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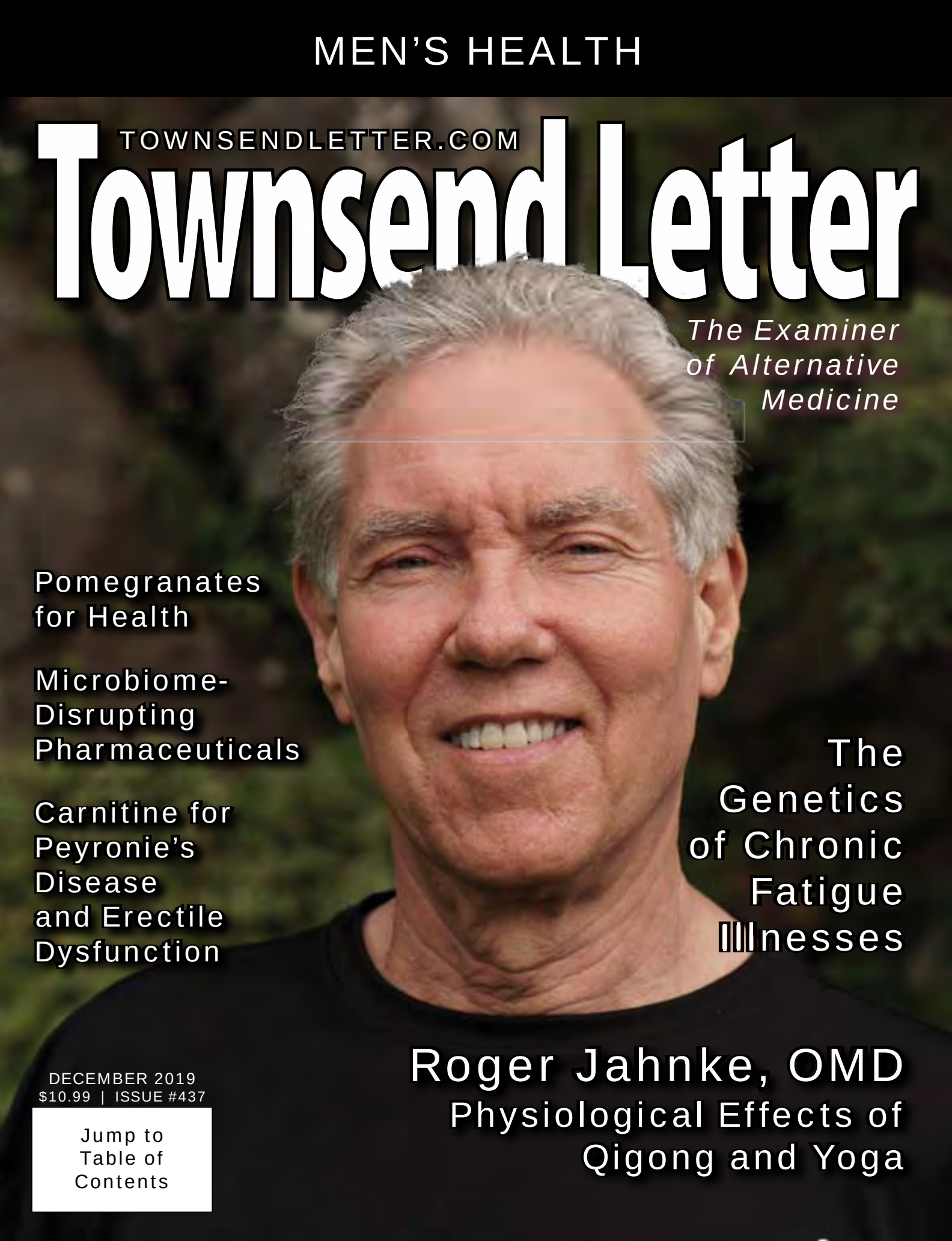

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The Genetics of Chronic Fatigue Illnesses

Roger Jahnke, OMD

Physiological Effects of Qigong and Yoga

DECEMBER 2019
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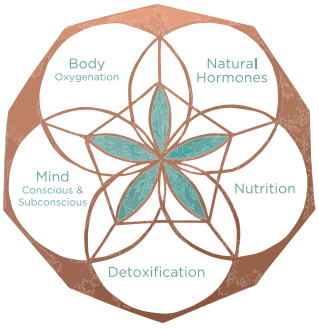

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From the Publisher

Stop the Thyroid Madness

I don't know about you but I have become frustrated by the repeated shortages of natural thyroid hormone medication. The company that I have worked with for nearly three decades first ran out of thyroid about six years ago and took nearly three years to restore its regular hormone supplies. In that time period it changed from 30-day packs to 90-day supplies with accompanying quadrupling price increases. However, hormone shortages began shortly thereafter, and currently they are unable to provide any dose thyroid hormone without a reliable date for when it will be available.

The dearth of natural thyroid hormone has been accompanied by a degradation of the quality of the hormone preparations. Jane Bowthorpe writes on the *Stop the Thyroid Madness* blog (*STTM*) about "The Sad Saga of Where We Are Today as Hypothyroid Patients" (Sept. 23, 2019). Bowthorpe thinks that all "natural desiccated thyroid (NDT) have gone south/changed from what they used to be." She reports that Armour Thyroid by Allergan underwent major changes in 2009. Patients who had been using Armour Thyroid saw a relapse of their hypothyroidism without a change in dose. Despite Armour's subsequent quality-control

continued on page 6 ➤

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Letter from the Publisher

➤ *continued from page 4*

improvement a similar faulty Armour product was noted by *STTM* bloggers in 2015. A Canadian brand of desiccated thyroid, ERFA, produced an adulterated product in 2014 causing many well-treated patients to become hypothyroid. Naturethroid by RLC Labs encountered manufacturing difficulties of its hormone for several years prior to 2018 when the newly released product led to relapsed hypothyroidism in many patients, according to an *STTM* blog. Bowthorpe reports that WP Thyroid by RLC Labs may have caused patient relapses as well. NP Thyroid by Acella Pharmaceuticals "seemed to change horribly in the summer of 2019," according to Bowthorpe. Not only were there hypothyroidism relapses but patients reported "a slew of other terrible symptoms ranging from nausea, burning in the stomach, allergic reactions, flu-like symptoms, and more." Her blog also reports that the product "had a highly repulsive taste and rank smell…comparable to cat pee or kitty litter." When patients complained of the change in effectiveness of the natural thyroid hormone preparations the companies' response invariably was that "we didn't change anything." None of the aforementioned pharmaceutical firms indicated that there would be any changes to restore their products back to their original quality established for decades.

The reason that integrative physicians and naturopathic doctors have prescribed desiccated thyroid hormone products is that they contained a natural blend of T4 and T3. The standard thyroid hormone prescription for hypothyroidism has been synthetic T4 only. Such treatment usually is not nearly as effective as the natural blend of T4 and T3. The reliance of endocrinologists and family practitioners on ordering TSH testing alone is also responsible for misdiagnosing many hypothyroid patients. An optimal level of free T3 (high normal, not mid-range) and free T4 (mid-range) is necessary for successful hypothyroidism treatment. Synthroid alone will rarely achieve such optimization.

Read and share Bowthorpe's blogged article: https://stopthethyroidmadness.com/2019/09/23/the-sad-saga-of-where-we-are-today-as-hypothyroid-patients/.

Cover Article: Qigong and Yoga – Underappreciated Healing for Serious Illness

For most men, health is frequently taken for granted. In our 20s we participate in extreme sports, exerting ourselves maximally, taking serious risks, and if we are lucky, survive to tell the tale – if not, we take time off to nurse serious injuries, but usually we recover sufficiently to take on the next big challenge. Our mantra is "pedal to the metal" and "sheets to the wind," and we ignore worries that we may fall to our death. In our 30s the body begins to show some lowered resilience, and we encounter minor injuries and mishaps that are not life-threatening but definitely hurt. There's a definite letting-up on the accelerator, and we do keep a watchful eye for some potential miscalculation that may end up in injury. We also begin to slow down on those pitchers of beer (street drugs) and don't try to ignore bronchitis while jogging at 5 a.m. In our 40s and 50s there is no doubt that the body will not suffer injury in silence; and when we are sick, we may not see the doctor, but we do stay home hopefully getting some TLC and not from a whiskey bottle. But we are aware that the aging process is upon us; and we do look at a better lifestyle, working out at the gym, tending not just to the job but the family

too, enjoying those weekend naps, and using some herbal and nutrient support. But by our 60s the aging process definitely has made its presence well known. If we're lucky, it's just some aches and pains; if we're not so lucky, there's one or more medical conditions we are nursing with one or more medications. The trouble is that medication only takes us so far; there's no cure, and too often there are some side effects, sometimes nasty side effects. What is one to do?

Roger Jahnke, OMD, and Nancy Faass, MSW, MPH, examine in this issue the "Physiology of Qigong and Yoga." Jahnke is a clinician in Traditional Chinese Medicine and is recognized as an expert in qigong. He has been studying Chinese medicine since the 1980s, travelling frequently to China as a lecturer and examiner of their health-care system. Jahnke would argue that integrating qigong and yoga practice in our daily lives would go far to prevent health deterioration. Even more, their implementation would augment the effect of pharmaceuticals in arresting disease and reversing physical impairment. Some would argue that qigong and yoga are not part of the Western lifestyle – if they were so important why didn't we get introduced to them by our grandparents? Jahnke would agree that these techniques were not part of healing methods handed down by our European ancestors. Medicine's "scientific approach" bases its healing on a military model where the germ needs to be killed, the cancer removed, and the degeneration arrested. The idea that a mindful form of exercise and meditation can rebalance the sympathethic/parasympathetic nervous system functioning is a difficult concept for men to swallow. Watching men pound themselves on the football field is much more enjoyable than disciplining ourselves to move mindfully or breathe with intention. Qigong and yoga might be the perfect medicine to incorporate in our daily lives not only to stave off the aging process but also to enhance the effectiveness of medical treatment.

Is Male Sexual Dysfunction an Issue of Low Testosterone?

Low testosterone and its treatment have become a cottage industry in the medical profession. Some clinics have established one-year prepaid programs, including monthly hormone testing and complete hormone treatment protocols. Undoubtedly supplementation of reduced hormone levels to optimized levels, particularly low testosterone, will revitalize one's health. Along with improved energetic functioning, cognitive ability, and muscular tone, sexual functioning will undoubtedly be enhanced. But enhanced enough that Viagra® or Cialis® would not be necessary? That is not so clear; some studies have shown that testosterone replacement is insufficient to improve depressed sexual performance and libido. Hence the marketplace is replete with a cornucopia of nostrums all touted to enhance erection and staying power. Might there be anything in our nutritional toolbox that may offer some succor for those suffering with E.D.?

In fact, there is. Jeremy Mikolai, ND, a naturopathic physician who has devoted much of his academic and clinical activities to cardiovascular medicine, writes in this issue about the amino ➤

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acid, carnitine's role in assuaging sexual dysfunction. We do get abundant carnitine if we are not vegan and are eating meat, foul, and fish. Carnitine is an important biochemical transporter of fatty acids into mitochondria and is critical for fat utilization and metabolism. Less well understood is carnitine's role in improving cardiovascular functioning, particularly in peripheral vascular disease, heart failure, and penile erection. Carnitine needs to be transformed into derivatives, proprionyl-l-carnitine (PLC) and acetyl-l-carnitine (ALC), to exert its maximal effect on restoring full vascular flow. Studies and clinical cases demonstrate marked improvement in a not uncommon disorder in men, Peyronie's disease, when PLC and ALC are prescribed. Except for difficulties with gastrointestinal distress, a frequent issue with vitamin supplements, carnitine is harmless. Why shouldn't it be a keystone in all protocols addressing male sexual dysfunction?

Pomegranates: The Wonder Fruit for Cholesterol, Hormones, and Cancer

Dr. D. Lindsey Berkson has made a career of understanding hormone functioning and nutrition. Her work has been recognized in collegiate and medical colloquiums where she has frequently presented. Dr. Berkson has written often for the *Townsend Letter*; in this issue she discusses a topic of personal interest – how daily pomegranate consumption is a mainstay for health and for preventing and reversing illness. How can a fruit, admittedly a complex fruit, exert powerful anti-cholesterol, anti-diabetic, anti-carcinogenic, and anti-inflammatory effects? Shouldn't that be the purpose of a drug agent? Berkson cites how pomegranate promotes kidney health, bone health, brain protection, and immune support. When she was seen by her Integrative-medicine cardiologist, he suggested a prescription of daily pomegranate.

Seriously. A genetic error with APOCIII is mitigated with pomegranate. So is an elevated LDL. So is oxidized cholesterol. From a physiological basis, pomegranate reduces the size of plaque! It lowers blood pressure, decreases blood clotting, increases nitric oxide, mitigates angina pain. Think about the cardiovascular patients coming in with a tub of cardiac drugs. Could pomegranate consumption enable stopping the daily prescriptions? That would be a major boon for those men (and women) who have had a heart attack or stroke and are shackled to a handful of pills. But pomegranates do more. For those men who have prostate cancer (and for those women who have breast cancer), pomegranate inhibits stem cell metastasis by modifying tumor signaling pathways and interfering with stem cell migration. One other boon from consuming pomegranate is improvement in kidney health; this could be a big benefit for those patients on dialysis.

But the benefit only comes to those who are willing to eat pomegranate daily. Drinking the juice is okay but eating the seeds, arils, (one-quarter to one-half cup daily) is even better.

Jonathan Collin, MD
Publisher

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Shorts

briefed by Jule Klotter
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GI Microbiome and Aging

Does aging lead to a less diverse (and therefore less beneficial) microbiome in the gastrointestinal tract, or does a less diverse microbiome contribute to signs of aging? Current evidence, although limited, does indicate a direct association between the two. A link between the GI tract and aging is not new; early in the last century, Nobel laureate Elie Metchnikoff suggested that regular consumption of probiotic-rich yogurt might "promote healthier aging." In a 2018 review, Ravinder Nagpal et al suggest that anti-aging probiotics may eventually be developed that slow the aging process.

Composition of the gut's microbiome in the elderly differs from that of healthy, younger adults: "Generally, the diversity of gut microbiota and the carriage of commensals such as bacteroides, bifidobacteria and lactobacilli are found to be reduced while the levels of opportunists such as enterobacteria, *Clostridium perfringens* and *C. difficile* are increased in elderly." However, this is not true in all geographical areas; diet and lifestyle play major roles in microbiome composition – regardless of age. Mobility issues, lack of exercise, medication use, and poor GI function can also decrease the numbers of beneficial bacteria.

