800%. For many patients suffering with brittle diabetes, insulin has skyrocketed in cost; patients frequently need to choose between insulin and groceries.

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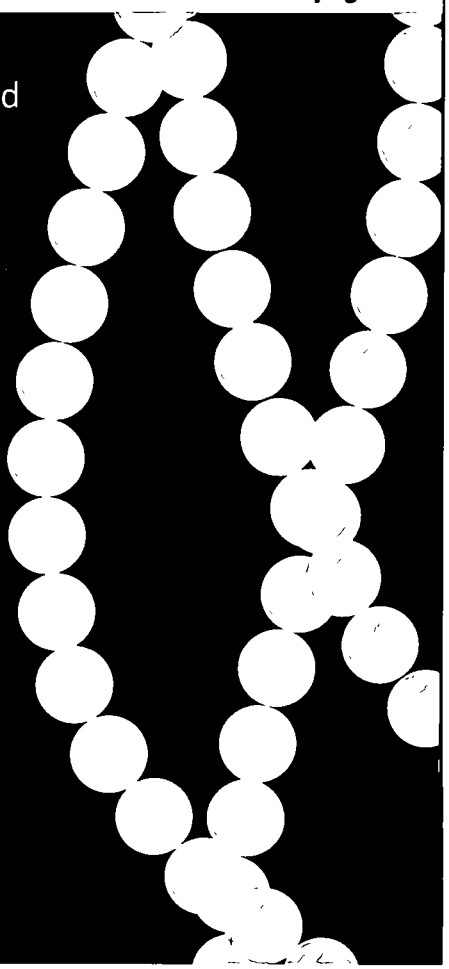

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Letter from the Publisher

➤ **continued from page 6**

Hefty price increases are hardly limited to treatments for rare diseases. The *Townsend Letter* has reported previously on an IV bag shortage in the US. While there has been a gradual improvement in IV solution availability, the price for fluids has increased 100% to 200% and even more. FDA oversight of compounding pharmacies, together with onerous injectable compounding requirements, has led to similar major price increases for vitamin and mineral injections. One company recently advertised 30 cc intravenous vitamin B complex at a price that was nearly 500% higher than it had been 5 years earlier. Injectable nutrients have become part and parcel of the integrative and naturopathic medical practice. The high cost of them will necessitate corresponding increase in IV infusion fees.

Should the US impose restrictions on drug pricing? Pharmaceuticals in most nations are limited to price controls set up by the government. In the US, there are limited price controls due to the carte blanche granted to drug manufacturers. Still, some contenders in the race for the presidency believe that drug price increases should be restricted.

Contact your legislators about drug price controls.

Mitch Gaynor, MD, Integrative Oncologist, Passes

New York City physician Mitchell Gaynor, MD, integrative oncologist associated with Cornell University/Weill Medical Center, died in September. He was a well-recognized author of several holistic wellness books including *Dr. Gaynor's Cancer Treatment Program, Healing Essence, The Healing Power of Sound, Sounds of Healing,* and *Your Health and the Environment*. Gaynor practiced in his center's oncology office, the Weill Medical Center, and New York Hospital. He was planning to promote his latest book, *The Gene Therapy Plan,* and had been invited to the *Dr. Oz Show* to explain how natural therapies could be used to reverse gene damage.

Gaynor was 59 years old and he was in excellent health; his death is considered suspicious, according to Health Nut News editor Erin Elizabeth. He was the 11th holistic physician to die since June. Newsmax states that among the 10 physicians who died, 4 were murdered, 2 were suicides, 2 were suspicious deaths, 1 is missing, and 1 in excellent health died from cardiac-related causes. Gaynor apparently was involved in an auto accident 2 days before his death.

Although not specifically stated, there is a suggestion that the high number of holistic physician deaths may not be coincidental. The *Townsend Letter* office oddly received an anonymous call advising us to initiate urgent security measures. As editorialized by me in the October issue, although there has been a "cluster" of deaths involving integrative practitioners, there is no basis to suggest a conspiracy. Holistic doctors are regrettably subject to premature death just like other practitioners and the public; sometimes deaths occur without diagnosed health conditions. Suicide is not uncommon in the health profession; when darkness haunts us, sometimes we slip over the edge. Unfortunately, sometimes our lives become entangled with unsavory souls who commit murder.

We need something more tangible to link all these deaths together characterizing them as "suspicious."

continued on page 15 ➤

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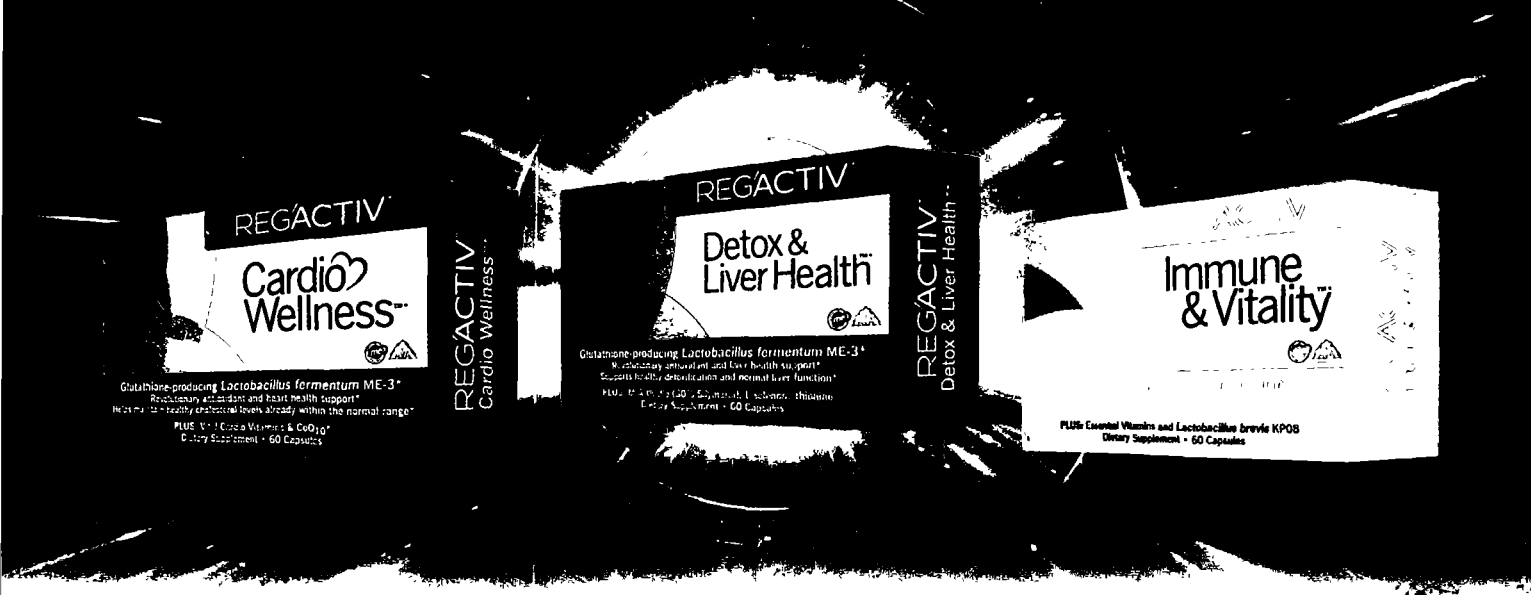

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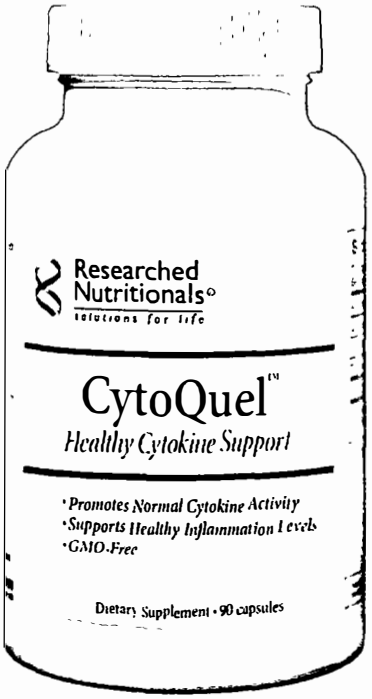

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With all the genetic testing available today, you may sometimes get more information that necessary. One way to home in on what is useful is to look at harmful genes than can be turned off (or prevented from turning on) with healthful diets and attention to key aspects of nutrition.

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ISSN 1940-5434

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

Letter from the Publisher

➤ continued from page 8

Green Smoothies and

In the January 2015 issue of the *Townsend Letter*, William Shaw, PhD, tantalized and challenged us with his provocative article "The Green Smoothie Fad: The Road to Hell is Paved with Toxic Oxalate Crystals." Shaw makes the convincing case that the current fad of drinking green smoothies may make a person more susceptible to kidney stones and related health problems. Surprisingly, we did not receive any letters rebutting Shaw's argument. Nearly a year later, Thomas Lodi, MD, MD(H), offers a rebuttal in his article in this month's issue: "Green Smoothie Bliss: Was Popeye Secretly on Dialysis?" Lodi admits that spinach and other green vegetables, as well as fruits, are loaded with oxalates. However, while Shaw makes the case that oxalate metabolism portends a high risk for stones, Lodi argues quite the contrary, that not only does the high consumption of oxalates in smoothies not increase the risk for stones, but the corresponding reduction in consumption of sugars, animal fats, and processed carbohydrates conveys substantially improved health.

Our esteemed contributing editor, Alan Gaby, MD, guides us on the integrative pathway, using nutrients in supporting chronic disease; for example, in his literature review in this issue, he reports on the intriguing nutritional diagnosis of iron deficiency in patients with coronary artery disease. Additionally, iron deficiency is a major consideration in treating patients with congestive heart disease. While Gaby writes for us to stay the course, Jacob Schor, ND, reports that some nutritional beliefs deserve revisiting with a healthy dose of skepticism. Schor notes that a 2014 paper in the *British Journal of Cancer*, reporting prospectively on the number of cases of cancer in over 600,000 UK women, failed to show any difference in those eating organic food versus those who did not. In fact, there was a statistically significant increased risk in the incidence of breast cancer in those women who primarily ate organic foods! How could this be – everyone "knows" that organic foods means better health?

Our December issue focuses on men's health and anti-aging. In that light, Sara Wood, ND, examines traumatic brain injury, a health problem that is becoming of increasing concern with the growing number of major injuries in high school, college, and professional football. Wood reviews nutritional supports helpful for mild head trauma; one unappreciated factor is progesterone.

Jonathan Collin, MD

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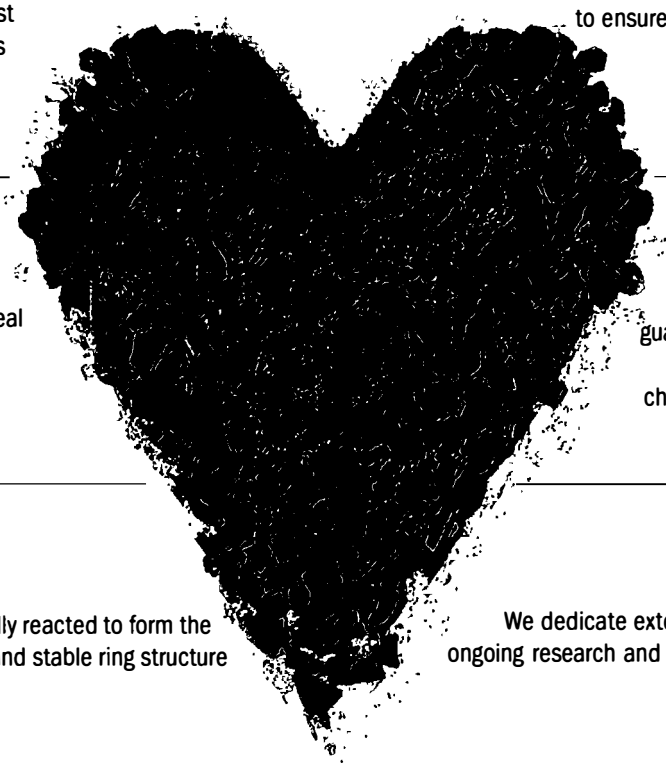

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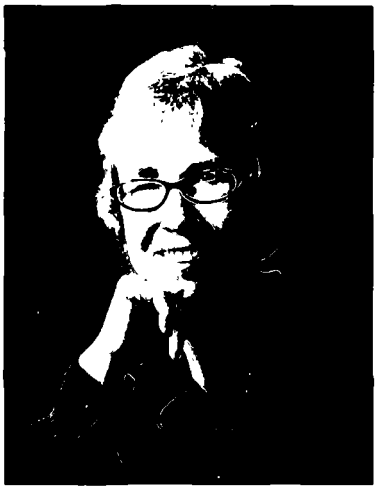

Shorts

briefed by Jule Klotter
jule@townsendletter.com

Circumcision, HIV, and STDs

Circumcision studies conducted on adult HIV-free African men show that removing the foreskin lessens the likelihood of their acquiring HIV from sexual partners. Circumcision, however, does not prevent the men from transmitting HIV to their partners. Although the exact reasons for this one-sided protection is unknown, researchers speculate that the foreskin's epithelial surface and microbiota may be involved.

Lance B. Price and colleagues found that the composition of penile microbiotas (collected at the junction between the shaft and glans) in 12 HIV-negative Ugandan men changed significantly after circumcision. Pre-circumcision samples were more heterogeneous with more anaerobic bacteria. The researchers suggest that anaerobic bacteria may stimulate genital mucosal inflammation and increase Langerhans cells' susceptibility to HIV infection. The foreskin's inner surface contains large numbers of Langerhans cells, a preferred target for HIV. Interestingly, circumcision has no effect on the prevention of other sexually transmitted disease rates, according to studies investigating *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae, Trichomonas vaginalis,* or *Chlamydia trachomatis* (Dinh et al).

The HIV-transmission studies of adult men in developing nations provide rationale for circumcision in adults, but should these studies be applied to male infants in developed countries? Unlike in adults, the neuron-rich foreskin in babies is typically fused to the glans penis; it does not retract. No one has studied the long-term physiological or psychological effects of cutting off an infant's foreskin. The Royal Dutch Medical Association, the British Medical Association, the Canadian Paediatric Society, and the Royal Australasian College of Physicians do not recommend routine circumcision in healthy infant boys, according to Angelika F. Na and colleagues. The Royal Dutch Medical Association views infant circumcision as "'a violation of children's rights to autonomy and physical integrity.'" The other countries say that there isn't enough consistent evidence of benefit to offset the risks of surgical complications and the medical cost.

The American Academy of Pediatrics 2012 policy statement does not recommend routine circumcision but does list prevention of urinary tract infections and HIV and STD prevention as benefits of infant circumcision. Na and colleagues point out that most UTIs occur in boys with underlying renal tract abnormalities and that UTIs respond to antibiotic treatment. They question the benefits of circumcising babies when most boys are not at risk for a treatable infection. As for HIV and STD prevention, no studies support a link between infant circumcision and HIV/STD prevention. Condoms, not circumcision, are the most effective way to prevent STDs.

Dinh MH, Fahrback KM, Hope TJ The role of the foreskin in male circumcision an evidence-based review *Am J Reprod Immunol* March 2011,65(3).279–283 Available at www.ncbi nlm nih.gov/pmc/articles/PMC3091617 Accessed October 3, 2015

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Benign Prostatic Hyperplasia, Nocturia, and Physical Activity

Standing more and sitting less may prevent benign prostate hyperplasia (BPH), according to a 2014 South Korean study. BPH is characterized by lower urinary tract symptoms such as increased frequency, increased urgency, a feeling of incomplete bladder emptying, and nocturia (excessive urination at night). Eight of 11 studies have found an inverse relationship between physical activity and BPH, according to Ho Won Lee and colleagues. In order to identify beneficial aspects of physical activity, the authors looked at frequency of exercise, exercise time, sedentary time, and nonsedentary time (e.g. light field work, washing windows, slow cycling) in 582 men, age 40 and older, without prostate cancer.

Unlike other studies, the Korean study found that high-intensity and longer-duration exercise does not reduce the risk of BPH (defined as ≥ 25mL of prostate volume and an International Prostate Symptom Score [IPSS] of ≥8). In fact, men who engaged in sweat-producing exercise 5

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or more times per week had an overall higher BPH risk (OR, 1.26; 95% CI, 0.68–2.33). However, sedentary time showed a significant linear relationship with BPH and with prostate volume: "Subjects with lower levels of sedentary time (4.5-7.0 hr/day) had a significantly lower risk of BPH (OR, 0.93; 95% CI, 0.52-1.67) than those with a higher sedentary time (>7 hr/day) (OR, 1.72; 95% CI, 0.96-3.09) (P for trend = 0.05)." Clinical trials are needed to confirm the relationship between sedentary behavior and BPH.

Although physical activity did not prevent BPH in the South Korean study, epidemiological evidence from a 2015 study indicates that activity might alleviate nocturia in some men. "Nocturia increases with age and is estimated to occur in over 50% of men over the age of 45 (regardless of BPH status)," say Kathleen Y. Wolin and colleagues. Excessive urination at night is associated with poor sleep and depression. Wolin and colleagues analyzed data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, an ongoing clinical study that is investigating the effects of cancer screening on cancer-specific mortality. The trial enrolled 76,705 men, aged 55 to 74, with no reported history of prostate cancer. Wolin and colleagues used data from the intervention arm of the study; these men completed questionnaires on lifestyle, BPH-related outcomes, and nocturia at baseline (c.1993) and an additional questionnaire on BPH, nocturia, and physical activity over 10 years later (2006–2008). The researchers found a weak association between physical activity and BPH but a strong inverse association between physical activity and nocturia. Nocturia was defined as waking 2 or more times a night to urinate. Men whose only complaint was nocturia showed a stronger correlation. The association between physical activity and nocturia was statistically nonsignificant for men with a BPH diagnosis, elevated PSA, or large prostate volume. As with the Korean study, the results of this study also need to be tested in a clinical trial.

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Rapamycin, an Anti-Aging Drug?

Rapamycin, an antifungal, anticancer, and immune-suppressing compound secreted by the bacterium *Streptomyces hygroscopicus*, is the basis for an anti-aging drug being developed by the Swiss pharmaceutical company Novartis. Animal research has shown that rapamycin delays the onset of several age-related conditions, including cancer, heart disease, bone loss, and Alzheimer's disease. It has also reversed cardiac aging and Alzheimer's. FDA approved rapamycin as a drug for transplant patients to help prevent organ rejection in 1999. Since then, patentable rapamycin derivatives have been FDA-approved to inhibit some kidney, lung, and breast cancers. Independent of its effects on disease conditions, rapamycin has lengthened lifespan in mice who began receiving the drug at 20 months (late middle age).

Rapamycin inhibits a cellular pathway that regulates growth and metabolism. This pathway, called TOR (target of rapamycin), works like a factory's circuit breaker, says science writer Bill Gifford: "When it's activated, the cell grows and divides, consuming nutrients and producing proteins. When mTOR [mammalian TOR] is turned down, the 'factory' switches into more of a conservation mode, as the cell cleans house and recycles old proteins. ..." This housecleaning phase has been linked to longer lifespans. When Roman V. Kondratov and Anna A. Kondratova gave rapamycin to mice genetically predisposed to premature aging, mTORC1 (which suppresses mTOR signaling) greatly increased and the mice lived 8 to 12 months longer than controls. Matt Kaeberlein and Daniel Promislow at the University of Washington plan to test rapamycin's ability to prevent age-related arterial stiffness and cardiac decline in middle-aged pet dogs.

Despite its anti-aging effects, scientists and physicians question rapamycin's use in older people because of its immune-suppressing properties. Rapamycin is known to impair wound healing. A 2014 study indicates that rapamycin may modulate rather than suppress immune activity. In this study, low doses of everolimus, a rapamycin derivative, increased antibody response to a flu vaccine in people 65 and older. However, vaccine response does not necessarily reflect the body's response to an actual infection, according to Janko Nikolich-Zugich, chair of the department of immunobiology at the University of Arizona and codirector of the Arizona Center on Aging.

At this point, too many questions about rapamycin's safety, dosage, and timing remain to use it as an anti-aging drug in healthy middle-aged people. Novartis spokesperson Mariellen Gallagher told Gifford: "'It is far too early to tell whether low-dose rapamycin will lengthen human life span. A favorable risk/benefit ratio needs to be demonstrated in clinic trials to be sure that mTOR inhibitors such as rapamycin have acceptable safety and efficacy in aging-related conditions in humans.'"

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Kondratov RV, Kondratova AA Rapamycin in preventive (very low) doses. *Aging* March 2014;6(3) 158–159 Available at www.ncbi.nlm nih gov/pmc/articles/PMC4012933. Accessed September 26, 2015

Service Dogs for Vets with PTSD

Although the US Veterans Affairs Department funds service dogs for physically disabled soldiers, the agency has not yet approved their use for soldiers with posttraumatic stress disorder (PTSD) or traumatic brain

injury (TBI). The agency is awaiting results from clinical trials that assess the effect of a service dog on a combat veteran with PTSD or TBI. Service dogs perform a variety of tasks for physically disabled veterans such as picking up and retrieving objects and opening doors. Service dogs can also provide active support for those with PTSD, such as waking their human partners from a nightmare. Perhaps most importantly, service dogs provide emotional support. Marguerite O'Haire at Purdue University's College of Veterinary Medicine is leading a placebo-controlled study involving 100 post-9/11 veterans, according to an article in *Military Times*. The researchers will be looking at service dogs' effects on medical symptoms, medication use, social anxiety, relationships, stress levels, and other factors. Meanwhile, a novel program at several veterans' medical facilities shows that, by training service dogs, veterans with PTSD can retrain themselves.

The Warrior Canine Connection (WCC) uses veterans with PTSD and TBI to train service dogs for soldiers with spinal cord injuries. This nonprofit organization has WCC programs at Walter Reed National Military Medical Center, Fort Belvoir, National Intrepid Center of Excellence, and the Palo Alto Veterans Administration Healthcare System. "WCC's training philosophy is based on positive methods of shaping behaviors and the premise that mastering the skills and patience required to train a service dog helps the WCC trainers regain control of their own emotions, focus their attention, and improve their social competence and overall sense of well-being," according to an article in *Psychiatric Annals*. Social worker and service dog trainer Rick Yount developed the program.

The mission of helping another disabled veteran, by providing a well-trained, valuable service dog free of charge, motivates trainer-veterans to surmount their own problems. These dogs are bred to be highly attuned to people's emotional affect, so their trainers must maintain confidence and a positive attitude. Trainers use praise and treats to teach the dogs that "the world is a safe place." Program participants have reported that the patience and positive techniques used in dog training have been highly useful in their interactions with their own children. Dogs in the training program are exposed to a wide variety of environments and experiences, requiring their trainers to move out into the community. Trainers also need to stay in the present moment in order to take advantage of "teachable moments." A veteran, triggered into remembering past traumas, cannot convince a startled dog that a backfiring car is not a threat. In addition to increased patience, emotional regulation, and impulse control, program participants report improved sleep, decreased depression, decreased use of pain medications, increased sense of belonging/acceptance, improved family dynamics, lower stress levels, and increased sense of calm.

The WCC program brings new meaning to the healing power of animal-assisted therapy.

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Yount RA, Olmert MD, Lee MR *Service dog training* program for treatment of posttraumatic stress in service members. *United States Army Medical Department Journal* April–June 2012,63–69 Available at http://www warriorcanineconnection org/how-we-help-warriors/research Accessed September 23, 2015

Yount R, Ritchie EC, St Laurent M, Chumley P, Olmert MD The role of service dog training in the treatment of combat-related PTSD *Psychiatr Ann* June 2013;43(6)·292–295 Available at EBSCO Host Accessed September 23, 2015.

Successful Aging

Successful aging entails more than freedom from disability and disease, according to Dilip V. Jeste, MD, and colleagues. Jeste et al. conducted a study to test the hypothesis that "older age would be associated with worse physical and cognitive functioning and lower [self-rated successful aging] SRSA scores." To their surprise, older age did not correlate with lower scores. "Perfect physical health is neither necessary nor sufficient for successful aging as defined by the older adults themselves," they state. Resilience and freedom from depression, however, are.

Their 2014 SAGE (Successful Aging Evaluation) study recruited 200 people in their 50s, 200 in their 60s, 250 in their 70s, 411 in their 80s, and 238 in their 90s. (Initially, they sought 325 participants for the 9th and 10th decades but could not get that many people in their 90s, so they added more in their 80s.) None of the participants required daily skilled nursing care, had a prior diagnosis

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of dementia, or had a terminal illness. The researchers questioned participants about their demographics, general health, depression and anxiety, and cognitive function in a structured 25-minute phone interview. A follow-up mail-in survey consisted of validated questionnaires to further assess physical and mental functioning, self-perceived cognitive deficits, depression, positive psychological factors (e.g., optimism), and self-rated successful aging. A total of 1006 out of 1300 participants completed the survey.

"Contrary to our hypothesis, older age was associated with higher SRSA, despite worse physical and cognitive functioning," say Jeste and colleagues. "... Possible explanations for this paradoxical result include acceptance of physical limitations, contentedness with overall accomplishments in life, a more realistic appraisal of one's own strengths and limitations, reduced preoccupation with social comparison (peer pressure), and greater emotional stability." The researchers noted an interesting correlation between physical function and depression: the SRSA scores of people with poor physical function (lowest tertile) and no or minimal depression were comparable to scores belonging to physically healthy people with moderate to severe depression. Similarly, SRSA scores of physically impaired people with high resilience scores were comparable to scores belonging to physically healthy people with low resilience. Resilience is the ability to cope with stress and adapt to change, such as the change in function and life circumstances that come with aging.

The study's results indicate that greater resilience, lower depression, better physical health, and older age are primary factors associated with successful aging. However, more research is needed to determine whether increasing resilience or reducing depression actually produces more positive SRSA scores. Although the SAGE study does not show causal relationships, it does challenge negative attitudes about aging. Instead of focusing solely on physical and mental functioning, clinicians can recognize that resilience, a sense of purpose, and other psychological factors may be equally important in successful aging. Clinicians can also use SRSA scores to measure outcomes.

Aldwin CM, Igarashi H An ecological model of resilience in late life *Ann Rev Gerontol Geriatr* January 2012 Available at www researchgate net Accessed September 24, 2015.

Jeste DV, Sayla GN, Thompson WK, et al Older age is associated with more successful aging role of resilience and depression. *Am J Psychiatry*. Feb 1, 2013;170(2):188–196 Available at www ncbi nlm.nih gov/pmc/articles/PMC3593664. Accessed September 24, 2015.

The Mitochondrial Free Radical Theory of Aging

The mitochondrial free radical theory of aging (MFRTA) attributes age-related decline to damaged cellular and mitochondrial DNA and RNA caused by high levels of reactive oxygen species (ROS) (e.g., hydrogen peroxide and superoxide). ROS are produced during metabolism and take part in cell signaling pathways that affect numerous processes, including proliferation, differentiation, and death. The theory that ROS-mediated oxidative damage is the cause of aging has not lived up to expectations. Researchers have failed to find predictable correlations between ROS production, ROS neutralization, or macromolecular damage, and lifespan. In a 2014 review, Jeffrey A. Stuart and Canadian colleagues discuss the theory's seeming failure to explain lifespan differences. Although the Canadians do not argue for discarding the theory, they suggest that it needs modification.

If ROS damage is the cause of aging, one would expect to find changes in ROS levels when animals eat a calorie-restricted diet. Calorie restriction is known to increase lifespan. Michael E. Walsh et al. reviewed data from decades of studies that examined tissues and diverse organs from rodents on calorie-restricted diets. Even though oxidative damage decreased, the researchers found no consistent effect on mitochondrial ROS production or antioxidant activity: "In a majority of studies, dietary restriction had little effect on mitochondrial ROS production or antioxidant activity. On the other hand, DR [dietary restriction] decreased oxidative damage in the majority of cases ... the effects of DR on endogenous antioxidants are mixed."

In addition to calorie restriction research, MFRTA has been tested using mice whose genetic expression of mitochondrial enzymes has been altered. Even though oxidative damage biomarkers rise or fall in correlation with antioxidant enzyme gene expression, "... there are seldom corresponding effects on longevity," report Stuart et al. Longevity has also failed to increase in most studies with mice with overexpression of base excision repair (BER) genes – a major pathway for repairing oxidative damage in DNA.

Stuart et al. propose "a more refined view of mitochondrial ROS." They suggest that age-related decline is due to ROS's role in signaling pathways that regulate aging and longevity rather than to oxidative damage alone.

Stuart JA, Maddalena LA, Merilovich M, Robb EL. A midlife crisis for the mitochondrial free radical theory of aging *Longev Healthspan* 2014,3(4) Available at www biomedcentral com/content/pdf/2046-2395-3-4.pdf Accessed September 18, 2015

Walsh ME, Shi Y, van Remmen H The effects of dietary restriction on oxidative stress in rodents *Free Radic Biol Med* January 2014;66 88–99 Available at http://europepmc org/articles/pmc4017324 Accessed October 9, 2015

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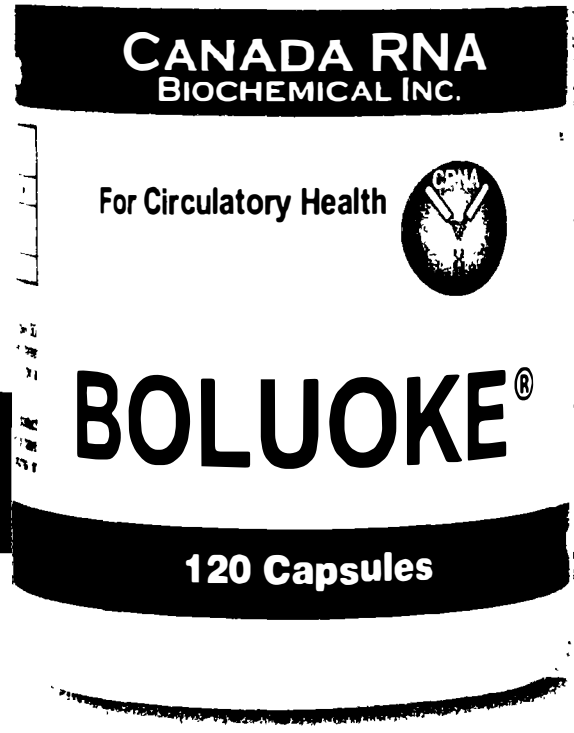
- ✔ No significant effect on INR or PTT



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Literature Review & Commentary

by Alan R. Gaby, MD
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Folic Acid, Vitamin B12, and Osteoporosis

In the B-vitamins for the PRevention Of Osteoporotic Fractures (B-PROOF) study, 2919 individuals aged 65 years or older (mean age, 74 years) living in the Netherlands who had an elevated homocysteine level (12–50 μmol/L) were randomly assigned to receive daily, in double-blind fashion, 400 μg of folic acid and 500 μg of vitamin B12 or placebo for 2 years. Both groups received 600 IU per day of vitamin D. The incidence of osteoporotic fractures was 4.2% in the vitamin group and 5.1% in the placebo group. Compared with placebo, B vitamins decreased osteoporotic fracture risk nonsignificantly by 16% in intent-to-treat analysis and by 19% among those who completed the trial. In prespecified subgroup analysis of individuals over age 80 who completed the trial, active treatment significantly decreased osteoporotic fracture risk by 70% ($p < 0.02$).

Comment: Individuals with the rare genetic disease homocystinuria have markedly elevated plasma homocysteine levels and develop osteoporosis at an early age. Homocysteine has been shown to interfere with collagen cross-linking, which is important for the stability and strength of connective tissue. Hyperhomocysteinemia might therefore decrease the integrity of the protein matrix of bone, thereby causing bones to become fragile. In a recent editorial in the *Townsend Letter*, I mentioned a study in which folic acid and vitamin B12 supplementation decreased the incidence of hip fractures by 78% in patients with a history of a stroke and high homocysteine levels. However, recently expressed concerns about possible scientific misconduct have cast doubt on the reliability of that study (Bauchner H, Fontanarosa PB. Expression of Concern: Sato et al. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA*. 2005;293:1082–1088. *JAMA*. 2015;313:1914). In a 2013 double-blind trial, patients with a recent stroke and a high prevalence of hyperhomocysteinemia received daily B vitamins (2 mg of folic acid, 25 mg of vitamin B6, and 500 μg of vitamin B12) or placebo. After a median of 2.8 years of treatment and 3.4 years of follow-up, the incidence of any osteoporotic fracture was nonsignificantly lower by 14% and the incidence of hip fracture was nonsignificantly lower by 6% in the vitamin group than in the placebo group. The results of the new study described above are similar to the findings from the 2013 study, and suggest that the effect of homocysteine-lowering on fracture risk is modest at best. However, the new study did identify a subset of participants (those over 80 who adhered to the program) that may benefit substantially from this treatment. The reduction of fracture risk in these elderly individuals appeared to be due to an improvement in bone quality, rather than an effect on bone mineral density.

Van Wijngaarden JP et al Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration B-PROOF, a randomized controlled trial *Am J Clin Nutr* 2014,100 1578–1586

Ubiquinol and Parkinson's Disease

Thirty-one patients with Parkinson's disease who were experiencing the "on-off" phenomenon while receiving levodopa (Group 1), and 33 other patients with Parkinson's disease who were not being treated with levodopa (Group 2) were randomly assigned to receive, in double-blind fashion, 300 mg per day of ubiquinol (the reduced form of coenzyme Q10) or placebo for 48 weeks (Group 1) or 96 weeks (Group 2). Among the patients in Group 1, treatment with ubiquinol resulted in an improvement in mean symptom severity, as determined by the Unified Parkinson's Disease Rating Scale ($p < 0.05$ compared with the change in the placebo group). Among the patients in Group 2, symptoms worsened in both groups, with no significant difference between groups.

Comment: With prolonged use of levodopa, disabling side effects such as random daily motor fluctuations (known as the "on-off" phenomenon) and random drug-resistant "off" periods occur in a large proportion of patients with Parkinson's disease. These abnormalities are thought to be due to erratic delivery of levodopa to the brain, which may result from the fact that large neutral amino acids (phenylalanine, tyrosine, methionine, leucine, isoleucine, valine, and tryptophan) compete with levodopa for intestinal absorption and for transport across the blood-brain barrier. One group of investigators found that, if protein intake at breakfast and lunch was severely restricted (i.e., a total of no more than 7 g of protein until the evening meal), then daytime plasma concentrations of large neutral amino acids remained relatively low, and the "on-off" phenomenon was eliminated in many patients. Although symptoms typically returned after the high-protein evening meal, many patients were able to function almost normally during the day.

Preliminary research suggested that coenzyme Q10 can improve symptoms in patients with Parkinson's disease, but several large follow-up studies concluded that coenzyme Q10 was of little or no value. The new study suggests that ubiquinol (and, presumably, coenzyme Q10 as well) can improve symptoms in a subset of patients: those experiencing the difficult-to-treat "on-off" phenomenon. It is possible that treatment with ubiquinol or coenzyme Q10 would also allow these patients to liberalize their very restricted diet.

Yoritaka A et al Randomized, double-blind, placebo-controlled pilot trial of reduced coenzyme Q10 for Parkinson's disease *Parkinsonism Relat Disord* 2015,21:911-916

Azelaic Acid for Acne

Fifty-five women (aged 18–45 years) with adult acne were randomly assigned to receive topical 15% azelaic acid gel twice a day or 0.1% adapalene gel once a day for 9 months. Both groups improved significantly. The improvement in lesion counts, acne severity, and Dermatology Life Quality Index score were comparable between groups, whereas dryness and scaling were significantly less ($p < 0.05$) with azelaic acid than with adapalene.

Comment: Azelaic acid is a 9-carbon straight-chain dicarboxylic acid that occurs naturally in some foods. It has both antibacterial and anti-inflammatory effects. In clinical trials that included patients with mild-to-moderate acne, topical application of azelaic acid (usually as a 20% cream) was significantly more effective than placebo and of comparable efficacy to other topical treatments (i.e., 0.05% tretinoin, 5% benzoyl peroxide, and 2% erythromycin). In the present study, azelaic acid was at least as effective as adapalene, another commonly used treatment for acne.

Thielitz A et al A randomized investigator-blind parallel-group study to assess efficacy and safety of azelaic acid 15% gel vs adapalene 0 1% gel in the treatment and maintenance treatment of female adult acne *J Eur Acad Dermatol Venereol* 2015,29 789–796

Iron Deficiency in Patients with Coronary Artery Disease

Bone marrow aspirates were obtained from the sternum in 65 patients with stable coronary artery disease during cardiac surgery, and from the iliac crest of 10 healthy controls. Bone marrow iron deficiency was found in 48% of the patients and in none of the controls ($p < 0.01$). Among the patients, iron deficiency was present in 10 of 16 (63%) with and 21 of 49 (43%) without anemia. Serum soluble transferrin receptor had the strongest association with bone marrow iron deficiency. Using the most accurate cut-off level of 1.32 mg/L or higher, the sensitivity was 67% and the specificity was 97%. For serum ferritin, using the most accurate cut-off level of 112 μg/L or lower, the sensitivity was 52% and the specificity was 79%. For transferrin saturation, using the most accurate cut-off level of 31.6% or lower, the sensitivity was 55% and the specificity was 90%.

Comment: The results of this study indicate that almost half of patients with stable coronary artery disease are deficient in iron. In addition to being a component of oxygen-carrying hemoglobin, iron is a cofactor for cytochrome oxidase, which is essential for mitochondrial energy production through its role in the electron-transport chain. Thus, iron deficiency might aggravate ischemic heart disease by 2 different mechanisms. Iron deficiency, with or without anemia, is a risk factor for poor outcomes in patients with congestive heart failure. Whether it is also associated with poor outcomes in patients with coronary artery disease has not been well studied. Nevertheless, it would seem like a good idea to test for iron deficiency in these patients, and to supplement with iron when appropriate. The results of the present study suggest that the most reliable noninvasive test for identifying iron deficiency in patients with coronary artery disease is serum soluble transferrin receptor.

Jankowska EA et al. Bone marrow iron depletion is common in patients with coronary artery disease *Int J Cardiol* 2015,182.517–522

Probiotic for Periodontal Disease

Thirty patients with chronic periodontitis and moderately deep pockets were treated with scaling and root planing and were randomly assigned to receive, in double-blind fashion, probiotic lozenges twice a day (morning and evening after toothbrushing) or placebo lozenges for 3 weeks. The probiotic lozenges (Prodentis; BioGaia, Lund, Sweden) contained at least 10^8 colony-forming units each of *Lactobacillus reuteri* strains DSM17938 and ATCC PTA 5289 (this information was not mentioned in the study, but came from a personal communication with one of the authors). Evaluations were performed at baseline and on days 21, 90, 180, and 360. Compared with placebo, probiotic treatment resulted in significant improvements in plaque index, gingival index, bleeding on probing, probing depth, and attachment gain at every time point. Biochemical studies on gingival crevicular fluid revealed a reduction in inflammatory markers in the probiotic group.

Comment: This study demonstrates that the use of lozenges containing *L. reuteri* was beneficial as an adjunct to scaling and root planing in patients with chronic periodontitis and moderately deep pockets. The beneficial effect of the probiotic lozenges persisted long after the treatment was discontinued. Although the mechanism of

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action is not certain, it may be related to an alteration of the oral bacterial flora.

Ince G et al Clinical and biochemical evaluation of lozenges containing Lactobacillus reuteri as an adjunct to non-surgical periodontal therapy in chronic periodontitis *J Periodontol* 2015,86 746–754

Curcumin for Ulcerative Colitis

Fifty patients with mild-to-moderate ulcerative colitis that had failed to respond sufficiently to mesalamine were randomly assigned to receive, in double-blind fashion, 3 g per day of curcumin (in 2 divided doses per day before meals) or placebo for 1 month, while continuing mesalamine. In intent-to-treat analysis, the proportion of patients who achieved clinical remission (defined as a score of 2 or lower on the Simple Clinical Colitis Activity Index [SCCAI]) was significantly higher in the curcumin group than in the placebo group (53.8% vs. 0%; $p = 0.01$). The proportion of patients who had a clinical response (defined as a reduction of at least 3 points in the SCCAI score) was also significantly higher in the curcumin group than in the placebo group (65.3% vs. 12.5%; $p < 0.001$). Endoscopic remission was seen in 38% of the patients in the curcumin group and 0% of those in the placebo group ($p < 0.05$). No significant side effects were seen.

Comment: Curcumin, a compound present in turmeric, has anti-inflammatory activity. In a previous study, administration of curcumin reduced the recurrence rate in patients with ulcerative colitis in remission. The results of the present study indicate that the addition of curcumin to mesalamine therapy was effective for inducing clinical and endoscopic remission in patients with mild-to-moderate active ulcerative colitis that had failed to respond to mesalamine alone.

Lang A et al. Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial *Clin Gastroenterol Hepatol* 2015;13 1444–1449 e1

Sugar-Sweetened Beverages and Fatty Liver

The association between intake of sugar-sweetened beverages or diet soda and fatty liver disease was examined in a cross-sectional study of 2,634 participants in the Framingham Offspring and Third Generation cohorts. After adjustment for age, sex, smoking status, energy intake, body mass index, and other potential confounding variables, the odds ratios for fatty liver disease were 1, 1.16 (95% confidence interval [CI], 0.88–1.54), 1.32 (95% CI, 0.93–1.86), and 1.61 (95% CI, 1.04–2.49) across sugar-sweetened beverage consumption categories (p for trend = 0.04). Sugar-sweetened beverage consumption was also positively associated with alanine aminotransferase levels (p for trend < 0.01). There was no association between consumption of diet soda and fatty liver disease.

Comment: In this study, increasing consumption of sugar-sweetened beverages was associated with an increased risk of fatty liver disease. Although observational studies cannot prove causation, the results are consistent with intervention studies in both animals and humans, in which high intake of fructose increased the amount of fat in the liver. In the present study, the results were adjusted for total energy intake and body mass index, which suggests that sugar-sweetened drinks cause harm by mechanisms that are at least in part unrelated to their high calorie content.

Ma J et al. Sugar-sweetened beverage, diet soda, and fatty liver disease in the Framingham Heart Study cohorts. *J Hepatol* 2015,63·462–469

Bad News About Bisphenol A Substitutes

A review of 32 studies (25 in vitro and 7 in vivo) revealed that bisphenol S and bisphenol F have endocrine-disrupting effects similar to those of bisphenol A.

Comment: Because of concerns that bisphenol A is an endocrine disrupter, this chemical has been removed from some consumer products. These products, which are often labeled "BPA-free," may contain other bisphenols, such as bisphenol S and bisphenol F. However, the evidence indicates that these other bisphenols may not be any safer than bisphenol A.

Rochester JR, Bolden AL Bisphenol S and F a systematic review and comparison of the hormonal activity of bisphenol A substitutes *Environ Health Perspect* 2015,123 643–650.

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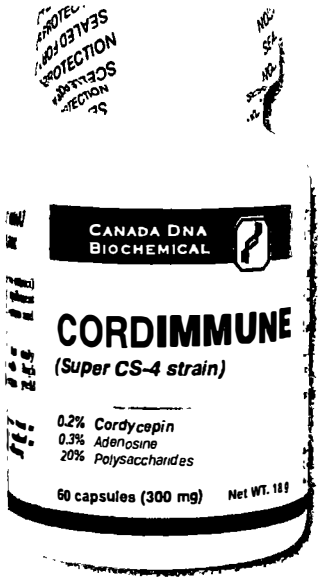

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Male Muscle Building

by Jade Teta, ND, and Keoni Teta, ND

You lose muscle as you age, there is nothing you can do about it, and it has devastating consequences for your health. For most people, this is not a surprising or controversial statement.

For years, study after study has told us that older populations have lower muscle mass. These same studies show that loss of muscle is also associated with fat gain, frailty, and negative health outcomes.[1]

But there is a problem: the statement is simply not true. Consider a September 2011 study out of the journal *The Physician and Sportsmedicine*.[2] This study looked at masters-level athletes ranging in age from 40 to 80 years old.

The researchers ran a battery of tests including in-depth questionnaires. Participants had muscle mass determined as well as muscle strength and fat percentage, among other tests. All the athletes maintained a rigorous training schedule of at least 5 days per week.

What did the researchers find? Not what you would think. Most of these highly active individuals maintained their muscle mass and strength and had little fat accumulation compared with their younger counterparts.

The one thing that the researchers did find is that after age 60, there was a slight decrease in muscle strength of the legs in both men and women. However, this change was small. Most remarkable is that even athletes in their 80s had maintained their muscle and strength compared with athletes in their 60s.

What Determines Muscle Loss as Men Age?

The results of this study, and others like it, calls into questions our old assumptions about muscle loss through the aging process.[3] The old way of thinking was, "Get old and lose it"; the new understanding brings us back to what we say to younger men, "Use it or lose it."

But there are two potential issues that we need to consider as health-care providers or savvy health consumers: (1) anabolic potential; (2) injuries and deconditioning

As muscle ages there does seem to be an "anabolic resistance" that develops largely as a result of protein absorption and utilization by the muscle. There has been debate about the mechanisms involved because older men tend to eat less protein compared with younger men.

However, there does appear to be a "blunted anabolic response" to protein consumption in older men.[4] Luckily, the research also gives us some good work-arounds to this issue. These include increasing protein intake, especially leucine-rich protein sources, and timing protein intake post workout.

Aging Muscle and Protein

While controversial in some circles, an acute bout of exercise has been shown to reverse this anabolic resistance. A fantastic review on all the particulars related to protein nutrition, as well as exercise type and timing in the elderly, was published in the November 2014 issue of *Sports Medicine*.

We highly recommend that health-care providers and savvy health consumers read this article if they have the time and education. But here is a brief synopsis of the findings of the review and current state of understanding.

It appears that postworkout protein ingestion is important and that this timing can be up to 24 hours after the session. This means that daily movement with adequate protein intake is key.

The question then becomes, what is "adequate protein intake" according to the studies? Several studies show that amount matters. Given the totality of the information gained in research so far, the threshold seems to be about 30 g or more per meal. Science has not yet given us an upper limit, but there are studies showing 40 g to be better than lower amounts. So, the consensus on amount of protein is 30 to 40 g per meal.

Another consideration is, large meals versus smaller meals? 30 to

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40 g per meal and at each meal during the day is better than doing lower amounts at some meals and higher amounts at others. One exception to this rule may be a very high amount of protein at one meal, 80 g in one study, can be effective too.

And then there are protein quality issues. Whey protein, with its quick absorption properties and high leucine content, reigns supreme in studies on protein quality. If we had to sum up the advice on protein related to overcoming anabolic resistance in an aging male, we would say the following:

1. Protein intake should be spread evenly over each meal;
2. each meal should contain 30 to 40 g protein;
3. whey protein is a convenient, highly effective protein delivery system;
4. daily exercise is critical to reverse anabolic resistance and works synergistically with protein intake in older men.

What about exercise?

As stated above, exercise is the critical component. Aging men have special challenges, especially if they have been inactive for any length of time. How do we make sure that we don't injure patients as we ramp up exercise intensity?

The first thing to realize is that weight training is crucial. While studies show that athletes who have stayed active with running and other pursuits can maintain muscle, weight training is essential to build muscle.

The concerns of weight training largely stem from the belief that heavy loads need to be employed to see benefit. This is an old belief. A 2012 study out of the *Journal of Applied Physiology* showed that workouts using light weights in higher repetition ranges (i.e., 3 sets of 30 reps) produced just as much muscle growth as did heavy weights in lower rep ranges.[2] That is very good news for older bodies, especially the deconditioned ones.

Three other tricks to accentuate muscle gains, be safer, and potentially repair damaged joints include training to failure, slow-motion weight lifting, and eccentric contractions.

For those less familiar with weight training, "failure" simply means lifting a weight until the muscle can no longer muster the force to complete the lift (i.e., muscle exhaustion). This style of training is more safely done on machines and has been shown to deliver similar muscle growth to very heavy loads.[7]

Slow-motion lifting usually involves slowing the weight-lifting movement down from a 1–2 second up-and-down cadence to a 4–10 second up-and-down cadence. This approach has been shown to produce size and strength gains similar to heavier load weight training but with less potential risk.[8]

Finally, eccentric contractions focus on the lowering portion of a lift. The idea in this style of training is to lower the weight under a slow controlled cadence. This style of contraction has shown special benefit toward tendons, including the Achilles and the tendons responsible for golfer's and tennis elbow.[9]

If you were to ask for our recommendation regarding a loading program for muscle development in this age population, it would go something like this:

1. Perform 3 sets of 10 reps of slow-motion lifts for each exercise.
2. Use a 4-second up cadence and a 7-second down cadence.
3. Do a fourth and final set to exhaustion.
4. Repeat this for all major muscle groups 1 to 2 times per week.

Final Thoughts

The idea that older men are destined to lose muscle and suffer all the well-known complications has been proved wrong in the science. We now know that much, if not all, of the muscle loss that occurs with aging is likely a result of inactivity and poor protein intake and utilization. It is not at all difficult to overcome the "anabolic resistance" of aging by correcting these shortcomings. Weight training is critical, as is getting sufficient protein at thresholds levels at each meal. Concerns regarding safety of weight training can be addressed while still providing the same benefits involved in heavier and riskier weight training.

Notes

1 Newman AB et al Strength and muscle quality in a well-functioning cohort of older adults the Health, Aging and Body Composition Study *J Am Geriatr Soc* March 2003;51(3) 323–330

2 Wroblewski AP et al Chronic exercise preserves lean muscle mass in masters athletes *Phys Sportsmed* September 2011,39(3) 172–178

3. Power GA et al Motor unit number estimates in masters runners. use it or lose it? *Med Sci Sports Exerc.* September 2010,42(9)·1644–1650

4 Moore DR Keeping older muscle "young" through dietary protein and physical activity *Adv Nutr* September 2014,5(5)·599S–607S

5 Wall BT et al. Dietary protein considerations to support active aging *Sports Med.* November 2014,44 Suppl 2.S185–194

6 Mitchell CJ et al Resistance exercise load does not determine training-mediated hypertrophic gains in young men *J Appl Physiol.* July 2012;113(1) 71–77

7 Schoenfeld BJ et al Effects of different volume-equated resistance training loading strategies on muscular adaptations in well-trained men *J Strength Cond Res* October 2014,28(10) 2909–2918

8 Tanimoto M et al Effects of whole-body low-intensity resistance training with slow movement and tonic force generation on muscular size and strength in young men *J* Strength Cond Res. November 2008,22(6).1926–1938

9 Murtaugh B et al Eccentric training for the treatment of tendinopathies *Curr Sports Med Rep.* May–June 2013,12(3)·175–182

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Green Smoothie Bliss: Was Popeye Secretly on Dialysis?

by Thomas Lodi, MD, MD(H)

There has been some confusion expressed on the Internet regarding the oxalate content in green smoothies along with a "dire warning" (in at least one article) to avoid drinking liquid sunshine.[23]

This sort of confusing rhetoric is intended to bewilder and baffle people rather than to enlighten them, and is always to be expected whenever a true healing modality directly from the loving hands of Nature (and nonpatentable) gains in popularity. And, although the compassionate intention of these commentaries to help mitigate the occurrence of calcium-oxalate kidney stones is appreciated, glaringly absent from these admonitions are warnings for people to avoid or at least reduce their intake of animal protein and refined carbohydrates which, for the population at large, should be of much greater concern than green smoothies.

Four Types of Kidney Stones

Four major types of kidney stones can form:

- Calcium stones are the most common and occur in two major forms: calcium phosphate and calcium oxalate.
- Uric acid stones result when the urine is consistently acidic. Eating purine rich food (animal protein) can result in calcium urate stones (or uric acid stones).
- Struvite stones are associated with kidney infections.
- Cystine stones are a consequence of a specific genetic disorder.

Oxalates in Human Food

There are many foods commonly found in the human diet that contain oxalates in significant concentrations including the following:

- Fruits
  - Mafuang (starfruit or carambola), berries, currants, kiwifruit, Concord (purple) grapes, figs, plums, and tangerines.
- Vegetables
  - Parsley, beet greens and roots, spinach, Swiss chard, collard greens, okra, leeks, celery, and rutabagas.
- Seeds and nuts
  - Pumpkin, squash, sunflower, poppy, quinoa (a seed), almonds, cashews, macadamia, filberts, etc.
- Legumes
  - Soybeans (tofu) and peanuts
- Grains
  - Wheat bran, wheat germ, and buckwheat
- Other
  - Cocoa, coffee, chocolate, and green and black tea.

Note. leaves contain higher concentrations of oxalates than do stems, stalks, and roots.

What are Oxalates?

Oxalates are the salts of oxalic acid, which occur naturally in many plants as a product of metabolism.

Salts (ions/charged) result from neutralizing acids and consist of positively charged cations in association with negatively charged anions in a solution, such as water. There needs to be a certain amount of water (solute) to keep the salt in its ionic form. Below a certain threshold amount of water, the cations and anions come together (precipitate) to form crystals (e.g., table salt).

Oxalates are divalent anions, which means that they can "grab" two monovalent cations, such as two atoms of potassium (see Figure 1), or one divalent cation, such as calcium, iron, magnesium, and so on (see Figure 2).

How Do Oxalates Produce Kidney Stones?

When ingested oxalates that are not bound by cations in the gut (e.g., calcium) can be absorbed directly into the blood and travel to

Figure 1
K2 Oxalate

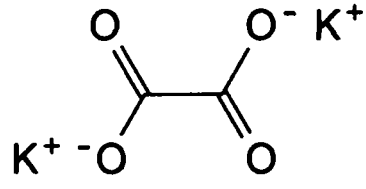
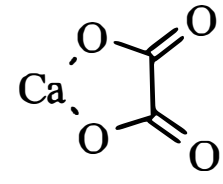


Figure 2
Calcium–Oxalate



the kidneys, where if the conditions are suitable and there is sufficient calcium present, calcium-oxalate crystals form. Whether the oxalate and calcium remain in ionic form or crystalize (precipitate) depends upon several factors, including pH (acidity), water content (hydration status), and the presence of other nutrients.

The point at which precipitation (crystallization) occurs is known as the saturation point and depends on a multitude of factors other than the oxalate content of food.*

In fact, the oxalate content of food actually has little relevance as to whether oxalate stones will form in the kidneys.

There are multiple studies on rats and humans indicating that high dietary intake of calcium actually reduces the incidence of oxalate kidney stones and, furthermore, that magnesium and potassium intake are inversely related to oxalate stone formation.

Hence, the more calcium, magnesium, and potassium that are in the diet, the more the ingested oxalates will be bound (in the intestines) and thereby excreted through the bowels rather than reabsorbed into the blood and subsequently excreted through the kidneys where they could precipitate to form crystals (stones). Additionally, the presence of adequate magnesium in the blood greatly reduces the likelihood of calcium-oxalate stone formation.

*The solubility (dissolvability) of oxalates varies greatly depending upon the cations present. The most soluble (dissolvable) are magnesium (Mg) and calcium (Ca) and the least soluble are the "heavy metals," such as lead (Pb) and mercury (Hg). Therefore, when oxalates are bound to magnesium or calcium, they are more likely to remain dissolved and not crystalize, whereas when bound to heavy metals, they crystalize quite readily

Dietary vs. Supplemental Calcium

A very important distinction needs to be emphasized between true dietary minerals (e.g., calcium) and supplemental calcium in pill or powder form. It has been shown that although high intake of dietary calcium decreases the risk of kidney stones, the intake of supplemental calcium can actually increase the risk of stone formation depending upon timing and amount.

The metabolic pathway (see Figure 3) represents the endogenous production (made by the body) of oxalates and clearly shows that kidney stones are related to dietary protein and refined carbohydrates, not to the oxalate content of food.

Furthermore, some foods that have quite high oxalate contents such as black and green tea actually appear to be preventative with regard to oxalate stone formation.

A very interesting study published in 1998 in the *Annals of Internal Medicine* evaluated just over 81,000 women aged 40 to 86 years who had no history of kidney stones. The results were quite confusing to these researchers, since for each cup of green tea consumed on a daily basis, the women's risk of kidney stones was actually reduced by 8%. In another study involving men, it was found that for each cup of tea consumed, their risk of kidney stones was reduced by 14%.

How Important are Dietary Oxalates?

It is well known that 80% to 90% of oxalates excreted in the urine are endogenously produced (made in the body), thereby decreasing the potential role of dietary oxalates to between 10% and 20%.[4,5,7,8]

Since dietary oxalate intake accounts for such a small amount of the oxalates actually found in the urine of people who form calcium oxalate stones, it is now fairly well accepted that dietary restriction of oxalate-containing foods is not a viable therapeutic intervention to prevent stone formation, except in a few rare circumstances: hypercalciuria type II and hyperoxaluria (primary and enteric).[4,5,7,8,16,21]

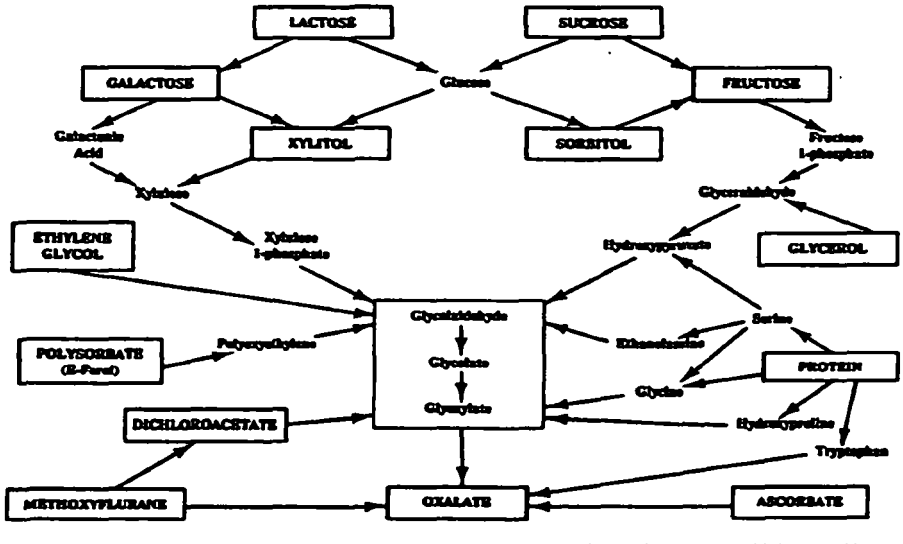
However, even in conditions involving fat malabsorption or inflammatory bowel disease (enteric hyperoxaluria), if probiotics are taken daily for 2 months, the saturation of the urine is reduced to such an extent that approximately 25% less calcium related (oxalate) stones are formed.

When any of these conditions do exist, however, the recommendation ➤

Figure 3

Schema linking carbohydrate and protein metabolism and therapeutic and toxic agent biotransformation with endogenous oxalate production.

Pathways are proved for xylitol, fructose, sorbitol, glycerol, protein, ascorbate, ethylene glycol, methoxyflurane, and dichloroacetate; pathways are postulated for polysorbate, galactose, lactose, and sucrose (see text).



Clinical Chemistry, Vol 36, No. 10, 1990 1725

Figure repnnted fron Conyers, Bela, Rolfe[6] with permission from the Amencan Association for Clinical Chemistry

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is that only about one-fourth cup of spinach or its equivalent should be consumed per day. That still leaves plenty for many smoothie recipes.

What Causes Kidney Stones?

Recent research indicates that the intake of refined carbohydrates, protein, calcium, and water are much more relevant to calcium oxalate stone formation than dietary oxalates.

The British Association of Urological Surgeons published the following, which is fully agreed on by the international medical community in all medical specialties: "Dietary advice to increase the consumption of fibre and reduce the consumption of sugar, refined carbohydrates and animal protein produced a significant reduction in the urinary excretion of calcium, oxalate and uric acid."

Animal Protein

Animal based diets generate large amounts of acid in the various fluid departments of the body, hence the kidneys respond by excreting all excess acids to maintain an alkaline pH in the blood and ECM (fluid bathing the cells).

Calcium, in the form of calcium bicarbonate (Ca[HCO3]2), calcium carbonate (CaCO3), and calcium phosphate (CaPO4), is released from the bones (in order to neutralize the excess acid), where it enters the blood, the extracellular fluid (ECM), and through the kidneys, thereby increasing the amount of urinary calcium available to precipitate with oxalates to form stones. This homeostatic response by the body to maintain functional integrity, however, results in a net calcium loss from the bones (osteoporosis).[11,17–19,21]

In other words, calcium is leached from the bones to neutralize the acids formed by consuming animal protein, resulting in supersaturation of calcium in the urine available for stone formation and less calcium in the bones (osteoporosis).[11,17–19,21]

Additionally, animal protein is the major dietary source of purines, which are broken down into uric acid that leads to uric acid kidney stones and excruciatingly painful crystals in joints (gout).

Of great import, it should be noted that dietary vegetable protein consumed in high amounts does not contribute to these same pathological changes in uric acid metabolism and calcium metabolism, hence does not lead to gout, osteoporosis, kidney stones, or kidney failure, as do large amounts of animal protein.

"A study conducted in the UK showed that a diet low in animal protein reduced the prevalence (occurrence) of urinary stone formation by 40–60%"[17]

"A high animal protein intake causes a significant increase in the urinary excretion of calcium, oxalate, and uric acid, 3 of the 6 main

urinary risk factors for calcium stone formation."[16]

"High amounts of dietary protein can lead to increases in both calcium and oxalate levels in the urine. The elevated protein results in lower urine pH – an acidic environment that makes it easier for calcium oxalate kidney stones to form. It also decreases citrate levels in the urine that help prevent kidney stones from forming. ..."[9,15,16]

Refined 'Naked' Carbohydrates

Refined carbohydrates are fruits, vegetables, and legumes or grains that have been stripped of most nutrients except the simple sugar. Nature does not produce isolated, simple carbohydrates (sugars) but rather complexes, which include all macronutrients (e.g., proteins and fats), enzymes, vitamins, and cofactors in sufficient quantities required to metabolize the natural, complex carbohydrates in that particular plant appropriately. There is no excess of these "cofactors" in plants, so that when carbohydrates are isolated (stripped) from their accompanying nutrients, the body must "borrow" the necessary cofactors in order to metabolize these "naked carbohydrates."[13,15,22]

Of note: Cooking vegetables, fruits, and grains is one method of turning a wholesome food into a "refined carbohydrate"; cooked vs. raw carrots is an example.