"The gut microbiota plays a central role in various host physiological functions including degradation of fibrous foods, energy supply and harvest, lipid storage and metabolism, synthesis of vitamins, suppression of harmful bacteria and maintenance of intestinal barrier integrity," say Nagpal et al. Fewer beneficial bacteria mean less short-chain fatty acids (SCFAs), which are end-products produced as the bacteria ferment complex carbohydrates (their food source). Our bodies require SCFAs (butyrate, propionate, and acetate) to maintain GI health. In addition, SCFAs have immune-modulating and anti-inflammatory effects. Altered microbiome composition can lead to a decline in immune system function, susceptibility to infections, increased inflammation, and other signs associated with aging.

The reviewers mention that probiotic supplementation, based on strains found in healthy elders and centenarians, may become possible in the future, but we don't have to wait for a magic pill. Since diet strongly influences the composition of the GI microbiome, regular consumption of complex carbohydrates that feed lactobacilli and bifidobacteria (prebiotics) is another option. Studies have shown that prebiotic consumption (eg, inulin, galacto-oligosaccharides, fructo-oligosaccharides) has positive anti-inflammatory and immune effects in elderly people.

Sources for inulin include asparagus, bananas, dandelion root, chicory root, Jerusalem artichokes, leeks, and onions. The list for oligosaccharides is more diverse, as reported in a mini-review from Belorkar and Gupta. Many edible plants contain oligosaccharides: garlic, onions, bananas, lentils, tomato, barley, rye, and wheat. In addition, honey is a rich source of fructooligosaccharides, preferred by *Bifidobacteria*; and mammalian milk is a source of galacto-oligosaccharides.

Because the US allows glyphosate-based herbicides to be sprayed on lentils and grains (ie, wheat, barley, rye) shortly before harvest to dry up the plants, it would be best to eat organic legumes and cereals. Glyphosate is a patented antibiotic – something to avoid if you are trying to increase the numbers of good bacteria.

Belorkar SA, Gupta AK. Oligosaccharides: a boon from nature's desk. *AMB Express.* 2016:6:82.
Nagpal R, et al. Gut microbiome and aging: Physiological and mechanistic insights. *Nutrition and Healthy Aging.* 2018;4:267-285.

Homeopathy for Upper Respiratory Infections

A 2019 review found evidence that homeopathy is effective in treating, and possibly preventing, upper respiratory tract (URT) and otorhinolaryngological infections, such as otitis, sinusitis, and tonsillitis. The Italian authors discuss 40 clinical trials and observational studies, cited by PubMed from 1981 through 2018, in their paper. The article is descriptive rather than one that gives quantitative conclusions or clinical recommendations, primarily because the studies vary in design and intervention. Classical homeopathy – even for the same disease condition – employs numerous possible remedies that are prescribed according to a person's symptoms and constitution. The homeopathic formulations typically contain

several different remedies (albeit in homeopathic dosages). Twenty-one different homeopathic remedies were used in these studies.

PubMed literature had only two randomized double-blind placebo-controlled studies of individualized (classical) homeopathic treatment for URT infections, and those gave conflicting results. Equivalence trials, however, found that recovery was faster in those who received homeopathy with fewer adverse effects than in those receiving conventional care. A 2001 multi-center observational study involving 456 patients with URT infections, lower respiratory tract infections, and/or ear complaints found that 82.6% of patients receiving homeopathy were healed or had major improvement after 14 days of treatment, compared to 68% receiving conventional treatment. In addition, the adverse side effect rate was higher in the conventional treatment group (22.3%) than in the homeopathy group (7.8%). This study was replicated in 2007 with 1557 patients; 857 received homeopathy, and 720 received conventional care (anti-inflammatories and antibiotics). Although no significant difference in response rate was found in the two groups after 14 days, signs of improvement occurred more quickly in the children and adults receiving homeopathy. Among adults, adverse drug reactions were higher in the conventional group (7.6%) than in the homeopathy group (3.1%); there was no statistically significant difference in children.

Although these two studies were not randomized, a 2005 study involving 169 children was. This study investigated whether individualized homeopathic care could prevent upper respiratory tract infections (URTIs) in children. Children with a history of diagnosed URTIs were randomly assigned to receive care from a homeopath or conventional care for 12 weeks. Children in the homeopathic group had symptoms for fewer days (8 days) than those in conventional care (13 days), and their symptoms were less severe: "There was a significant difference in the median total symptom score in favor of homeopathic care (24 points) compared to the control group (44 points) (p=0.026)."

Although individualized treatment with a professional homeopath is preferred, proprietary homeopathic products to treat the symptoms of URTIs are available; and some of these have been tested in clinical trials. A 2015 randomized, controlled multinational clinical trial tested the effects of German-manufactured Influcid (Aconitum 3D, Bryonia 2D, Eupatorium perfoliatum 1D, Gelsemium 3D, Ipecacuanha 3D, and Phosphorus 3D). All 523 patients (ages 1-65 years) had access to on-demand conventional treatment for symptoms (paracetamol syrup, ambroxol syrup, and oxymetazoline nasal spray), but half also received Influcid: "The conclusion was that homeopathic treatment shortened URTI duration, reduced the use of symptomatic medication and was well tolerated." A similar 2016, randomized, controlled clinical trial, involving 261 children, also found that Influcid "reduced global disease severity, shortened symptom resolution, and was safe to use."

The Italian authors advocate for "more modified approaches" to assess the value of integrating homeopathic care when treating respiratory and otorhinolaryngologic illnesses:

> What emerges from this overview is an efficacy/effectiveness paradox, similar to that found in several other areas of complementary medicine research, with weak evidence in favor of homeopathy when studies are done in randomized and double-blind conditions, yet documented effectiveness in equivalence studies comparing homeopathy and conventional medicine, and documented usefulness in general practice through observational studies: the therapy seems useful when applied in open practice and produces substantive effects, even in patients with chronic diseases.

Bellavite P, Marzotto M, Andreoli B. Homeopathic treatments of upper respiratory and otorhinolargyngoloci infections: A review of randomized and observational studies. *J Altern Complement Integr Med.* 2019;5:073.

NHF Battles at Codex

Industry-backed proponents are using a new tactic to gain the Codex Alimentarius Commission's approval for standards that would allow worldwide use of potentially unsafe additives and products in food, according to Scott C. Tips. Tips has long attended Codex meetings as the National Health Federation's delegate. National Health Federation (NHF) is a non-profit association that lobbies for health freedom and consumer safety interests.

Tips says that Markus Lipp, the FAO/Codex science officer and former Monsanto employee, is attempting to use "scientific consensus" as an acceptable basis for over-riding the concerns of delegates from Codex member nations. When 55 African countries objected to the proposed standard for milk additives (emulsifiers and stabilizers) at the July 2019 meeting, Lipp argued that "scientific consensus" supported the new standards. Tips told those at the meeting that "'consensus' without any qualifiers" is the term in the Codex Procedural Manual: "a dangerous precedent would be set by using a contrived term to push through a standard so strongly opposed." The milk stand-off was resolved through mediation;

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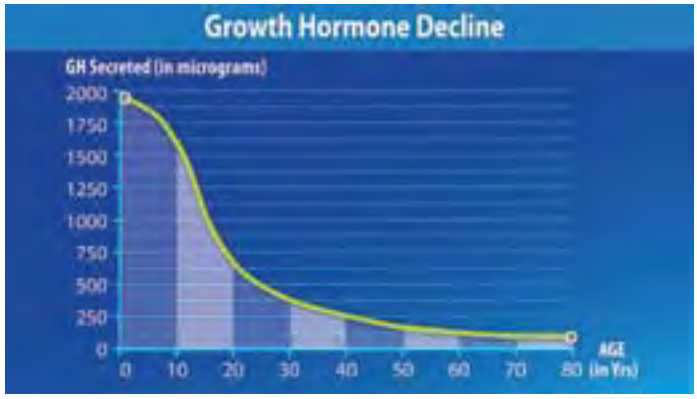

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* Sattler FR. Growth hormone in the aging male. *Best Pract Res Clin Endocrinol Metab.* 2013;27(4):51–55.

Garcia JM, Merriam GR, Kargi AY. Growth Hormone in Aging. 2019 Oct 7. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279163/

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the Codex Committee on Food Hygiene agreed to study the additive trisodium citrate further, and the African countries agreed to adopt the other standards.

Tips expects the "scientific consensus" argument to show up again at the May 2020 vet drug residue committee meeting when the adoption of a worldwide standard for zilpaterol hydrochloride (Zilmax®) will be discussed...again. Zilpaterol, made by Merck, is a beta-adrenergic agonist given to cattle and other food animals to increase lean muscle. Although it was approved by US FDA, Merck pulled the drug from the US and Canadian markets in 2013, after numerous reports of cardiac disease and high death rates in the animals. Beta-adrenergic agonists in humans have produced elevated heart rates, arrhythmias, myocardial infarctions, and death. Merck has been pushing Codex to set an approved worldwide residue standard for zilpaterol in meat for some time so that the company can sell overseas.

The US, Mexico, Japan, Australia, New Zealand, and some African and South American countries want a standard for zilpaterol residues in the food supply. They claim that the science, provided by the Joint FAO/WHO Expert Consultation on Food Additives (JECFA), attests to its safety. Unfortunately, JECFA relies on studies and data from industry to assess the risks. Not surprisingly, JECFA's "science" has support from industry front groups, such as Health for Animals (Merck). It's hard to see any benefit to consumers if zilpaterol residues are permitted in the meat supply.

Shorts

In his article about the July 2019 Codex meeting, Scott Tips writes: "At this most recent Codex meeting – the most important one of the year – the National Health Federation was there to remind fellow delegates that Codex science can be mistaken, misguided, and even corrupted, and that we should not blindly accept whatever swill we have been given to swallow." His Codex experience makes me wonder if the term "scientific consensus" is being appropriated by other industries in their battles to institute financially beneficial policies.

The National Health Federation's work is supported by donations. For more information, go to https://thenhf.com.

Tips SC. NHF Shouts Down "Scientific consensus" Scheme in Flames. July 2019.
Tips SC. Victory at Codex Over Dangerous Vet Drug! July 31, 2018.

Maternal Fluoride and Infant IQ

JAMA Pediatrics recently caused a stir by publishing a study that found maternal fluoride exposure during pregnancy is associated with decreases in offsprings' IQ scores; boys were particularly affected. Fluoridation of drinking water is considered "one of the top 10 public health achievements in the 20th century," according to US Centers for Disease Control and Prevention. It is credited with protecting against dental caries.

continued on page 70 ➤

Functional Gastroenterology Bolus

by Steven Sandberg-Lewis, ND, DHANP

Common Confusion – Fermentable Foods vs Fermented Food

I have been told by dozens of patients that they were avoiding all fermented foods based on our diet handouts for SIBO treatment and prevention. Was that really in our recommendations? I sure didn't believe it was correct. It is true, some highly sensitive people react to fermented food. Perhaps this is due to histamine sensitivity, because the fermentation and aging process may produce histamine. Others might react to acids (acetic, butyric, etc.) or traces of yeast, ethanol or some other fermentation metabolite; but barring an individual response, there seems no reason to remove these foods from the diet of patients with bacterial and yeast overgrowth. I now think that many of us, including some healthcare professionals, conflate foods that have high fermentation potential with fermented foods.

Highly Fermentable Foods

Researchers and clinicians such as S. Haas, E. Gottschall, N. Campbell-McBride, SJ Shepard and PR Gibson, M. Pimentel, A. Siebecker, N. Jacobi and N. Robillard have developed the modern dietary concepts underlying low fermentation diets. These diets organize common foods into various degrees of fermentation potential, allowing patients to reduce in vivo fermentation. Some of our patients can partially or completely control their IBS or IBD symptoms by using one of these low fermentation diets. It is unlikely that these approaches cure bacterial overgrowth (although this has not been studied) but can effectively control the fermentation of carbohydrates and the symptoms caused by the byproducts of this process: painful distention of the GI lining, stool frequency and consistency changes, abdominal bloating, reflux, nausea, etc. The more highly fermentable carbohydrates are fructans, oligosaccharides, disaccharides, monosaccharides (opinions vary) and most sugar alcohols.[1] These fall into the general categories of prebiotics/fiber. Bacteria, archaea, and yeast ferment these carbohydrates into hydrogen, methane, hydrogen sulfide, and carbon dioxide gas.[2] In addition, acids such as acetic, lactic, and butyric as well as ethanol are common metabolites of these processes.

Fermented Foods

The same biochemistry applies to fermented foods. The big and essential difference is that this is an in vitro process. Although the same gases and metabolites are produced, the gases escape into the environment. Fermentation airlocks or water-sealed crocks are used to keep contaminants and oxygen out of the mix and allow the gases to escape during the process of fermentation in vitro. Unless the patient is sensitive to some other metabolite, the usual problems induced by gas pressure and chemistry are not an issue with fermented food. All the health benefits of fermentation—organic acids, anti-microbial agents, bioactive peptides, probiotics and nutrients[3]—can be ingested without the in vivo issues of gas accumulation.

The common list of fermented foods includes beer, wine, yogurt, kefir, cheese, sourdough, fermented meat (salami, etc.), pickles, olives, sauerkraut, kimchi, fish sauce, tempeh, miso, soy sauce and kombucha (fermented tea). Cocoa and various ethnic foods may also be fermented.

Health Benefits of Fermented Foods

Although it is believed that the probiotic organisms in fermented foods are "just passing through" and not creating an ecological niche in the gut flora, there is plenty of evidence of their benefits.[3] It is thought that they do not persist in the gut for more than a few days. Frequent consumption of fermented foods leads to a "transient microbiome." They are thought to influence the diversity and function of the gut microflora.[4] Common organisms include various species of Lactobacillus, Leuconostoc, Streptococcus, and Bifidobacteria. Even if the bacteria are not viable, there is significant benefit. These probiotics and their benefits include the following:

- Fermented dairy and metabolic syndrome[5]
- Yogurt and type 2 diabetes mellitus[6]
- Fermented soy and hypertension[7]
- Yogurt and body weight and blood lipids in obese individuals[8]
- Yogurt and bladder cancer incidence[9]
- Yogurt and body weight[10]
- Fermented food and atopic dermatitis[11]
- Kefir and allergy[12]
- Yogurt and lactose intolerance (due to in vivo beta-galactosidase production)[13]
- Chinese kefir, glutathione and superoxide dismutase upregulation[14]
- Yogurt containing *L. rhamnosus* and antibiotic-associated diarrhea in children.[15]

Additional benefits are improved mineral absorption by bacterial degradation of phytates via phytase production in breads[16] and increased polyphenols production in beer[17] and antimicrobial compounds in fermented milk.[18]

Some so-called fermented products are "fake" in that they are not truly fermented. Instead they are processed with lye, salt, or vinegar. This includes some pickles, olives, and sauerkraut; and these are not expected to have the same health-promoting effects as true fermented foods.