Calcium

Hypercalciuria (excess calcium in the urine) is thought to be partially mediated through the insulin/glucagon pathways, which are required to metabolize carbohydrates and can result in hypersaturation of urinary calcium with a concomitant increase in calcium-oxalate stone formation (as well as calcium urate and calcium phosphate). Calcium-oxalate stone formation is specifically increased in individuals with an abnormal insulin response.[10,13,15]

Other variables that mediate calcium saturability are magnesium, potassium, and water.

Magnesium

Refined carbohydrates (e.g., sucrose) disturb magnesium balance in the body by depleting magnesium levels in the metabolic requirements necessary to process simple sugars. Magnesium is required for ATP (energy) formation. Magnesium is essential for stimulating hormonal and enzymatic responses to put calcium into the bones and out of the blood and urine (kidneys). Another one of magnesium's many functions is to keep calcium in solution, which prevents it from crystalizing; hence, even when dehydrated, if there is sufficient magnesium, calcium will stay in solution. Finally, magnesium directly binds to oxalate in the gut, allowing it pass through without being reabsorbed.[7-10,14]

Green Smoothie

➤

If there is not enough magnesium to keep calcium in solution, various forms of calcification will occur from stones, muscle spasms, fibrositis, fibromyalgia, and atherosclerosis (calcified plaques in the arteries). In fact, magnesium has been used effectively to prevent recurrent kidney stones.

Chlorophyll-Magnesium

Every green plant derives its color from chlorophyll, the molecule that transforms sunlight into biologically available energy, ATP. Even those plants that are not green have chlorophyll that is being masked by higher concentration of anthocyanins (red/purple) or carotinoids (yellow/orange), the other two pigments found in plants.

Chlorophyll is chemically a porphyrin ring, just like the "heme" in our hemoglobin (blood). But, unlike our blood, which has iron in the center, the chlorophyll molecule has magnesium in the center of every porphyrin ring.

Clearly then, every plant, green and otherwise (including spinach) has abundant magnesium and calcium and potassium. In fact, this combination of minerals certainly contributes to the universal finding that vegetarians have significantly less kidney stones (including calcium oxalate) than humans who have "derailed" and gone astray down the omnivore path, eating diets not dissimilar from their canine friends who are certainly much further away on the phylogenetic tree than their close cousins, the tailless primates who refrain from such indiscriminate scavenging.

"Vegetarian diets are associated with low excretion of calcium, oxalate, and uric acid and may lower the risk for urolithiasis in a number of ways. These include the absence of animal protein and provision of higher amounts of magnesium and potassium, both of which are associated with lower risk for stone formation."[14]

Water

All of these substances in the blood are contained in the "water" portion of the blood. Water, keep in mind, is the "universal solvent."As the proportion of water increases, crystals "disappear" and then reappear when the relative amount of water decreases. In the biological system, this is referred to as "hydration" and "dehydration" As the Mayo Clinic advises, "Not drinking enough water each day can increase your risk of kidney stones. People who live in warm climates and those who sweat a lot may be at higher risk than others."

Another one of the numerous benefits of eating uncooked (raw) vegetables and fruits is that they have not had the water removed via the cooking process. Even when food is cooked with water, such as boiling or steaming, it is the water within the cells of the food (plant or animal) that is removed, thus removing the milieu necessary for life.

So, in a soup where all the ingredients are "drowning" in water, it is the "intracellular water" that has been removed by the heating process and along with it, the "life force," or electromagnetic tension that defines life.

This is the reason that people are not thirsty after eating fruit or a purely vegetable salad. The food is completely hydrated; hence the hydration status of the eater is not changed. Dehydrated food, through the law of osmosis (thermodynamics), extracts water from the body to satisfy this nonnegotiable law of nature and hence the body's homeostatic mechanisms elicit "thirst" to compensate for the water loss.

So, God's Wearing a White Coat These Days?

The European Molecular Biology Organization in 2011 published an article, "Molecular Breeding of Healthy Vegetables," to provide a rationale for why science is in the process of usurping God's (Nature's) role.

The purpose of the article was to "[discuss] recent attempts to characterize and modify phytochemicals in vegetable crops by using molecular approaches, focusing on those modifications that are of interest to consumers."

The article explains how scientists are attempting to "hide" what they have determined as important and eliminate what they have determined is unnecessary in fruit, vegetables, and nuts (seeds).

This way food producers can "attempt to break into the US $18 billion snack-food industry," like they did in 2010 with "creation" of "baby carrots."

Greed and outrageous arrogance are easily concealed under the pretense of beneficence whose rhetoric hypnotizes the gullible with words such as, "About 3 billion people in the world are malnourished due to imbalanced diets. Vegetables can contribute to the prevention of malnutrition disorders. Genetic engineering enables vegetable breeders to incorporate desired transgenes into elite cultivars, thereby improving their value considerably."[23]

These plant breeders and scientists have determined that certain foods contain "antinutrients" defined as "naturally occurring compounds with inhibitory effects on the nutritive potential of plants." The goal, then, is to reduce certain nutrients and increase others according to their understanding of nature.

Nature is incomprehensibly complex; hence altering one aspect will only induce the biological imperative to maintain homeostasis and purpose. Even the scientists recognize this, citing "specific function of calcium oxalate accumulation in plants is not known; it might have a role in calcium regulation, ion balance, plant protection, detoxification or light gathering."[23] Nevertheless, since 1994, there have been attempts to lower the oxalate content of certain vegetables.[1,3]

continued on page 38 ➤

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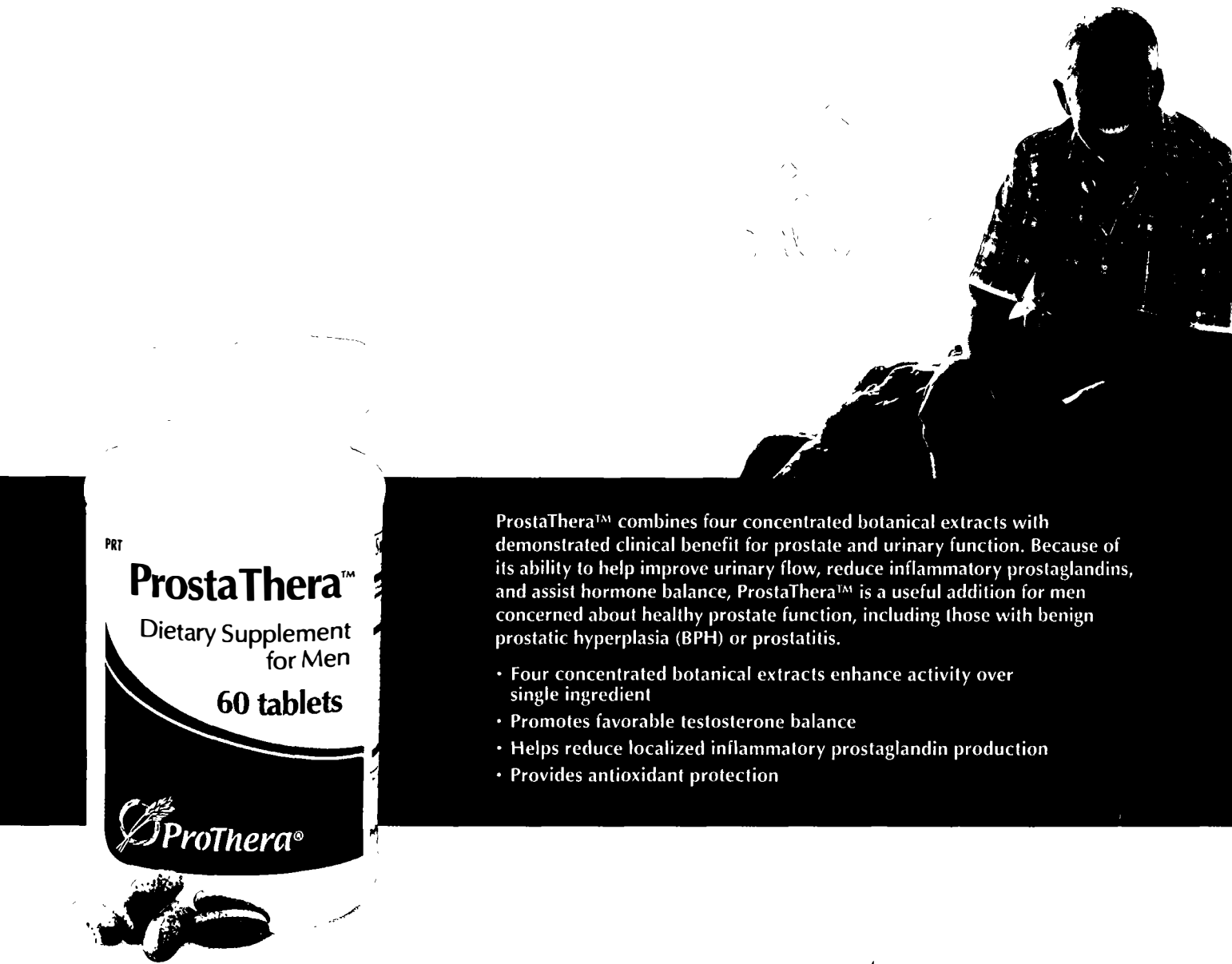

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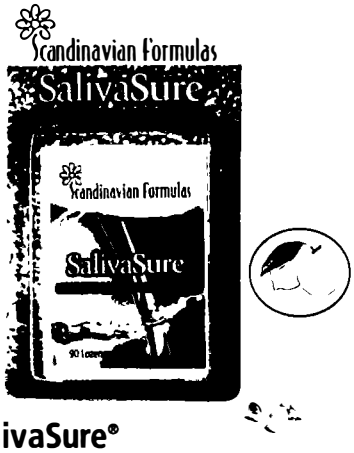

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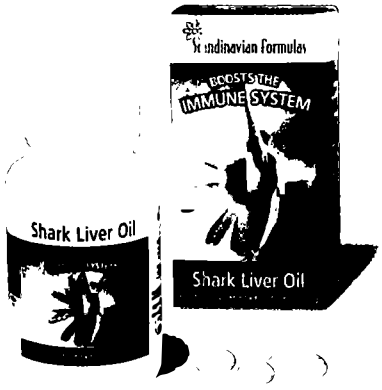

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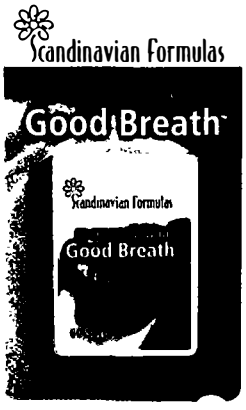

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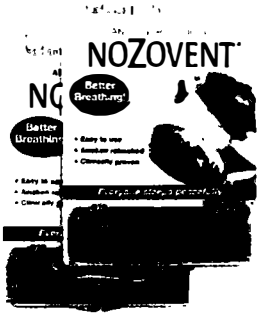

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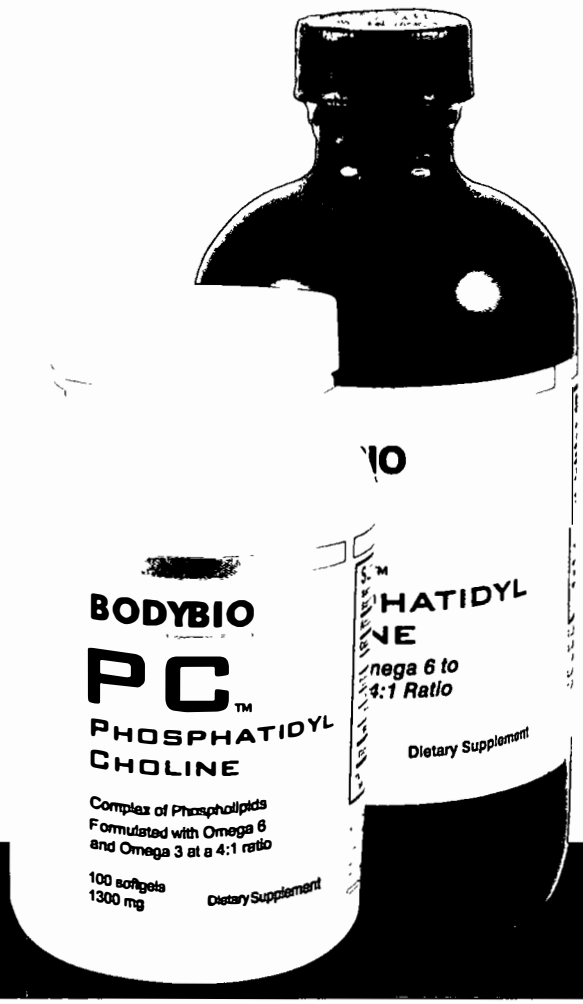

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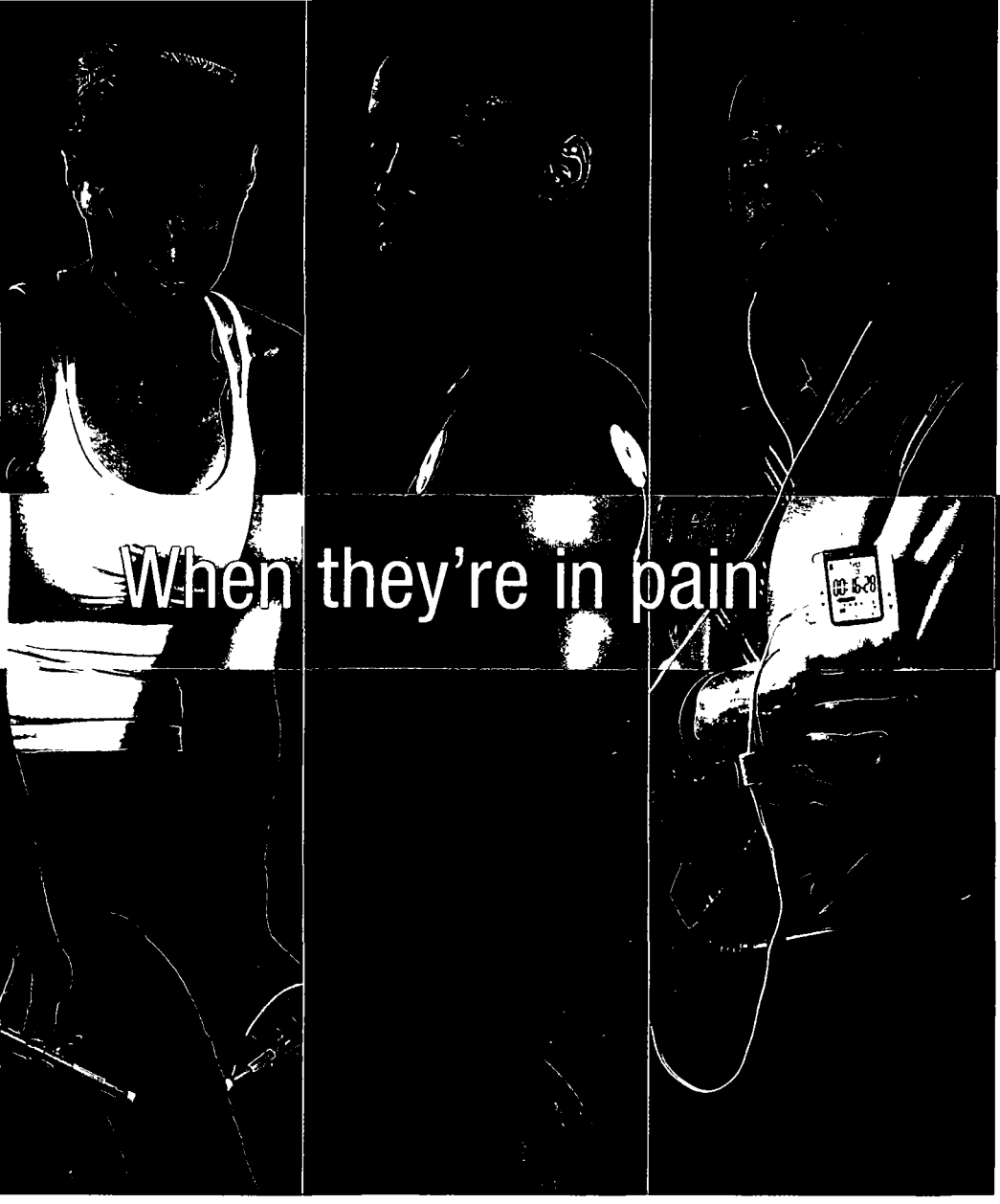

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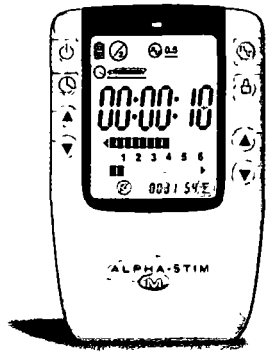

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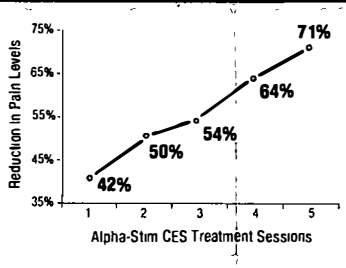

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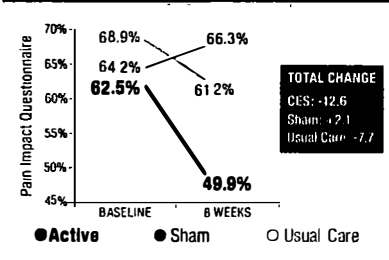

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Green Smoothie

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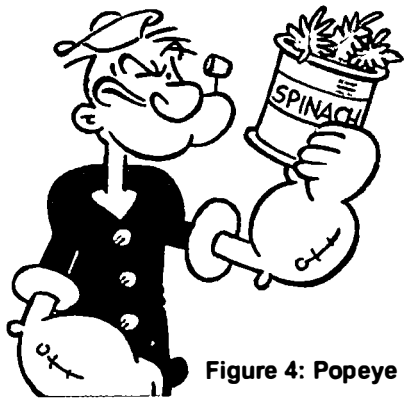

Figure 4: Popeye

Molecular biology labs around the world have been highly involved with the "molecular cloning of oxalate decarboxylase gene to remove nutritional stress (oxalic acid) from plants" since the 1990s.

Dire Warning

Whether or not articles on the Internet are meant to obfuscate and overwhelm the reader with disinformation or are merely a product of naïve ignorance or are driven by ego requirements, it is imperative at this time in human history that we maintain a vigilant stance to protect our biology and life on planet Earth.

Clinical Experience

Over the past 10 years, we have designed and supervised over 1000 green juice "feasts" wherein people mostly with advanced stages of cancer (some early stages) would stop eating solid food and drink 3 to 5 quarts per day of freshly prepared juice for a duration of 1 to 4 weeks.

Although the juice recipe was adjusted occasionally for individual taste, each was a slight variation of our primary recipe of spinach, kale, celery, cucumber, green apple, and lemon.

After the "feast," these people transitioned into a raw, vegan diet, which included green smoothies each morning. They are given the knowledge and tools to continue this dietary regimen after leaving the center and are followed closely for approximately 9 to 12 months, after which they modify their diets to include 20% to 30% cooked, vegan food. This modified 80:20/70:30 regimen always includes daily green smoothies and green juice along with a diet of abundant unprocessed fresh vegetables, fruits, and nuts.

During this 10-year period, we have had zero incidences of calcium oxalate or calcium urate stones. Furthermore, I began this program 4 years prior in New York where, again, we had zero incidences of calcium oxalate crystal formation in the kidneys of our patients.

The experience at our center is not unique. There are five well-known centers in the US (and many lesser known) providing the same services and countless others in Canada, Europe, Australia, and New Zealand. Furthermore, we are seeing this awakening occur in Singapore, Malaysia, Philippines, Thailand, Hong Kong, and China.

Note: May I refer the reader to an easy-to-locate video which follows two very unhealthy, obese men for 60 days of juice "feasting" (and the sequel), *Fat, Sick & Nearly Dead* (1 & 2) Again, no stones!

Conclusion

Unless one has hypercalciuria type II and hyperoxaluria (primary and enteric), there is no reason to avoid healthful foods that contain natural oxalates found in plants. And, in fact, the research corroborates our clinical findings (over 15 years) that drinking green juices and smoothies is not only

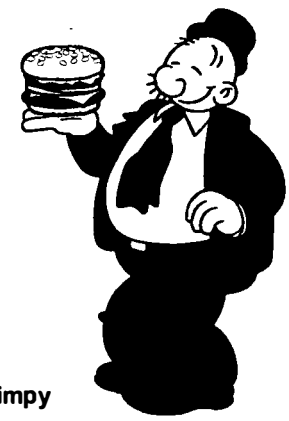

Figure 5: Wimpy

health-promoting in multitudinous ways but actually protective against the development of kidney stones, both calcium-oxalate and urate varieties.

The vast majority (80% to 90%) of oxalates found within the body are produced endogenously (from within) in the liver as an aspect of glycolate (carbohydrate) metabolism.

Precipitation of oxalates to form calcium-oxalate crystals (coalesce into "stones") only occurs under very specific conditions related to hydration (water) status, pH of the urine, and the concentration of calcium, magnesium, and potassium.

The biochemical milieu in the blood and kidneys that favor stone formation is directly correlated to the intake of refined carbohydrates and animal protein and inversely correlated with amount of natural sources of calcium, magnesium and potassium (fresh green vegetables, fruit, and seeds/nuts).

Happily, Then

Our staff and patients (>1000 people) have remained oxalate and uric acid stone free over 15 years by drinking a minimum of 1 to 2 quarts per day of fresh green vegetable juice, enjoying a green smoothie, and eating abundantly of the green leafy vegetables, fruits and nuts/seeds that are, for the most part, prepared without employing the destructive force of fire (not cooked).

This daily dietary regimen is augmented 3 to 4 times per year with green juice "feasts" for on an average of 10 to 14 days.

Thomas Lodi, MD(H), MD, CNS, is the founder of An Oasis of Healing in Arizona (Integrative Oncology Center) as well as the founder of the Institute of Integrative Oncology in Asia, which consults and certifies various cancer centers throughout Eastern and Southeast Asia. In addition to using an integrative approach with regard to medical interventions, he both teaches and provides training in life-style to modify the body's biochemistry and align the mind-body-sprit continuum such that malignancies and other chronic "diseases" resolve back into a healthy homeostasis.

Finally

We don't have a lot of biographical information regarding Popeye; however, looking at his image (Figure 4), one can see that he was thin, energetic, affable, and strong; and, considering his competence in battle, apparently quite healthy. Furthermore, there were no dialysis catheters inserted into his bare arms in all of the images ever produced of our spinach-obsessed hero, who may have been a vegetarian ... for all we know.

J. Wellington Wimpy, on the other hand (Figure 5), ate substantial amounts of animal protein and refined carbohydrates with apparently little or no vegetables (spinach). Furthermore, he always wore a long-sleeved coat, perhaps to conceal his dialysis catheters ... one can only speculate.

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Nutritional Antioxidants and Testosterone Secretion: Natural Methods to Increase Testosterone in Men

by Michael J. Glade, PhD; Kyl Smith, DC; and Michael M. Meguid, MD, PhD

Keywords: Low testosterone, Leydig cells, oxidative stress, antioxidants, phosphatidylserine

"Low normal testosterone status" ("Leydig cell impairment"), with midmorning serum total testosterone concentrations between 7 nmol/L and 14 nmol/L), is affecting an increasingly large proportion of men who are middle-aged and older.[1] A relatively recently recognized clinical condition, low normal testosterone status is associated with lack of energy, motivation, initiative, self-confidence, concentration, and memory; poor sleep quality; replacement of muscle bulk and strength and skeletal structure with body fat; impaired work performance; depressed outlook; and increased systemic inflammation and oxidative stress. These overt signs and symptoms are accompanied by reduced life expectancy that is associated primarily with increased risks for developing any form of cardiovascular disease, especially fatal or nonfatal cardiovascular events.[1]

It is becoming increasingly evident that chronically elevated systemic oxidative stress is a "root cause" of low normal testosterone status, exposing the primary testosterone-producing Leydig cells of the testes to oxidative damage that inhibits the synthesis and secretion of testosterone. Equally convincing evidence demonstrates that reducing oxidative stress releases Leydig cells from oxidative inhibition, allowing testosterone synthesis in response to luteinizing hormone (LH) to recover and reestablish normal-for-age circulating testosterone concentrations. The available reliable data obtained from well-designed studies show that otherwise healthy men who consume dietary nutrients and phytonutrients with antioxidant properties can enjoy the combined and mutually beneficial health advantages of oxidative stress reduction and enhanced androgenic status. In a society embracing the attitude that "60 is the new 40," maintaining healthy testosterone status through dietary oxidative stress reduction is eminently sensible.[1]

Oxidative Stress Impairs Leydig Cell Testosterone Secretion

Leydig cells experience increased levels of oxidative stress during aging, after exposure to environmental prooxidants, and when testosterone synthesis is stimulated.[2-9] Because the mitochondrial electron transfer system supplies the energy that drives testosterone synthesis in response to LH, producing a surge of oxidizing free radicals that themselves can overwhelm an underprepared antioxidant defense system, additional chronic endogenous factors (such as aging) and environmental stressors act in concert to suppress testosterone status.

The aging-associated decline in testosterone status is a consequence of cumulative oxidative stress within Leydig cells.[2,3,9-11] Oxidatively damaged Leydig cells and Leydig cells in aged testes exhibit suppression of antioxidant enzyme activities, reduced intracellular glutathione content, accelerated lipid peroxidation and oxidative modification of DNA, and loss of the mitochondrial membrane potential required for testosterone synthesis.[2,3,9-17] In addition, they become less sensitive to LH, with fewer LH receptors per cell and impaired ability of LH to activate steroidogenic acute regulatory (StAR) protein-catalyzed transport of cholesterol from the outer mitochondrial membrane to the inner mitochondrial membrane, a rate-limiting step in testosterone synthesis.[16,18-22] Furthermore, the activities of several enzymes of the testosterone biosynthetic pathway are reduced and testosterone synthesis is inhibited in oxidatively stressed adult human testes.[23] In contrast, a reduction in systemic oxidative stress in mice reduces oxidative stress within Leydig cells and increases the rate of testosterone secretion.[24]

➤

Nutritional Support for Healthy Testosterone Synthesis

The body of scientific evidence indicates that oxidative stress reduction sustains and restores testosterone production. Consistent with this hypothesis, several nutritional antioxidants (e.g., the phytonutrients in pomegranates, vitamin C, vitamin E, α-lipoic acid, zinc, selenium, and phosphatidylserine) contribute to a reduction in systemic and local oxidative stress, stimulation or reversal of inhibition of testosterone synthesis, and enhancement of androgenic status.

Pomegranates. In adult rats, intraperitoneal injection of pomegranate polyphenols prevented carbon tetrachloride (CCl4) inhibition of testicular antioxidant enzyme activities and promoted LH-stimulated testosterone synthesis.[25] The consumption of the pomegranate polyphenol, ellagic acid, blocked adriamycin-induced testicular lipid peroxidation and inhibition of testosterone synthesis in young male rats.[26]

Vitamin C. Vitamin C directly stimulates LH secretion by the pituitary, testosterone synthesis by Leydig cells, and increased serum total testosterone concentrations in healthy male rats.[27–29] Vitamin C supplementation prevents oxidative suppression of testosterone synthesis in animals exposed to cadmium, lead, cyclophosphamide, or arsenic trioxide, and upregulates testicular testosterone synthesis.[30–35]

Vitamin E. Vitamin E (α-tocopherol), a powerful chain-breaking lipid-soluble dietary antioxidant, attenuates oxidant-induced lipid peroxidation in adult male rat testes in vivo.[36,37] Dietary vitamin E prevents the oxidative inhibition of testicular testosterone synthesis induced by exhaustive exercise, cadmium, chromium VI, and sodium azide.[30,38–42] Combined dietary supplementation with vitamin E and vitamin C prevents oxidative inhibition of testosterone synthesis by arsenic trioxide.[43] Leydig cell responsiveness to LH is proportional to the amount of vitamin E that is present.[37] Supplemental vitamin E (483 mg daily for 8 weeks) increased testosterone synthesis an average of 20% in healthy men.[44]

α-Lipoic Acid. Exposure to bisphenol A (BPA) inhibits the activities of antioxidant enzymes in Leydig cells, increases intracellular lipid peroxidation, and attenuates testosterone synthesis in adult rats and in cultured rat Leydig cells.[45,46] In contrast, dietary supplementation with α-lipoic acid has prevented or attenuated these detrimental effects on testosterone status.[45]

Zinc. Chronic zinc deficiency produces testosterone deficiency and, in healthy men, the serum total testosterone concentration is directly correlated with dietary zinc intake. Increased dietary zinc intake can stimulate testosterone synthesis in men and improve testosterone status.[48,47]

Selenium. Dietary selenium deficiency impairs testosterone synthesis in response to LH.[49] However, supplemental selenium attenuates or prevents the inhibition of testosterone synthesis caused by exposure to several oxidants, including cadmium, sodium azide, or di(2-ethylhexyl) phthalate.[42,50–52]

Phosphatidylserine. Testicular cells are enriched in phosphatidylserine and require phosphatidylserine for full activation of testosterone synthesis.[53–55] By initiating androgenic signaling cascades and through direct stimulation of testosterone synthesizing enzymes, dietary phosphatidylserine directly enhances testosterone status.[54–56] For example, in a double-blind, randomized, placebo-controlled study, healthy men with initially "desirable" resting plasma free testosterone concentrations and participating in a prescribed exercise regimen supplemented their diets with 600 mg of phosphatidylserine daily for 10 days.[57] Supplemental phosphatidylserine produced a 60% greater increase in resting plasma free testosterone concentration than was produced by placebo.

Conclusions

Human aging often is accompanied by excessive endogenous and exogenous oxidative stress. Oxidatively damaged Leydig cells exhibit decreased responsiveness to LH and impaired testosterone synthesis. On the other hand, antioxidant defenses that can be augmented by dietary supplementation with specific antioxidant nutrients can reduce oxidative damage to Leydig cells, removing oxidative inhibition of testosterone synthesis, increasing testosterone secretion, and safely improving testosterone status with beneficial effects on human male health.

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Traumatic Brain Injury: Recognition and Treatment Options for Mild Injury and What Can We Learn from Failed Clinical Trials

by Sara Wood, ND

Over the past several years, there has been increasing media coverage of the dangers of head trauma and especially of the repeated traumas seen in many professional sports and experienced by deployed military troops. Symptoms attributed to chronic head trauma include depression, apathy, anxiety, cognitive changes, attention issues, and aggression. Damage occurs in two parts during a traumatic brain injury (TBI); the cumulative insult to brain tissue is generally attributed to both the primary injury (mechanical damage from shearing, tearing or stretching of neurons, blood vessels, and other cellular structures) and secondary injury mechanisms, including the release of excitatory neurotransmitters, mitochondrial dysfunction, depolarization, and the initiation of inflammatory and immune processes that can compromise the blood–brain barrier (BBB) and contribute to edema, increases in intracranial pressure, and ischemia.[1,2]

There is emerging evidence that the disruption in the BBB allows passage of a protein into the immune system where it triggers an inflammatory autoimmune response, and that even subconcussive hits to the head contribute the levels of this protein as well as autoantibodies.[3] In other words, a significant portion of the damage done in a TBI occurs in the hours/days/months after the event and repeated head trauma that is *too minor to cause* a *concussion* is causing an inflammatory reaction in the brain, which leads to a wide array of symptoms, including many that are among the most commonly reported mental health issues faced by Americans in general.

Many have taken the headlines and high-profile stories of injury as reasons to keep their children from playing high-contact sports, or called for changes in regulations for the use of safety gear, which are all good efforts to prevent the primary event from occurring.[4] However, regardless of precautions taken, head injuries remain remarkably common even in the general population, with falls, motor vehicle accidents, and assaults among the most common causes.[5] Most people have had at least one, and possibly several, incidences of concussion or head trauma in their lives. There are some populations in which the incidence of brain injury is higher than average, including children under age 4, teens, and the elderly. Concussion rates are as high as 4% in children and adolescents, although these events are often underreported, as the signs and symptoms can be subtle, delayed, and varied.[6] Mild brain injury is underdiagnosed even among those who seek treatment in trauma centers, and it is still estimated that more than 1.7 million people in the US suffer from a TBI annually.[7,8] Additionally, 10% to 20% of returning veterans have

Primary Injury	Secondary Injury
Occurs at the moment of initial trauma and may include	Consequences of the immune reaction to the initial trauma and may include
• Direct force to the head	• Edema and compression of the brain
• Impact of the brain against the skull	• Ischemia and hypoxia causing cell death
• Shearing or physical tearing of the neurons or blood vessels	• Increase in intracranial pressure
• Damage to the blood brain barrier	• Release of excitotoxic neurotransmitters
• Bruising or intracranial bleeding	• Formation of oxidative free radicals

Glasgow Coma Scale

	Eye Movement	Verbal Skills	Motor Skills
1	Doesn't open eyes	Makes no sounds	Makes no movement
2	Opens eyes in response to painful stimuli	Incomprehensible sounds	Extension to painful stimuli
3	Opens eyes in response to voice	Utters inappropriate words	Abnormal flexion to painful stimuli
4	Opens eyes spontaneously	Confused, disoriented	Flexion / Withdrawal to painful stimuli
5	N/A	Oriented, converses normally	Localizes painful stimuli
6	N/A	N/A	Obeys commands
	Severe: < 9	Moderate: 9-12	Minor: >13

Teasdale G Jennett B Assessment of coma and impaired consciousness A practical scale Lancet 1974 13(2)81-4

suffered a traumatic brain injury, the majority of which are classified as mild but can still lead to postconcussive syndromes that increase the risk for PTSD and suicide.[9]

Recognizing these injuries and providing proper care as soon as possible is imperative for recovery, as secondary injury mechanisms can continue far beyond the original incident, and symptoms can persist for months. Early intervention requires accurate and prompt diagnosis, and while severe TBI patients are likely to be seen in trauma centers, those experiencing mild trauma may not even realize that they have experienced a brain injury. Assessment of the severity of a TBI is typically done using the Glasgow Coma Scale (GCS), a 3–15 point scale that assesses a patient's level of consciousness and neurological function, although this scale is not as sensitive to mild injuries.[10] Common symptoms of mild brain injury often include vague symptoms such as fatigue, headaches, sleep disturbances, depression, irritability, anxiety, and cognitive changes. These symptoms may not appear for days or weeks after the injury, making diagnosis difficult, and in up to 20% of patients they may persist beyond a year following the injury.[11,12]

The primary immune defense mechanism in the central nervous system (CNS) is the stimulation of microglial cells, specialized macrophages that when activated, secrete inflammatory cytokines, free radicals, and excitotoxins such as glutamate and aspartate.[13] Once activated by an initial event, these cells remain primed and, when they receive subsequent stimulation, can be hyperreactive, requiring a smaller stimulus to release even higher levels of pro-inflammatory substances.[14] The subsequent stimulation may be additional trauma, but may also be a toxic insult, infection, or inflammatory immune signals from elsewhere in the body, and these incidences may be separated by several months.[15]

Initial treatment for those who are identified as having experienced a brain injury typically involves avoiding vigorous activities, the use of NSAIDs or other anti-inflammatory methods, and close monitoring. Much of the ongoing research in treating TBIs is focused on limiting the secondary injury processes, including inflammation and excitotoxicity; however, more than 30 phase III clinical trials for TBI treatment have failed, despite exhibiting promising preclinical data.[16,17]

Progesterone

One of the seemingly promising areas in treatment of TBI has been the administration of progesterone. Born of the observation that gender influenced clinical outcomes in TBI cases, a hormonal influence on brain inflammation was investigated.[18,19] Progesterone, a steroid hormone produced primarily in the ovaries in women and the testes in men, but also in small quantities in the adrenal glands and in the neurons, has been recognized in several protective mechanisms in regard to neurodegeneration.[20–22] Progesterone receptors are present in the CNS of both men and women.[23]

Progesterone has been shown to reduce cerebral edema, downregulate the inflammatory cascade, decrease postinjury ischemia, reduce glutamate-related excitotoxicity, enhance the effects of GABA, and protect mitochondrial function in animal models.[24,25] Early human models included several randomized, double-blind, placebo-controlled phase II clinical trials, and they showed an improved outcome in progesterone-treated patients. with a lower 30-day and 6-month mortality rate than the controls. These studies didn't consider mild TBI cases; however, the difference between the treatment and control groups was more dramatic in the moderate traumatic brain injury survivors than in those who had experienced severe brain injury.[26,27] Additionally, neither of these phase II trials discovered any complications or adverse events associated with the administration of progesterone. These studies, though small, indicate that progesterone shows great promise as a neuroprotective agent following traumatic brain injury and have led to some larger phase III trials.

Unfortunately, the phase III clinical trials for progesterone were not as promising as their preclinical studies. The two studies released early this year seem to have joined the growing body of failed clinical trials in treatments for TBI.[28,29] While it is possible that progesterone simply doesn't have the beneficial effects that it was thought to have after the first several hundred investigational studies, numerous other factors may influence the outcome of these studies, as well as the findings in phase III trials for other TBI treatments, including the immense variance in the types of injuries that the subjects have experienced, the part of the brain affected, the participants' overall health to start with, potential delays in the initiation of treatment, the subjectivity of diagnosis, and insensitive outcome measures.[30] The participants in both of the failed phase III progesterone trials were severe or moderate TBI patients, with whom recovery is generally slower (and may not be detectable at the 6- or 12-month mark) as well as less likely overall. ➤

Suggested therapies for mild TBI

Therapy	Recommended Dosages	Mechanism of Action in TBI
Progesterone	25-50 mg transdermally or 100-200 mg orally for women 10-20 mg transdermally or 50-100 mg orally for men	• Reduces cerebral edema • Reduces glutamate excitotoxicity • Protects mitochondria
Omega-3 Fatty Acids	3000-4000 mg/day *(dosage may need to be altered in those using blood thinning agents)	• Reduces lipid peroxidation and maintains cell membrane integrity • Stimulates brain derived neurotrophic factor (BDNF) • Enhance production of anti-inflammatory leukotrienes
Vitamin D	5000-10,000 iu/day or dosage required to achieve 60-80 ng/ml in serum	• May reduce IL-6 • Regulates calcium flux • Modulates immune response
Curcumin	2-4 g/day of Menva or other highly absorbable form	• Reduces oxidative damage • Stimulates BDNF • Reduces cerebral edema • Reduces microglial activation and neuronal death

While much additional research is needed in the treatment of all TBI cases, including those that are moderate to severe, it may be time to revisit basic anti-inflammatory and neuroprotective strategies, especially those that can be easily employed for the large percentage of TBI cases that are mild, including those "minor" head injuries that may be overlooked due to their delayed and vague symptom presentation. Limiting damage from secondary injury mechanisms is the most important step in controlling symptoms and preventing additional neuronal destruction. In addition to continuing to prevent primary injury to the brain, including wearing protective gear when engaging in higher-risk behavior, it is important to ensure the brain is getting adequate perfusion, that the BBB integrity isn't compromised, and that free radicals and reactive oxygen species produced as part of the immune response are quenched as to not propagate neuronal damage. Many of the following nutrients may be used reactively in the event of a random head injury such as a fall or car accident, as well as proactively for those who are regularly engaging in behavior that puts them in danger, including contact sports or active military combat.

Omega-3 Fatty Acids

Omega-3 fatty acids, including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexanoic acid (DHA), are essential to maintaining the structural balance of cell membranes throughout the body and have reduced lipid peroxidation and protein oxidation in TBI models.[31] Additionally, omega-3 fatty acids have been shown to increase the levels of brain-derived neurotrophic factor (BDNF), which is required for the survival of neuronal cells, and omega-3 fatty acids are precursors to anti-inflammatory leukotrienes and promote modulation of inflammation in general and neuroinflammation specifically.[32,33]

Vitamin D

A potent regulator of the immune system and inflammatory responses, circulating vitamin D can cross the BBB and therefore limit an inflammatory response.[34] Though there have been few studies on the effects of vitamin D alone on TBI, there has been a favorable outcome using vitamin D in conjunction with progesterone as well as an established relationship between vitamin D deficiency and increased inflammatory cytokines in general.[35,36] Animal studies indicate that vitamin D deficiency correlated with elevated IL-6 and other inflammatory markers post injury compared with vitamin D-replete subjects.[37] Additionally, vitamin D regulates intracellular calcium throughout the body and can downregulate voltage sensitive calcium channels, altering calcium flux that affects neurogenesis, synaptogenesis, myelination, and neurotransmitter release in the brain.[38] Unfortunately, up to one-third of the US population may be deficient in vitamin D.[39] Repletion of this important nutrient preinjury as well as treatment at the time of insult may improve recovery from a TBI and reduce symptoms associated with postconcussive syndrome.[40]

Curcumin

Curcumin is the principal antioxidant found in turmeric, a plant that is part of the ginger family. There are several mechanisms through which curcumin limits the damage caused by TBI. Supplementation with curcumin prior to injury has been demonstrated to reduce oxidative damage, normalize levels of BDNF, and counteract cognitive impairment after TBI.[41] Acute TBI often results in significant cerebral edema, increased intracranial pressure (ICP), and decreased blood flow. Curcumin has shown promise in reducing cerebral edema, both when given prophylactically and immediately following injury by reducing glial cell activation and increasing the activity of specific aquaporins, which are channels that regulate fluid levels.[42] And even when only administered after an injury, curcumin has been shown to improve patient outcomes by reducing microglial activation and neuronal cell death.[43] Curcumin is safe even at relatively high doses (12 grams/day), although there are some reported issues with the bioavailability of the molecule due to poor absorption and rapid metabolism. Advances in curcumin supplements, including the use of liposomal curcumin, curcumin nanoparticles, and the complementary use of agents that interfere with the metabolism, have greatly improved the clinical efficacy of curcumin.[44] Randomized, double-blind, crossover trials of the lecithin formulation of curcumin (Meriva) have discovered a 29-fold higher total curcuminoid absorption compared with standard curcumin mixtures.[45]

Traumatic brain injuries remain quite common, and while ongoing research is being conducted to find safer and more effective treatments for moderate to severe TBIs, there is much that can be done to prevent and treat mild brain injury beyond increasing helmet use. Because much of the damage in any TBI is due to secondary mechanisms, lowering inflammatory potential in at-risk groups and treatment with agents that help to control secondary insult in the event of a brain injury are needed. Proper screening and diagnosis of subconcussive and mild injury is imperative so that the proper action can be taken. Though there have been many failed phase III trials for TBI treatment, the patients enrolled in those studies were primarily in the moderate to severe category, which not only decreases their chance of recovery but also makes their clinical progress difficult to track. By taking a proactive approach with at-risk populations as well as a more active role in the treatment of mild brain injury, there are many ways we can reduce the chronic effects of head trauma that contribute to the depression, anxiety, and cognitive dysfunction that affect so many people. Additionally, as we learn more about the ongoing inflammatory component of TBI, and especially as

we look at that in the context of long-term effects on mood, behavior, and cognition, it's important to acknowledge that there are many things beyond physical trauma that can contribute to inflammation in the brain and CNS, including infections and diet. While it's possible that many people who are experiencing fatigue, depression, anxiety, and difficulty concentrating may be doing so as a result of repeated head trauma, others may be experiencing these symptoms due to the chemicals they have been exposed to, infectious agents, or systemic inflammation. Reducing inflammatory processes in the central nervous system is a likely to be of benefit regardless of the source of insult.

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Dr. Wood grew up in Colorado and obtained her undergraduate degree in biochemistry from Colorado College. An enthusiasm for science but a passion for people led her to medicine, and a desire to treat the cause of disease, not just the symptoms, led her to naturopathy. After completing her doctorate at the National College of Naturopathic Medicine, Dr. Wood stayed in Oregon and has a private practice focused on endocrine imbalance, digestive dysfunction, immune support, and cardiovascular health.

In addition to her clinical practice, Dr. Wood is a staff physician with Labrix Clinical Services Inc., where she educates physicians and health care providers around the country about hormonal balancing through development of educational materials, contributions to a webinar series, and lectures at local and national conferences. In 2008 she coauthored a book on andropause titled *His Change of Life: Male Menopause and Healthy Aging with Testosterone.*

Applying Nutrigenomics to Cardiovascular Medicine: Prevention and Treatment

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

Nutrigenomics provides us with an expanded perspective on the prevention and treatment of cardiovascular disease. In cardiovascular management, nutrigenomics encompasses genetic testing, metabolomics, the identification of single nucleotide polymorphisms (SNPs) and nutrient-genetic interactions, and the newest concept, gene expression testing. These tests provide indication of whether or not your patients' genetics are expressed and their risk of cardiovascular disease.

Most genetic expression is driven by inflammation, and the majority of the genes, once turned on, promote an inflammatory response. Most of the loci on genes associated with MI, CHD, and CHF are expressed through inflammation, oxidative stress, and immune-vascular dysfunction. This dynamic starts in the vascular endothelium, vascular smooth muscle, and cardiomyocytes, leading to angina, coronary artery vasospasm, obstructive coronary heart disease, diastolic and systolic dysfunction, and cardiomyopathy. Regardless of the type of insult, blood vessels respond to insults via three fundamental mechanisms: inflammation, oxidative stress, and immune-vascular dysfunction.

Consequently, the inflammatory pathways have become the primary focus in the management of genetic expression and of genetic risk for CVD. That management goes beyond an emphasis on the top five traditional risk factors such as hypertension, dyslipidemia, diabetes, obesity, and smoking. It is probable that 80% or 90% of outcomes in cardiovascular disease are not genetic per se, but actually reflect environmental influences on genetic expression. Reduction and prevention of CHD is not likely to improve without using genetic markers and gene expression testing to identify these underlying risk factors.

Nutrients. Nutritional factors provide information that determines whether our genes are turned on or turned off, with a corresponding beneficial or detrimental outcome. One change in a single ubiquitous nutrient such as magnesium may cause 300 or 400 different changes in downstream metabolic pathways and cardiovascular function and health. This is just one example of environmental influences and the importance of genetic expression. When there is interference with a metabolic pathway, a single area of abnormality can result in a myriad of defects and a spoke-like effect, resulting in a ripple of downstream changes in many metabolic pathways.

Epigenetics. There are several issues we want to define when we initially examine patients. One is their genetic profile, the genes they were dealt. The genetic profile includes their proteome, transcriptome, metabolome, and to some extent the gut microbiome. The gut has a tremendous influence, obviously, on cardiovascular illness.

Genetic Trends in Cardiovascular Disease

- Genetic predisposition to CHD accounts for less than 50% of the susceptibility to CHD depending on gender, age, ethnicity and other factors.
- Positive family history increases risk of CHD by less than 3%.
- If onset of heart disease occurs before age 46, genetics account for approximately 100% of risk.
- There are 30 to 60 loci associated with MI and CHD, but only a minority of loci mediates effects on CHD through the known top five risk factors.
- More than 50% of these genetic variants occur in over 50% of the population. Ten of the risk variants occur in over 75% of the population.
- Homozygotes for 9p21 SNP have 100% increase in risk and heterozygotes have 50% increase in risk.
- In the Swedish Twin Registry, genetic factors accounted for 57% of risk for CHD in men and 38% in women.

There are also epigenetic influences that are not genetic such as DNA methylation, histone modification, and non-coded messenger RNA. These influences are not in the genetic code, but can be passed on from mother to fetus and from generation to generation. The final aspect is gene expression, as genes express themselves in response to nourishment or insults from different types of information coming in from the environment. Genetic polymorphisms and transcription factors must also be included in the general workup to determine if a patient is at risk for cardiovascular disease. Genetics have become important in determining not only dietary intake, but also medication intake in many patients, based on their genetic profile.

There are more than 400 known risk factors for cardiovascular disease. Aggregating all these risk factors, regardless of their mechanism of action, it becomes clear that they all ultimately result in the same three finite responses in the body: inflammation, oxidative distress, and/or immune dysfunction. These risk factors ultimately translate into vascular disease.

Diet

Mediterranean Diet. We know the Mediterranean diet (MedDiet) turns on numerous beneficial genetic pathways that can reduce risk for cardiovascular disease, as well as risk for type II diabetes, so this is currently one of our best strategies for disease prevention. If our patients consume a Western diet, that will result in totally different outcomes in terms of gene expression, since most of the foods included in a Western dietary pattern have been shown to express 30 to 40 different inflammatory and immune pathways.

The MedDiet has an advantageous effect on genes such as transcription factor 7. If you can turn off that one gene, you can reduce the risk of diabetes by as much as 40%. In a clinical trial of this diet, other prevalent beneficial effects were related to atherosclerosis and hypertension. The Mediterranean diet, in combination with CoQ10, has been shown to be the most beneficial intervention for healthy aging, and preventing processes and diseases related to chronic oxidative stress and CHD. Changes in genetic expression toward a protective mode were often associated with improvement in systemic markers for inflammation, immune function, oxidative stress, hypertension, and CHD:

- Modulating 43% of genetic pathways, including nine pathways in response to diets emphasizing olive oil, and four pathways with diets emphasizing nuts.
- Decreasing oxidative stress, high sensitivity C-reactive protein (hsCRP), and interleukin 6 (IL-6).
- Increasing oxidative defenses, enzymes, hippurate, and phenols, while improving mitochondrial function, fatty acid beta oxidation, and ATP energy production.
- Preventing cardiovascular diseases with a relative risk reduction of 30% and reduced diabetes mellitus by 40%.

Pritikin and DASH Diets. The Pritikin diet is one of the most effective ways to turn off the gene expression that increases risk for cardiovascular disease. As reported in recent *Annals of Internal Medicine*, the Pritikin diet can reduce risk of cardiovascular disease by as much as 30% to 35%. That benefit is directly correlated with the diet itself, but is also enhanced when supplementing with nutrients such as CoQ10. The DASH-1 and DASH-2 diets have also been found beneficial in relation to changes in inflammatory genes and improved response to the types of medications prescribed for hypertension.

Specific Nutrients

Electrolytes. These nutrients, particularly sodium, potassium, and magnesium, can change genetic expression, salt sensitivity, intravascular volume, blood pressure, risk for heart disease, risk for coronary heart disease, heart attack, cardiac arrhythmias, and congestive heart failure. In terms of salt sensitivity, for example, there are genetic variations between Caucasians and African Americans. One of the most important is cytochrome P4A11 (expressed as CYP4A11), which relates to sodium and water diuresis and the role of the epithelial sodium channel (ENaC) function. ➤

Top 25 Environment and Functional Risk Factors for Cardiovascular Disease

- Hypertension (24 hour ABM)
- Dyslipidemia (advanced lipid testing)
- Hyperglycemia, metabolic syndrome, insulin resistance, and diabetes mellitus
- Obesity/body composition
- Smoking/tobacco
- Hyperuricemia
- Renal disease
- Elevated fibrinogen
- Elevated serum iron/ferritin
- Trans fatty acids and refined carbohydrates
- Low dietary intake of omega 3 fatty acids and omega 3 index
- Low dietary potassium and magnesium with high dietary sodium intake
- Micronutrient deficiencies
- Caffeine intake with CYP 1A2 SNP, IF/IF allele
- Inflammation: increased hsCRP
- Increased oxidative stress and decreased oxidative defenses
- Immune vascular dysfunction/imbalance
- Lack of sleep
- Lack of exercise/sedentary lifestyle
- Stress, anxiety, and depression
- Hyper-homocysteinemia
- Subclinical hypothyroidism
- Hormonal imbalances in both genders
- Chronic clinical or subclinical infections
- Heavy metals
- Environmental pollutants

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Patients who have resistant hypertension due to CYP4A11 who are treated with the drug Amiloride, have dramatic reductions in blood pressure and often can discontinue or reduce the dose of other anti-hypertensive drugs.

Omega Fatty Acids. Omega 3 fatty acids affect huge numbers of genes that reverse changes in our metabolic profile and in our transcriptome, genes that can improve beta oxidation, mitochondrial health, mitochondrial biogenesis, and transcription factors. As a result, ATP production goes up, cells are healthier, and patients live longer. We know that omega 3 fatty acids by themselves have dramatic effects on PPARs and many nuclear receptor proteins that function as transcription factors such as retinoid X receptors, liver X receptors, and farnesoid X receptors. These receptors can have dramatic influences, reversing inflammation, oxidative stress, blood pressure, and risk for heart disease. It is also very important to balance omega 3s and omega 6s in a way that achieves these beneficial effects and reduces inflammation. Assessing the omega 3 pathway and determining the omega 3 index in the red blood cell can lead to specific treatments to improve CVD:

- In specific studies, omega 3 fats changed expression of 610 genes in men and 250 genes in women.
- Omega 3s improved cardiovascular markers, decreasing saturated GPC (glycerol phosphocholine) and LPC (lysophosphatidylcholine), and increasing oxidative stress defense factors, nuclear transcription factors, acylcarnitines, hexose, and leucine.
- Polymorphisms contribute to the complexity of nutritional effects seen with omega 3s and their role in reducing cardiovascular disease, inflammation, glucose levels, and lipids.

Monounsaturated Fats. Lipids such as olive oil that contain oleic acid can also have a positive impact on different SNPs and PPAR receptors, improving coronary heart disease and diabetes mellitus, while reducing oxidized LDL. Even without the MedDiet, olive oil given as a supplement can have dramatic and highly beneficial influences on genetic expression related to the three finite vascular responses for reducing cardiovascular disease.

- Extra virgin olive oil (EVOO), taken for 6 weeks at 20 grams (<1 1/2 tablespoons) per day in healthy adults improved 133 of 238 proteomic biomarkers for CHD, CKD (chronic kidney disease), dyslipidemia, and DM.
- EVOO down-regulated CHD genes; reduced oxLDL, glucose levels, AGEs (advanced glycation end products), HbA1C, ROS (radical oxygen species), collagen peptides, and inflammation; and prevented some forms of atherosclerosis.
- EVOO upregulated cholesterol efflux capacity (CEC), improved reverse cholesterol transport (RCT), and increased HDL-C.

Gut Metabolites. We've also known that changes in the gut microbiota, particularly those various microbiomes that metabolize phosphatidylcholine, L-carnitine, and other vital nutrients, can produce changes that are relevant to cardiovascular disease. This is another example of why the gut is so important in determining what happens within the cardiovascular system.

- Gut microbiota signatures (GMS) act as important determinants in the pathogenesis of inflammatory-induced obesity, CHD, atherosclerosis, and T2 DM.
- High-fat intake and elevated glucose in the presence of altered GMS promote increases in lipopolysaccharides (LPS), endotoxins from the cell walls of gram negative bacteria that can lead to ED and atherosclerosis. LPS crosses the enterocyte barrier coupled with lipoproteins, stimulating the innate immune system, TLR4 in adipocytes, and vascular tissue, activating NFkb, and increasing inflammation, oxidative stress, and immune dysfunction.
- A diet of saturated fatty acids (SFA) and/or high refined carbohydrates (CHO) increased LPS concentration by 70%, as well as gram negative concentration in the gut.
- SFA and CHO decreased bifidobacteria levels. Similar reductions occurred in association with obesity, DM, MS, and NAFLD, promoting alterations in the intestinal barrier and enterocytes leading to increased intestinal permeability.
- Increases in the abundance of *Pseudomaoadaceae* were observed in CVD patients compared to healthy individuals.
- *Firmicutes* species are lower in CVD patients, and CHD plaque also has higher ratio of *Pseudomaoadaceae* to *Firmicutes* bacteria and DNA.
- Higher *Prevotella* species relative to *Bacteroides* are reported in patients with high TMAO and CHD.
  Healthy flora becomes very important in maintaining a healthy gut microbiome, and of course, one must nourish the flora with good prebiotics to assure health.
- Diets with fermentable fibers, prebiotics, probiotics, and plant polyphenols favorably regulated microbial activities and decreased gram negative bacteria within the gut.
- *Saccharomyces boulardii* increased HDL and improved serum lipid levels.
- Certain probiotics were found to reduce blood pressure.

Genes Relevant to Cardiovascular Risk

Gene 9p21. One of the primary genes we are now measuring is the 9p21 gene, which increases the risk of atherosclerosis and coronary heart disease. Patients who have a heterozygote SNP for 9p21 have a risk for MI that is increased by 50%. When a patient has a homozygote SNP, risk goes up to approximately 100%, so this is one of the top genetic risks that we measure for CHD and MI. The 9p21 gene is associated with coronary heart disease and MI, but also with cancer through the MTAP (methylthioadenosine phosphorylase) pathway. However, there are many other genes that should also be evaluated, not just for coronary heart disease, but also for hypertension and dyslipidemia. A gene called GLU 1q25, for example, increases the risk of heart disease in diabetics, related to glutamic acid, glutamine synthesis, and insulin levels.

Apo E4 Genotype. The Apo E genotype is not new information, but we must remind ourselves that this genotype increases risk for CVD and people with the genotype have varied responses, particularly to different types of fats in their diet. Consequently, it is important that their genotype be identified before starting these patients on specific types of nutrients such as omega 3 and 6 fats. Management of risk factors for patients with the APO E4 allele addresses issues such as:

- Increased cholesterol absorption and delayed clearance, resulting in higher serum LDL.
- Increased CVD risk with smoking and alcohol intake and overall increased incidence of CHD, CVD, MI, Alzheimer's, and dementia.
- Inability to repair vascular endothelium to produce nitric oxide.
- Less response to statins.
- Best reduction of LDL occurs through dietary restriction of carbohydrates, with low fat diets, and omega 3 fatty acids.
- Response to phytosterols and cholesterol absorption

COMT Polymorphisms. One of the newest genes that we're looking at is COMT (catechol-O-methyltransferase) which provides instructions for the breakdown of norepinephrine and epinephrine. If this genetic SNP is present, the patient will have higher levels of norepinephrine and epinephrine and increased risk of hypertension and coronary heart disease. There is a variation in response depending on which of the specific COMPT SNPs the patient carries; for example, aspirin or vitamin E may be beneficial for patients with one type of COMT SNP, but detrimental if one of the other SNPs is present.

Glutathione-Related SNPs. The risk of myocardial infarction can be increased by 71% if a SNP affecting glutathione metabolism (GSH-Px) is present. This selenium-dependent enzyme expresses different capacities to neutralize hydroxyl radicals and other oxidative molecules related to increases in oxidative stress and CVD. For these patients, glutathione peroxidase and selenium levels would be key measurements to track for the risk of CVD:

- Low GSH-Px is a major CHD risk factor.
- Higher levels of glutathione peroxidase support more rapid recycling of glutathione, resulting in higher availability of glutathione.

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Testing for Early Detection and Prevention of Cardiovascular Disease

1. Genetic Expression Scoring and Testing: Corus CAD.
2. Top five CHD Risk Factors treated to new goals:
   a. Hypertension: 24 hour ambulatory BP monitor (ABM).
   b. Dyslipidemia: Advanced lipid testing.
   c. Dysglycemia: FBS, 2h GTT, HbA1c, insulin, proinsulin, C-peptide.
   d. Obesity: BW, BMI, WC, WHR, body impedance analysis (BIA).
   e. Tobacco: stop all forms.

Genetic Testing

1. 9p21 (GG/CC) (inflammation, plaque rupture, thrombosis, AAA, ASCVD, CHD, MI, DM, IR)
2. 6p24.1 (CHD and DVT)
3. 4q25 (atrial fibrillation)
4. ACE I/D (DD allele) (HBP, LVH, CRI, nephroangiogenesis microalbuminuria. carotid IMT, CHD, MI)
5. COMT: Val/Val or Met/Met allele (CHD, MI, HBP and use of ASA and vitamin E)
6. 1q25 (GLUL) (CHD in DM)
7. APO E (E4/E4) (CHD, lipids, dietary response, omega 3 FA)
8. MTHFR (A1298C and C677T) for methylation (endothelial dysfunction, hypertension, thrombosis, CVD, CHD, MI, CVA and hyper-homocysteinemia).
9. CYP 1A2 (IF/IF) and caffeine (HBP, MI, CHD, tachycardia, stiff aorta, PWV, AI, SBP, PP, vascular inflammation, increased catecholamines)
10. Corin (hypertension, volume and sodium, CHF with ANP and BNP, CRF, CVD, eclampsia)
11. CYP 11 B2 (TT allele) (HBP and aldosterone)
12. GSH-Px (glutathione peroxidase) (ALA-6 alleles, selenium) (CHD and MI)
13. NOS 3 (Nitric oxide, HBP and CHD)
14. ADR B2 (AA allele vs GG allele) (HBP, PRA and DASH diet and RAAS drugs)
15. APO A1 and A2 (lipids)
16. HETE CYP4AII and CYP4F2 (HBP, sodium and volume overload, ENac) (amiloride)
17. MMP-2, MMP-9, and TIMP-1 (cardiovascular remodeling, DD, LVH, CHF, and hypertension)
18. AGTR1, NR3C2, HSD11B1, and B2 (HBP, potassium) and AGTR1 (AA/AC) and ARB response
19. AT1R-AA (AT1R autoantibodies); hypertension (ARB vs ACEI)
20. Blood group type A, B, and AB (vWF and thrombosis)

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- Increased glutathione peroxidase (GSH-Px) decreases BP, MI, LVH, and CHF.
- GSH-Px confers more cell, tissue, and organ protection than SOD (superoxide dismutase) or catalase, or the combination of both.

Hypertension. There is a whole host of genetic influences on blood pressure, probably 30 different genes that we have recognized to date, all of which are helpful in determining both risk for hypertension and risk for cardiovascular target organ damage, as well as response to nutrients, caffeine, medications, and various types of diets. We know, for example, that someone who consumes large amounts of caffeine and has the SNP cytochrome P-450-1A2 will increase their risk of tachycardia, hypertension, aortic stiffness, and myocardial infarction. Of course, one could have the right type of SNP for caffeine detoxification and that will reduce their risk. Approximately 60% of the population has cytochrome P-450-1A2FF, which is the wrong kind of gene to have, because they are slow metabolizers and their risk for CHD and MI actually go up with caffeine consumption. Before you tell patients it's okay to be drinking caffeine, you need to check the gene for cytochrome P-450 function.