I am not a microbiologist and certainly do not consider myself an expert on probiotics. I wrote this column to take a closer look at this common misconception of fermentation potential of foods versus fermented foods. I welcome your comments on the information included in this article. Direct any comments to editorial@townsendletter.com.

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	More Fermentable	Less Fermentable
Vegetables	Artichoke, asparagus, cauliflower, garlic, peas, leeks, mushrooms, onion	Bok choy, bell pepper, carrot, cucumber, eggplant, green beans, lettuce, potato, tomato, zucchini
Fruits	Apples, cherries, dried fruit, mango, pears, stone fruits, watermelon	Banana, cantaloupe, grapes, kiwi, mandarin, orange, pineapple, strawberries
Dairy products	Cow/goat/sheep milk, ice cream, soy milk, cashew milk, hard cheeses, lactose-free milk,	Nut milk (other than from whole soybeans or cashew), yogurt
Non-dairy proteins	Most beans/legumes, some processed meats and marinades	Eggs, most meats, poultry, seafood, tempeh
Grains	Wheat, rye, barley, most breakfast cereals and baked goods	Corn flakes, corn pasta, oats, quinoa flakes/quinoa, rice, plain rice cakes, sourdough spelt bread, gluten-free breads
Sweeteners	High fructose corn syrup, sugar alcohol sweeteners (ie, sorbitol), honey (opinions vary on this), inulin	Dark chocolate (if made with low fermentation sweeteners), maple syrup, rice malt syrup, liquid stevia, sucrose
Nuts and seeds	Cashews, pistachios	Small portions – almonds, Brazil nuts, coconut, filberts, pecans, sunflower; less fermentable – macadamias, peanuts, pumpkin seeds, walnuts

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In this Issue

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Our January issue will feature articles on Lab Testing and Diagnostics, Detox Protocols, and Weight Management.

ON THE COVER: Roger Jahnke, OMD – Physiological Effects of Qigong and Yoga (pg. 28); Carnitine for Peyronie's Disease and Erectile Dysfunction (pg 38); Pomegranates for Health (pg. 56); Microbiome-Disrupting Pharmaceuticals (pg. 62); The Genetics of Chronic Fatigue Illnesses (pg. 74)

Literature Review & Commentary

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

Does Skipping Breakfast Promote Heart Disease?

The association between skipping breakfast and cardiovascular and all-cause mortality was examined in a prospective cohort study of a nationally representative sample of 6,550 US adults (mean age 53 years) participating in the National Health and Nutrition Examination Survey III (1988 to 1994). During 112,148 person-years of follow-up, 2,318 deaths occurred, including 619 from cardiovascular disease. After adjustment for age, sex, race/ethnicity, socioeconomic status, dietary and lifestyle factors, body mass index, and cardiovascular risk factors, participants who never consumed breakfast, as compared with those who consumed breakfast every day, had hazard ratios of 1.87 (95% confidence interval [CI], 1.14 -3.04) for cardiovascular mortality and 1.19 (95% CI, 0.99-1.42) for all-cause mortality.

Comment: In this study, skipping breakfast was associated with a significantly increased risk of mortality from cardiovascular disease and from all causes. Although observational studies cannot prove causation, the possibility that skipping breakfast promotes the development of cardiovascular disease is biologically plausible. Skipping breakfast would presumably put downward pressure on morning blood glucose levels, forcing the body to secrete more epinephrine and cortisol in order to prevent hypoglycemia. Both of these hormones appear to have adverse effects on the cardiovascular system. In addition, breakfast skippers may eat relatively large meals later in the day, potentially resulting in periods of hyperinsulinemia, which itself may be atherogenic. In a previous randomized controlled trial, skipping breakfast was found to increase insulin resistance,[1] which is another risk factor for heart disease.

Rong S, et al. Association of skipping breakfast with cardiovascular and all-cause mortality. *J Am Coll Cardiol*. 2019;73:2025-2032.

Plant-Based, Raw-Food Diet Improves Heart Failure

Three patients with heart failure received conventional therapy and also consumed a plant-based diet, consisting of raw fruits, vegetables, avocado, seeds, and small amounts of raw oats and buckwheat. Patients were advised to eliminate all animal products, cooked foods, free oils, soft drinks, alcohol, and coffee. The diet was followed for 53 to 95 days (mean, 79 days). Mean left ventricular ejection fraction increased from 22% at baseline to 42.2% at follow-up. Mean left ventricular mass decreased by 21%, mean stroke volume increased by 62%, and mean cardiac output increased by 17%. One of the patients had had a 90-95% ostial stenosis of the left anterior descending artery, which almost completely regressed. All patients reported subjective improvements, including a reduction in angina, less shortness of breath, and less fatigue. The authors stated that such dramatic and rapid improvements in heart morphology and function would be highly improbable with conventional treatment alone.

Comment: Plant-based diets are known to improve serum lipid concentrations, reduce blood pressure, decrease inflammation and, as part of a lifestyle intervention, lead to the regression of atherosclerotic lesions. However, there has been little research on the use of plant-based diets in patients with heart failure. These case reports are encouraging and warrant larger, controlled trials. If plant-based, raw-food diets are beneficial for patients with heart failure, they may work by decreasing inflammation (heart failure has a significant inflammatory component) and by providing abundant amounts of cardioprotective nutrients such as magnesium, potassium, flavonoids, vitamin C, and essential fatty acids.

Najjar RS, Montgomery BD. A defined, plant-based diet as a potential therapeutic approach in the treatment of heart failure: A clinical case series. *Complement Ther Med*. 2019;45:211-214.

Vitamin K and Arterial Calcification

Sixty-eight patients (mean age, 69 years) with type 2 diabetes and cardiovascular disease were randomly assigned to receive, in double-blind fashion, 360 µg per day of menaquinone-7 (MK-7; a form of vitamin K_2) or placebo for six months. Calcification of the femoral artery was assessed at baseline and after six months by two different methods: ^{18}sodium fluoride positron emission tomography (^{18}F-NaF PET) and computed tomography (CT). After six months, compared with placebo, MK-7 nonsignificantly increased arterial calcification by both assessment methods ($p = 0.06$ with ^{18}F-NaF PET and $p = 0.18$ with CT).

Comment: Arterial calcification is an independent risk factor for myocardial infarction and stroke. Matrix Gla protein (MGP) is a vitamin K-dependent protein that inhibits vascular calcification. Some studies have suggested that vitamin K is a cardioprotective nutrient, but the research is conflicting. In a previous trial, supplementation with 500 µg per day of vitamin K_1 (the form of vitamin K found in plants) slowed the progression of coronary artery calcification in elderly volunteers.[2] In contrast, the present study found that MK-7 (which is found in cheese, butter, egg yolks, meats, and natto [fermented soybeans]) did not prevent arterial calcification, and may even have made it worse. The findings from these two trials conflict with those of an observational study, in which higher vitamin K_2 intake was associated with a lower risk of cardiovascular mortality, whereas no association was found between vitamin K_1 intake and cardiovascular mortality.[3] Thus, the effect of vitamin K on cardiovascular disease risk remains unclear.

In recent years, many practitioners have been recommending large doses of vitamin D (such as 5,000 IU per day or more) for various purposes. I have pointed out in the *Townsend Letter* and elsewhere that high-dose vitamin D has not been shown to be more effective than moderate doses. Furthermore, large doses of vitamin D caused atherosclerosis in experimental animals. Proponents of high-dose vitamin D argue that vitamin K can prevent the potential adverse effects of vitamin D on the cardiovascular system. As far as I am aware, there is no clinical evidence to support that argument. Moreover, atherosclerosis and arterial calcification are separate (though possibly related) pathological processes. The present study underscores the point that vitamin K may not be effective for preventing the side effects of high-dose vitamin D.

Zwakenberg SR, et al. The effect of menaquinone-7 supplementation on vascular calcification in patients with diabetes: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2019 Aug 6 [Epub ahead of print].

***Serenoa repens* (Saw Palmetto) for Benign Prostate Hyperplasia**

A meta-analysis was conducted on 15 randomized controlled trials and 12 observational studies (including a total of 5,800 patients) that examined the effect of an extract of saw palmetto berries (*Serenoa repens*) (Permixon; Pierre Fabre Medicament, Castres, France) at a dose of 320 mg per day on lower urinary

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tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH). Articles studying *Serenoa repens* extracts other than Permixon were excluded. Compared with placebo, Permixon was associated with a mean of 0.64 fewer voids at night ($p < 0.001$) and a mean increase in maximum urinary flow rate (Qmax) of 2.75 ml per second ($p = 0.01$). When compared with alpha-blockers, Permixon showed similar improvements in the International Prostate Symptom Score (IPSS) and in Qmax. After six months of treatment, efficacy (as determined by IPSS) was similar between Permixon and 5-alpha-reductase inhibitors. Prostate volume decreased slightly with Permixon. The treatment did not adversely affect sexual function and was generally well tolerated, with gastrointestinal symptoms being the most frequent adverse effect (mean incidence, 3.8%).

Comment: Extracts of *Serenoa repens* inhibit the enzyme 5-alpha-reductase and also have anti-androgenic and anti-inflammatory effects. Each of these actions would be expected to be beneficial in the treatment of LUTS/BPH. The results of the present meta-analysis provide strong evidence that at least one of the many commercially available *Serenoa repens* products is effective. Current American Urological Association practice guidelines state that there is not sufficient evidence to recommend *Serenoa repens* as a treatment for BPH. This conclusion may have resulted in part from the negative results in some studies. For example, a 2011 study published in the *Journal of the American Medical Association* found that an extract of *Serenoa repens* (Prosta-Urgenin Uno; Rottapharm/Madaus, Cologne, Germany) did not improve symptoms of BPH.[4] In other research, different *Serenoa repens* products were found to differ in their physiological effects. Therefore, some *Serenoa repens* products may be more effective than others.

Vela-Navarrete R, et al. Efficacy and safety of a hexanic extract of *Serenoa repens* (Permixon®) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH): systematic review and meta-analysis of randomised controlled trials and observational studies. *BJU Int*. 2018;122:1049-1065.

Sambucus nigra (Black Elderberry) for Influenza and Colds

A meta-analysis was conducted on four randomized controlled trials (including a total of 180 participants) that examined the effect of *Sambucus nigra* (black elderberry) on cold or flu symptoms. In the pooled analysis, *Sambucus nigra* significantly reduced upper respiratory symptoms ($p < 0.001$), with a large effect size.

Comment: *Sambucus nigra* has been used traditionally to treat cold and flu symptoms, but there have been no large-scale studies examining its effectiveness. The results of this meta-analysis indicate that *Sambucus nigra* is indeed an effective treatment for colds and influenza. It may work in part by exerting a direct antiviral effect. In test-tube studies, extracts of *Sambucus nigra* inhibited the replication of influenza virus types A and B and decreased the infectivity of human influenza virus H1N1.[5]

Hawkins J, et al. Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: A meta-analysis of randomized, controlled clinical trials. *Complement Ther Med*. 2019;42:361-365.

Selenium for Cancer-Related Lymphedema

Twenty-six women who had undergone surgery for breast cancer up to three years previously, most of whom had received chemotherapy, radiation therapy, or both, were randomly assigned to receive, in double-blind fashion, five intravenous infusions of selenium (500 µg in each infusion, as sodium selenite) or placebo (0.9% saline) over a two-week period. All patients were taught manual lymphatic drainage. The severity of lymphedema was assessed before and at the end of selenium treatment, and one month after the end of treatment. At the end of treatment, as compared with before selenium treatment, 75% of women receiving selenium were improved, whereas there was no change in the placebo group. At follow-up one month later, the proportion of women who had improved from stage III to stage II was 83.3% in the selenium group and 10% in the placebo group ($p = 0.002$).

Comment: In this study, short-term intravenous administration of selenium decreased the severity of breast cancer-related lymphedema, and the benefit persisted for at least 1 month after the treatment was discontinued. Previous studies found that selenium, given orally or intravenously, decreased the severity of chronic lymphedema resulting from radiation therapy, and accelerated the improvement of acute lymphedema following surgery and lymph node removal for cancer of the oral cavity.[6] The mechanism of action of selenium is not known.

Han HW, et al. Sodium selenite alleviates breast cancer-related lymphedema independent of antioxidant defense system. *Nutrients*. 2019;11:E1021.

Curcumin Enhances the Effect of Chemotherapy in Patients with Colorectal Cancer

In a phase IIa trial, 28 patients (mean age, 68 years) with metastatic colorectal cancer were treated with folinic acid/5-fluorouracil/oxaliplatin chemotherapy (FOLFOX) and were randomly assigned in a 2:1 ratio to receive or not to receive (control group) 2 g per day of curcumin. Curcumin was found to be safe and tolerable (the primary outcome), with similar adverse events occurring in both groups. Median progression-free survival time was 291 days in the curcumin group and 171 days in the control group (hazard ratio for progression-free survival = 0.57; $p = 0.2$). Median overall survival time was 596 days (range, 323 days to still alive [13 of 18 still alive]) in the curcumin group and 200 days (range, 9-563 days; 9 of 9 dead) in the control group (hazard ratio for overall survival = 0.27; $p = 0.004$). Note: The numbers for overall survival were taken from the text, which differed from the numbers in the abstract.

Comment: Curcumin is a compound found in the spice, turmeric. Curcumin has demonstrated anticancer effects *in vitro* and in animal studies; and preliminary evidence suggests that it may be useful for preventing or treating certain types of cancer in humans. In the present study, curcumin was safe when used in combination with chemotherapy in patients with metastatic colorectal cancer, and it appeared to increase survival times.

Howells LM, et al. Curcumin combined with FOLFOX chemotherapy Is safe and tolerable in patients with metastatic colorectal cancer in a randomized phase IIa trial. *J Nutr*. 2019;149:1133-1139.

Eggs and Cardiovascular Disease

The association between dietary cholesterol or egg consumption and cardiovascular disease (CVD) and all-cause mortality was examined by pooling individual participant data from six prospective US cohorts. These cohorts included a total of 29,615 participants whose mean age at baseline was 51.6 years. During a median follow-up period of 17.5 years, there were 5,400 CVD events (a composite of fatal and nonfatal coronary heart disease, stroke, heart failure, and other CVD deaths) and 6,132 all-cause deaths. Each additional 300 mg of dietary cholesterol consumed per day was significantly associated with a higher risk of incident CVD (adjusted hazard ratio [HR] = 1.17) and all-cause mortality (adjusted HR = 1.18). Each additional half an egg consumed per day was significantly associated with a higher risk of incident CVD (adjusted HR = 1.06) and all-cause mortality (adjusted HR = 1.08).