Conclusions and Key Take Away Points

- Evaluate and treat the Top 5 CHD Risk Factors utilizing the new definitions and testing methods.
- Evaluate and treat the Top 25 Modifiable CHD Risk Factors.
- Evaluate micronutrient testing (MNT).
- Evaluate specific genetics, SNP's, genetic expression testing (Corus CAD, GET, and GES), epigenetics and metabolomics for CVD, CHD, hypertension, and dyslipidemia.
- Obtain noninvasive CV testing (Endopat, CAPWA, TMT, CAC, CTA, Carotid IMT, rest and exercise ECHO, MCG, ABI, AAA, 24 hr ABM).
- Traditional Mediterranean diet (TMD) with 5 tablespoons EVOO/day (50 grams) and CoQ10.
- Modified low glycemic DASH 2 for hypertension. B2-AR AA/GG alleles.
- 10 servings of fruits and vegetables per day (6 veg/4 fruit).
- High mixed fiber (40 grams), prebiotics, and probiotics general and specific species (alternating species).
- Omega 3 fatty acids for all patients, dose dependent (1- 5 grams per day of balanced DHA, EPA, GLA and gamma-delta tocopherol).
- 2 grams sodium, 5-10 gram potassium and 1000 mg magnesium/day.
- Avoid caffeine in CYP 1A2 SNP (IF/IF and IF/IA alleles).
- Selective use of ASA, vitamin E depending on COMT phenotype (met/met).
- 5 methyl folate and B vitamins depending on MTHFR genotype.
- Selenium with GSH-Px (ALA 6 alleles).
- Specific anti-hypertensive drug selection based on genotypes such as ACE I/D, Corin, CYPII B2, HETE and CYP 4A11, AGTR1, and AGTAA.

Lab Testing

You want to be able to measure whether your patients' genes are expressing inflammation, oxidative stress, or immune dysfunction, which will put them at increased risk for cardiovascular disease.

Measuring Genetic Expression. A test is now available that measures gene expression; this evaluation, with the acronym Corus CAD, is available from a company in Southern California, CardioDx. The evaluation uses a score of 0 to 40, expressing the patient's risk for obstructive coronary heart disease. This evaluation is very accurate, highly sensitive, has published studies, and good medical background information. We use not only genetic testing for SNPs, but also the Corus gene expression test to determine patients' risk at baseline. Once you have established the baseline, you can do an intervention, and then repeat the test in about six months to see if that intervention is reducing the gene expression testing score, which implies that you are reducing the risk for future cardiovascular events.

Metabolomic Testing. Changes in endothelial physiology and biochemistry, reflected in metabolites, often precede hypertension by decades. One strategy applied in a series of studies evaluated just 36 of the known 4,229 metabolites, primarily dicarboxylacylcarnitines, medium- and long-chain acyl carnitines, and fatty acids. Successful prediction of various forms of CVD risk were made in study after study, in patients at risk of CHD, coronary artery disease, adverse events after coronary artery bypass grafting, and those at increased risk due to the effects of aging. Metabolic measurement predicted CVD beyond any degree possible using readily available clinical characteristics and other CHD risk factors.

Cardiovascular SNPs. Obviously, there are large numbers of cardiovascular SNPs that we could check. At this point I recommend testing for those that have the best validation, the highest correlation with risk prediction, and those that are easily attainable. Currently 23andMe provides far too much information. The genetic tests listed in the table here define risk for coronary heart disease, arrhythmias, heart failure, and hypertension; these are the genetic factors I recommend that you look at in all your high-risk cardiovascular patients. From these tests and the Corus gene expression test, you will be able to determine the nutritional programs, medications, and other interventions the patient requires. Most of these tests can be obtained through Boston Heart Lab, Cleveland Heart Lab, Vibrant America Lab, Quest Labs, Doctor's Data, Genomics, Genova, or Pathway Genomics; there are also a number of companies that offer various test panels. I use a checklist of the companies that provide the best genetic testing, and for each patient, I simply check off the relevant tests for that individual and submit the list.

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Dr. Mark Houston is an author, teacher, clinician, and researcher, currently Associate Clinical Professor of Medicine at Vanderbilt University School of Medicine, Clinical Instructor in the Department of Physical Therapy and Health Care Sciences at George Washington University, Director of the Hypertension Institute and Vascular Biology and Medical Director of the Division of Human Nutrition at Saint Thomas Hospital in Nashville, TN. Dr. Houston was selected as one of the Top Physicians in Hypertension in the US in 2008–2014 by the Consumer Research Council, and by USA Today as one of the Most Influential Doctors in the US in both Hypertension and Hyperlipidemia twice in 2009–2010. He was selected for The Patient's Choice Award in 2010–2012 by Consumer Reports USA. He is triple boarded certified by the American Board of Internal Medicine (ABIM), the American Society of Hypertension (ASH) (FASH) and the American Board of Anti-Aging and Regenerative Medicine (ABAARM, FAARM). He holds two Master of Science degrees, one in Human Nutrition from the University of Bridgeport, Connecticut, and another in Metabolic and Nutritional Medicine (University of South Florida School of Medicine-Tampa). Dr. Houston has presented over 10,000 lectures nationally and internationally and published over 250 medical articles and scientific abstracts in peer reviewed medical journals, as well as book chapters and books.

Books

Stephen T. Sinatra and Mark C. Houston (editors). *Nutritional and Integrative Strategies in Cardiovascular Medicine*. Boca Raton, FL: CRC Press; 2015.

Dr. Stephen Sinatra and Dr. Houston are coauthors of a book on integrative cardiovascular medicine published in spring 2015 by CRC Press, available on Amazon.com and in various book stores. This is one of the first and only books that takes an integrative approach to cardiovascular medicine from the perspective of functional medicine, metabolic medicine, nutrition, nutritional supplements, and pharmacology. The book discusses all the essential aspects of cardiovascular disease, written for health care providers.

Other best-selling books by Dr. Houston include *What Your Doctor May Not Tell You About Heart Disease* (Grand Central Publishing, 2012); *What Your Doctor May Not Tell You About Hypertension* (Time-Warner Books, 2003); *The Handbook of Hypertension* (Wiley-Blackwell, 2009); and *Vascular Biology in Clinical Medicine* (Hanley and Belfus, 2002).

Workshop — January 27, 2016
Scripps Natural Supplements: *An Evidence-Based Update*
Preconference in San Diego
Integrative Cardiovascular Symposium
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Editorial

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Bovine Colostrum: The Anti-Aging Revolution: What Athletes Can Teach Us About Staying Young

Part 1

by Douglas A. Wyatt
Director, Center for Nutritional Research

Aging is generally accepted as a normal and inevitable part of the human experience. And, the quest for longevity is almost equally normal and inevitable. We are more determined than ever to avoid the physical and mental ravages of modern diseases and to enhance quality of life. The end of humans' long search for the Fountain of Youth may be well within reach, not to mention sitting right in front of us all along. My argument has always been that athletic performance and staying young are essentially the same concept, and that anyone can employ similar strategies to maintain their youthfulness as do athletes trying to improve their performance. A more complete understanding of the connection between aging and athletic performance will demonstrate the beneficial role of bovine colostrum supplementation in both.

Professional athletes have always sought ways to enhance their performance, achieve better results, and gain an advantage over their competitors. The Olympian, or "superathlete," takes this to new heights, and in a world where performance is measured in milliseconds, any natural substance that enhances endurance and strength and reduces recovery time determines who wins the gold and who wins the silver. Many of today's superathletes are turning to bovine colostrum as a means to that coveted edge. The growth hormones in bovine colostrum help burn fat, build lean muscle, build strength, shorten recovery time, balance blood glucose levels, and prevent illness after vigorous exercise. Colostrum's ability to maintain lean body mass, facilitate fat loss, repair tissue, and accelerate healing is just as significant for an athlete as for an aging person. 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, sagging skin, and wrinkles, as wells as a plethora of autoimmune conditions. Is it possible that the poorly aged adult is simply an untrained, underperforming athlete?

Decline in Growth Hormone Production

The outward signs of aging are the result of the body's beginning to taper off its production of growth hormone following maturity, at around age 20 with a 15% decline every decade. By late adulthood, growth hormone levels are generally less than half the levels during early adulthood. Although this is normal, both athletes and aging adults have been lured by the promise of youth, vitality, and increased muscle mass from synthetic human growth hormone (HGH). Contrary to popular belief that HGH injections will increase muscle mass, growth hormone does not possess anti-aging properties in and of itself. Instead, growth hormone stimulates insulinlike growth factor (IGF-1 and IGF-2) production in the liver, which is responsible for cellular reproduction in all tissues. Furthermore, manufactured HGH by nature of its recombinant DNA origins is only 70% bioidentical to natural growth hormone. As a result, HGH injections may lead to cancer, joint pain, carpal tunnel syndrome, arm and leg swelling, glucose intolerance, increased risk of diabetes, and gynecomastia. Conversely, growth hormones in bovine colostrum are nearly bioidentical to growth hormones in the human body, many of which actually help prevent cancer, improve glucose tolerance, and reduce inflammation and pain. Colostrum is the only food source of all the growth hormones required by the human body.

Unlike injectable HGH and synthetic IGF-1, colostrum is not a banned substance. The International Olympic Committee (IOC) launched an inquiry into whether powdered bovine colostrum was a potentially banned substance following a higher than anticipated number of medals won by the Australian Olympic

team in the 2000 and 2004 games.[1] The Australians claimed that their winning advantage was attributable to their athletes' colostrum supplementation during training.[2,3] The IOC determined that colostrum was instead a superfood, and their ruling provided athletes with a safe, viable, and legal alternative to doping and other banned substances. The only downside to colostrum supplementation was that athletes needed 60 grams/daily, a rather large dose, to achieve results.

Growth hormones in bovine colostrum, such as IGF-I, IGF-2, and transforming growth factor (TGF-alpha and TGF-beta) have regenerative effects that 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.[4,5]

Because the body produces fewer growth hormones and fewer antioxidants with age, reactive oxygen species can damage DNA, proteins, and lipids, thereby accelerating aging. Insufficient antioxidant production is believed to be a contributing factor in cancer, cardiovascular disease, cataracts, brain dysfunction, and immune system decline.[6] It's also been hypothesized that telomeres are the key to aging and cancer by the role that they play in maintaining the structural integrity of DNA. Chronic oxidative stress compromises telomere integrity.[7] As DNA strands become shorter with aging, they eventually become too badly damaged to replicate new cells, and senescence is associated with aging, cancer, and shorter lifespan due to an overall increased risk of death.[8-10] Geneticists have found that people over age 60 who have shorter telomeres were 3 times more likely to die from heart disease and 8 times more likely to die from an infectious disease than people with longer telomeres.[11] Bovine colostrum contains telomerase, an enzyme that helps preserve telomeres, thereby allowing identical, undamaged cells to replicate over and over.

Increasing Lean Body Mass/Burning Adipose Tissue

Increasing lean body mass and burning adipose tissue is critical for the high-caliber athlete, and it also plays an important anti-aging role in preventing those extra pounds from accumulating as metabolism slows and inactivity becomes more common. Once again, growth hormone and IGF-1 enter the equation, and increasing these naturally (and legally) can only be achieved in one or two ways: first, by performing weight-bearing exercise 1 to 2 hours daily, every day of the week, which does cause the body to increase IGF-1 production, but not significantly; second, by supplementing a sensible exercise program with bovine colostrum, which is certainly more realistic. Studies with Colostrum-LD showed that a dose of just 20 grams/day was necessary for the growth hormones to exert their fat-burning action.[12] Due to significant developments in colostrum processing, results could be achieved at one-third the dose used in earlier studies. Additionally, the desired results occur after 4 to 8 weeks of supplementation, and maintenance of health benefits requires consistent daily use.

The IGF-1 in colostrum is the *real growth hormone* that promotes muscle growth and favors adipose stores over glucose as a fuel source.[13] IGF-1 is primarily produced by the liver and production is stimulated by growth hormone. IGF-1 is the only natural hormone capable of promoting muscle growth by itself. Although synthetic IGF-1 is banned by the IOC, naturally occurring IGF-1 in bovine colostrum supplements is not, and IGF-1 is abundant in bovine colostrum. During vigorous exercise, colostrum slows protein breakdown and stimulates glucose transport in muscle. Muscles are then able to make more efficient use of the fuel available to them, which results in an increase in lean muscle mass without a corresponding increase in adipose tissue. Long-term colostrum supplementation increases IGF-1 levels.[14] Daily colostrum supplementation benefits skeletal muscle tissue by reducing the oxidant-induced damage during exercise.[15]

Colostrum supports maintaining a healthful body weight, whether it be keeping the weight on or keeping it off. Approximately one-third of adults over 60 suffer from sarcopenia, a major cause of falls and subsequent disability.[16] Colostrum contains nine essential amino acids and nine nonessential amino acids that spare and synthesize muscle tissue. Leucine, of which colostrum contains significant quantities, promotes muscle synthesis by activating a signaling pathway that stimulates the body's anabolic drive.[17,18] As aging muscle becomes resistant to leucine stimulation, colostrum supplementation can help overcome the deficit, prevent further muscle

degradation, and promote new muscle tissue. Colostrum also benefits individuals with muscle wasting syndrome due to cancer, rheumatoid arthritis, AIDS, or other malignant disease by boosting muscle mass.

Conversely, colostrum supplementation can be a potential therapeutic treatment/prevention strategy for obesity. Bioactive peptides and amino acids enhance hormone release which leads to increased satiety and thus decreased food intake. Colostrum contains leptin, and elevated leptin levels accelerate the satiety signals from the stomach to the brain, thereby curtailing overeating and excess calorie consumption. It is, however, important to note that many people initially experience minor weight gain when they first begin supplementation, which is due to the increase in lean muscle mass.

Blood Glucose Homeostasis

Keeping blood glucose levels consistent throughout the day avoids catabolism, in which muscle protein is broken down into amino acids for fuel. When a person's glucose level begins to drop within two hours of the last meal, those amino acids are converted to glucose in order to raise the blood glucose back into homeostasis to ensure that the brain has a consistent fuel supply. The body is very efficient in this process, but rather self-defeating if the goal is to preserve or increase muscle tissue. During the fasting state between meals, the body is essentially consuming its muscle tissue to fuel the brain. Anabolism is the buildup of muscle protein from amino acids. Having some protein in the body's gas tank keeps the brain fueled and maintains muscle tissue. IGF-1 plays a critical role by preventing catabolism and promoting anabolism.

The blood glucose homeostasis benefit may be more easily recognizable to athletes in training, yet it can have a significant impact on aging well, particularly in terms of improving glucose tolerance, boosting insulin sensitivity and even reducing the risk of type 2 diabetes.[19] Diabetes is a major aging disease characterized by significant cellular damage caused by the generation of reactive oxygen species. In most cases, a high-fat diet, excessive weight gain, and obesity lead to an increased risk of type 2 diabetes and non-alcoholic fatty liver disease. Research shows that bovine colostrum can decrease levels of blood glucose and ketones, as well as reduce cholesterol and triglycerides, all of which may cause complications in type 2 diabetic patients.[20]

Bovine colostrum is the only medicinal food that can offer Fountain of Youth benefits without the financial and health costs of synthetic growth hormone. This is not to say that colostrum is a "magical anti-aging pill," but it is a significant game-changer in the arena of anti-aging medicine by virtue of its naturally occurring growth hormones. Regular physical activity and healthful lifestyle behaviors must not be overlooked. Colostrum supplementation is most effective when muscle fibers are subjected to repeated injury during exercise, such that lean body mass is maintained or increased. Trained muscles are more efficient at utilizing glucose and bigger muscles utilize more stored fat for energy. It's a win-win for people who want to age well and maintain a more youthful appearance.

Douglas Wyatt is the founder of Sovereign Laboratories LLC, a Sedona-based company dedicated to developing natural products that provide the public with the best solutions for optimal health. He is honored to be listed as the leading expert in colostrum and is credited with reintroducing bovine colostrum into human use. Additionally, he serves as the research director of the International Center of Nutritional Research, a not-for-profit institute dedicated to nutritional health, and is one of the leading figures in the natural products Industry. Doug is a leader in the research and a proponent of colostrum's unique and powerful healing components that show incredible promise for turning the tide on the prevention and treatment of the world's increasing chronic disease endemic. As a publisher, author, writer, scientist, and public speaker, Doug has appeared nationwide on television and radio shows and at health conventions worldwide. He is dedicated to the prevention of chronic disease through natural nutritional intervention and is working with the WHO (World Health Organization) and other internationally recognized research organizations on clinical trials on HIV/AIDS other infectious disease, autoimmune disease, and bowel health issues.

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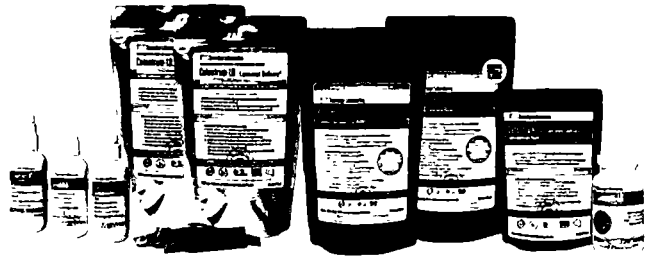

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See article in this issue: Bovine Colostrum: The Anti-Aging Revolution – What Athletes Can Teach Us About Staying Young: Part 1

The Neuroendocrine Theory of Aging: Minimizing Chronic Stress to Prevent the Degenerative Diseases of Age

by Chris D. Meletis, ND, and Kimberly Wilkes

The neuroendocrine theory of aging is a fascinating explanation for why we develop many of the diseases of our time, from depression to obesity to diabetes and many more, along, of course, with aging itself. Russian scientist Vladimir Dilman, MD, PhD, DMSc, first proposed the neuroendocrine theory of aging in 1954 in a master's thesis. Ward Dean, MD, began communicating with Dilman, and in 1992 they coauthored a book, *The Neuroendocrine Theory of Aging and Degenerative Disease*.[1] Dean deserves the credit for helping to bring Dilman's theory before the American public.

When Dilman first proposed that neuroendocrine factors were involved with aging, it was a pioneering theory. Dilman and Dean built the foundation for the theory, and now researchers are filling in the gaps and expanding upon it. The reason that this theory is appealing and why we wanted to write about it is because it gives us a lens to look at the human body as a symphony put on by all the members of the orchestra. If we only focus on the brass or the strings, we're missing the bigger picture. In the same way, all the systems of the body work in harmony, and any disharmony in any part of the bodily cycles causes us health challenges.

There are too many components to the neuroendocrine theory of aging to discuss them all in one article; therefore, here we're going to discuss one aspect: stress. More specifically, we're going to discuss what Dilman called the *adaptive homeostat*, the system that the body uses to cope with stress. But first, let's briefly talk more about the neuroendocrine theory of aging overall.

An Explanation for Why We Age

The main line of thought behind the neuroendocrine theory of aging is that as we age, receptors in the body begin to ignore the effects of hormones and other messenger substances. Normally, when the body is overproducing a hormone or other substance, there are mechanisms established to shut off the overproduction. However, when receptors become desensitized to those signaling substances that tell them to stop overproducing, more and more of those signaling substances are needed for the receptors to understand the message. It's the same concept as an elderly person who is hard of hearing. When they were younger they could hear a whisper. But now, people may have to talk really loudly or even shout for that elderly person to hear them. Thus, when your receptors become desensitized, your hormones and signaling substances must increase their "volume" more and more for the cells to understand the directions that they are being given. At some point, the cells may become completely deaf to the message that the hormones and signaling substances are sending.

This process is what Dilman referred to as loss of hypothalamic and peripheral receptor sensitivity. When there is a loss of this sensitivity, your body's homeostasis – its balance – begins to shift in a way that is unfavorable to your health. The resulting imbalanced levels of hormones, neurotransmitters, and cell signalers contribute to aging and degenerative diseases.[2]

Stress: Not Always the Villain

Balanced cortisol levels are healthy. Cortisol, when released in high amounts in short spurts, acts as an anti-inflammatory. It helps make glucose and fatty acids available to produce energy and nourish many bodily tissues.

Thus, we need some stress in order to survive. Stress results in a number of reactions that give us an advantage in times of danger. It's what helped our ancestors survive their encounters with a saber-toothed tiger.

When our ancestors encountered danger, it was often short lived. Cortisol levels rose to help them deal with the danger and then returned to normal after it was over.

However, when we are exposed to chronic stress such as the emotional demands of work deadlines, financial challenges, raising children, and countless other stressors, our cortisol levels tend to rise, and to remain elevated longer than normal. These types of stressors are "the saber-toothed tigers" of our time.

There's no doubt that chronic stress is often an *aging accelerator*. Just look at how much older the president of the US appears after eight years in one of the most stressful jobs that anyone can have.

During chronic stress, cortisol levels stay high. When the body overproduces cortisol for an extended time, it becomes harmful. At some point, after extended periods of producing too much cortisol, the adrenal glands may even become exhausted and stop producing cortisol altogether, which also leaves the body vulnerable to disease and fatigue.

The Neuroendocrine Theory and Stress

The neuroendocrine theory of aging proposes a reason *why* stress ages us and causes disease. The theory also lays out solutions for minimizing the effects of stress. Based upon Dilman's theory, stress-related damage occurs due to dysfunction in the adaptive homeostat, the hypothalamus-pituitary-adrenal (HPA) axis.

When you're stressed, it normally causes the hypothalamus to release corticotropin-releasing hormone (CRH). The release of CRH triggers pituitary production of adrenocorticotropic hormone (ACTH), which then triggers the adrenal cortex to produce DHEA and the glucocorticoid cortisol and the adrenal medulla to release epinephrine and norepinephrine, typically called "fight or flight" hormones.

During stress, as cortisol levels rise, this signals the hypothalamus and pituitary to slow the output of CRH and ACTH. On the other end of the spectrum, falling cortisol levels cause an increase in hypothalamic activity, which stimulates the production of CRH while ACTH production once again increases in the pituitary, causing the adrenal cortex to increase levels of cortisol. And so the cycle continues, ensuring that the adaptive homeostat works in a balanced manner.

However, cortisol levels don't stay the same throughout the day. They're usually at their peak in the morning and lower in the afternoon and evening. These daily fluctuations in cortisol are governed by changes in CRH and ACTH production and by alterations in the sensitivity of the hypothalamus and the central nervous system to cortisol. Normally, between 3 to 6 a.m., when ACTH levels increase, this results in an increase in cortisol. Throughout the day, cortisol levels fall until at night they are at their lowest. If the adaptive homeostat is working properly, basal morning cortisol levels should be twice those of nighttime.[2]

Age Is Not the HPA's Friend

Being exposed to high levels of cortisol for long periods of time can tip the scales in favor of disease. This is what Dilman called *hyperadaptosis*. Chronic high cortisol levels are linked to diabetes, hypertension, suppressed immunity, gastric ulcers, headaches, osteoporosis, cardiovascular concerns, and death of brain cells. This is similar to what is seen in people who have Cushing's syndrome, a disease marked by high cortisol levels. In these patients, the high cortisol levels lead to insulin resistance and obesity. It is a vicious circle, because high cortisol levels cause the loss of more hypothalamic cortisol receptors, making the body even less sensitive to the effects of cortisol.[2]

All of these effects appear to worsen with age. Dilman proposed that as we grow older, the hypothalamic receptors become less sensitive to high levels of cortisol. This means that it is more difficult for the receptors to understand when to shut off or slow cortisol production. Increasingly higher and higher levels of cortisol are needed to stop production of cortisol and return the body to a balanced state.[2]

Dilman's original research on this subject has been confirmed by recent studies. In one study published in August 2014, researchers looked at how bereavement affected the cortisol:DHEAS ratio and immunity in younger and older adults. The study included 41 subjects with a mean age of 32 years and 52 older adults with a mean age of 72 years, and compared bereaved and nonbereaved study participants. The researchers found raised stress hormone levels (a higher cortisol:DHEAS ratio) in the older bereaved participants compared with their age-matched controls. By contrast, the younger subjects had a low cortisol:DHEAS ratio even though, like all the bereaved subjects in the study, the younger ones were suffering from symptoms of depression and anxiety. The neutrophils (immune cells) of younger bereaved subjects also functioned effectively, whereas in the older bereaved subjects, there was weakened neutrophil function.[3]

Hyperadaptosis can actually alter physical appearance. Dilman noted that in many people who are over age 40, hyperadaptosis is characterized by a moonlike appearance to the face and the buildup of visceral fat in the waist.

How Stress Affects Testosterone

Throughout Chris Meletis's clinical career working from the foundational base of the neuroendocrine theory of aging, he has postulated a concept that he terms the NeSID (neuroendocrine stress-induced dysfunction) effect, which incorporates the role of stress on both the 5-alpha reductase and COMT pathways. Stress elevates levels of 5-alpha reductase, the enzyme that converts the androgen testosterone to dihydrotestosterone (DHT) as well as serves to help break down cortisol to its metabolites: allo-tetrahydrocortisol (5α-THF) and 11β-hydroxyandrosterone (OHAN) and corticosterone to allo-tetrahydrocorticosterone. Receptors for androgens have a greater sensitivity for DHT than they do for testosterone, and testosterone breaks apart from the receptors more easily than does DHT. This is not advantageous to health because DHT is linked to male pattern baldness, benign prostatic hyperplasia (BPH), and prostate cancer.[4]

It has been shown in studies of obese patients – both male and female – that 5-alpha reductase levels rise in response to the development of insulin resistance and that the rise in the 5-alpha reductase levels is associated with inactivation of cortisol levels in the liver. It is believed that this rise in 5-alpha reductase is a compensatory mechanism to protect against cortisol levels' rising too high. Although this increase in 5-alpha reductase protects against cortisol, it leaves the body wide open for the other negative effects of the DHT produced.[4,5]

The Genetic Link

Everyone has a different tolerance for stress. What is stressful for one person may not bother someone else. Researchers are now discovering ➤

➤

that the activity of an enzyme called catechol-O-methyltransferase, which is encoded by the COMT gene, may explain why some people are more resilient to stress than others.

The COMT gene directs the body to produce two versions of catechol-O-methyltransferase. One version – membrane-bound catechol-O-methyltransferase (MB-COMT) – is a longer form and is primarily produced in the brain's nerve cells. A shorter version of catechol-O-methyltransferase – soluble catechol-O-methyltransferase (S-COMT) – is produced in the liver, kidneys, and blood and plays a role in regulating levels of some hormones.[6]

Catechol-O-methyltransferase plays an important role in the inactivation of catecholamine neurotransmitters (dopamine, epinephrine, and norepinephrine) in the brain. The type of genotype of the COMT gene that a person possesses dictates how well he or she can adapt to stress. In a study of 321 healthy college volunteers, male participants with the COMT Met-present genotype were significantly more resilient to stress than those with the Val/Val genotype.[7]

Increasing activity of COMT may also unfavorably influence metabolism of estrone, one of three major endogenous estrogens found in humans along with estradiol and estriol. Estrone is converted in fat tissue from estradiol and adrenal androstenedione. Estrone has a higher affinity for an estrogen receptor found in breast cancer cells, the estrogen receptor alpha. Estrone can be procarcinogenic in women and also is linked to hypertension, leg cramps, and breast tenderness.[8] In men, estrone is linked to erectile dysfunction.[8]

Epigenetic Effects on the Adaptive Homeostat

Epigenetics refers to changes in gene expression that involve the process of methylation, which acts like a switch to turn genes on and off. Studies have shown that epigenetic changes to the gene for the type II glucocorticoid receptor (NR3C1) are a likely mechanism explaining the neuroendocrine effects of chronic stress (for example, having a stressful childhood). In fact, adults who have a history of childhood adversity have been found to show reduced cortisol responses to a standardized neuroendocrine challenge test. This reduced cortisol response was found to be due to epigenetic changes.[9]

How Stress Causes Weight Gain

Obesity is responsible for many of the diseases of our time. The neuroendocrine theory offers an explanation as to *how* obesity – especially weight gain around the abdomen – causes disease. The theory also provides a basis for effective weight management solutions and may explain why conventional weight-loss programs are often ineffective.

Obesity is known to cause changes in the hypothalamus. Furthermore, in obese humans and animals, there is evidence of neuronal injury in the hypothalamus, a brain area involved in body weight control.[10] Additionally, chronic stress, primarily by disrupting the hypothalamic-pituitary-adrenal axis, encourages visceral fat accumulation.[11] Visceral fat tissue is a key endocrine organ that helps regulate insulin action and plays a role in insulin resistance.[12] One study found that in depressed women, stress was responsible for almost 11 pounds per year of weight gain. The explanation for this goes beyond the fact that people tend to eat more – and eat more unhealthful foods – when they're stressed. The bodies of people who are stressed actually react differently to a high-fat meal. Depressed subjects who are under more stress have lower postmeal resting energy expenditure and higher insulin levels compared with subjects who are not stressed.[13]

The weight gain that occurs after chronic stress also involves disrupted cortisol levels. Higher cortisol levels have been found in obese subjects compared with nonobese subjects.[14]

Further supporting the connection between stress and weight gain is the link between cortisol and the metabolic syndrome, a cluster of risk factors for heart disease. Metabolic syndrome is characterized by the accumulation of visceral fat, which is also a characteristic of cortisol excess. Studies have associated abnormalities of cortisol secretion and metabolism with the development of metabolic syndrome.[15]

Natural Solutions for Hyperadaptosis

Dilman's work showed that the way to restore optimal function of the adaptive homeostat, relieve hyperadaptosis, and ultimately reduce the damaging effects of stress is to restore hypothalamic (and peripheral) receptor sensitivity and to use hormone replacement therapy to restore hormone levels to what they were when the body was younger. This can be accomplished by using a number of natural substances.

Adaptogens

A combination of herbs known as adaptogens can be used effectively to resensitize the hypothalamus and restore the adaptive homeostat. These include:

- Siberian ginseng (*Eleutherococcus senticosus*)[16]
- Manchurian thorn tree extract[2]
- hawthorn extract[17]
- *Echinopanax elatum*[18]
- schisandra[19]
- *Rhaponticum carthamoides*[20]
- *Ajuga turkestanica*[2]
- *Aralia mandshurica*[21]
- *Rhodiola rosea*[16]
- myricetin[22]
- *Magnolia officinalis*[23]
- *Phellodendron amurense*[23]
- Ashwagandha[24]

Each of these adaptogens has been studied extensively and used clinically for its ability to protect the body from stress. Many clinicians have used these adaptogenic botanicals in clinical practice with great success.

New research continues to be published on these adaptogens, building upon and lending even more support to Dilman's theory. For example, an animal study published in August 2014 showed that *Schisandra chinensis* reduced serum cortisol and blood glucose levels in rats undergoing stress.[19] According to the researchers, "It appears to protect the cell structure of the adrenal cortex, and offset the

negative effects of psychological stress and strenuous exercise related to immune dysfunction."

A study published in August 2013 investigating 56 stressed human subjects showed that a combination of magnolia and phellodendron reduces cortisol exposure and perceived daily stress, while improving mood, reducing fatigue, and increasing vitality.[23]

Other Ways to Restore Cortisol Receptor Sensitivity

In addition to adaptogens, there are other substances that can increase the body's ability to deal with stress. One of those substances is phosphatidylserine. Supplementation with phosphatidylserine normalizes the dysregulations of the hypothalamus-pituitary-adrenal axis caused by stress.[25]

Dean has also used the drug metformin (Glucophage) to restore cortisol receptor sensitivity as well as metformin's nutritional relatives, berberine and mulberry. It is also important to note that goat's rue (*Galega officinalis*) is the herbal progenitor upon which metformin is based. All four of these substances are known for their ability to improve insulin sensitivity and reduce insulin resistance.[26–29] There is an intricate interplay between cortisol and insulin. Cortisol opposes the blood–sugar balancing effects of insulin and is responsible for the development of hyperglycemia (high blood sugar). Cortisol also blocks the peripheral utilization of glucose, thereby contributing to insulin resistance. Therefore, any substance that can restore insulin sensitivity also has the potential to restore cortisol receptor sensitivity.

Natural Hormone Replacement Therapy

To rejuvenate the adaptive homeostat, Dilman also advocated supplementing with natural hormones to restore them to their youthful levels. Melatonin, DHEA, and pregnenolone are three hormones that fall with age and which also play a critical part in the body's stress response.

Melatonin is produced by the pineal gland of the brain, primarily after exposure to darkness. Although best known for its ability to promote sleep, melatonin is a regulator of regulators and plays a critical role in maintaining the diurnal rhythm of many body processes. Melatonin also counteracts stress and is a powerful adaptogen due to its ability to suppress the release of cortisol. In stressed animals, nighttime melatonin administration significantly reduced the memory problems and depression that typically occur after chronic stress.[30] In human studies, after exposure to light at night, cortisol levels rise as melatonin levels drop.[31]

Dosages of melatonin from 750 mcg to 6 mg per day, taken before bed, can be effective at restoring melatonin levels.

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DHEA, which originates in the adrenal glands, is another hormone that declines with age and chronic stress. Depending on the results of a salivary hormone test, supplementing with 12.5 to 50 mg of DHEA per day in the morning can help your adrenal glands adjust to stress. Women usually need less DHEA than men.

Pregnenolone also is produced by the adrenal glands and is important in regulating the adaptive homeostat. In one study, researchers investigated the effects of DHEA sulfate or pregnenolone sulfate in mice introduced into an environment where they had previously received an electric shock to their feet. Normally, these mice would halt in fear when exposed to this environment. However, when the mice were given DHEA and pregnenolone sulfate, the animals' usual fear response was reduced.[32]

As part of his adaptive homeostat protocol, Dean recommends 10 to 100 mg of pregnenolone per day, taken in the morning.

Support for Adrenal Exhaustion

As noted earlier, when the adrenal glands overproduce cortisol due to exposure to chronic stress, over time, they can become burned out and stop producing cortisol. When this happens, it's necessary to replenish cortisol levels in one of two ways. First, if an adrenal function salivary hormone test indicates that your cortisol levels are depleted, with a doctor's supervision you can try low-dose hydrocortisone treatment.

Another option to nourish exhausted adrenals is to supplement with adrenal glandular and/or glycyrrhizin, which is extracted from licorice. Glycyrrhizin affects cortisol metabolism and can raise cortisol levels, giving exhausted adrenals a much-needed break.[33] Glycyrrhizin should be taken for 1 or 2 weeks at a time, alternating with 2 or 3 weeks of nonuse, to eliminate the risk of adverse effects and to maximize its beneficial properties.

Conclusion

One component of the neuroendocrine theory of aging, the adaptive homeostat, provides us with many solutions for protecting our bodies from the damaging effects of stress. Thanks to Dilman and Dean's work, we have a blueprint we can follow for balancing cortisol levels and restoring hypothalamic sensitivity, thereby inhibiting the diseases of aging.

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Red Yeast Rice in the Treatment of Hyperlipidemia

by Douglas Lobay, BSc, ND

This article discusses the use of red yeast rice (RYR) in the treatment of hyperlipidemia. It begins with a brief overview of the history and folk use of this natural product from Asia. It provides information on its chemical composition and active ingredients, pharmacology, and mechanism of action. It then provides analysis of clinical studies and scientific research in the use of RYR to treat hyperlipidemia, hypercholesterolemia, and cardiovascular disease. It also discusses other potential clinical uses of RYR. It reports on adverse side effects and toxicology. It concludes with a discussion of this author's personal experience of using RYR in the treatment of hyperlipidemia and has specific dosage recommendations.

History and Folk Use

Red yeast rice has been used in China for over 1200 years. It has been used to flavor, color, and preserve foods and as a traditional medicine. RYR has been included in fermented rice products, rice wine, rice vinegar, pickled tofu, Peking duck, and Chinese pastries. RYR was first mentioned in traditional Chinese medicine during the Tang dynasty at about 800 AD to invigorate the body, aid in digestion, and revitalize the blood. RYR was included in the Chinese Pharmacopeia of the Ming dynasty in the 1300s.[1] It is still widely used in China and other Asian countries, including Japan and Thailand. In more modern times RYR has been used in the treatment of dyslipidemia, high cholesterol, coronary heart disease, diabetes, osteoporosis, cancer, non-alcoholic fatty liver disease, fatigue, poor memory, Alzheimer's disease, and dementia.[2]

Chemical Composition and Active Ingredients

Red yeast rice is created by fermenting rice with a fungal species called *Monascus purpureus*. Rice is a food staple that consists of approximately 80% carbohydrates, 7% protein, 2% dietary fiber, and 1% fat. It contains trace amounts of B vitamins, including vitamin B1, B2, B3, B5, and B6, and minor amounts of minerals including calcium, magnesium, potassium, phosphorus, iron, and zinc.[3]

Monacolins have been identified to be the active ingredients in RYR for its lipid-lowering effects. Fourteen different monacolins have been isolated from RYR with HPLC (high-performance liquid chromatography) and MS (mass spectroscopy). The concentration of the monacolin varies. Monacolin K has been identified to be structurally identical to the cholesterol-reducing drug lovastatin (Mevacor). Twelve different commercial products of RYR were analyzed for monacolin content by HPLC and MS at an independent lab. There was wide variability in total monacolin content ranging from 0.31 to 11.15 milligrams per 600 mg capsule of RYR. There was also wide variability of monacolin K content ranging from 0.10 to 10.09 mg per 600 mg capsule of RYR.[4]

RYR also contains sterols including beta-sitosterol, campesterol, stigmasterol, sapogenin, isoflavones, monounsaturated fatty acids, decalins and other biphenolic compounds, azaphilones and other lactone ring compounds, GABA (gamma aminobutyric acid), dimerumic acid, and citrin.[5,6]

Pharmacology

Detailed pharmacodynamics and pharmacokinetics on RYR are lacking in the scientific literature. Extrapolation of the data from studies of monacolin K or lovastatin has been suggested. Lovastatin, also known as monacolin K, is a naturally occurring molecule consisting of two bound phenolic rings known as naphthalene and one lactone ring with one or more attached substituent groups. It has a molecular formula of C24H36O5 and a molecular mass of 404.54 grams per mole. Its oral bioavailability has been shown to be less than 5%. Once absorbed it shows 98% protein bound. It has a biological half-life between 2 to 5 hours. It is mainly altered through hepatic degradation via the cytochrome P450 pathway, specifically CYP3A4 and CYP2C8. It is excreted 83% through fecal elimination and 10% through urine excretion.[7] One study compared the dissolution rate and oral bioavailability of lovastatin in lovastatin tablets and RYR. The results showed that the lovastatin from RYR was higher and faster than lovastatin tablets alone.[8] In another study, the plasma clearance of lovastatin was

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compared with RYR in 11 healthy volunteers who were randomized to receive 20 mg of lovastatin versus 2400 mg of RYR. The results suggested that the effect of RYR on cholesterol concentration might be caused by the additive or synergistic effects of monacolin K with the other monacolins in RYR.[9]

Mechanism of Action

Lovastatin or monacolin K inhibits the enzyme hydroxyl methylglutaryl coenzyme A (HMG CoA) reductase that catalyzes the reduction of HMG-CoA to mevalonate during the initial synthesis of cholesterol. There is a naphthalene-lactone complex that forms the basic structure of the monacolins and other allied statin drugs. In the liver, it is believed, the lactone ring of that naphthalene-lactone structure opens and binds to the HMG-CoA reductase enzyme, thereby inhibiting the incorporation of acetate molecules into forming a cholesterol molecule. The other monacolins probably exert cholesterol-lowering effects. RYR also contains phytosterols, isoflavones, and monounsaturated fatty acids that might also contribute to lipid-lowering effects.[10]

Clinical Studies in Hyperlipidemia

In one study, 40 children between ages 8 and 16 years with familial hyperlipidemia were treated with a product that contained 200 milligrams of RYR with 3 milligrams of monacolins for 8 weeks. Total cholesterol decreased 18.5% on average and LDL decreased 25.1%. Apolipoprotein B decreased 25.3%, and both HDL and Apo A showed no significant changes. No adverse effects were observed when liver and muscle markers including AST, ALT, and CK were monitored.[11]

In a double-blind, placebo-controlled trial, 52 physicians and their spouses with a total cholesterol greater than 200 milligrams were randomly assigned to receive RYR extract or placebo for 8 weeks. The primary outcome was to measure lipid before and after treatment. Total cholesterol decreased by an average of 37 mg/dl or 15%. LDL cholesterol decreased by an average of 36 mg/dl or 22%. No marked difference in CK levels or other side effects were noted between the groups. The authors concluded that RYR may be an attractive and well-studied alternative in patients who are intolerant to statins or who have objections to pharmacologic lipid lowering.[12]

In another study, a Mediterranean diet was compared with RYR supplementation for the management of statin-intolerant patients with and without type 2 diabetes. A total of 171 patients were observed over 24 weeks. 46 diabetic patients were treated with MD alone, 44 diabetic patients were treated with MD and RYR, 38 patients with dyslipidemia were treated with MD alone, and 43 patients with dyslipidemia were treated with MD and RYR. The results showed that RYR was superior in lowering LDL levels in both groups. In the diabetic group treated with MD alone, LDL decreased an average of 7.4%. In the diabetic group treated with MD and RYR, LDL decreased an average of 21.0%. In the dyslipidemic group treated with MD alone, LDL decreased 12.5%, and in the dyslipidemic group treated with MD and RYR, LDL decreased an average of 22.0%. RYR was superior to MD alone in modifying lipid parameters in diabetic and nondiabetic dyslipidemic patients. [13]

The beneficial impact of a RYR product on cardiovascular events and mortality was studied in 1530 elderly hypertensive patients greater than 65 years of age who had a previous myocardial infarction. 772 patients took the RYR product and 758 patients took a placebo for an average of 4.5 years. 68 cases (8.8%) of coronary events occurred in the RYR-treated group and 108 cases (14.3 %) in the placebo group. This translated to a 38.2% risk reduction of coronary events in the RYR-treated group. There were 49 cases (6.4%) of death due to coronary heart diseases in the RYR-treated group and 68 cases (9.0%) in the placebo group. This translates to a 29% risk reduction in the RYR-treated group of death by coronary heart disease. The researchers concluded that this RYR product could effectively and safely reduce cardiovascular events and all-cause death in Chinese elderly hypertensive patients who have had a previous myocardial infarction.[14]

In an assessment of 93 randomized controlled trials, three different RYR products were compared with placebo on lipid modification in primary hyperlipidemia. A total of 9625 participants were involved in these trials. Total cholesterol decreased an average of 0.91 mmol/L or 35.0 mg/dl, LDL decreased 0.73 mmol/L or 28.1 mg/dl, triglycerides decreased 0.41 mmol/L or 36.3 mg/dl, and HDL increased 0.15 mmol/L or 5.8 mg/dl. No serious adverse side effects such as dizziness and gastrointestinal disturbance were noted. Lipid modification of RYR was similar to statin medication. RYR was superior to fish and vitamin B3 in modifying lipid levels. The researchers concluded that RYR was similar to statins and that more rigorous trials are needed, including long-term safety effects. [15]

In a clinical prospective trial, the effect of RYR on coronary events was studied in a Chinese population with previous myocardial infarction. Nearly 5000 patients were given a RYR extract or placebo and followed for primary end points of lipid levels and cardiovascular events. 5.7% of the RYR-treated patients experienced a cardiovascular event contrasted to 10.4% of the placebo group. The absolute difference of CV events between the two groups was a 4.7% reduction in the RYR group. The relative different of CV events was a 45% reduction in the RYR group. The RYR group experienced a decrease in cardiovascular and total mortality of 30% and 33%. The need for coronary revascularization also decreased by 33% in the RYR-treated group.

The authors concluded that long-term therapy with this RYR product significantly decreased the recurrence of coronary events and the occurrence of new cardiovascular events and death, improved lipoprotein regulation, and was safe and well tolerated.[16]

Other Potential Clinical Effects

RYR attenuated the development of angiotensin II-induced abdominal aortic aneurysm and the development of atherosclerosis in experimental mice models. RYR suppressed angiotensin II, decreased atherosclerotic lesion in the intima lining, decreased vascular cell adhesion, and regulated inflammatory responses independent of its lipid-lowering effects.[17] RYR supplementation upregulated endogenous nitric oxide expression in vascular endothelium and red blood cells, increased plasma nitric oxide, and improved abnormal rheology in high cholesterol–diet induced atherosclerotic rats.[18] RYR also has been shown to increase excretion of bile acid by up to 3 or 4 times in hamsters.[19] RYR supplementation decreased cellular proliferation and induced apoptosis in colon cancer growth. Epidemiological studies show that individuals who take statins have a lower risk of colon cancer. The chemoprotective effects of RYR were postulated to exist beyond the effects of the monacolins alone.[20] RYR supplementation inhibited prostate cancer cell growth in mice. RYR decreased tumor volume in both androgen-dependent and -independent prostate tumor lines. RYR decreased expression of androgen-synthesizing enzymes and cholesterol-dependent hormones. These effects were postulated to be independent from monacolins in RYR.[21] Several azaphilones from RYR showed selective toxicity against various human cancer cell lines in in vitro experimentation.[22] RYR supplementation enhanced bone formation through improved osteoblast cell proliferation and differentiation. Alkaline phosphatase enzyme activity increased, reflecting improved bone activity.[23] RYR supplementation improved collagen matrix and bone formation in rabbits.[24]

Adverse Side Effects

Monacolin K and other statins can potentially cause hepatotoxicity, nephrotoxicity, and peripheral neuropathy. Myopathy was reported in 4 individuals from 2002 to 2007 in the Italian Surveillance System of Natural Products.[25] Another report discussed a middle-aged man with joint pain and myopathy who had been taking RYR for several months. Laboratory testing showed moderately elevated CPK levels. His symptoms and lab abnormalities returned to normal after the RYR was discontinued.[26]

A case of rhabdomyolysis was reported in a stable renal transplant recipient who had been taking a RYR product. The muscle damage stopped once the RYR product was discontinued. The interaction of the immune-suppressing transplant drugs and the RYR on the cytochrome P450 pathway was believed to be the cause of this problem. It was further recommended that transplantation patients should use caution when using RYR products.[27] One 63-year-old female who had been taking RYR for several months showed acutely elevated liver enzymes and hepatotoxicity. The liver enzymes and inflammation returned to normal after the RYR product was discontinued.[28]

RYR use is likely unsafe during pregnancy and is not recommended while breast-feeding. It has caused birth defects at high doses in animal models. It should be used with caution in patients with liver and kidney disease. It uses the cytochrome P4503A4 pathway and can potentially interact with other drugs and foods. These drugs include gemfibrozil, cyclosporine, protease inhibitors, acetaminophen, amiodarone, carbamezapine, isoniazid, methotrexate, methyldopa, fluconazole, itraconazole, erythromycin, phenytoin, lovastatin, pravastatin, and other statin drugs. These foods include alcohol, grapefruit, and herbal medicines such as St. John's wort.[29]

Toxicology

Citrin is a mycotoxin that is produced by several genera of fungal species, including *Monascus*. Citrin has been shown to be nephrotoxic to certain animal species. Its LD (lethal dose) 50 is 100 milligrams per kg in animal models. Its effect on humans is not clearly known. It has shown to be genotoxic to human lymphocytes in in vitro experiments. The EFSA (European Food and Safety Authority) has suggested that the daily citrin content be limited to an average of 30 mcg/kg in children and 60 mcg/kg in adults.[30] In an independent evaluation of 12 commercially available RYR products, 4 showed variable amounts of citrin. The citrin content ranged from 0 to 114.2 mcg/capsule. The four products showed 14.3, 57.5, 70.4, and 114.2 mcg/600 mg capsule of RYR. The other 8 products showed 0 mcg of citrin. Increasing the temperature by several degrees Celsius during the fermentation process of RYR dramatically stops the production of citrin.[4] Red yeast rice can contain a trace amount of arsenic.[3]

Personal Use in Clinical Practice

I have been using RYR in my practice for about 15 years. I have used RYR alone or mixed with other natural supplements as policosanol, guggulipid, milk thistle (*Silybum marianum*), and coenzyme Q10. I currently have RYR manufactured in capsular form for my patients. Each capsule contains 500 milligrams of RYR standardized for 0.4% monacolin K levels and 100 milligrams of milk thistle seeds. I have seen RYR consistently lower elevated cholesterol and triglyceride levels in patients. I try to monitor lipid levels before and after treatment. I have observed that total cholesterol and

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Red Yeast Rice

LDL levels decrease about 20% to 30%, HDL increases 5% to 15%, and triglyceride decreases 10% to 30%. This is consistent with the reported data in the scientific literature. I have prescribed RYR to over 400 patients and have dispensed about 80,000 capsules. Patients are usually very happy with the results. They can go back to their doctors with a lab test that shows decreased lipid levels. I have noted that patients on RYR have less incidence of myocardial infarction when compared with patients who do not take it or other statin therapy. I usually prescribe 2 to 4 capsules of the RYR product per day with food or meals. I also like to give some nutritional advice about diet and lifestyle changes that are beneficial for controlling elevated lipid levels along with RYR supplementation. I have observed minimal adverse side effects. Most patients do not report any side effects at the recommended dosage. I usually tell the patients to supplement with coenzyme Q10. Occasional stomach upset occurs, and rarely muscle aches and myalgia occur. I observe that about 1% to 2% of my patients taking RYR report unusual muscle pains and myalgia. I try to monitor liver and kidney function tests and also test for CPK levels in patients complaining about muscle pains. I have been very satisfied with the clinical results of using RYR to help control hyperlipidemia.

Dosage and Recommendations

I recommend using 2 to 4 capsules per day of a product that contains 500 to 600 milligrams of RYR powder standardized to contain 0.4% monacolin K content. I advise patients to take the supplement with or just after meals or food for best absorption, and to concomitantly take coenzyme Q10. I monitor lipid levels, liver and kidney function, and muscle markers such as CPK, before and during RYR supplementation.

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The Shifting Paradigms of Diet and Cancer

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Over the past 50 years, scientific belief as to how diet might affect cancer risk has undergone dramatic shifts, moving (some would say evolving) from one worldview to another with such regularity that a close examination of these changing ideas may be useful to us to not only inform our understanding of what to eat (or not to eat) but also to illustrate how much scientific "truth" shifts over time and how we may need to be flexible in interpreting "facts" as we sometimes, perhaps out of habit, cling to discredited beliefs as if they were immutable truths.[1]

Back in the 1950s and 1960s, scientific suspicion focused on things in food as the cause of cancer. First to be blamed were chemicals added to foods, the preservatives, food colorings, nitrates, pesticide residues, and smoke flavorings: food itself was not thought to affect disease; rather, it was the additions to food that were the problem.[2-7]

In the 1960s the vision shifted slightly to the idea that perhaps food itself could be carcinogenic; the high-temperature grilling of meat became the prime suspect. Cooked meat and heated fats were the new cause of cancer; a burger and fries had to be avoided for one to stay cancer free.[8,9] Coffee was thought to cause kidney cancer, and nuts were a danger because they might contain aflatoxins.[10] Broiled meat was the source of benzopyrenes, heterocyclic amines, and polynuclear hydrocarbons, chemicals that certainly sounded dangerous.[11]

The once strong association between cooked meat and cancer, in particular colon cancer, has grown weaker over the years. For example, Kampman et al. wrote in a 1999 paper, "The frequency of fried, broiled, baked, or barbecued meat, use of drippings, and doneness of meat were not significantly associated with risk."[12] Heterocyclic amines may still increase risk, but less so than once thought. Cooked meat is not the cause of all cancer.

While science has by and large dropped this "additive" theory, the idea persists strongly. Many people avoid certain foods that contain additives, especially preservatives, out of fear that eating them will cause cancer.

There is a near universal belief that consuming organic food, produced without pesticides and processed without chemical additives, will lower risk of cancer. Those of us who routinely see cancer patients have heard the line all too often, "How can I have cancer? I only eat organic food!"

Exposure to pesticides in large quantities, for example by the farm workers who apply them, is linked to higher risk of certain cancers, in particular non-Hodgkin's lymphoma, soft tissue sarcoma, and breast cancer.[13,14] Yet a 2012 meta-analysis of 17 human studies and 223 studies of nutrient and contaminant levels in food concluded, "The published literature lacks strong evidence that organic foods are significantly more nutritious than conventional foods."[15] Nor is there much evidence that eating organic does much to lower risk of cancer.

A 2014 article in the *British Journal of Cancer* reports that in a large prospective study that followed 623,080 middle-aged UK women for 9.3 years, the reported cases of cancer (n = 53,769 cases) did not differ significantly by the amount of organic foods the women reported eating. Actually, risk for breast cancer was slightly higher in those reporting that they always or usually chose organics (breast cancer [RR = 1.09, 95% CI: 1.02–1.15]; a finding that we want to ignore, as it clashes with our view of the world). Non-Hodgkin's lymphoma was about 21% lower in the organic eaters.[16] Otherwise there were no significant differences.

By the way, sales of organic food in the UK have grown from £100 million/year in 1994 to £2 billion in 2008. In the US the jump is staggering: organic sales have gone from under $4 billion/year in 1997 to over $39.1 billion in 2014.[17] Despite the lack of strong evidence of a health benefit, people remain strongly drawn to the idea that our food is to blame for cancer.

This idea that chemicals in foods cause all cancer, to quote Dr. Walter Willet of Harvard School of Public Health, "was the first paradigm."

Willet sees our understanding of how diet affects cancer as slowly evolving from one principle culprit to another, or as he sees it from one paradigm to another.

In Willet's view, the second paradigm "was the idea that fat in the diet is a major cause of cancer."[18]

Fat was, in both scientific and popular belief, the culprit, the cause

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of cancer. The highest goal of dietary counseling a quarter-century ago was to achieve and maintain a low-fat diet.[19] Clinical trials of low-fat, high-carbohydrate diets were undertaken to prevent diseases ranging from breast cancer to actinic keratosis.[20,21]
Yet, in Willet's words,

> There was never any strong evidence for this idea, but it was repeated so often that it became dogma in the 1980s and 1990s. For conditions such as heart disease and diabetes, the type of fat in the diet is quite important. But the hypothesis that the percentage of calories from fat in the diet is an important determinant of cancer risk, at least during midlife and later, is not supported by the data.

In a 2004 PBS *Frontline* interview, when asked whether low-fat diets have made us fat, Willet famously answered,

> This campaign to reduce fat in the diet has had some pretty disastrous consequences. ... One of the most unfortunate unintended consequences of the fat-free crusade was the idea that if it wasn't fat, it wouldn't make you fat. I even had colleagues who were telling the public that you can't get fat eating carbohydrates. Actually, farmers have known for thousands of years that you can make animals fat by feeding them grains, as long as you don't let them run around too much, and it turns out that applies to humans. We can very easily get fat from eating too many carbohydrates, and the public was really directed to only focus on fat calories, when we really have to keep an eye on calories no matter where they're coming from.[22]

"The third paradigm" according to Willet, "was that fruits and vegetables dramatically reduce risks of cancer." Along with this we could include the idea that certain nutrients found in these foods would provide ample protection. Instead of things added to foods being the problem, it was deficiency of some of the chemicals found in foods that was to blame for cancer. We needed more of these chemicals such as antioxidants or phytonutrients, minerals, or enzymes. Many of us still see the world from this perspective.

Recall the famous CARET and WHEL trials that failed so abjectly, studies based on the notion that we understood what was missing from the diet, things that could stop cancer.

The B-Carotene and Retinol Efficacy Trial (CARET) was such a surprising failure, it should be taught in naturopathic school as a lesson in humility and as a cautionary warning about leaping to conclusions based on epidemiological evidence. Recall that the trial followed 18,314 study participants who, because of heavy smoking, were at high risk for lung cancer. Recall also that the study was halted far earlier than planned, back in 1996, because the participants taking beta-carotene supplements had a 28% increase in lung cancer incidence and a 17% increase in death compared with the placebo group. The study participants who had taken beta-carotene remained at higher risk than the placebo group even five years after stopping supplementation.[23] It was not supposed to work this way.

The Women's . Healthy Eating and Living (WHEL) Trial on breast cancer recurrence started recruiting women in 1995 and followed them to 2006, during the transition from the "fat paradigm" to the "phytonutrient deficiency paradigm." Of the 3088 women recruited, all of whom had been diagnosed and treated for breast cancer, 1537 were assigned to a combination low-fat and high-vegetable and -fruit diet. During a mean 7.3 years' follow up, recurrence of new primary invasive breast cancer diagnosis or death in the two groups was tracked. In the end, 16.7% of the women in the intervention group and 16.9% in the control group experienced an event; that is, cancer occurrence, recurrence, or death. These differences are not significantly different. In simple words, the extreme dietary interventions based on both the low fat and high phytonutrient theories had no measurable impact on what mattered most: cancer.[24]

While some trials have demonstrated positive results, the overall benefits of adding food nutrients via the diet have been less than we had hoped for.

In Willet's words, "That's not to say there's no benefit from fruits and vegetables, but [the benefit is] probably very small and limited to certain foods and certain cancers."

We have now emerged into what Willet describes as the fourth paradigm: "that a major cause of cancer is excessive adiposity [obesity]." Talking about weight is a tricky subject these days, filled with politically correct terminology; obesity is now euphemistically described as a "positive energy balance." In simpler terms, the theory is that too many people are too fat. Not just too fat but because they expend too few calories as a result of inactivity, they are insulin resistant and so produce excessive amounts of insulin hormone. Current thinking is that because insulin may bind to some IGF-1 receptor sites, it acts as a growth factor for many types of cancer cells.

I frequently describe a Danish study to patients as an illustration of the relative impact of fruits and vegetables compared with dietary starch on cancer.[25] It examined diet and lung cancer survival times and is helpful to illustrate our new focus on energy balance, blood sugar, and insulin.

The Danes followed a large cohort, 57,053 subjects, and reported that those with the highest intake of fruit and vegetables had a lower risk of dying, while the people with the highest intakes of potatoes had an increased risk of dying. High intake of vegetables decreased risk of dying by 16%, and of fruit by 19%, but high intake of potatoes increased risk of death by 51%. Potatoes have a very high glycemic index. Harvard's Glycemic Index of Foods, as impossible as it sounds, lists baked potatoes as raising blood sugar levels more than eating pure glucose.[26]

Evidence supporting these "new" ideas regarding energy balance and

cancer was there a quarter-century ago yet seems to have been ignored, probably because it didn't fit the working paradigm of the time.[27]

This current positive energy balance paradigm is, in Willet's opinion, here to stay, at least for the time being, as the evidence seems more consistent than earlier theories.

High glycemic load is associated with greater risk for colon cancer recurrence. A 2012 paper reported that in stage III colon cancer patients, those consuming the most blood-sugar raising carbohydrates in their diet had a nearly 80% higher risk of recurrence than those patients consuming the least (highest quintile of dietary glycemic load vs. lowest quintile: HR 1.79 for disease-free survival).[28]

Willet's current assessment is that obesity is the most important dietary culprit, "On a population level, the number of cases of cancer attributable to people being overweight and obese is about equal to the number attributable to current smoking. This is in part because smoking is going down and obesity is going up; in terms of importance within a population, they are in the same ballpark. ..."

Yet there are already holes developing in the new paradigm.

The "obesity/hyperinsulinemia effect" may not be as large as the researchers want us to believe. A March 2015 meta-analysis of prospective cohort studies looked at data on dietary patterns and risk of breast cancer and reported "a dietary pattern with a high glycemic index was associated with a summary relative risk (SRR) of 1.05 ... and a high glycemic load with a SRR of 1.06. ..." While these effects are statistically significant, they are minor.[29]

Once again, the paradigm of the day may not be as permanent as we first believed.

Perhaps we have been going about this the wrong way. We have been seeking both a cause for and a cure for cancer as if there will be a simple straightforward answer, as if cancer were a disease like scurvy. (Scurvy, as everyone now knows, is caused by vitamin C deficiency. This is a simple causal relationship and easy to understand; yet even so for hundreds of years, people, particularly sailors, died from the disease. Scottish surgeon James Lind is credited with reporting the cure for scurvy in 1753. The fact that it wasn't until 1867 that the British Navy began to supply daily rations of lime juice to sailors is often used to illustrate how slow it takes medicine or society to incorporate advances in science into common practice.)[30]

Diet and Cancer

There are two lessons we must learn. The first is that cancer generally defies simple explanations.

We keep looking to find the "vitamin C" that will prevent or cure cancer. It is time to face the fact that this disease is in most cases multifactorial, that there are many

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different factors that interact and together trigger cancer. It's not like scurvy. For the majority of cancers there are no simple solutions.

Admittedly in the few cancers for which there are clear solutions, we, or at least the public, hesitate to act forcefully; take lung cancer and smoking for example. Smoking is responsible for about 140,000 lung cancer deaths in the US each year. One might think that this would provoke a strong reaction on par with our efforts to invest in eating organic foods, but this clear threat hasn't stopped people from smoking. Government data tell us that *17.8%* of all adults in the US still smoke (42.1 million people).[31] This is the elephant in the room, so to speak, so let's take a moment to acknowledge the facts:

"Cigarette smoking is responsible for more than 480,000 deaths per year in the United States, including nearly 42,000 deaths resulting from secondhand smoke exposure. This is about one in five deaths annually, or 1,300 deaths every day."[32] This reality has led us to what is perhaps the greatest oxymoron of all time: the smoker who only eats organic food.

We also have to face the fact that identifying and removing one of these factors does not necessarily cure the disease. It's usually more complicated.

Some of the explanations for cancer are true some of the time, for some cancers, but they can't be applied generally. For example, just because *H. pylori* infections are strongly associated with gastric cancer does not mean that *H. pylori* causes all cancers or that eradicating these infections will prevent more than a narrow group of cancers.[33]

Some of the explanations that we thought true years ago have turned out to be of less significance than originally thought, or in some cases, as with fat, not to blame at all. It's easy to get set in our ways, to think of what we learned years ago, perhaps even during our naturopathic training, as an enduring truth. Yet inherited beliefs that have been proved to have no merit are superstitions, a term that is maybe too strong. Maybe we could call these past-paradigm ideas that are no longer accepted "old scientists' tales"?

Lots of ideas have waxed then waned over the years. Some have decreased in importance while others have grown. If we truly want to reduce suffering and prevent cancer, we need to keep our minds open and adjust what we tell patients as the science and the evidence shifts. What we thought was true a few years back is not necessarily true today.