Comment: In this study, higher consumption of cholesterol or eggs was associated with a higher risk of CVD and all-cause mortality in a dose-dependent manner. However, the study did not consider the possibility that the effect of dietary cholesterol and eggs on CVD risk depends on the way in which these foods are cooked. Research in animals has shown that feeding pure cholesterol does not cause atherosclerosis, whereas oxidized cholesterol in food is highly atherogenic.[7] Cholesterol is an unstable molecule, and the cholesterol in food is susceptible to spontaneous oxidation, even in room air. The extent to which cholesterol in food becomes oxidized (and, by implication, the atherogenicity of the food) presumably varies with different cooking and storage methods. For example, breaking the yolk of an egg during cooking exposes the cholesterol to high temperatures and oxygen (room air), which might accelerate the formation of cholesterol oxides. In contrast, the cholesterol in boiled or poached eggs, or fried eggs with an intact yolk, would be shielded from room air and might therefore be less susceptible to oxidation and less atherogenic. Similarly, butter left exposed to room air might be more atherogenic than butter kept covered and refrigerated.

Zhong VW, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. *JAMA*. 2019;321:1081-1095.

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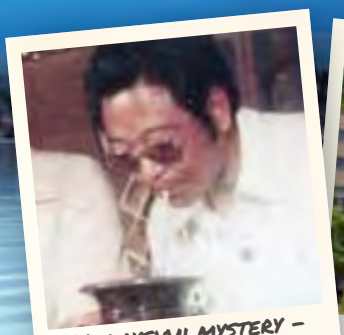
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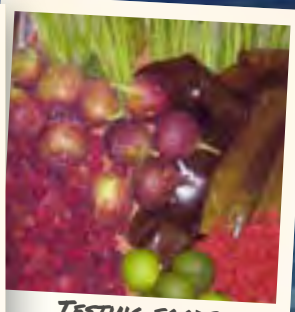
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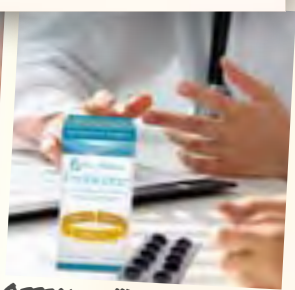
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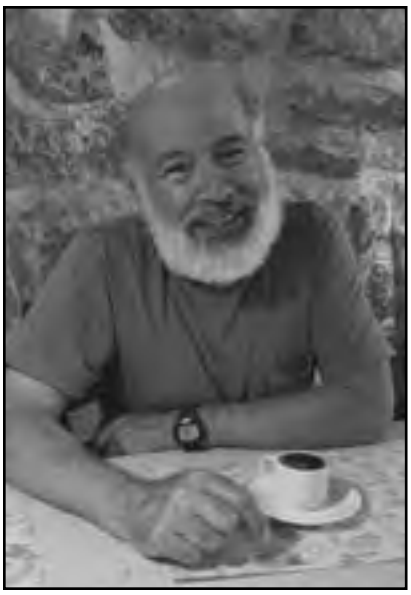

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Useful Pharmacy

Over the years I've come to dread the yearly chore of collecting pharmacy continuing education hours to fulfill the requirements for my Oregon naturopathic physician's license renewal. I've practiced the last 28 years in Colorado. Most of that time it has been illegal to practice naturopathic medicine here. Although our law was passed a few years back, our pharmacy scope remains limited; we can inject vitamin B-12 and B-6 but that's about all we can do legally.

Learning about how to prescribe new drugs that are being added to other states' scopes of practice has not helped me practice better or safer naturopathic medicine.* Thus, in the last three decades I've sat through a lot of pharmacy lectures that were a waste of my time.

If I had wanted to prescribe drugs in the first place, I wouldn't have gone to naturopathic school. I still like the idea that we are drugless practitioners. I've never been in a rush to add drugs into my practice and I don't see that changing. The modern reliance on drugs and intravenous therapies by my colleagues has never resonated with me.

I've been trying to steer our CE conversations away from "Learn how to use more drugs" to "What can we learn from drugs to practice better naturopathic medicine?" What can we learn from drugs that can be translated into knowledge to advance our naturopathic practices? That's what I would like to hear at conferences.

I think this concept is fundamental to what we naturopathic doctors do reflexively in practice. We are always translating new drug information and scientific advances into simpler, greener, more natural therapies. We strive to stay on the cutting edge of science and well ahead of the curve of modern medical practice, yet practice with our 'natural tool chest.' In part, this tendency defines naturopathic medicine and sets us apart from other natural medicine or holistic practitioners.

So, here's one example of what I would call 'useful' pharmacy C.E. that I came across this year.

There's a long-used drug called isosorbide mononitrate that is used to treat angina chest pain secondary to cardiovascular disease. This drug belongs to a class of drugs called nitrates. Another drug in this class and used for a somewhat similar purpose is nitroglycerin. Isosorbide is slower acting and will provide symptom relief for hours where nitroglycerin is fast-acting. Supplying the body with nitrates leads to an increase in nitric oxide (NO) and this, in turn, causes vasodilation and increased blood flow. The rapid increase in nitric oxide is what leads to symptom relief.

These nitrate drugs have been used for a long time: nitroglycerin since 1847.[1] Various slower acting nitrates have been employed for more than half a century.

The idea that slow-release nitrates might be useful for treating cardiac arterial disease has been adopted in our naturopathic world. Beet juice and beet powders are so high in nitrates that some studies simply refer to them as dietary nitrates; and until you read the full text, you may not realize that the nitrates the participants are taking are powdered beets.[2]

Beets aren't the only trick we employ to raise nitric oxide production. There is the business of using l-arginine to treat CVD because it supplies the body with the required nitrates needed to produce NO.[3] The fact that nuts are super high in l-arginine has been suggested as the reason why eating them lowers risk for heart disease.[4] This idea that supplying nitrates is good for the heart because of increased NO production is old news for most of us.

But there's something we can learn from studying the way this drug isosorbide mononitrate is used. Recall a lot of people have been taking it for many years. Some clinical tricks have been figured out over this time. This drug is supposed to be prescribed once a day. If twice, then at breakfast and lunch,

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*After listening to Alan Gaby lecture about Armour Thyroid a few decades ago, we did start supplying thyroid hormones to many of our patients. All the thyroid we sold never came close to paying the fees of the lawyer who eventually defended us when we got in trouble for doing this.

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but not evenly spread out over the day. A person's vascular walls quickly build up a tolerance to nitric oxide, and they stop dilating in response to exposure.

If you take isosorbide once a day, it works quite well at reducing angina.[5] If nitrates are administered around the clock, tolerance to their effects develops rapidly.[6,7] If you take it three-to-four doses per day, the drug doesn't work nearly as well. Thus, the recommendation is to have 12-14 hours per day that are drug-free to avoid tolerance. Is it the drug itself that creates tolerance or is the tolerance to nitric oxide? It appears that the tolerance is to the NO triggered vasodilation.[8] Thus an educated guess would be that NO made from any substrate would still trigger tolerance.

Now if we were to be prescribing these nitrate drugs we should be cautioning patients to be sure that for half the day they need their serum concentration to drop back to normal. When it comes to the supplements that we use to raise NO levels, as far as I can tell, the same cautions should apply. If we spread doses of our natural nitrates across the day, we will likely see diminished effects. Thus, for l-arginine, l-citrulline, beet powder and other clever natural NO strategies we choose to enhance NO production, we need to make sure that this is a half-time strategy, that half the day we are doing nothing that will increase NO.

Someone is going to ask me about nuts. I now consider them as a once a day snack rather than something to tell patients to graze on all day long.

There is one other interesting thing we should note regarding isosorbide and NO. At least with isosorbide, the NO tolerance is prevented by treatment with N-acetylcysteine (NAC).

Going back to 1989, Svendsen et al reported that doses of NAC increased exercise tolerance in people taking isosorbide mononitrate and prevented tolerance. Their study used large doses, nearly 5 grams per day.[9] Although Parker had been unable to demonstrate this effect in 1987, a 1994 study by Mehra did confirm benefits, reporting a "… substantial NAC-mediated potentiation…" of isosorbide's effect.[10] Nizomov reported that a combination of l-arginine and NAC was helpful in 1995 against acute coronary syndrome.[11] In a 2008 report we see the NAC and l-arginine combination being helpful in lowering blood pressure by improving vascular function.[12]

What can we learn from all these drug trivia?

If you have patients taking slow release prescription nitrate drugs, make sure they get that daily drug break. Consider adding NAC to reduce the development of tolerance if the drug breaks allow symptom recurrence. Perhaps a single serving a day of nuts in the morning or mid-day might have a better effect than grazing on nuts all day long? We don't know that as no one has likely ever considered the possibility before. We should translate this into naturopathic medical practice: if using supplements such as l-arginine or beets to increase nitric oxide, to treat CVD, consider this same daily break to allow NO to fall and so prevent tolerance. Also, consider the addition of NAC to a range of supplements that are attempting to provide benefit through increasing nitric oxide.

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HYPERCOAGULATION

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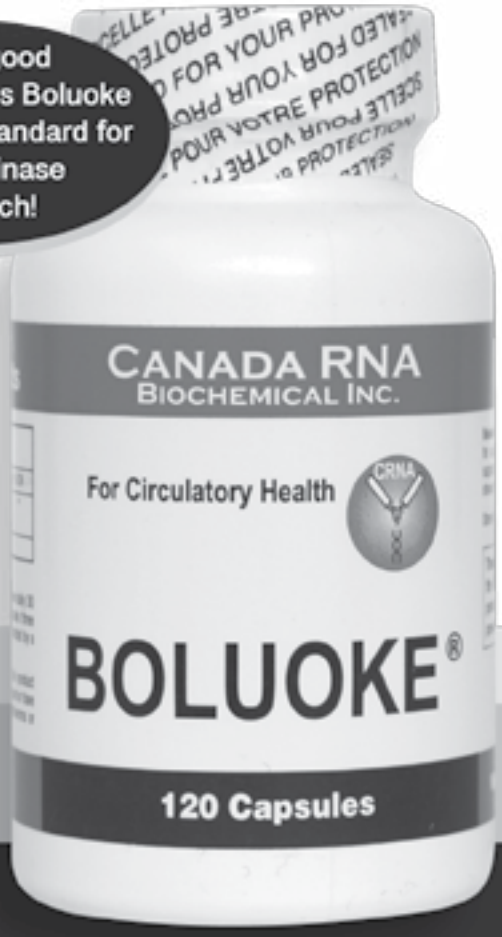

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On the cover

Physiology of Qigong and Yoga

by Roger Jahnke, OMD, and Nancy Faass, MSW, MPH

Qigong and yoga are ancient methodologies developed and refined over thousands of years, designed to sustain the inherent healing systems of the body by maximizing restorative energies, termed chi or qi in China and prana in India. Research indicates that these therapeutic practices promote a range of beneficial physiological effects involving mechanisms currently well understood in Western biomedicine (Oschman, 2000; Jahnke, 2002).

Reviews of clinical studies on qigong and tai chi have reported improvement in the management of cardiovascular, respiratory, musculoskeletal, and immune function and pain disorders, as well as improved muscular strength, stamina, posture, flexibility, balance, and mood (Li et al, 2001; Klein & Adams, 2004; Wang et al, 2004). Therapeutic exercise also enhances the production and delivery of co-enzymes and antioxidants, connective tissue repair, and the enhancement of stem cell development. Ongoing research promises to further clarify these effects.

Clinical Research

The National Library of Medicine Medline database currently lists 167 clinical trials on qigong, and 429 on tai chi (the most well-known form of qigong), and at least 400 of these studies have been performed in the past ten years. This surge of new research has focused not on stress or relaxation, but on the leading causes of premature morbidity and mortality in our time – heart disease, cancer, respiratory disease, stroke, Alzheimer's disease, diabetes, kidney disease, and obesity. Recent clinical trials on qigong have explored specific applications in disease management.

Heart disease. A study conducted in Taiwan involving 100 patients with a history of heart failure evaluated the benefits of qigong for these patients. Researchers found that those practicing Chan-Chuang qigong achieved significantly greater improvement than the control group in terms of six-minute walk distance and quality of life at two, four, and 12 weeks after the intervention and depression at 12 weeks after the intervention. (Note that participants' ability to walk and their quality of life had begun to improve by the two-week evaluation, but changes in depression were not reported until the 12-week evaluation).[1]

Breast cancer. Randomized research at a Chinese university hospital evaluated 86 breast cancer survivors to assess the benefits of qigong. After six months of intervention, heart rate variability and shoulder range of motion were significantly improved in the Baduanjin qigong group, compared to the control group. There were also significant improvements in depression, QoL (quality of life), and four QoL dimension scores (physical well-being, social well-being, functional well-being, and breast cancer subscale).[2]

Cancer survivors. A five-center clinical trial in Shanghai enlisted cancer survivors to explore the benefits of a 21-day intervention that provided supportive-expressive group participation, cognitive-behavioral therapy (CBT), and Guolin Qigong in tandem. A total of 388 cancer patients were enrolled to either receive the 21-day intervention (n = 129) or a waiting-list comparison (n = 259). The intervention group showed significant improvements in the QoL score. However, there were no clinically relevant

changes in subscales of emotional, cognitive, or physical functioning, pain, or insomnia. (It would be interesting to see the response to those measures at 240 days in comparison with the 21-day outcomes. A six-month study pairing CBT and qigong is summarized below).[3]

Housebound elders. A joint study by two Chinese universities evaluated the progress of 120 housebound elders who were randomly assigned to one of three interventions: Baduanjin qigong training, qigong combined with CBT, or CBT alone. Interventions were conducted by means of home visits over six months. Quality of life (QoL) and self-reported health status were significantly improved in the qigong-and-CBT group as compared to the qigong-only group or the CBT-only group. Participants reported less difficulty with activities of daily living (ADL); and loneliness and depression were significantly lowered in the group receiving joint qigong-and-CBT intervention (at both 3 months and 6 months), as compared to the qigong-only group or the CBT-only group.[4]

Breast cancer survivors with decreased cognitive function. A randomized interventional pilot conducted at five centers in Kansas City and Pittsburgh compared 1) qigong, 2) gentle exercise, and 3) survivorship support. Participant self-report of cognitive function improvement was greatest for those in the qigong group, who also indicated the most reduction in distress.[5]

Diabetes and obesity. A recent Chinese study evaluated 40 middle-aged female obese diabetic patients (average age 57 years old), randomly divided into a control group and an exercise group (n=20). The fitness training group performed eight new Baduanjin qigong exercises for 24 weeks, whereas the control group did not exercise. Qigong was found to reduce blood sugar and blood lipid indicators of obese patients with diabetes. After the intervention, the waist measurements, waist-to-hip ratio, and levels of triglycerides, HbA1c, HDL, and retinol-binding protein (a marker for insulin resistance) in the experimental group were decreased significantly compared with their test results before the intervention.[6]

Obstructive sleep apnea. A Turkish study conducted at four medical centers tracked the effect of qigong and tai chi (a form of qigong) on patients with obstructive sleep apnea in a randomized controlled study. In the intervention group, there was a statistically significant decrease in the apnea-hypopnea index and in percentage and duration of stage N2 sleep, as well as an increase in percentage and duration of stage N3 sleep when compared with the controls.[7]

Healthy aging in midlife. A pilot study performed in Austria examined the effects of qigong in 12 subjects (average age 52 years) who performed qigong for eight weeks (60-minute sessions, 3 times/week). Part 2 of the study evaluated the detraining effects 12 weeks after cessation of qigong. These results suggest that performing qigong exercise effectively improved attention, brain processing speed, blood pressure, and maximal workload. However, these improvements disappeared 12 weeks after cessation of qigong. Consequently, performing qigong regularly is important in order to maintain related health effects.[8]

Parkinson's disease. Researchers at a Korean university hospital evaluated the benefits of qigong for Parkinson's disease patients applying a randomized, waiting-list control design. Participants were assigned to a group performing Turo (qi dance) or a waiting-list group. The qi dance group showed statistically significant improvements on the Unified Parkinson's Disease Rating Scale and Parkinson's Disease Quality of Life questionnaire as compared to the control group.[9]

Attention deficit and behavioral disorders in children. A pilot study conducted in Portugal evaluated the efficacy of Taiji Quan and qigong for four children (ages 6 to 10) suffering from attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD). Researchers reported:

> Results showed very interesting improvements in symptoms of CD, ODD and ADHD-HI (hyperactive-impulsive), while ADHD-PI (predominantly inattentive) showed only minor improvements. The overall symptom improvement was 43% across pathologies, which demonstrates that Taiji Quan and qigong may be promising treatment for behavioral disorders.[10]

Mechanisms of Action

When the goal is to mobilize healing capacity or reduce health risk, research suggests that moderate exercise is often preferable to vigorous exercise (Blair et al., 1995). To contrast therapeutic exercise such as qigong with more vigorous aerobic exercise such as running and cycling, it is useful to trace the oxidation and energy cycle, lymphatic function, and neurological activity.

Oxygen

In both vigorous and moderate exercise, the body produces a powerful mix of metabolic resources. However, in vigorous exercise, this energy production serves as endogenous fuel to support muscle activity and is spent to feed hungry muscles. In the less intense fitness systems of ancient cultures, this inner resource has historically been considered therapeutic or medicinal and is conserved, so it can be circulated throughout the body as an internal healing resource referred to in ancient China as "the inner medicine" or "the healer within." This resource is not completely expended but is circulated internally and utilized as a reserve of self-repair factors to sustain and heal tissues, organs, and glands in support of optimal function, recovery, and longevity. Increased oxygen availability from the practice of therapeutic exercise offers at least three potential benefits:

- Support for energy production,
- Cellular and intracellular hydration, as a by-product of energy metabolism, and
- Enhanced immune function.

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Energy production. The energy necessary to fuel cellular processes and regulate body heat is supplied through the metabolic interaction of oxygen and glucose in the presence of ATP (adenosine triphosphate), which serves as a catalyst in the release of energy, obviously a critical factor in vitality and stamina. In contemporary Chinese research it has been observed that blood levels of ATP increase with therapeutic practices such as qigong, which efficiently activates the Krebs cycle (Wang et al, 1988).

Hydration. A second critical benefit of increased oxygen metabolism is linked to the cellular metabolism of water as a byproduct of the Krebs cycle (Shields, 1990). Through this process, water is incorporated into various types of fluids throughout the body, including lymph, blood, serum, cerebrospinal fluid, synovial fluid, tears, and perspiration. This internal hydration supports a range of immune and repair functions, particularly those associated with the lymphatics. Both the production and circulation of this fluid are increased in therapeutic mind-body exercises.

Oxygen and immune function. The scientific evidence indicates that immune function is dependent on oxygen. Mild to moderate exercise (including breathing exercise) has been found to increase immune function, mobilizing natural killer cells (Pedersen et al, 1988), production of white blood cells and lymphocytes (Lee et al, 2003a), favorable T-cell ratios (Yao, 1989), and increased production of interleukin-4 (Carlson et al, 2003).

Immune function is decreased in individuals who exercise so vigorously that they exceed aerobic levels and cross the anaerobic threshold (Brahmi et al, 1985). Reduced lung volume and oxygen capacity are associated with less resistance to disease and increased risk of mortality (Gordon & Kannel, 1970; Cullen et al, 1983). In studies of elderly patients, for example, reduced oxygen metabolism was associated with immunodeficiency (Saltzman & Peterson, 1987). Oxygen deficiency has also been implicated in a range of disorders, including cancer cell proliferation, confirmed in the research of Nobel Prize recipient Otto Warburg (1966). Therapeutically, relaxation and breathing exercises as in yoga have been found beneficial for patients with lung cancer (Corner et al, 1996).

Lymphatic System

The human body contains approximately 500 to 600 lymph nodes with clusters found in the neck, chest, underarms, abdomen, and groin. We now know that physical activity and deepened breathing enhance circulation and function of the lymphatic system through a number of beneficial mechanisms:

- Lymph generation and propulsion,
- Circulation of cerebrospinal fluid,
- Transport of nutrients, and
- Support for immune function.

Lymph generation. A significant portion of the water in the body's fluids is produced by the same physiological process that generates the body's biological energy (Shields, 1980). For each gram of glucose metabolized, in excess of a gram of water is produced. In a moderately active human weighing about 155 pounds (70 kg), engaging in therapeutic exercise such as qigong, yoga, or walking can produce as much as 1400 cc (1.5 quarts) of additional aerobically generated fluid daily (Shields, 1972). With moderate physical activity, as much as one half of the water propelled through the lymph system is a by-product of cellular metabolism, accelerating the elimination of metabolic by-products and bacterial toxins, and increasing the circulation of immune factors.

Lymph propulsion. The lymph system has no distinct heart in humans. (Interestingly, both birds and reptiles have a specific lymph heart, per Shields, 1980.) In humans, the lymph is propelled by a *composite lymph heart*; and circulation of lymph against gravity is accomplished by the contraction of skeletal muscles, propelling the lymph through the lymphatic vessels via one-way valves. "Spontaneous, intrinsic pulsator contraction of the peripheral lymphatic vessels" has been demonstrated in humans (Smith, 1949; Reimenschneider & Shields, 1981), which occurs through several mechanisms:

1. Aerobic propulsion. Fluid volume and holding capacity of interstitial spaces between the cells are naturally limited. As that limit is reached, due to aerobic production of water, the overflow drives the excess fluid into terminal lymphatic vessels (Yoffe & Courtice, 1970; Shields, 1980; Adair & Guyton, 1985; Olszewski, 1985). Like a cup that is running over, the interstitial space fills, building volume and pressure, and then flows over into the lymphatics.
2. Intrinsic smooth-muscle contraction. Within the lymphatic vessels and peripheral lymphatic capillaries, the autonomic response of smooth muscle tissue is to contract when filled and stretched to a certain tolerance (Olszewski, 1985). This contraction moves the lymph forward through the lymphatic vessels. Functioning as a systemic pump, this mechanism acts in a manner similar to the contractions of the heart as it pumps blood through the arteries (Bradbury & Cserr, 1985).
3. Striated skeletal-muscle contraction. Even slight contractions of the skeletal muscles propel the lymph through this unidirectional system. During aerobic exercise, the pumping of the skeletal muscles and compression of the tissues increase the flow of interstitial fluid. In contrast, in qigong and yoga, this mechanism is triggered by relaxation and contraction of striated muscles through purposeful patterns of movement entailed in these practices.
4. Gravitational propulsion. An inversion of the limbs or lying in the prone position allows for freer flow of lymph due to the reduced force of gravity. This is one of the reasons that elevation of the limbs is frequently

prescribed for health problems characterized by pooling of the interstitial fluids (edema). In therapeutic practices, various postures and movements create this dynamic, promoting the circulation of lymph by gravity. For example, in certain walking forms of qigong (tai chi and guo lin qigong are the most well-known), the individual moves all the limbs in beautiful circular motions, slowly and continuously, to activate this inversion mechanism. In yoga, a number of the postures (asanas) invert the limbs: for example, in both the head stand and shoulder stand almost the entire body is inverted.

5. Mechanical lymph propulsion through the process of breathing. One of the most powerful aspects of the lymph heart mechanism occurs through the action of the lungs and diaphragm (Shields, 1980). Located below the diaphragm is a substantial, expanded portion of lymphoid tissue known as the cisterna chyli. This cistern-like structure collects lymph from multiple incoming lymphatic vessels in an expanded balloon-like area of the vessel, which functions as a holding chamber, with the most substantial accumulation of lymph anywhere in the body. Another major repository of lymph fluid is concentrated in sponge-like webs of lymphoid tissue throughout the abdominal organs. With the downward movement of the diaphragm, particularly in deeper breathing, a wave of lymphatic fluid is compressed from the cisterna chyli and the sponge-like webs of tissue. This lymph is moved forward in the system through the one-way valves in the lymphatic vessels and propelled upward into the thoracic duct (Adair & Guyton, 1985).
6. Transformation. The thoracic duct collects lymph from the organs within the rib cage and from lymph-rich areas in the abdominal cavity. Lymphatic fluid accumulates centrally and is then propelled by the action of the diaphragm and the lungs in a final rush through the thoracic lymph duct into the blood at the subclavian vein. There it merges with blood to become a component of blood serum (Shields, 1980). The lymph-borne by-products of metabolism are then detoxified in the liver, filtered through the kidneys, and discharged from the body in bile and urine.

Lymph and immune function. The role of the lymphatic system in immune activity is well documented in the scientific literature (Drinker & Yoffe, 1941; Bradbury & Cserr, 1985; Olszewki, 1985; Van Rooijen, 1987). Lymph delivers immune cells originating from a number of sources:

- Transported to the lymph from immunogenic tissues and organs (spleen, thymus, and bone marrow),
- Exchanged from blood circulating through the lymph nodes, and
- Formed within the lymph nodes themselves (Bradbury & Cserr, 1985).

Lymph contents include lymphocytes, macrophages, and antibodies (Olszewski, 1985). Both qigong (Lee et al, 2004) and yoga (Lee et al, 2003a) have been found to increase levels of these immune components. Further, when lymph flow or volume is increased, greater numbers of these cells are diffused into the system (Adair & Guyton, 1985).

Qigong and yoga mobilize the body's self-regulatory systems required for healing and good health.

- *Immune modulation.* A review of clinical trials on qigong reported a range of immune modulating effects. The results were particularly noteworthy when participants sustained the practice for a period of five months or longer (Ryu, 1995a).
- *Lymphocytes*. The concentration and functionality of lymphocytes, monocytes, and neutrophils have been found to increase following qigong training (Lee et al, 2003b & 2004). We also know that neurotransmitter receptor sites on lymphocytes interface with neuropeptides that drive immune function (Smith et al, 1985). This reflects an important link between lymphatic function, neurochemistry, and neuroimmunity.
- *CD4/CD8 ratios*. A review of clinical trials on qigong and immunity reported on four studies in which the number of CD4 lymphocytes were significantly increased and CD4+/CD8+ ratios were significantly improved (Ryu et al, 1995a; Yao, 1989; Lee et al, 2006; Yu & Wang, 2007).
- *Antibodies*. The development of antibody-generating cells in lymph nodes has been delineated, localized, and quantified in the research (Van Rooijen, 1987). Clinical studies found that both qigong and meditation supported desired increases in antibody titers in response to a vaccine (Ryu et al, 1995a; Davidson et al, 2003). Two more recent studies of qigong practice reported increases in secretory IgA levels (Bayat-Movahed et al, 2008), one also documenting decreased salivary cortisol (Chan et al, 2013).

The pathological presence of leucocytes is comparable to the pathological absence of leucocytes – a deficiency of functional capacity. Thus, according to the paradigms of Chinese medicine, when the individual implements qigong, the practice will optimize function. Performed with intelligence and moderation, health enhancement practices increase functional potential. Similarly, the fact that one person has too many antibodies and another person has too few does not have an impact on the potential for the practice to enhance functional capacity in both parties. The effect is ultimately adaptogenic.

Circulation of cerebrospinal fluid. Historically, cerebrospinal fluid (CSF) was perceived as a closed system. However, it has been acknowledged for several decades that CSF travels along the cranial and spinal nerves and into the perineural lymphatics (Kimber & Kimber, 1977; Bradbury

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& Cserr, 1985). The effects of pressure and posture on this flow suggest that certain types of movement, postural adjustment, and deep breathing activate the CSF/lymphatic interaction (Bradbury & Cserr, 1985).

Nutritive function. The role of the lymphatic system in the delivery of nutrients was little known before 1972 (Shields, 1972). More recent findings indicate that the lacteals in the small intestine mediate this nutritive mechanism (Adair & Guyton, 1985). Chyle (milky fluid with high nutrient contents) is absorbed from chyme in the small bowel and then passed into the circulating blood. During deep inspiration, diaphragmatic activity appears to significantly improve the function of the cysterna chyli and abdominal organs and enhance absorption in the small intestine. In traditional Asian systems of medicine and self-care, breath practice and therapeutic exercise are enlisted to improve circulation and the absorption of micronutrients from therapeutic diet and medicinal herbal formulas. Therapeutic practices such as qigong maximize the nutrifying potential of lymphatic fluid by increasing volume and flow rates of the lymph. In individuals whose health is compromised, these functions can be enhanced through therapeutic exercise such as qigong (Lee et al, 2003b, 2004).

Neurological Function

Traditional healing systems emphasize the restoration of *homeostasis.* In Chinese medicine, the importance of equilibrium between the sympathetic and parasympathetic systems is conveyed in the metaphor of energy balance (yin and yang). Research on mind-body practices suggest that this equilibrium enhances neurological function through a number of mechanisms, including the following:

- Initiation of the relaxation response,
- Shift to a more beneficial neurotransmitter profile,
- Increased microcirculation,
- Support for neurological aspects of immune function, and
- Promotion of alpha/theta brain wave activity.

Initiation of the relaxation response. When the autonomic nervous system is primarily in the sympathetic, adrenergic mode, the system is expending rather than conserving energy. In the extreme, this is the *stress response* with increased heart rate, blood pressure, and breathing. Catabolic activity can occur in this mode, associated with elevated cortisol levels (Girod & Brotman, 2004). The stress response, if protracted, can lead to adrenal dysfunction (Selye, 1978) or hypothalamic-pituitary-adrenal dysregulation (Kresser, 2017). Potential clinical consequences of biological stress include functional disorders such as depression, hypertension, arrythmias, immune deficiency, and/or inflammation (Benson, 1975).