Notes

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A Case of Essential Tremor Resolving with Reduction of Toxic Metals

by Davis W. Lamson, MS, ND
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Benign essential tremor is a somewhat common disorder of tremors, mostly in the upper extremities and neck, resulting in shaking of the head. In most cases it is of unknown origin. There are several reports of association between essential tremor and high lead levels in blood, but none showing the lessening of tremor with reduction in lead level.[1-4] This may be the first report on such resolution.

A female patient aged 77 consulted regarding several problems including previously diagnosed essential tremor. She had pronounced shaking of the head with impaired handwriting.

In the course of workup, a thyroid profile revealed elevated reverse T3 of 41 (range 6.7–21.8 ng/dL), which correlates tightly at this clinic with five or more toxic metals' being highly elevated (unpublished). Intravenous chelation challenge was performed with both EDTA (ethylenediamine tetraacetic acid) and DMPS (dimercaptopropanesulfonic acid), followed by a 6-hour urine collection for metal analysis (January 2014). The metal analysis (by Doctor's Data) showed high levels of nine toxic metals with aluminium, cadmium, gadolinium, lead, and platinum in the highest range. (She was previously treated with platinum chemotherapy.) Mercury, nickel, thalium, and uranium were midrange.

Chelation therapy was continued on a 2-times monthly schedule with occasional mineral replacement and with the urine collection for analysis performed about every 4 months. After 22 chelation treatments (to April 2015), the periodic urine analyses for metals showed almost no change instead of the usual reduction of levels. (This phenomenon is presently interpreted as having such high metal levels that reduction in levels thus far may be small compared with the total body burden.)

However, after 22 chelation treatments, there was complete resolution of head tremor with notable (to the patient) improvement in handwriting. Therapy is being continued to observe whether further benefit to hand tremor can be achieved and if laboratory indication of reduced metal levels occurs.

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Davis W. Lamson, MS, ND, practices at Tahoma Clinic in Tukwila, Washington (near Seattle), with particular interests in autoimmunity and cancer. He has published over 35 research and review papers, on subjects including hepatitis C, controling MRSA, stimulating immune function, emphysema, autism, diabetes, gastroesophageal reflux, kidney failure, autoimmunity, and various cancer-related topics. After a career in chemistry research and university instruction, Dr. Lamson enrolled in the first naturopathic medicine class at Bastyr University, receiving the doctorate in 1982. The career change was successful, and the previous training in chemistry seems of great value in locating causes of medical problems. He was adjunct faculty and coordinator of oncology education for 17 years at the Medical School of Bastyr University from 1997 through 2013. In addition, he supervised ND medical students in a hospital oncology setting.

Dr. Lamson received the 2004 Bastyr University Distinguished Alumnus Award and the 2005 President's Award of the Oncology Association of Naturopathic Physicians on its founding. In 2015, he received the Lifetime Achievement Award of that association. Dr. Lamson has served on the boards of directors of the Washington Association of Naturopathic Physicians, the Botanical Medicine Academy, and the Naturopathic Academy of Primary Care Physicians. Presently he serves on the conference committee of the Oncology Association of Naturopathic Physicians.

A Possible Treatment for Ebola

by Walton Ferris
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There is a treatment for Ebola, and other viruses. Try it.

It is safe, inexpensive, available, nonspecific, and unlikely to breed resistance.

It is the inducing of a high enough level of the ascorbate ion in one's plasma, often enough, and for long enough.[1-5]

Normal levels of ascorbate in the well-fed are 34 to 114 umol/L but are quickly used up by an infection.[27] Normal levels in the poorly fed are likely under 40 umol/L. The kidneys flush ascorbate levels above 80 umol/L in a few hours.

Maximum levels with repeated oral intake are 220 umol/L, and may provide some resistance to infection, achieved by 2 or 3 grams of ascorbic acid or sodium ascorbate every 4 hours – or 12 grams in a water bottle drunk through the day.[7] Repeated oral intake of liposomal ascorbate may achieve continuous levels above that.

Treatment of symptoms needs thousands of umol/L, and maintaining that level until resolution, achieved regularly by IV of sodium ascorbate in doses of 20 to 100 grams. Possibly oral liposomal ascorbate in doses above 5 grams could help.

Note that humans, primates, and fruit bats are considered the vectors for Ebola – and they are also the only animals (besides guinea pigs) that don't make endogenous ascorbate, in gram amounts.

Some reasons for considering ascorbate to be antiviral are:

Robert F. Cathcart, MD, said: "My experience with giving massive doses of ascorbic acid orally to over 30,000 patients and with giving intravenous sodium ascorbate to over 2,000 patients would indicate that with Ebola and other viral hemorrhagic fever diseases that intravenous sodium ascorbate should be used in doses beginning with at least 180 grams per 24 hours. If the fever is not controlled or the symptoms are not reduced, the dosage and the rate of administration should be increased until they are controlled." When given in a hospital, the administration should be constant, around the clock at the rate and amount to eliminate the symptoms. If the fever does not abate in the first 3 or 4 hours, the rate should be increased to whatever necessary to break the fever. However, when the fever and other symptoms abate then the rate of administration can be reduced.[2]

"Interestingly, the symptoms of avian flu include hemorrhages under the skin, and bleeding from the nose and gums. These are also classical symptoms of clinical scurvy, which means a critical vitamin C deficiency is present. This means that vitamin C (ascorbate) is needed to treat it. Severe cases may require 200,000 to 300,000 milligrams of vitamin C or more, given intravenously by a physician. This is similar to ebola."[3]

W. M. Wassell, MD, said: "To prevent Ebola and other plague like diseases you need to up your vitamin C levels to match those animals that produce their own vitamin C by taking orally at least 10g vitamin C daily in spaced out doses throughout the day. To cure Ebola, 50g IVC daily for 3 days should do for most. Rule of thumb is to give enough vitamin C to keep the fever away for 72 hrs."[8]

Belfield and Stone (1975) reported enormous success in the treatment of a variety of viral infections in animals: "The intravenous use of ascorbate is especially valuable in the therapy of viral diseases as it appears to be an effective, non-specific, non-toxic virucidal agent. We have not seen any viral disease that did not respond to this treatment. Successful therapy appears to depend on using it in sufficiently large doses."[4]

As far back as 1948, Fredrick R. Klenner, MD, cured 17 out of 17 cases of viral pneumonia and 60 out of 60 cases of polio using the unheard-of IV doses of 350 to 700 mg/kg, and went on to find a wide range of results for such high, frequent doses.[5] His 25 years of successes are a great proof of this approach.

Steve Hickey, PhD, has a good article.[12]

A dramatic case of cure with sodium ascorbate (SA) in 2009 was Alan Smith, who was at death's door from swine flu. See video: https://www.youtube.com/watch?v=vTXSTGGRvKY.

A great lecture by Levy is available at https://www.youtube.com/watch?v=GpptUsJFCEY; he mentions Ebola

at 11 minutes. He has cured two cases of West Nile virus and one of dengue fever.[16]

There are at least three methods of application:

1. infusion of SA, most proven (IVC);
2. oral application of liposomal ascorbic acid, (LA) easiest to use in the field;
3. oral application of ascorbic acid (AA) and/or its salts, useful as a preventative.

1. The infusion method is most effective, raising levels up to peaks of 15,000 to 25,000 umol/L (= 441 mg/dl) .[6] It is rapidly excreted in the urine, returning to baseline in 4 to 6 hours, and will also be used up in reducing the virus, so reapplication must be done in hours, keeping the minimum level above, say, 1000 umol/L. These high levels produce a high redox action, attack the virus, replace ascorbate body stores, strengthen the tissues that were hemorrhaging, and rejuvenate other antioxidants. One prediction showed the following graph of level vs. time *when there is no active oxidative factor and no lowered body store of ascorbate*[7]:

From Figure 1, one can see that a 10 gram dose might have to be repeated in 2 hours to keep the level high, whereas a 50 gram dose would last for 4 hours.[7] Klenner said to repeat every 2 to 6 hours until the patient recovers.[8] He kept their temperature going downwards. (See also Figure 4 of note 6.)

The infusion rate should preferably be 0.5 gram/minute (no more than 1 gram/minute).[9] The dilution can be 18 ml/g normally (no less than 10 ml/g for large doses).[11] The dose/infusion should be between 350 mg/kg and 1200 mg/kg.[11] For the first IV for acute infection, Levy suggests a dose between 1000 and 1500 mg/kg. Adding some oral divided doses, around 180 mg/kg, would help. One study found a synergistic effect in adding oral alpha-lipoic acid.[10]

These large doses are contraindicated if the patient has reduced renal function or urinary output. Use caution with G6PD deficiency, sickle-cell anemia, or high levels of unbound iron or copper, although large doses of vitamin E may help against hemolysis.[13]

Do provide much hydration. And, since Ebola breaks down ground substance and collagen, provide whey or some other nutrient that contains glycine, lysine, and proline, if possible.[14] Selenium deficiency increases susceptibility, as does vitamin D deficiency.[25]

Read the details and precautions from the Riordan Clinic, which has done over 40,000 infusions, up to 1000 mg/kg, on pages 13–18 of their protocol at http://www.doctoryourself.com/RiordanIVC.pdf. Pages 11–12 tell of the Phase I clinical trials. Note that they are not treating a raging infection, so do *not* follow their schedule of 2 or 3 infusions per week; it might require closer to every 6 or 8 hours.

Note also, "Due to the chelating effect of IVC, some patients may complain of shakiness due to low calcium or magnesium. An additional 1.0 mL of MgCl added to the IVC solution will usually resolve this. If severe, it can be treated with an IV push of 10 mL's of calcium gluconate, 1.0 mL per minute."[6]

In the field you could prepare stock solution of sodium ascorbate by the following method: http://www.vitamincfoundation.org/pdfs/civprep.pdf.

Note: USP sodium ascorbate sells for under $4.00/100 grams. Cathcart talks about this at http://www.youtube.com/watch?v=Zgi-7xPrCAg.

Figure 1

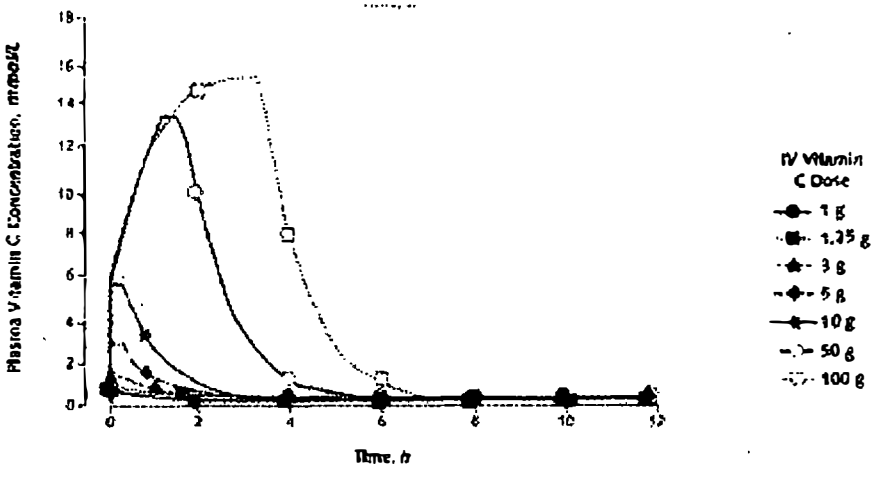
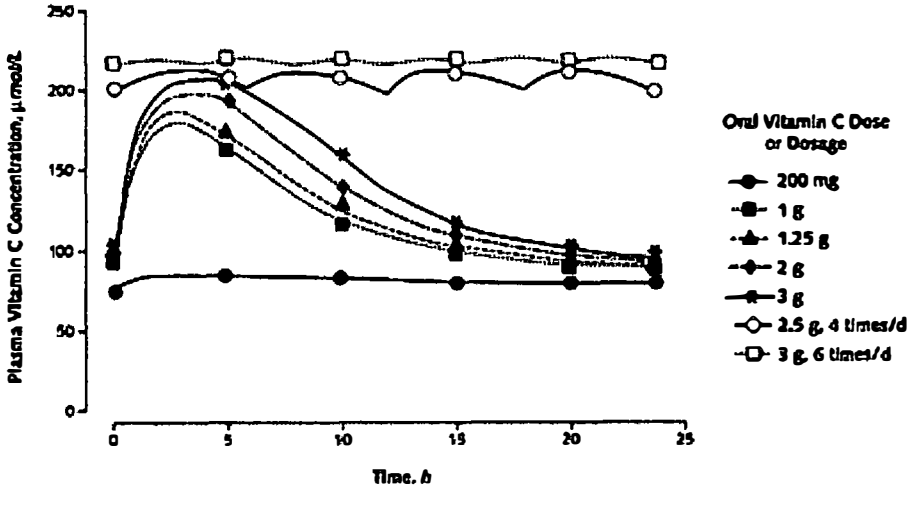


Figure 2



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2. Levy finds that *liposomal* ascorbate taken orally is effective and does not cause bowel or kidney problems.[15] He cured one case of hemorrhagic dengue fever with 10 grams.[16] One might start with 2 to 5 grams, and repeat until the desired response is achieved, at 4 to 8 hour intervals. Higher cost but very easy. Try it.

It might have shorter shelf life at high temperatures.

A very good US source is LivOn Labs (www.livonlabs.com), and Swanson (http://www.swansonvitamins.com) just added a liposomal vitamin C as SWU904. There are probably some vendors that are less competent.

3. Oral dosage of ascorbic acid or sodium ascorbate may raise one's resistance to disease, but for someone already seriously ill, it would take massive doses to do any good, and for Ebola it's unlikely to be enough. See www.doctoryourself.com/titration.html.[17]

The digestive system does not accept large doses (over 3 grams) well; thus many 1 or 2 gram doses, taken often, are better absorbed. Each person will find some limit, usually over 20 grams/day, that will cause some diarrhea. Cathcart said that being near that limit was necessary for effectiveness in treating acute conditions and that the limit rises as one feels sicker. One man took 4 grams every 20 minutes!

Under normal circumstances, 3 grams every 4 hours would produce the maximum (220 umol/L) blood level, but toxins such as Ebola can use up ascorbate quickly. See Figure 2 (p. 73) for oral dosing results.[7]

Such a dose rate may help as protection, and if one checked urinary AA levels daily and they remained high, it should be an indication that one is still healthy.[26]

If the level drops, immediately increase dosage or go back to steps 1, 2, or 4.

In fact, a field test for presymptom Ebola (or other serious conditions) might be to take 1 gram of AA orally then test urinary AA 4 hours later, when it should peak. A low level suggests that something is amiss.[26]

4. Levy also suggests that in difficult cases the best treatment results can come from a combination of IVC sodium ascorbate 25 to 150 grams, liposomal 1 to 5 grams, oral ascorbate to tolerance, and ascorbyl palmitate 1 to 3 grams.[18]

It has not been determined what would be an adequate preventative dosage for a health worker. A 20 gram IV every 8 hours? 3 grams of liposomal every *x* hours? 2 grams of oral AA every hour? Perhaps the 3 grams every 4 hours would be sufficient.

Background

Ascorbic acid is remarkably safe.[19] The LD50 is 11,900 mg/kg (oral, rat) according to the Wikipedia entry on ascorbic acid. The Riordan clinic did over 40,000 infusions of sodium ascorbate, up to 1000 mg/kg with only a few minor reactions. (Don't use other mineral salts; you might get too much mineral.) Cathcart did 20,000 infusions. Follow the contraindications and provide sufficient hydration.[9]

Ascorbate has been used for thousands of years. Most mammals have an intact enzyme system that converts glucose into ascorbic acid in daily amounts up to 185 mg/kg/day when healthy, and many times that when under oxidative stress.[20–22] (A 154 lb animal, when well, might produce 13 grams a day; when sick, on the order of 50 grams a day – in the bloodstream.)

This action is endogenous for most mammals, but fruit bats, guinea pigs, primates, and humans lack an enzyme, thus lack the endogenous ascorbate, and thus are ripe for virus infection and to act as a vector of the virus.[23] An easy test would be to compare the response of a guinea pig vs. a mouse or rat to an Ebola sample.

AA has been used clinically, curing viral diseases since 1948 in published reports.[5]

There are two present-day experts in ascorbate use:

Thomas E. Levy, MD, JD, has spent over 20 years using ascorbate and has written several books on the subject, including *Curing the Incurable* (2002) and *Primal Panacea* (2011). Each has 1200 references and shows the wide range of benefits, including cardiovascular. His 2013 book, *Death by Calcium*, is about both AA and the body's difficulties dealing with calcium. His website is www.peakenergy.com; e-mail televymd@yahoo.com. He has made many YouTube videos, including https://www.youtube.com/watch?v=GpptUsJFCEY and https://www.youtube.com/watch?v=YTW9x91RWnY.

Ron Hunninghake, MD, is chief medical officer at the Riordan Clinic in Wichita, which has done 40,000 IVCs and research. Its website is www.riordanclinic.org.

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All accessed October 1, 2015.

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A background reference:
The Healing Factor: Vitamin C Against Disease. Available at http://www.vitamincfoundation.org/stone. (A full book by a pioneer of ascorbate, Irwin Stone, a chemist who really studied it – and benefited from it.)

Another good papers on ascorbate use is:
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Notice

This article is not in any way offered as prescription, diagnosis, or treatment for any disease, illness, infirmity, or physical condition. This is just publicly available information gathered from many sources and a few common-sense guesses. Persons needing medical care should obtain it from a physician. That said, I do report that several sources suggest that 2 or 3 grams of vitamin C, 4 times a day may be near optimum for *healthy* adults, normally. Irwin Stone and Linus Pauling, both of whom had really investigated this, took 18 grams/day, just to add a safety factor.

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Walton C. Ferris, BSc in physics and math, had a 47-year career as electronic design engineer, including one patent; he is now retired. He has 24 years' experience in reading medical material following his wife's death from kidney cancer.

Breaking Free from Sugar

review by Katherine Duff

The Complete Guide to Beating Sugar Addiction, by Jacob Teitelbaum, MD, and Chrystle Fiedler
Fair Winds Press; 100 Cumming Center, Suite 406-L, Beverly, Massachusetts 01915-6101
©2015; softcover; $19.99; 304 pp.

Sweets were once considered a treat, but now the average American adult consumes one-third of their calories in sugar and white flour. This anomaly in human history has created the problem of sugar addiction and its adverse health effects in bodies that were never designed to handle such large quantities. In describing the nature of sugar addiction, author Jacob Teitelbaum, MD, calls sugar the energy loan shark whose credit line eventually runs out, in his book *The Complete Guide to Beating Sugar Addiction.* Initially, the sugar gives energy but then crashes, leaving the person wanting more sugar to raise energy levels again. Eventually, this vicious cycle results in any number of health issues, such as heart disease, hormonal problems, and irritable bowel syndrome.

With the goal of supporting change to a low-sugar diet, the author has identified four types of sugar addict. Each type is driven by different needs to consume more sugar for more energy. Type 1 is for the "chronically exhausted and hooked on quick hits of caffeine [including energy drinks] and sugar." This behavior is exhibited by Type A individuals who may be sacrificing good sleep. The resulting fatigue is addressed with sugar, and the later crash is addressed with even more sugar. Eventually the Type 1 person develops health problems associated with reduced immune function.

The Type 2 person is in perpetual crisis or makes a crisis out of small events. This could also be the person who has too much work to do and is stressed to keep up. The adrenal gland is overworked trying to keep up with the constant stress until it no longer is able and adrenal function becomes low. The Type 2 person then turns to sugar to increase energy level. Some problems associated with this are diabetes, high blood pressure, and chronic fatigue.

A high-sugar diet, antacids, steroids, and antibiotics can lead to yeast overgrowth. Type 3 people finds themselves in a situation where once having developed the yeast overgrowth, they are constantly craving sweets that are in turn feeding more growth of the yeast. The resulting health problems include sinusitis, spastic colon, and food allergies.

Depression as a result of low hormonal levels in men and women can drive a person to consume more sugar. The Type 4 woman can be experiencing a deficiency of estrogen, progesterone, and/or testosterone; the man, testosterone. Low hormone levels can also lead to insulin resistance. The sugar, which is unable to enter the cells to provide energy, circulates in the blood, leaving the person with cravings for even more sugar for energy.

"Sugar addiction is the canary in the coal mine. It usually points to a larger problem that is also dragging you down."

In order to "cut out sugar," there are general instructions for all types. Learn to identify sugar under all of its names, and never eat processed foods that have any type of sugar as one of the first three ingredients. There is information on the natural and chemical sugar substitutes and advice for getting through the withdrawal period. Getting adequate sleep is imperative, as it does more than give us energy: it reduces sugar cravings and decreases appetite.

The solutions are tailored for each type. Type 1 calls for quality sleep that may involve treating sleep disorders. Hypothyroidism may be a cause of the fatigue, so treatment with a natural form of thyroid may be needed. Since infections are common to the Type 1 person, supplements to support the immune system are listed. The challenge for the Type 1 person is to change the diet to healthful foods from junk food eaten on the run. In addition, nutritional supplements that emphasize the B vitamins are listed. One of those supplements is ribose, which may be a great help for all types attempting to stop a sugar addiction. It is a sugar that does not raise blood glucose or promote yeast growth and in fact has a negative glycemic value. It does provide an energy boost and satisfies sugar cravings.

Other types may need bioidentical hormones, as in the case of adrenal fatigue and hormone deficiencies. Yeast overgrowth can be treated with natural supplements and pharmaceuticals when needed. And sleep, being such an important factor in preventing fatigue, may require pharmaceuticals for problems such as insomnia.

In what the author calls the side effects of sugar addiction, we see a long list of chronic conditions that are among our most common health problems, such as heart disease, obesity, and diabetes. In what may be an unexpected inclusion on the list are chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS). The discussion of CFS and FMS shows us the snowball effect of sugar addiction. While these conditions may have started from a severe case of flu, the treatment of antibiotics could cause the overgrowth of yeast. In an attempt to overcome the fatigue of CFS, a person could use sugar for energy, further exacerbating the yeast growth. The constant stress of coping with the increasing problems can lead to hypothalamic dysfunction

which in turn affects the adrenal, thyroid, ovarian, and/or testicular hormones. Unusual infections could also occur. Teitelbaum offers his SHINE protocol for treating CFS and FMS, which he has found effective in treating his patients as well as himself. SHINE is an acronym that stands for the five areas that need addressing: Sleep, Hormonal Support, Infections, Nutritional Support, and Exercise.

Obviously, sugar addiction has become a common problem. Teitelbaum show us that it may not be enough to just cut out the sugar. A comprehensive approach may be needed to resolve not only the addiction but also the underlying factors and consequences. This book takes what could be an overwhelming task and presents the solutions in manageable steps. Whether it is recommended supplements or a list of low-glycemic foods, the author explains why and how they will help. There is advice for finding a knowledgeable practitioner, pertinent testing companies, and resources for quality products. There are even recipes for each type. The layperson and especially the health practitioner should find this book a most helpful and convenient resource.

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Acid Reflux, Asthma, and Recalcitrant Cough

review by Jule Klotter

The Chronic Cough Enigma, by Jamie Koufman, MD
Katalitix Media; New York
www.katalitix.com.
© 2014; softbound; 140 pp; $14.95.

For years, New York laryngologist Jaime Kaufman has successfully treated thousands of patients with hard-to-diagnose, recalcitrant chronic cough – coughs that have no pulmonary cause and do not respond to acid suppression. She presented histories, diagnostic test results, and treatments of 50 consecutive patients at the American Broncho-Esophagological Association 2012 annual meeting. No peer-reviewed journal, however, would publish the paper because her findings challenge the assumption that chronic coughs are asthma related. In her experience, silent airway reflux (laryngopharyngeal reflux) is the cause in 40% of chronic cough, and vagal neuropathy (neurogenic cough) accounts for another 14%. The remaining 46% of her chronic cough patients have both reflux-related and neurogenic issues. Her book *The Chronic Cough Enigma* is an expanded version of the unpublished paper. She wrote the book to help frustrated patients and to educate doctors about diagnostic tests and chronic cough treatment.

Unlike acid reflux, silent reflux occurs without signs of heartburn or indigestion. Instead, people with airway reflux experience hoarseness, postnasal drip, difficulty swallowing, and shortness of breath. "Aspiration of even a small amount of a neutral-pH refluxate causes cough," Koufman explains. She uses a spit-in-the-cup pepsin assay and high-definition airway and esophageal ISFET pH monitoring to detect signs of stomach refluxate in the throat and to diagnose airway reflux. Silent airway reflux is often mistaken for asthma. People with asthma, however, have difficulty with expiration (breathing out), while people with airway reflux have difficulty with inspiration (breathing in). Also, airway reflux does not respond to asthma medication.

Treatment for silent airway reflux consists primarily of lifestyle modification, such as not eating within 3 to 4 hours before bedtime and not wearing tight clothing. Dietary recommendations include avoiding reflux-inciting foods and high-acid foods that trigger activation of inflammation-producing pepsin found in the throat and esophagus. Koufman says, "As inflammation and reflux improve, vavular and esophageal function improve and there is subsequently less reflux."

Most doctors ... think that reflux is an incurable, chronic disease for which the only treatment is lifelong medication. Not true. Reflux is curable with healthy diet and lifestyle: and by the way, it is the single most common cause of chronic cough.

Neurogenic cough usually stems from damage to the vagus nerve that occurs during upper respiratory infections. Branches of the vagus nerve control all respiratory and digestive functions. "Sometimes after the nerves heal, there are crossed wires, and those improperly directed nerves can lead to cough, pain, or other neurogenic symptoms," Koufman explains. A neurogenic cough can be triggered by talking, singing, changes in temperature, air conditioning, and perfume or other fumes. Unlike the reflux-related cough, the neurogenic cough is almost always dry. A chronic burning tongue and/or throat are other symptoms. Larnyngeal electromyography is the definitive test for diagnosis.

Koufman uses medication, such as low-dose amitriptyline, for 3 to 9 months to reset the vagus nerve control center in the brain. "When a person has a neurogenic cough, the coughing sparks a cascade of nerve and brain responses like a string of firecrackers," says Koufman. "The key to effectively curing neurogenic cough is to stop the cough and the neural cascade. If that can be done for three to nine months, the brain can reset."

The Chronic Cough Enigma is a straightforward, clearly written explanation of the pathophysiology, diagnosis, and treatment of a medical puzzle that afflicts millions. I highly recommend it.

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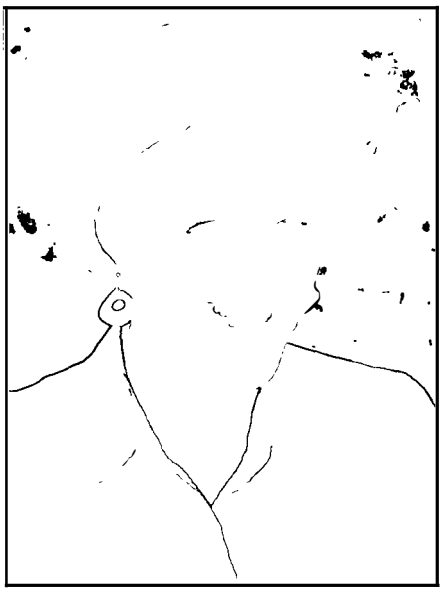


Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

Spirituality as an Age-Well Strategy

I liked the pulse of the 2015 Healthy Aging Summit in Washington, DC. It presented a mix of research, clinical medicine and advocacy, which I wrote about in my November 2015 *Townsend Letter* column. With this month's theme of men's health in aging, I write about something the conference didn't cover: a role for spirituality in supporting the aging process.

Attendees weren't afraid to look chronologic aging squarely in the eyes. They weren't going to give an inch to the ageist attitudes of our youth-obsessed culture. One outspoken person said that he disagreed with the conference introduction video wherein the elderly stated their age as "years young." "What's wrong with being old?" he asked. "We should feel proud of the age we've achieved." Attendees bandied phrases such as "Don't sugarcoat age," "Sweet-talk adds to discrimination," and "Sixty-five is the new 65." Even the opening talk was about achieving potential. My favorite was, "We should have a Peace Corps for older people. We do. It's called the Peace Corps." What I didn't hear in the "age well" messaging was the spiritual aspect of vibrant health.

The Healer

As a medical student, I was taught that *health* is not the absence of disease but the presence of physical, mental, and social well-being. The only shortcoming I saw to the WHO definition of health is that it seemed static – an answer for standardized tests, not one for the ER in the midst of a medical crisis. Or so I thought.

Imagine my surprise when that static definition helped me save lives on three continents. Working in a hospital in the headwaters of the Amazon, I was on a medical team to stem the outbreak of yellow fever. Using the jungle's rivers like roads, we canoed to distant villages. At each site we had to first meet with the traditional healer to receive permission to screen and immunize the villagers.

Later during a humanitarian mission in the Horn of Africa, I waited on giving a blood transfusion to a young man until his village's healer could speak with me. In a remote Native American community the night before I was to serve as their doctor, there was a knock at my door. I was asked to join members of the community at their sweat lodge. During the sweat they prayed for me to be blessed and guided while serving as their doctor.

Not only did the WHO definition of health help me tailor my medical services to diverse communities, as I tried to integrate it, I changed. The image of the medical doctor whom I wanted to be had become more organic, connected with humanity, and tuned to the invisible forces of healing.

Spirituality for Life

The largest body of published medical literature for spirituality in medicine is focused on end-of-life care. But spirituality can help people live to their potential, too, empowering them to make healthful choices.

I'm very interested in how spirituality can inspire us to be vibrant. I've watched spirituality help people get off the couch and out of the junk-food aisles. Another struggle common among those with excess weight is feeling judged or blamed, as if their condition is fully due to them personally. Can spirituality help them receive grace, mercy, and self-acceptance? Can the social networks that we form around our spiritual beliefs help us become more informed about the health effects of certain foods and medications? And what about the silver lining; can spirituality help patients find purpose in their journey through illness and harness their experience to come alongside others?

Most cultures around the globe and across time have harmonized the spiritual with the physical. The explanations may not have been scientifically sound, which was obviously detrimental to the patient. But that

doesn't mean that the method by which health care was provided was not effective. In contrast, the US system offers a fragmented form of health care. The scientific advances may have bigger impact if we can reunite them with the spiritual aspects that have withstood the test of time.

Is Spirituality Necessary?

I asked my colleagues attending the conference if they had heard discussions about the connection between spiritual and physical well-being. They hadn't, but they were interested in engaging in the topic.

For example, I spoke with the physician scientist who invented a clinical criterion for cognitive decline. His criteria didn't include spirituality, but in his opinion, preserving someone's mental functioning so that they can experience their spiritual beliefs is very important, and personally very satisfying to him.

One plenary speaker explained how our parents' aging process influences our own perception of aging. When she reached the young age at which her mother had died, it was emotional. The milestone was one that she clearly felt deeply and she reached deep inside to work through it.

The most common response from attendees was that the question of spirituality in healing was interesting, but was it really necessary?

"Necessary for what?" I asked. If health care were a ship, the captain would call all hands on deck, because of the widespread chronic diseases. Spiritual beliefs can inspire people toward nourishing choices, regular exercise, and stress reduction. So in a utilitarian way, spirituality is necessary.