Balancing sympathetic activity is the parasympathetic (cholinergic) phase of rest and repair, also described as the relaxation response (Benson, 1975). This conservative, anabolic repair phase of metabolism is characterized by decreased blood pressure and heart and breath rate, which can neutralize the potentially harmful effects of sympathetic overactivity. The parasympathetic profile can be engaged consciously, simply through deep, slow breathing coupled with the intention to relax (Benson, 1975). Traditional Asian health maintenance practices also provide effective techniques for generating the relaxation response (Benson, 1975; Chang et al, 2004) and the biofeedback response (Green & Green, 1977), normalizing blood pressure and heart rate (Lee et al, 2003b).

Improved neurotransmitter profile. Certain characteristic profiles of neurotransmitter dominance are typically associated with mood states such as pain, anxiety, or depression (Lechin et al, 1996), in contrast to profiles associated with positive emotions (Ornstein & Sobel, 1987; Rein et al, 1995). Research indicates that therapeutic mind-body exercise can promote a more favorable neurotransmitter profile, moderating sympathetic function through the hypothalamus, characterized by decreased norepinephrine, and elevated cholinesterase and beta endorphins (Brown et al, 1995), as well as elevated melatonin. The neurotransmitter profile of the predominantly parasympathetic and more anabolic environment has been documented to improve clinical outcomes in a number of debilitating conditions:

- Reducing cravings for addictive substances (Kovacs & Telegdy, 1988),
- Mitigating depression (Lechin et al, 1996),
- Improving postoperative distress (Levin et al, 1987),
- Enhancing control of acute pain (Heffline, 1990), and
- Supporting pain management in conditions such as fibromyalgia (Creamer et al, 2000).

Increased microcirculation. During the stress response, arterioles in the skin, muscles, and certain organs constrict. The systematic deactivation of sympathetic function in the relaxation response, typical in qigong and yoga, promotes vasodilation with accompanying warmth of the skin surface and enhanced microcirculation (Wang et al, 2001). This can result in significant increases in oxygen, nourishment, immune components, and other self-healing factors. Biofeedback research has further confirmed an association between elevated skin temperature and the relaxation response (Green & Green, 1977). A number of studies from China have explored microcirculatory mechanisms and concluded that this effect can be promoted through qigong and other health practices (Wei et al, 1988; Xiu et al, 1988; Zhao et al, 1988), further confirmed in Chinese clinical studies (Wang et al, 2001; Liu et al, 2003).

Neurological aspects of immune function. Research in psychoneuroimmunology has demonstrated that mental and emotional states alter resistance to infection and disease (Ornstein & Sobel, 1987; Pert, 1997). Lymphocytes

and macrophages have receptors for neurochemicals produced by the nervous system, the brain, the gut, and the endocrine glands, including catecholamines, serotonin, and endorphins, as well as prostaglandins (Roxman et al, 1985; Ornstein & Sobel, 1987). The hypothalamus appears to be a nexus for these various interrelated influences, since it contains 40 times more receptor sites than any other area of the brain or nervous system (Pert et al, 1985; Pert, 1986). Studies have confirmed the effects of the hypothalamus on immune function (Ornstein & Sobel, 1987). The practice of qigong and yoga influences these relationships via the hypothalamus by down-regulating sympathetic activity (Green & Green, 1977; Benson, 1975). Clinical research has corroborated the positive effect of mind-body exercise on immune function (Shannahoff-Khalsa, 1988; Xiu et al, 1988).

Induction of alpha/theta brain wave activity. Research conducted on practitioners of yoga (Green & Green, 1977) and qigong (Beijing College of Traditional Chinese Medicine, 1988) has shown that these practices elicit the relaxation response with brain wave frequencies toward the alpha range and, in certain cases, the theta frequency. Alpha brain wave function is a result of relaxation and is conducive to healing, slowing heart rate, reducing blood pressure, increasing skin temperature, and improving circulation. In qigong and yoga, the goal is to achieve the lowest possible frequency of brain wave activity through the practice. In standing qigong (which involves no movement), this quiescent meditative state has been found to promote the theta range of brain activity, confirmed in EEG studies from China (Pan et al, 1994). The dynamic forms of qigong can also be effective in promoting alpha or theta states. In general, mind-body practices tend to promote favorable neurological activity.

Conclusion

The efficacy of these techniques can now be explained through our scientific understanding of the body's basic self-regulatory mechanisms. Qigong, tai chi, yoga, and mind-body systems such as the Feldenkrais method and the Alexander technique increase efficiency of the lymphatics and circulatory system, improve sympathetic-parasympathetic balance, optimize immune function, and enhance neurotransmitter production.

The vast majority of clinical trials on therapeutic exercise have reported enhanced quality of life and health improvement. Now that we have ample evidence to confirm the value of these practices, it is apparent that they are practical, timely, inexpensive tools for improving health and healing. Applied in the management of chronic disease, therapeutic exercise could potentially reduce the burden of illness and the cost to millions of individuals with chronic health conditions. If lifestyle medicine were applied more broadly, the fiscal savings could be significant.

Source: portions of this article have been adapted from Jahnke R. Physiology of qigong, tai chi, and yoga. In Rakel D, Faass N. *Complementary Medicine in Clinical Practice.* Sudbury, MA: Jones & Bartlett; 2006, courtesy of Roger Jahnke © 2006, 2019.

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Institute of Integral Qigong and Tai Chi: http://IIQTC.org

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Men's Heart Health: An End to Heart Attacks

by Joel Kahn, MD

Your chest slowly begins to tighten up, and you feel it in your throat and left shoulder. It is not a pain but a dull and scary pressure. Your breathing is heavy, and your skin is moist. You feel slightly dizzy and cannot figure out what is happening. It has been 20 minutes, and the feeling has gotten more intense. You are having a heart attack, also known as myocardial infarction (MI), and your heart muscle is dying. Your very life is at risk. You are joining one of nearly 800,000 persons every year in the USA alone that suffer a MI.[1] In terms of death, heart disease is the leading cause of death for men in the United States, killing 321,000 men in 2013 – that's one in every four male deaths.[2] At younger ages, men face a greater risk of heart disease than women. On average, a first MI, the most common manifestation of this prevalent disease, strikes men at age 65.

Nearly 10% of men have a diagnosis of coronary heart disease (CHD), which is a term for clogged heart arteries causing angina chest pressure, a MI, and the need for heart stents and bypass surgery. Tragically, half of the men who die suddenly of coronary heart disease, hundreds of thousands, have no previous warning symptoms and no chance in the traditional medical model to be diagnosed before death. The key message of research statistics is that even if a man has no symptoms, he may still be at risk for CHD and heart death.

After World War II the number of cases of CHD began to rise. Until the early 1950s, CHD was largely regarded as a feature of aging. Certain keen observers like Paul Dudley White, MD, of the Harvard Medical School disagreed and felt a large proportion of MI and cases of CHD could be predicted by "risk factors" developed from research studies like the Framingham Study initiated in the late 1950s.[3] These studies identified that high blood pressure, high LDL cholesterol, and smoking were the key risk factors for CHD. About half of Americans (49%) have at least one of these three risk factors.[4] Several other medical conditions and lifestyle choices can also put a man at a higher risk for heart disease, including diabetes, overweight and obesity, a diet high in processed foods, physical inactivity, and excessive alcohol use.[2] This science led Dr. White to conclude from the 1950s onward that "Death from a heart attack before the age of 80 is not God's will, it is man's will."[5] The matter of heart attack prevention is pressing because over 1,000 people a day in the US alone experience a heart death judged to be preventable by the Centers for Disease Control in Atlanta.[6] The following steps are suggested as a comprehensive and effective strategy to identify CHD in men before a heart attack occurs.

Step 1: Clinical Clues to Silent CHD

CHD progresses silently for years before a MI or death occur, but there are clues to "sick" blood vessels in other parts of the body that can be an early warning system to CHD.

Erectile dysfunction (ED). Some men have a built-in warning system for silent CHD. When achieving an erection is difficult or impossible, it can be a sign of clogged arteries in the pelvis that presents before a MI hits a few years later. There are, on average, three to five years between the onset of ED and the finding of CHD, which is plenty of time to detect and to work on preventing heart issues.[7] Unfortunately, the norm in clinical practice is a Rx for an erectile dysfunction drug without a consideration of the risk of CHD. A full evaluation for silent CHD has been recommended by expert panels.[8]

Baldness. In a comprehensive study of almost 37,000 men, severe baldness at the crown of the head strongly predicted the presence of silent CHD at any age.[9]

Gray hair. A new study presented in Europe at EuroPrevent 2017 found that a high amount of gray hair is a risk factor for silent heart atherosclerosis. A total of 545 adult men without known heart disease had a CT angiogram of their heart arteries, a very accurate way to identify silent problems. Having equal amounts of gray and dark hair, or mainly gray and white hair, correlated with finding silent heart blockages. The researchers hypothesized that atherosclerosis and hair graying occur through similar biological pathways.[10]

Diagonal ear lobe crease. One of the strangest of markers, a crease in the earlobe (specifically, an angled crease in the ear that runs diagonally from the canal to the lower edge of the earlobe) has been mentioned in medical research reports as a sign of silent CHD. The

ear lobe crease may result from poor circulation or a nutritional deficiency in collagen production. Although some medical professionals have argued that a crease is just a general sign of aging, researchers used the most sophisticated CT scan method to measure silent CHD and found that ear lobe crease predicted CHD even after accounting for other risk factors, such as age and smoking.[11]

Calf pain on walking. This is known as claudication (from the Latin for "to limp"). Atherosclerosis can block leg arteries, particularly in smokers, before CHD is diagnosed. This symptom requires an evaluation without delay. An examination of the pulses in the legs and simple measurements of leg blood pressure and blood flow can confirm a diagnosis of poor circulation and increased MI risk.[12]

Step 2: Determine Arterial Age

The concept of "arterial age" to predict longevity goes back to the 1600s when a leading English physician, Thomas Sydenham, MD, wrote that "a man is as old as his arteries." While there are recommendations to search for breast and colorectal cancer, there is no routine screen to identify silent CHD.[13] The American Heart Association recently updated its guidelines for the management of cholesterol to consider a simple CT scan of the heart known as a coronary artery calcium score (CACS) as pivotal in deciding on therapy.[14] In addition, a large analysis of the predictive power of the CACS and the use of cholesterol lowering statin medication was published that makes it clear that getting a CACS is the most important step to assess the risk of a heart attack.[15]

A CACS was developed as a screening test for silent calcified heart arteries using specialized CT scanners called EBCT but is now performed on the widely available multi-slice scanner at most hospitals and even some larger clinics.[16] The test simply requires holding one's breath and is independent of heart rate or blood pressure. A second type of heart CT scan called a coronary CT angiography or CCTA requires that contrast agents be injected and is not used as a screening tool. The CACS test takes under 30 seconds and is painless. With modern software algorithms and CT scanners, the radiation exposure is about 1 mSv, or on par with a mammogram. The CACS is not a yearly examination and might be repeated every 5-10 years (or never) so the radiation exposure is considered low. It is a screening test for silent CHD so it is not appropriate for persons with a prior MI, stent, coronary bypass, or known atherosclerosis of other parts of the body like a carotid endarterectomy. Additional considerations are the potential incidental findings (pulmonary nodules, enlarged lymph nodes, and thoracic aortic aneurysm).

The CACS requires calcification of heart arteries, sometimes called hard plaque. Soft plaque that is not yet calcified may also threaten the health of men but will not be identified on a CACS. A digital carotid ultrasound called a carotid intimal-medial thickness (CIMT) can show both hard and soft carotid plaque years before an event.[17] A CIMT is a 20-minute ultrasound of the neck that uses advanced software measurements to examine carotid arteries for plaque and also measure the thickness of arteries, another sign of aging. The biggest drawback of the CIMT is finding a quality center that offers it.

Step 3: Measure Advanced Labs

The standard annual wellness examination or even executive physical generally involves the same laboratory evaluation that was obtained 20-30 years ago. The field of lab testing for genetic and acquired heart risk is advancing rapidly and widely available. Here are some tests to consider.

Advanced lipid profile. Rather than a calculated LDL cholesterol level, advanced panels measure LDL particle number and size directly, which are more accurate and predictive of future heart and stroke events.[18] Two people with the same total and calculated LDL cholesterol levels can have widely different particle and size measurements, making for very different risks.[19]

hs-CRP. The high sensitivity C-reactive protein is a blood test patented by Harvard Medical School to measure inflammation or the "fire" that results from an irritated immune system. The higher the hs-CRP the greater the risk for atherosclerosis, heart attack, stroke and even other conditions like cancer and dementia.[20]

Lipoprotein (a). This is a genetic form of cholesterol that's elevated in about 20% of those tested and unaffected by most lifestyle measures or statin medication. It's rarely drawn even though hundreds of research studies indicate that if it's high, the risk of heart attack and stroke skyrocket. It runs high in many families that have been decimated by heart disease.[21]

Early identification of men with coronary heart disease allows them to take preventive measures before a heart attack occurs.

Homocysteine. This amino acid is produced by a process called methylation. It can injure arteries when elevated. It may be due to a genetic defect in the MTHFR gene, which is easily measured or due to nutritional deficiencies of B vitamins. Homocysteine can be lowered with B-complex vitamins.[22]

TMAO. This is a newly described marker of heart and kidney health that's elevated after eating meat- and egg-heavy diets with an altered gut microbiome. It has been shown to cause heart and kidney damage and is associated with worsened prognosis.[23]

apoE. This is a genetic marker related to cholesterol metabolism that is measured from a blood sample. For the few that inherit a pattern called apo E 4/4, the risk of heart disease and Alzheimer's disease is high and may have an onset 15-20 years earlier than average.[24]

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Step 4: Calculate an Astro-CHARM Score.

A major advance in 2018 was the publication of the application called the Astro-CHARM score.[25] The online risk calculator is a collaboration of NASA and the University of Texas Southwestern Medical Center and is the most advanced tool available. It permits entering the CACS, the hs-CRP and more traditional measures (age, smoking status, total cholesterol, HDL-cholesterol, and blood pressure) to predict the 10-year risk of fatal and non-fatal MI and stroke.

Step 5: Review New Prevention Guidelines

The approach to avoiding a MI and CHD may seem complex as outlined here but the core activities of day to day self-maintenance are quite simple. The key recommendations to prevent heart issues have been organized in the 2019 Primary Prevention of Cardiovascular Disease guideline from the American College of Cardiology/American Heart Association (ACC/AHA).[26] An even simpler version of the guidelines is available and may be more appropriate to share with patients.[27]

Step 6: Apply Strategies to Reverse Disease

Even though prevention is the ideal goal of health care, heart disease or otherwise, for the millions with CHD clinically evident or found by the testing protocol described, an attempt to halt and reverse the process is crucial. Although this may sound like a fantasy, for nearly three decades it has been known that just as arteries can worsen with time, they can also improve rapidly. Some of the measures to achieve this are presented here.

Statin medications. There is concern for the long-term use of cholesterol-lowering statin medications and careful assessment of the medical literature is mandatory. A recent study analyzed a database of 13,644 asymptomatic patients studied for heart artery disease by a CACS and followed for over nine years.[28] The data was analyzed as to whether a statin was used or not during that time period. The findings indicated that when the CACS was over 100, being treated with a statin was associated with a lower risk of bad outcomes. For example, when the CACS was over 100, only 12 patients needed to receive a statin to prevent one event like a heart attack, stroke, or death. Of course, an intensive program of lifestyle measures should proceed the decision to use a statin in most patients.

Nutrition. Atherosclerotic CHD was shown to be reversible using a whole food plant diet and lifestyle measures in 1990.[29] Patients were taught to eat a plant-based diet without added fats and were also asked to walk, manage stress with meditation, and gather as a group for social support. It was demonstrated that the patients who adhered to this "lifestyle program" felt better and showed reductions in the amount of narrowing in their arteries. Since those first reports, the data that heart disease can be reversed by intensive lifestyle changes emphasizing a plant-based diet low in added fats has become so robust that the Ornish Lifestyle program was recognized by Medicare in 2010 for reimbursement as a therapy of CAD. Another similar program, based out of the Pritikin Longevity Center in Miami, Florida, received the same Medicare designation for intensive therapy and reversal of heart disease with plant-based dietary therapy.

Aged garlic. The ability of garlic to lower blood pressure, cholesterol, and blood clotting has been recognized for some time. There have actually been a surprising number of studies testing the ability of aged garlic extract to halt CHD progression. For example, in a study published in early 2016 that used baseline and follow-up CT angiograms of heart arteries, aged garlic extract reduced areas of plaque in heart arteries at the one-year follow-up.[30] In addition to the sulfur content of garlic, onions also provide a source of sulfur in the diet that may be crucial for maintaining optimal amounts of antioxidants.

Pomegranate. Pomegranate juice and seeds both have powerful antioxidant properties that may improve the function of HDL cholesterol. In studies of mice, pomegranates can reduce atherosclerosis although translating animal research to human health can be misleading. In humans with increased stress at risk for CAD, pomegranates can reduce evidence of arterial damage. In a study using pomegranate juice for three years, the degree of narrowing in carotid arteries of five study subjects was reduced.[31]

Chelation. Over 60 years ago some data surfaced that chelation therapy using disodium ethylene diamine tetraacetic acid (EDTA) could reverse heart artery disease. It took many decades but the Trial to Assess Chelation Therapy (TACT) was published in 2013 and demonstrated an improvement in outcomes in post-myocardial infarction (MI) patients following IV EDTA versus a placebo.[32] The TACT showed a particularly large reduction in CVD events and all-cause mortality in the subgroup of patients with diabetes. A second phase (TACT2), limited to patients with heart disease and diabetic mellitus type 2, is ongoing and has enrolled hundreds of patients.

There is an interesting oral agent containing EDTA and additional agents that has data for lowering the calcification of coronary arteries in peer reviewed data.[33] Other components of the novel combination may attack the mechanism of calcification and lead to reversal of plaque.

Nutraceuticals. In a recently published randomized study from China, 76 patients with carotid atherosclerosis were treated with either nattokinase (NK) 6,000 FU or simvastatin 20 mg.[34] In both groups cholesterol fell, and in the NK group HDL rose; but reversal of atherosclerosis over 26 weeks was profound with NK and plaque volume fell by 37%.

In another study from China in 2009, 60 patients with carotid plaque received aspirin and atorvastatin.[35] Thirty of the patients also got lumbrokinase, two capsules three times a day for six months. Lumbrokinase is an enzyme extracted from earthworms. Measurements of CIMT were lower in the group treated with lumbrokinase as were measures of cholesterol fractions and platelet

aggregation. The use of lumbrokinase was safe in this small study.

Bergamot was studied in patients with atherosclerosis over 6 months without randomization.[36] Lipid fractions improved as anticipated during therapy with bergamot, and there was a stunning decrease in the CIMT from 1.2 cm to 0.9 cm.

Vitamin E has eight forms, and four of them are classified as tocotrienols with properties far more favorable than the more common tocopherols. In a study of 50 patients with carotid disease, half were treated with a source of gamma tocotrienol from palm oil.[37] Over 18 months of therapy, regression of plaque was seen in seven of the 25 patients treated with the vitamin E preparation while in the control group none regressed and 10 showed worsening.

A promising combination therapy has been reported to promote the reversal of carotid atherosclerosis.[38] The study combined pycnogenol with *Centella asiatica* and followed 391 patients with ultrasound measurements of plaque for over four years in a randomized trial. The progression of plaque over time was least in the patients treated with the combination nutraceutical, and there was reduction in the number of angina episodes and myocardial infarctions in the treated cohort.

Conclusion

Further advances in the detection, prevention, and reversal of atherosclerosis are needed. Prevention of heart disease as outlined by the recent ACC/AHA guideline must be the focus of medical education and patient care. Once the disease is present, natural therapies can give hope to patients with even advanced disease; nutrition, and nutraceutical therapies can improve their quality and quantity of life. There is no reason that the vision of Paul Dudley White, MD, cannot be achieved and make CHD an option and not an inevitable outcome for so many men.

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Carnitine Derivatives in Integrative Treatment of Peyronie's Disease and Sexual Dysfunction in Men

by Jeremy Mikolai, ND

Carnitine is a general term used to refer to the amino acid derivative L-carnitine (LC) and its closely related metabolic counterparts, acetyl-l-carnitine (ALC), and propionyl-l-carnitine (PLC). Participation of LC/ALC in shuttling of fatty acids into mitochondria for beta-oxidation is well known and largely understood, but its participation – and that of its derivatives – in other body processes is less completely understood. However, the therapeutic applications for these agents in diverse pathologies of any age and gender cannot be overstated. Their efficacy has been demonstrated on important pathologies of the cardiovascular system, peripheral vascular system, nervous system, in the redress of infertility in both males and females, and in several conditions that are specific to the male urogenital organs. We will consider two of these areas: Peyronie's disease (PD) and erectile dysfunction (ED).

Propionyl-l-carnitine (PLC) is a derivative of L-carnitine. As a manufactured agent, it is most often delivered as glycine propionyl-l-carnitine (GPLC). Its therapeutic effect has several important applications in the vascular system, including in the treatment of peripheral vascular disease (PVD), healing of ulcers from PVD, improved walking distance in intermittent claudication, congestive heart failure, and angina.[1-5] Repeated studies show PLC supplementation increases circulating nitrate.[6] More nitrate does not prove increased vasodilation or conclusively elucidate one or more mechanisms of action for the therapeutic effect of PLC, yet its effect on diseases of ischemic pathophysiology are demonstrable.

Peyronie's disease (PD) is a fibrotic disorder of the tunic albuginea (TA) of the penis resulting in pain, penile deformity (especially during erection), and palpable changes/nodularity at the areas of local fibrosis. The causes of PD are incompletely understood, but several risk factors are known including local ischemia and previous trauma. PD is not uncommon and may affect 3-9% of the male population, likely more. PD is characterized by an acute phase of 12 months, which often includes pain, and a chronic phase thereafter in which pain may resolve but in which deformity and plaque formation may progress. Erectile dysfunction is a common co-morbidity of PD.[7]

Interlesional injections appear to be the present minimally invasive treatment of choice for PD with interferon preparations showing significant effects on penile curvature, plaque size, penile pain, and erectile function. Surgical correction is typically reserved for disease that has progressed over at least 12 months and results in penetrative inability or other severely impaired sexual satisfaction. The procedure of choice is often incision and grafting, especially with multifocal disease, severe curvature, or desire not to suffer loss of penile length resulting from other procedures.

Cavallini et al (2002) evaluated the efficacy of PLC (2 g/day) versus tamoxifen (40 mg/day) for three months in 60 patients, all of whom were also receiving interlesional verapamil infiltrations (10 mg/wk) for 10 weeks. Another group of 15 individuals with resistant PD were treated with the verapamil/PLC regimen. In both groups taking PLC, significant improvements were seen in penile curvature, plaque size, disease progression, and International Index of Erectile Function (IIEF) scores. None of these effects were seen in the tamoxifen group.[8]

While Cavallini study above was published in 2002, the Gokce et al review (2013) of Peyronie's disease demonstrates no significant effect on PD from either interlesional verapamil injections or oral tamoxifen.[7] A 2007 study by Safarinejad demonstrated no significant effect from PLC versus vitamin E on similar outcomes in PD.[9] More recent data supports a dose of 3-3.5 grams/day of PLC as necessary for likely improvement in PD.[7]

Biagiotti and Cavallini previously studied the effect of ALC in 48 PD patients randomized to two groups, one taking ALC 1 g two times/day, one taking tamoxifen 20 mg two times/day, each for three months. Their results

demonstrated significant improvements in pain and disease progression, penile curvature, and plaque size in the ALC group versus only decreased plaque size in the tamoxifen group, which also had significantly more side-effects.[10]

Acetyl-l-carnitine (ALC) is derived from the acetylation of carnitine and is used as a coenzyme A (CoA) donor in the mitochondria as acetyl CoA combines with carnitine to form ALC, which is transported out into the cytosol leaving CoA available for further beta-oxidation of fatty acids.

ALC has diverse and complex action upon the nervous system ranging from antiapoptotic effects to nerve regenerative properties, including increased neuronal structural element synthesis, increased growth factor sensitivity, and analgesic action that may be attributable to a reduction of glutamate in the neuronal synapse.[11]

ALC is a neuropathy intervention par excellence; it demonstrates effect in nerve damage repair and nerve regeneration in primary trauma as well as in chronic neuropathies such as diabetic neuropathy. A 2017 review by Veronese et al demonstrated that, in a review of 711 patients with diabetic neuropathy, ALC oral supplementation resulted in improved pain perception as well as improved motor and sensory nerve conduction velocities and amplitudes. In other words, ALC resulted in improved nerve function.[12]

Vasodilator activity may explain the role of PLC in the improvement of male sexual dysfunction, erectile dysfunction, and some symptoms of decreased sex hormone production with age ("andropause"); but that mechanism does not seem to explain all of the effects of the combination of PLC and ALC in the treatment of these disorders. None the less, oral supplementation of 2 grams/day each of ALC and PLC has demonstrated profound effects on male sexual function and associated symptoms.

Compared to supplementation with either high dose testosterone intramuscular injection or placebo, supplementation of ALC/PLC for six months demonstrated significantly superior results compared to testosterone on improvements in nighttime erections and IIEF score. Both testosterone and ALC/PLC were superior to placebo on numerous outcomes, including peak end systolic and diastolic blood flow velocities, resistive index, nighttime erections, IIEF score, Depression Melancholia Scale score, and fatigue scale score.[13]

Peyronie's disease, which affects 3-9% of men, can improve with supplemental acetyl-l-carnitine/propionyl-l-carnitine treatment.

It is important to note that the Huo et al (2016) review found that there is no significant benefit to sexual function, mood, psychological well-being, or cognitive function resulting from testosterone supplementation in men with low testosterone.[14]

Erectile dysfunction is a common disorder in men, especially aging men, and may be primary or secondary in its cause or often both. While psychological factors are virtually ubiquitous as contributing or propagating factors, the initiating insult may be psychological, metabolic, vascular, nervous system, or primary urogenital in origin. It may be secondary to trauma, iatrogenic intervention, T2D, high blood pressure, high cholesterol, vascular disease, nerve damage and other issues.

The development of 5-phospho-diesterase inhibitors (5-PDEi) such as sildenafil and tadalafil revolutionized the treatment of erectile dysfunction in men, though these agents do not work for every individual. Intracavernosal injections of trimix (combination of alprostadil-prostaglandin, papaverine-vasodilator, and phentolamine-alpha adrenergic blocker) are effective for some men who fail oral 5-PDEi therapy.

Prostatectomy is a primary iatrogenic cause of erectile dysfunction in men with a history of prostate cancer or severe benign prostatic hyperplasia. Regardless of the method of resection, nerve damage and erectile dysfunction are always risk factors. Cavallini et al (2005) studied 96 patients who had undergone bilateral nerve-sparing radical retropubic prostatectomy in three groups. Group 1 took a placebo, group 2 took 2 grams/day each of PLC and ALC as well as sildenafil 100 mg as needed for sexual activity, while group 3 took only 100 mg sildenafil as needed.[15]

While both groups 2 and 3 had significant improvement in IIEF score, group 2 scores were significantly greater than group 3 in erectile function, satisfaction, orgasm, and sexual well-being. The percentage of each group reporting satisfactory sexual intercourse were 7%, 88%, and 51%, respectively. Moreover, only the ALC/PLC treatment group demonstrated improvements in intracavernous injection tests after the treatment period – again, signaling that ALC/PLC is affecting an improvement of this natural function, a healing, which is not occurring in other treatment contexts.

Case Reports

Case 1: Mike was a 41-year-old male with a six-year history of Peyronie's disease, which he felt began with a flare of psoriasis. He reported extreme pain and phimosis for the first year, followed by a severe hour-glass restriction circumferentially around the shaft of the penis just proximal to the glans penis with painful erection, limitation of erection size, and sexual satisfaction. A 1 mm round palpable nodule fixed within the TA was appreciable. His history was also significant for untreated mild-moderate recurrent major depression, type 2 diabetes mellitus (T2D) that was moderately controlled through diet and exercise, moderate plaque psoriasis, and a remote history (11 years prior) of penile fracture, which was treated with non-surgical conservative management and presumed to have healed completely.

Mike started GPLC 1,500 mg twice daily and ALC 500 mg twice daily. He reported increased libido and decreased depression and fatigue

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within the first week of use. At four weeks follow up, he reported a 25% improvement in erection size and early signs of resolution of his fibrosis, including painless erections, lack of skin breaks, and resolution of some fibrosis. At eight-weeks follow up, Mike had near resolution of all symptoms with continued improvements in fatigue and depression. While his TA nodule was still palpable at eight weeks, it was resolved completely by the six-month follow up visit. Mike had no reported negative off-target effects.