Spirituality is part of how we define ourselves, even in a secular society. *Secular* means that all spiritual beliefs should be respected. In my opinion, suggesting that patients check their beliefs at the clinic entrance, alongside muddy boots and wet umbrellas, falls short of that respect.

Is Spirituality Politicized?

One day I accidentally became the envy of lobbyists. I had been a state page and a congressional intern, so when invited to be "doctor of the day," I returned to the central nerve of politics with a Tanita brand bioimpedance scale. I set it up at the first aid station and offered legislators personalized printouts of their body composition. The scale works best when metal is removed. I didn't hesitate to use white-coat authority to say, "Senator, empty your pockets. You can hand me your wallet."

While I got laughs, I didn't get funding. I returned the wallets, and my moment in politics ended as abruptly as it started.

I can be lighthearted about politics but I couldn't feel the same way about my scientific research. What if new jargon or catchphrases changed my research funding? That's the challenge that some of my colleagues faced. In the Bush era, public health funding was tied to faith communities. The 2015 Healthy Aging Summit's phrase was "social networks." There was no funding or mention of faith communities.

Whatever we call them, new health programs are often most effective when they build on existing social networks such as faith communities. Faith communities, the social networks arising from our spiritual beliefs, have shown themselves effective in promoting health. Examples include social gatherings for physical activity, intergenerational activities, and civic engagement.

Summary

Although spirituality got short shrift at a leading health and wellness forum that I attended in Washington, DC, attendees were interested in engaging in the topic. Enduring despite political tides, spiritual aspects of health can help us better understand what it means to be human. In practical public health and preventive medicine, spirituality can help patients toward more healthful ways of being.

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

Anti-Aging Medicine

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

An Anti-Aging Approach for Men's Health

Warning that physical inactivity is the fourth leading risk factor for death worldwide, the World Health Organization (WHO) issued *Global Recommendations on Physical Activity for Health* – in an effort to provide guidance on the frequency, duration, intensity, type, and total amount of physical activity needed for the prevention of noncommunicable diseases. Among adults ages 18 to 64 years, the recommendations are fourfold:

1. Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity.
2. Aerobic activity should be performed in bouts of at least 10 minutes' duration.
3. For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity.
4. Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.

Indeed, physical activity is the quintessential anti-aging practice. Ulf Ekelund and colleagues from the University of Cambridge (UK) assessed the link between physical inactivity and premature death. The team analyzed data collected on 334,161 men and women across Europe, enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. Over an average of 12 years, the researchers measured height, weight, and waist circumference, and used self-assessment to measure levels of physical activity. Data analysis revealed that the greatest reduction in risk of premature death occurred in the comparison between inactive and moderately inactive groups. The investigators estimated that daily exercise burning between 90 and 110 kcal ("calories") – roughly equivalent to a 20-minute brisk walk – would take an individual from the inactive to moderately inactive group, and reduce their risk of premature death by between 16% to 30%. The impact was greatest amongst normal-weight individuals, but even those with higher BMI saw a benefit. In further calculations, the team reveals that 337,000 of the 9.2 million deaths amongst European men and women may be attributed to obesity (classed as a BMI greater than 30) – with double this number of deaths (676,000) attributable to physical inactivity. The study authors report: "The greatest reductions in mortality risk were observed between the 2 lowest activity groups across levels of general and abdominal adiposity, which suggests that efforts to encourage even small increases in activity in inactive individuals may be beneficial to public health."

The role of exercise as an anti-aging approach is biological, as postexercise levels of irisin, a hormone released from muscle after exercise, correlate to telomere length. James Brown and colleagues from Aston University (UK) enrolled 81 healthy men and women, aged 18 to 83 years with a mean body mass index (BMI) of between 20 and 30 kg/m2, in a study to assess whether a molecular link exists between circulating irisin levels and the length of telomeres – the end caps of chromosomes which are thought to be a marker of aging. The team found that those subjects with higher levels of Irisin also had longer telomeres. Writing, "relative telomere length can be predicted by age and plasma irisin levels," the study authors conclude: "Irisin may have a role in the modulation of both energy balance and the ageing process."

This month's column reviews recent studies that reinforce the life-enhancing, life-extending importance that physical activity confers – particularly among men.

Ekelund U, Ward HA, Norat T, et al Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women the European Prospective Investigation into Cancer and Nutrition Study (EPIC). *Am J Clin Nutr* January 14, 2015

Global Strategy on Diet, Physical Activity and Health World Health Organization 2010 Available at http //www who.int/dietphysicalactivity/factsheet_recommendations/en. Accessed 27 August 2015

Rana KS, Arif M, Hill EJ, et al Plasma irisin levels predict telomere length in healthy adults. *Age.* January 2014

Daily Exercise Lowers Death Risk

Exercising for 30 minutes a day, 6 days a week, is linked to a 40% lower risk of death from any cause in older men. Professor Ingar Holme and colleague Sigmund Alfred

Anderssen of the Department of Sports Medicine at the Norwegian School of Sport Sciences (Oslo, Norway) studied data obtained from men taking part in the Oslo Study, which began in the 1970s. A total of 14,846 men born during 1923–1932 took part in the first study (Oslo I) in 1972–1973. Participants had their height, weight, cholesterol, and blood pressure assessed, and they were asked whether they smoked. They were also asked to respond to a validated survey (Gothenburg questionnaire) on their weekly leisure time physical activity levels. In 2000 the 5738 surviving men repeated the process (Oslo II) and were then monitored for almost 12-years to determine whether physical activity level over time was associated with a lowered risk of death from cardiovascular disease, or any cause. Results showed that during the 12-year follow-up, 2154 participants died. Further analysis showed that 30 minutes of physical activity, regardless of intensity, 6 days a week, was associated with a 40% lower risk of death from any cause. In addition, men who regularly engaged in moderate to vigorous physical activity during their leisure time lived 5 years longer on average than those who were classified as sedentary. The researchers say that the impact of regular exercise in elderly men seems to be as good for health as quitting smoking. "Public health strategies in elderly men should include efforts to increase physical activity in line with efforts to reduce smoking behaviour," they concluded.

Holme I, Anderssen SA Increases in physical activity is as important as smoking cessation for reduction in total mortality in elderly men: 12 years of follow-up of the Oslo II study *Br J Sports Med* 2015;49:743–748

Tai Chi Linked to Longevity

Chinese men who practiced tai chi, a form of mind-body exercise that originated in ancient China, were less likely to die over a 5-year period, as compared with sedentary men. Xianglan Zhang and colleagues from the Vanderbilt University School of Medicine (Tennessee, US) studied data collected on over 61,000 middle-aged and elderly men in Shanghai, China. Researchers tracked their health and lifestyle for more than 5 years: nearly 22,000 participants reported that they exercised at least once a week, and the rest were considered nonexercisers. Factoring in the men's age, health conditions, and whether they smoked, exercise was tied to a 20% lower likelihood of dying. Similarly, whereas 6.2% of the nearly 10,000 men who practiced tai chi died during the study, after adjusting for confounding factors, the team found that they were 20% less likely to die than men who didn't exercise. Further, the researchers observed that men who walked regularly were 23% less likely to die during the study, and men who jogged were 27% less likely to die. The study authors write: "The present study provides the first evidence that, like walking and jogging, practicing Tai Chi is associated with reduced mortality."

Wang N, Zhang X, Xiang Y-B, et al Associations of Tai Chi, walking, and jogging with mortality in Chinese men. *Am J Epidemiol*. June 27, 2013

Two Bone-Building Exercises

Weight-lifting and jumping exercises may improve bone density and reverse age-related bone loss among middle-aged men. Pam Hinton and colleagues from the University of Missouri (US) enrolled 382 physically active, middle-aged men who completed either a weight-lifting program or a jumping program for a year. Both programs required participants to complete 60 to 120 minutes of targeted exercises each week. The participants took calcium and vitamin D supplements throughout their training programs. The researchers measured the men's bone mass at the beginning of the study and again at 6 and 12 months using specialized X-ray scans of the whole body, hip, and lumbar spine. The researchers found that participants' bone mass of the whole body and lumbar spine significantly increased after 6 months of completing the weight-lifting or jumping programs, and this increase was maintained at 12 months. Hip-bone density only increased among those who completed the weight-lifting program. As well, the participants reported minimal pain and fatigue after completing their exercises, and these ratings decreased over the year. The study authors write: "[Resistance training] or [jump training], which appeared safe and feasible, increased [bone mineral density] of the whole body and lumbar spine, ➤

Anti-Aging Medicine

➤

while [resistance training] also increased hip [bone mineral density], in moderately active, osteopenic men."

Hinton PS, Nigh P, Thyfault J Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass A 12-month randomized, clinical trial *Bone*. 2015 Oct,79 203–212

Taking Up Exercise Late in Life

Fortunately (for many of us), it is never too late to start exercising. Mark Hamer and colleagues from the University College London (UK) assessed data collected on 3454 healthy senior men and women, enrolled in the English Longitudinal Study of Ageing. Participants reported how much they exercised at the start of the study, with researchers following them via regular health surveys for the next 8 years. At follow-up, 90% of the subjects were considered to be healthy agers, as they did not develop any major chronic diseases and had not experienced deterioration of their physical or mental status during the study period. The men and women who were active at least once a week at the study's start and remained active were the most likely to age healthily. Additionally, those who started exercising during the study period enjoyed health benefits as well: they were 3 times more likely than inactive adults to age well. Overall, men and women who remained active during the full 8 years of the study were over 7 times more likely to be aging well. Observing, "Sustained physical activity in older age is associated with improved overall health," the study authors conclude: "Significant health benefits were even seen among participants who became physically active relatively late in life."

Hamer M, Lavoie KL, Bacon SL Taking up physical activity in later life and healthy ageing the English longitudinal study of ageing *Br J Sports Med*. 2013 Nov 25

To stay updated on the latest natural approaches that may help to promote men'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, your weekly health newsletter featuring wellness, prevention, and biotech advancements in longevity. ◆

Calendar

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.

NOVEMBER 20-21: INTEGRATIVE THERAPIES INSTITUTE presents ADVANCING MEDICATIONS & INTEGRATIVE THERAPIES IN CLINICAL PRACTICE in Scottsdale, Arizona CONTACT www itiscottsdale com

DECEMBER 5: ORGANIC ACIDS WORKSHOP FOR DISCOVERING UNDERLYING CAUSES OF CHRONIC ILLNESS with Kurt Woeller in Los Angeles, California. CONTACT· www.organicacidworkshop com

DECEMBER 5: A DIFFERENT LOOK AT THYROID, CHOLESTEROL, & DIABETES USING BLOOD CHEMISTRY in Pineville, North Carolina. CONTACT. 800-231-5777, https //www facebook com/BioticsResearch

DECEMBER 5-6 NUTRITIONAL INTERVENTIONS YOU WILL USE EVERY DAY in Windsor Locks, Connecticut. CONTACT 800-231-5777, https //www facebook com/BioticsResearch

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

JANUARY 22-24: INTEGRATIVE THERAPIES INSTITUTE presents GENOMICS, NEUROPSYCHIATRIC THERAPIES, AND CHRONIC ILLNESS, IMMUNE & AUTOIMMUNE CONDITIONS & ADVANCED INTEGRATIVE THERAPIES IN CLINICAL PRACTICE in Irvine, California. CONTACT: www.iti2016.com

JANUARY 23-26: WALSH RESEARCH INSTITUTE presents PHYSICIAN EDUCATION WORKSHOP: MASTERING BRAIN CHEMISTRY (nutrient protocols for autism, behavioral/learning and mental disorders) in Irvine, California CONTACT Sue at 630-400-3400, www walshinstitute org/practitioner-education.html

JANUARY 29-31: 13th ANNUAL NATURAL SUPPLEMENTS: AN EVIDENCE-BASED UPDATE in San Diego, California CONTACT www Scripps org/NaturalSupplements

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

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

JANUARY 30: ORGANIC ACIDS WORKSHOP FOR DISCOVERING UNDERLYING CAUSES OF CHRONIC ILLNESS with Kurt Woeller in Tampa, Florida CONTACT www organicacidworkshop.com

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

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

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

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

MARCH 12: ORGANIC ACIDS WORKSHOP FOR DISCOVERING UNDERLYING CAUSES OF CHRONIC ILLNESS with Kurt Woeller in Atlanta, Georgia CONTACT www.organicacidworkshop com

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

APRIL 14-16: 14th ANNUAL INTEGRATIVE ONCOLOGY CONFERENCE @ Town & Country Resort in San Diego, California CONTACT: www bestanswerforcancer org/annual-conference/2016-conference/

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

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

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

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

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

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

Women's Health Update

by Tori Hudson, ND and
womanstime@aol.com

Green Tea: Three More Uses

Green Tea Reduces Bacteria in Dental Plaque

Streptococcus mutans is one of the most common bacteria that cause dental disease, including dental plaque. Germicidal mouthwashes such as chlorhexidine do reduce bacteria in the mouth but can also cause staining and an unpleasant taste. New research points to green tea as having benefits for oral health. The polyphenols in green tea have been reported to suppress glucosyltransferase, which is used by oral bacteria to feed on sugar. The authors of the current study conducted a randomized, controlled, single-blind, crossover trial to evaluate the effects of rinsing with green tea, and the effects on *Streptococcus mutans* in plaque, and then compared that with chlorhexidine mouthwash and plain water.

Students at a dental institute were selected (n = 30, mean age of 22.4). If they scored 1 on the plaque index, which indicates a film of plaque adhering to the free gingival margin adjacent to the tooth, they were eligible. Baseline plaque samples were collected.

Students were then randomly assigned, 10 each in the green tea group, the chlorhexidine group, and the plain water group. Chlorhexidine (0.12%), a commercially available product, was used, plain water was used as the negative control, and fresh green tea bags were used. A 2% green tea mouthwash was prepared by dipping a tea bag weighing 2 grams in 100 mL warm water for 5 minutes.

10 mL of the mouthwashes was given to the students, and they were told to rinse with it for 1 minute. After 5 minutes, plaque samples were again collected. After a 7-day washout period, the participants returned to repeat the procedure with a different mouthwash. The same procedure was repeated until all 30 students tried all 3 mouthwashes.

Reductions in *S. mutans* colony counts after rinsing with chlorhexidine and with green tea were almost identical. No significant reductions in *S. mutans* levels were observed after rinsing with the plain water mouthwash. There were no differences seen between the green tea mouthwash and the chlorhexidine mouthwash, and both were significantly more effective than plain water.

Comment: Reductions in *S. mutans* count in plaque were seen in both the green tea and chlorhexidine groups. Although the reductions were only slightly greater in the chlorhexidine group, green tea has certain advantages due to no staining, no aftertaste, no allergic reactions, and no bacterial resistance. Even though this study had a small sample, this is a very desirable strategy, an easy practice to explain, and an easy habit to acquire for individuals to use.

Neturi RS, Srinivas R, Vikram Simha B, Sandhya Sree Y, Chandra Shekar T, Siva Kumar P. Effects of green tea on *Streptococcus mutans* counts – a randomised control trail [sic]. *J Clin Diagn Res*. 2014;8(11):ZC128-ZC130.

Green Tea's Effects on Weight Reduction

Green tea has been studied for its beneficial effects on cardiovascular and metabolic diseases. Epigallocatechin gallate (EGCG) is the most abundant green tea catechin and is considered the most bioactive constituent that can reduce body weight by decreasing fat cell differentiation and proliferation. One study has demonstrated that green tea extracts and drinks could reduce body weight and body mass index in obese individuals in 2 months. (Basu A et al. Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. *J Am Coll Nutr*. 2010;29:31–40.) On the other hand, a previous study found that 302 mg of EGCG daily did not reduce weight in obese women. (Hsu C, Sai T, Kao Y, et al. Effect of green tea extract on obese women: a randomized, double-blind, placebo-controlled clinical trial. *Clin Nutr*. 2008;27:363–370.) This current study set out to increase the concentration of EGCG to a daily dose of 856.8 mg/day to see if this increased amount would result in weight loss in obese individuals.

This randomized, double-blind trial was conducted in 115 women with central obesity, with 102 of them having a body mass index (BMI) ≥ 27 kg/m^2 and a waist circumference ≥ 80 cm. Women were randomized to either a high-dose green tea group or placebo group for 12 weeks. One capsule of green tea or placebo was give 3 times per day, 30 minutes after meals for a total daily dose of 856.8 mg EGCG. ➤

➤

Body weight decreased from 76.8 kg to 75.7 kg after 12 weeks in the EGCG group. BMI and waist circumference were reduced from 31.0 cm to 30.6 cm and 95.1 cm to 92.8 cm respectively. In the placebo group, only waist circumference and hip circumference reached significant reduction from 95.7 cm to 91.5 cm and 107.2 cm to 103.7 cm respectively. No differences were seen in weight or BMI.

The study also demonstrated a trend of decreased total cholesterol and decreased LDL cholesterol. Significantly lower ghrelin levels and elevated adiponectin levels were also seen in the green tea group than in the placebo group.

Comment: Obesity is one of the most challenging issues in women's health care. No single strategy produces consistent results in all women. Nutritional modifications, exercise programs, behavioral therapy, and agents that can affect insulin resistance, fat burning, fat oxidation, and metabolic rates occupy central roles in efforts. Green tea and its main components, the catechins, including EGCG, are thought to influence body weight through mechanisms of thermogenesis and fat oxidation. The results of the current study with significant weight reduction and decreased ghrelin levels after EGCG treatment imply that a high dose of EGCG might increase energy metabolism and interrupt lipid accumulation and directly inhibit ghrelin secretion.

For perspective on dosing, one might look for a capsule of green tea extract of approximately 330 mg of which 45% is EGCG. If 2 capsules are taken 30 minutes after each meal (3 times per day), this would then be 900 mg of EGCG per day, slightly more than the 856.8 mg in the current study.

Chen I, Liu C, Chiu J, Hsu C Therapeutic effect of high-dose green tea extract on weight reduction: a randomized, double-blind, placebo-controlled clinical trial *Clin Nutr*. Epub May 2015.

Green Tea Catechins for Xerosomia (Dry Mouth)

The perception of dry mouth (known as xerostomia) affects up to 40% of adults in the US and can have a significant effect on quality of life. Causes can include medications, diabetes, Sjögren's syndrome, and hormonal changes such as menopause. Previous animal and laboratory studies provided evidence that green tea polyphenols could be beneficial for xerostomia.

The current human study used a double-blind, placebo-controlled, randomized design comparing green tea with xylitol. The study involved 60 individuals (58 women and 2 men) with the complaint of dry mouth and who had Sjögren's syndrome-mediated salivary gland hypofunction, with 30 taking the placebo and 30 taking the green tea medicine. The green tea proprietary formula contained green tea catechins and other ingredients (amounts not given; Internet search reveals xylitol, sorbitol, natural flavors, green tea [leaf], acacia gum, jaborandi extract (leaf), magnesium stearate, silicon dioxide, sucralose). The placebo contained 500 mg xylitol and other nonplant ingredients. Participants took 1 lozenge every 4 hours for a maximum of 6 lozenges per day, over an 8-week period. Quality of life assessments and saliva collection with volume determined were used to evaluate response.

After 8 weeks of therapy, the xylitol-containing placebo failed to affect saliva output while the green tea catechin containing formula resulted in a statistically significant increase in saliva output with a 3.8-fold increase in unstimulated saliva output and a 2.1-fold increase in stimulated saliva output, compared with baseline. This occurred within 1 week. Both groups experienced a quality of life score demonstrating significant improvement with no significant difference between groups.

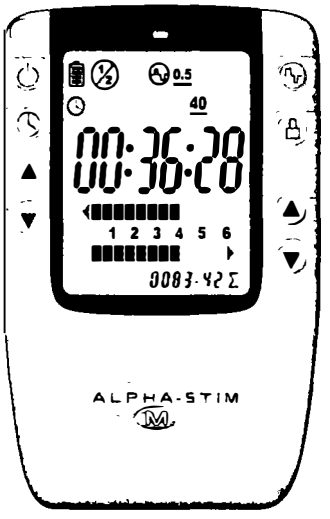
Comment: Most commercial products for xerostomia contain xylitol, although it has not been known if xylitol does in fact play a role in saliva output. A xylitol chewing gum, a sorbitol-containing lozenge, and a xylitol-containing spray previously showed no efficacy in stimulating saliva in patients with xerostomia. Other research using a maltose-containing lozenge found a potential benefit for xerostomia, and another with a 1% malic acid spray did show a modest increase in salivary flow rates. It is not clear why there is a discrepancy between salivary output increase in the treatment medication compared with placebo vs. the similar effects on subjective quality of life measures. A longer study with more participants would hopefully clarify and produce greater results in the treatment group not only in objective measures of salivary output but also in subjective quality of life values.

De Rossi S, Thoppay J, Dickinson D, et al. A phase II clinical trial of a natural formulation containing tea catechins for xerostomia. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014;118.447–454.

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. ◆

The Alpha-Stim M for Anxiety, Insomnia, Depression, and Pain

The Alpha-Stim M is a cranial electrotherapy stimulation (CES) and microcurrent electrical therapy (MET) medical device that uses low-level electrical current to safely and effectively treat anxiety, insomnia, depression, and pain. Alpha-Stim treatments are cumulative; however, most patients show some improvement after their first treatment. Alpha-Stim can be used as a stand-alone treatment or as an adjunct with other modalities and pharmaceuticals. Alpha-Stim has a unique and patented waveform that has been proved safe and effective in numerous double-blind studies. The Alpha-Stim, FDA-cleared for the treatment of anxiety, insomnia, depression, and pain, is available for your patients now.



Mushroom Wisdom Celebrates 25 Years

As we enter into the New Year, Mushroom Wisdom is pleased to be celebrating its 25th anniversary of bringing you the finest, grounded-in-research medicinal mushroom products available. It all started with the introduction of the maitake mushroom to the West, which led to the development of the powerful immune-supporting, one and only Maitake D-Fraction. This was followed by discoveries showing that another compound in the maitake mushroom, called SX-Fraction, supported healthy blood sugar and serum insulin levels. As medicinal mushrooms are being recognized more and more for a varied array of promising health benefits, beyond supporting immune health, MWI has been leading the way with research on the lion's mane mushroom and the introduction of the clinically tested standardized proprietary extract Amyloban 3399. Its research has focused on healthy nerve and brain support as well as benefits for sleep, mood, and mental health. MWI looks forward to serving you for 25 more years.

Dr. Ohhira's Probiotics Honored as a Seven-Time Winner of *Better Nutrition* Magazine's 2015 'Best of Supplements' Award

In Japan, the number seven (7) is regarded as lucky and holy. In the Bible, seven is the number of physical and spiritual completeness, and positive renewal. So the seventh "Best of Supplement" award designation corresponds significantly to Dr. Ohhira's renowned and respected probiotic formula.

Dr. Ohhira's Probiotics originated from a reverence for nature and is widely recognized for bestowing transformative and replenishing good health. It all begins with an abundance of fresh herbs, fruits, mushrooms and vegetables, and, of course, clean, clear, spring water. A diversity of bacterial strains are added and encouraged to flourish through the patience of a multiyear natural temperature fermentation process that produces a probiotic like no other on the market today.

Better Nutrition magazine selected Dr. Ohhira's Probiotics innovative formula as 2015 "Best of Supplements" Award Winner in the "Probiotic" category for the *seventh* time, making Dr. Ohhira's Probiotics the only probiotic supplement ever to achieve this honor. A representative from *Better Nutrition* presented the award during the Natural Products Expo East held September 17–20 in Baltimore, Maryland.

To select the winning products, the editors of *Better Nutrition* conducted retailer surveys, as well as tallied up readers' and staffers' votes. The Better Nutrition Supplement Advisory Board, consisting of naturopathic physicians, health writers, and nutrition educators, considered the nominated supplements' quality of ingredients and reputation, and the science behind the products. The award winners were featured in the November 2015 issue of *Better Nutrition.*

Iichiroh Ohhira, PhD, one of Japan's leading microbiologists, formulated this product, and over 30 years of university-based, scientific research studies have proved it to be strong, safe, and effective in dealing with digestive distress. Established in 2000, Essential Formulas Incorporated is the sole distributor of Dr. Ohhira's Probiotics in the US and has now expanded its line to Reg´Activ, containing ME-3, the glutathione-generating probiotic that allows your body to produce this "master antioxidant" needed to heal itself. ◆

Study Shows Taking Sustamine L-Alanyl-L-Glutamine May Reduce Muscle Protein Breakdown After Resistance Exercise

A University of Texas at Austin study showed that taking sustamine L-alanyl-L-glutamine inhibits signaling proteins that activate protein degradation, which helps to maximize muscle protein buildup after resistance exercise.[1]

The study, published April 3 in the journal *Amino Acids*, included 89 male Sprague Dawley rats 2 to 3 months of age who performed resistance exercise. Immediately post exercise, the rats were given whey protein (0.4g/kg), low-dose Sustamine (0.1g/kg), high-dose Sustamine (0.5g/kg), or placebo, in random order. Sixteen rats were used as sedentary controls.

The primary findings were that "Sustamine altered, immediately post exercise the phosphorylation state of signaling proteins in a manner that theoretically should reduce muscle protein breakdown, while whey protein accelerated the phosphorylation of proteins in the mTOR-dependent signaling pathway thereby theoretically activating muscle protein synthesis."

Sustamine is a dipeptide of glutamine that provides several substantial benefits such as enhanced recovery, immune system support, and increased metabolic rate. This was one of the first studies to demonstrate its benefit on inhibiting muscle protein breakdown.

About Sustamine

Sustamine L-alanyl-L-glutamine is vegetarian, allergen free, and the only GRAS L-alanyl-L-glutamine. It is also tasteless, odorless, and stable in liquids. Sustamine is a dietary supplement and an ingredient used in food and beverages.

Sustamine is an ingredient that works on multiple levels to help rehydrate the body and sustain energy levels during exertion. It combines L-glutamine (the most important amino acid for stimulating muscle protein synthesis) and L-alanine (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.*

Sustamine is a registered trademark of Kyowa Hakko Bio Co. Ltd.

* 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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The 'Structure-Function' Dysfunction

I recently presented a webinar that discussed current research on the use of nutritional supplements for the prevention and treatment of common illnesses. A company that sells dietary supplements to health-care practitioners contacted me and asked if I would be willing to repeat the webinar for its clients. Well, not exactly repeat it; in order to comply with Food and Drug Administration (FDA) regulations, I would have to change all references to diseases and health conditions into "structure-function" language. I told the company that using structure-function language makes it difficult to teach anything useful, and that converting my presentation to such language would ruin it. The company was not surprised by my reply, because it had been forced to deal with the structure-function demon for many years.

FDA regulations prohibit the dietary supplement industry from claiming on product labels or on any accompanying literature that a supplement may be useful for preventing or curing a disease. There are some exceptions to this rule; for example, claims that calcium can prevent osteoporosis and that folic acid can prevent neural tube defects are allowed. However, there are hundreds of other health benefits of dietary supplements for which the FDA restricts the dissemination of truthful scientific information. As a rather pathetic consolation prize, the FDA does allow various structure-function claims. Thus, while you are not allowed to say that St. John's wort relieves depression, you can say that it helps improve mood. It is acceptable to claim that magnesium helps maintain a healthy circulatory system, but not that it can prevent cardiovascular disease. It is permitted to say that a supplement supports the immune system, but not that it can help prevent or treat colds or influenza.

The problem with structure-function language is that its lack of precision often renders it nearly useless. For example, research suggests that saw palmetto is beneficial for benign prostatic hyperplasia, that flower pollen can be used to treat prostatitis, and that high-selenium yeast may help prevent prostate cancer. However, because FDA regulations limit the claims for each of these products to something vague like "supports prostate health," there is no way of knowing which products may be helpful for a particular person. Similarly, a product that "helps maintain a healthy circulatory system" may or may not be effective for specific conditions such as intermittent claudication, hypertension, high cholesterol, congestive heart failure, or

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Editorial

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cardiac arrhythmias. The FDA's restrictions on the dissemination of truthful scientific information prevents people from learning about treatments that could help them, impedes medical progress, and causes some individuals to waste money on products that are not appropriate for them.

Some supplement manufacturers have taken the FDA to court, claiming that the restrictive language required by the FDA interferes with freedom of speech. So far, these legal challenges have mostly been unsuccessful. However, it may now be the time for the supplement industry to mount another challenge against the FDA. In 2012, the United States Second Circuit Court of Appeals ruled on a case regarding the FDA's right to prohibit drug companies from disseminating scientific evidence about off-label uses of approved drugs. According to the ruling, the truthful promotion of off-label drug use is constitutionally protected free speech that is not subject to FDA regulation. The court noted that prohibiting this type of speech "interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions." The FDA tried to do an end run around this ruling by requiring that drug companies allow the FDA to edit off-label marketing materials prior to their release. However, a drug company challenged that regulation in court, and a judge recently ruled that the FDA has no authority to restrict the drug company's First Amendment rights.[1]

I am not a lawyer or constitutional scholar, but it seems that these recent court rulings have set a precedent that could also apply to the supplement industry. A new court challenge might finally put an end to the FDA's arbitrary and harmful restrictions against truthful speech about dietary supplements. If the industry could successfully reign in the FDA, then I would be able to repeat my webinar without making any changes. I would not have to change "reverses actinic keratoses" to "promotes skin health," or change "decreases the mortality rate in patients with congestive heart failure" to "helps maintain a healthy circulatory system," or change "decreases the symptoms of multiple sclerosis" to "contributes to normal functioning of the nervous system."

Alan R. Gaby, MD

Notes

1. A free-speech clinic for the FDA. *Wall Street Journal*. August 15–16, 2015:A10.

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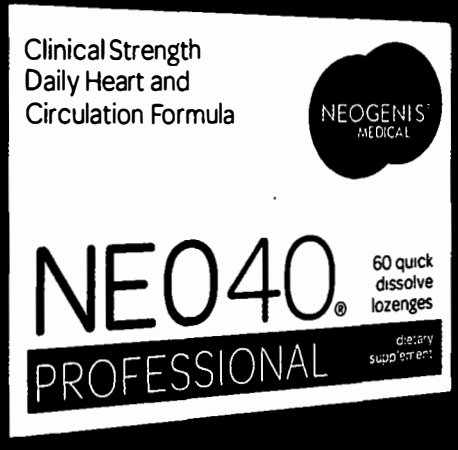

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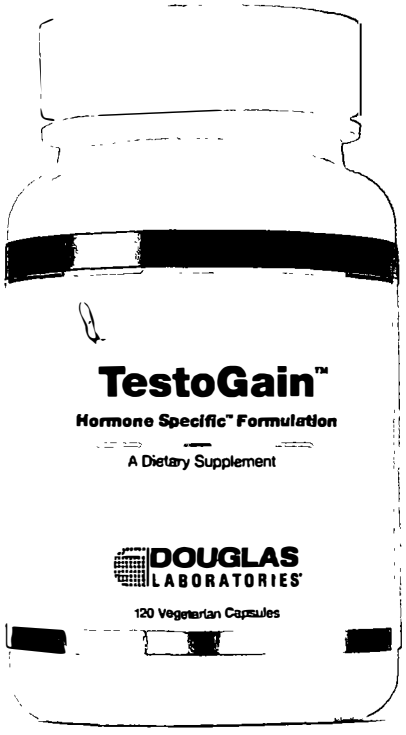

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