Case 2: Patrick was a 23-year-old male newlywed and recently graduated engineer with ADHD that was well-controlled on guanfacine, 2 mg every night at bedtime. He complained of erectile dysfunction, including difficulty reaching full tumescence, difficulty maintaining tumescence, and anorgasmia as well as premature ejaculation. He continued to have nighttime erections. He had no significant physical exam or laboratory abnormalities. He had a history of incompletely controlled irritable bowel syndrome without red flags and no other significant personal, social, medical, or family history.

Patrick started ALC/PLC, 1/1.5 grams two times per day. Within one week he reported complete improvement in sexual function and also reported significant gastrointestinal side effects, primarily loose stools. He stopped the ALC/PLC protocol, and we addressed this acute issue. He continued to have improvement in sexual function for several weeks and then decided to resume ALC/PLC, which he did without side effects and with return to what he considered to be full improvement for several more weeks of treatment. He was then able to discontinue treatment with continued full satisfactory function.

Case 3: Clint was a 59-year-old male who was referred to me for cardiac evaluation after he was found to have unexplained fluctuating NT-proBNP levels; our work-up revealed severe asymptomatic three-vessel coronary artery disease. He had only recently sought care and was under treatment but, at this time, was severely hypertensive, hyperlipidemic, and diabetic with a HgbA1c over 10%. He was seen by a cardiothoracic surgery, had a very successful three-vessel bypass surgery, a very rapid recovery, and was seen for follow up less than three months after surgery with no pain, exercising daily, controlled blood sugar and blood pressure, on 10 mg of rosuvastatin, but no other medications and asking to address erectile dysfunction. He had tried Trimix, which had worked for him but was not of routine interest to him; he had failed sildenafil oral tablet at an unknown dose. He began ALC/PLC 1/1.5 gram, two times per day; after one month without improvement, he doubled his dose. After two months of treatment, he was lost to follow up without known improvement.

I discussed with this patient that it would be optimistic to expect the ALC/PLC protocol to show significant results in less than six months, but I certainly do expect that he would have had appreciable improvement over a longer treatment period. The logical next step in his case would have been to clear him for sexual activity (with his cardiologist or surgeon, or to order or perform an exercise tolerance test) and then prescribe a 5-PDE inhibitor of adequate dose and dosage form for an adequate trial as he may well benefit from combination treatment even having previously failed 5-PDEi alone.

In the integrative management of Peyronie's disease, as well as in almost every case of erectile dysfunction, there is a central place for the therapeutic application of ALC and PLC. Moreover, in virtually every case necessitating these agents, the skilled clinician will likely find their appropriate application leads to the improvement of one or more important comorbid conditions.

Jeremy Mikolai graduated with highest honors from the National College of Natural Medicine in Portland, Oregon in 2010. He then completed three years of clinical residency training, including one year as chief resident. His clinical training focused on family practice integrative medicine with extensive additional training in cardiovascular diseases. Following residency, he completed an additional year of integrative cardiology fellowship.

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Does Testosterone Cause Prostate Cancer?

by Geo Espinosa, ND, LAc

Testosterone is a cholesterol-derived hormone in the body responsible for male sexual differentiation. It is tightly bound to sex hormone-binding globulin and loosely bound to albumin; about 2% is free and bioavailable.

As a man ages, a steady decline in testosterone production or bioavailability, via several pathways, can happen. One, peripheral aromatization can occur resulting in the conversion of testosterone to estrogens. Two, testosterone binds the androgen receptor (AR) on the cell nucleus to produce proteins for cellular function. Three, testosterone undergoes conversion to 5α-dihydrotestosterone (DHT), a more potent androgen, by the enzyme 5α-reductase.[1]

For close to seven decades, it's been thought that testosterone (or its metabolites) "is the gasoline that lights the prostate cancer fire."

Briefly, prostate cancer is the fifth leading cause of death from cancer in men, with an estimated 307,000 deaths representing 6.6% of total male cancer mortality. This estimate accounts for 15% of the cancers diagnosed in men, with almost 800,000 occurring in more developed regions. The likelihood of developing prostate cancer increases with age with the average age at diagnosis being 66 years.[2]

The notion that testosterone participates in prostate cancer development is counterintuitive as most men have a decline in testosterone as they age. That would mean that the highest rate of prostate cancer is 25 years old, not 66.[3]

So, then why do many still think higher testosterone increases prostate cancer risk?

Let's begin with a little history.

Low testosterone levels are associated with more aggressive prostate cancer and higher Gleason scores.

A Short History of the Testosterone/ Prostate Cancer Confusion

It all started with the work of Dr. Charles B. Huggins, an urologist at the University of Chicago, circa 1940.

Dr. Huggins began experimenting on the effects of castration on dogs with enlarged prostates (BPH). (After all, dogs are the only non-human animals we know of that naturally develop prostate problems.) Huggins observed that the dogs' prostates shrunk after castration. But that was not all he observed. Dr. Huggins also noticed that dogs with cancerous-appearing areas also demonstrated prostate shrinkage. When their prostates were removed, the cancerous areas cleared up.

As an experiment, Huggins and his research team then removed the testicles or applied estrogen to a group of men who had metastatic prostate cancer to their bones. At the time the PSA test did not exist; and a blood test called acid phosphatase, typically high in men with prostate cancer that had spread to their bones, was used to determine the progression of the disease. Indeed, Huggins and his team showed that acid phosphatase dropped substantially within days of lowering testosterone; and injecting testosterone into men with prostate cancer caused acid phosphatase to rise. They concluded that reducing testosterone levels caused prostate cancer to shrink and that raising testosterone levels caused it to grow.[4]

Is Testosterone the Fuel for Prostate Cancer?

In test tubes, testosterone demonstrates an increase in prostate cancer in numerous cancer cell lines but apoptosis (programmed cancer cell death) once androgens are removed.[5]

A similar response is found in rat studies: androgens promote tumor progression until androgens are withdrawn – then causing regression of prostate tumor cells.[6]

From test tubes and rat studies, one can easily think, "that's it, case closed. Testosterone fuels prostate cancer, thus low testosterone in men is best for prostate cancer prevention." But in analyzed human studies lies the paradox.

A meta-analysis of three prospective studies controlling for testosterone, estradiol, sex hormone binding globulin (SHBG), age, and body mass index (BMI) demonstrated an increase in prostate cancer for men in the highest levels of serum testosterone but no association with DHT or estradiol.[7]

Another meta-analysis called the Endogenous Hormones and Prostate Cancer Collaborative Group included 3886 men diagnosed with prostate cancer and 6438 controls. The results

demonstrated no direct association between endogenous serum androgens and the development of prostate cancer.[8]

Yet another, well-designed human clinical trial looked at 3255 men in the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events trial, also known as the REDUCE trial. Prostate biopsies performed at two and four years revealed no relationship between testosterone or dihydrotestosterone (DHT) levels and prostate cancer risk.[9]

Here's the kicker: not only is there no causal relationship with high endogenous testosterone and prostate cancer, but low testosterone may cause the disease.

One such clinical trial demonstrated a high incidence rate of aggressive, more deadly type of prostate cancer among men with low testosterone defined as >7.6nmo/l (220ng/d).[10]

Similarly, a group of Chinese men, 110 total, showed greater high-grade prostate cancer (higher Gleason score) in men with low testosterone.[11]

Beyond analyzing staging with Gleason grade on biopsy, a high-risk disease has been associated with low testosterone after prostatectomy. For example, almost 700 men undergoing prostatectomy had their morning testosterone levels taken with surgical pathology outcomes and observed a significant risk of advanced disease that included seminal vesicle invasion in severely hypogonadal men.[12]

Where Are We Now?

It is apparent, based on research, that optimal levels of testosterone do not induce prostate cancer but protect against it. Optimal levels, based on my experience, are a total between 600 to 800 ng/dl with SHBG levels no higher than 40 to 50 nmol/l.

Moreover, higher estrogen levels in aging men might be a contributing factor as shown in some studies.[13] This hypothesis is inconclusive as other studies suggest no association between estrogen and prostate cancer.[14] The role of estrogen in prostate cancer development and progression is complex and multifactorial, incorporating more than one of the mechanisms already described and with interplay between them.

Lastly, some patients can benefit from testosterone therapy after prostate cancer diagnosis. One meta-analysis looked at about 2300 men with low risk prostate cancer (≤ Gleason 6) who underwent testosterone treatment and showed short-term safety with no prostate cancer progression regardless of route of administration.[15]

Testosterone replacement therapy after prostate cancer diagnosis is a viable option in hypogonadal men, but such patients need close monitoring by a knowledgeable physician to assure against cancer progression. As always, natural and lifestyle options to increase testosterone and overall health, particularly in men with prostate cancer history, should be exhausted before considering exogenous testosterone use.

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Multivitamins and Prostate Cancer

by Jacob Schor, ND

I was sitting with a patient the other day, who came in for advice about his prostate cancer. We had already covered the rather long list of cancer-specific supplements he takes. Last on his list was a question about the multivitamin I had suggested a few years back and whether I still thought it his best choice. His question caused me to pause. A pause so long that it felt like when your computer screen freezes and you need to 'force quit' whatever you were doing. I didn't know what to tell him.

I'm no longer sure whether prostate cancer patients should take a multivitamin.

A year ago, in an article on prostate cancer, I wrote, "Taking a multivitamin is safe and probably useful." At the time, I cited the Physicians' Health Study randomized trial of regular multivitamin use that reported a modest but significant (8%) reduction in total cancer incidence in men. The men with a history of prior cancer had a 27% reduction in total cancer during the study. Yet there had been significant effect on risk of prostate cancer.[1]

I am no longer sure that my thinking was accurate. Research results on nutrition and prostate cancer tend to be erratic and often conflict from one study to the next. In one study a nutrient appears helpful and another the same substance seems harmful. What's good one day is bad the next.

This confusing situation was summed up in a review paper by Pao-Hwa Lin, William Aronson and Stephen Freedland published in 2017. They started by pointing out the obvious concern everyone is aware of with prostate cancer, that high doses of beta carotene may increase risk of getting prostate cancer. But in addition, they summed up a confusing series of other studies by stating that a "U" shape relationship may exist between folate, vitamin C, vitamin D and calcium with [prostate cancer] risk."[2]

Rather than a straight-line dose response relationship these nutrients may trigger a hormetic response in which their effect on prostate cancer changes with dose, initially hindering growth but then at higher doses promoting growth.

Folate is a good example of how confusing this is. Recall first that researchers often make distinctions between dietary folate and total folate as these chemicals are not the same. "Folate is a naturally occurring water soluble B vitamin that is found as various polyglutamated forms in fruits, vegetables, and liver products. Folic acid is the synthetic, fully oxidized, monoglutamyl form of folate that is more stable and therefore used in dietary supplements and fortification of whole grains and cereals"[3]

Half a dozen years back the National Cancer Institute's website suggested that folate is a possible protective factor that may decrease the risk of prostate cancer, while folic acid, the synthetic version of folate used to fortify foods and contained in supplements, is a nutrient that may increase the risk of prostate cancer. Their thinking goes back to the findings of the Aspirin/ Folate Polyp Prevention Study[4]:

> … a placebo-controlled randomized trial of aspirin and folic acid supplementation for the chemoprevention of colorectal adenomas… In a secondary analysis, the authors addressed the effect of folic acid supplementation on the risk of prostate cancer. …. Supplementation with 1 mg of folic acid was associated with an increased risk of prostate cancer. However, dietary and plasma levels among non-multivitamin users were inversely associated with risk.[3,]

If we look at recent research on folate and prostate cancer, we find three meta-analysis that will only serve to confuse us. Two of them reported that dietary folate was not associated with risk of prostate cancer. Yet in 2013, Collin reported that folate levels were positively associated with an increased risk of prostate cancer. (five studies, OR = 1.18; 95% CI 1.00, 1.40; P = 0.02).[6] Tio and colleagues reported in 2014 on the results of their own meta-analysis that looked at folate blood levels and also dietary folate intake. They found no statistically significant association between dietary folate (15,336 cases, 11 studies) [OR of 0.97 (95% CI 0.89-1.06)]. Nor did they find an association with total folate (5 studies, 7,114 cases) [OR of 0.99 (95% CI 0.82-1.19)]. However, they did find a significant association when they examined blood folate measurements (7 studies, 6,122 cases) [OR of 1.43 (95% CI 1.06-1.93)]. One might sum this up as that it didn't matter how much folate one ate as food or swallowed as pills, but only the folate

that stayed in the blood was what made the difference.[7]

A third meta-analysis, published in 2014 by Wang et al, also found no association between dietary intake and risk, but it did report that serum folate was positively associated with risk of prostate cancer (RR = 1.21; 95% CI = 1.05-1.39; P = 0.008).[8]

A 2014 California randomized controlled trial (RCT) was more relevant as it reported on folate's impact on disease recurrence risk in men already treated for prostate cancer. In general, there was no impact from dietary or total folate, well except in the men who had been treated with surgery, and who had low folate intake; they had a 2.6-fold increase in the risk of recurrence (HR 2.56, 95% CI 1.23-5.29, p = 0.01). This association was not seen in men treated with radiation therapy.[9]

How do we translate that into patient instructions? If you've had prostate surgery be careful, but if you were treated by radiation, go ahead, eat all the folate you want?

Not all the research suggests folate supplements are bad; Roswell's 2013 study on micronutrients and prostate cancer risk, done in a prospective cohort of Danish men, reported that folate supplements were associated with a significant decrease in risk, [HR 0.88 (95 % CI 0.79-0.98) per 100 µg increase/day].[10] We should remember the obvious, that disease prevention does not inform us about risk of disease recurrence in men already treated or disease progression in men following a "wait and watch" routine.

Of course, some multivitamin manufacturers have switched their folate ingredients from folic acid to more exotic forms and at this point we have little outcome data to inform opinions about what they will do to prostate cancer. Nor do we have adequate data to tell us whether we are looking at a U-shaped hermetic curve.

Someday the research may determine which man might benefit from folate supplements and give us a target blood level to aim for. But what do we do until we have that knowledge? Is the variation in response to folate due to genetics, dosing, or some other factor? That phrase about *primum non nocere*, while not Hippocratic in origin, still resonates with me. I want to avoid anything that might increase risk.

Vitamin D is probably the best example for which conflicting data might be best explained by a hormetic U-shaped curve of dose response. We're all familiar with the studies that look at circulating vitamin D levels and prostate cancer risk. Nelson reported in 2017 that D deficiency (<20 ng/ml) is associated with triple the risk for aggressive prostate cancer in African American men.[11]

Then there are the papers that report higher vitamin D levels are associated with lower risk for prostate cancer, lower disease severity[12-15] and lower cancer specific mortality. We are all familiar with these and other arguments in support of what most would consider a no-brainer idea, that men with prostate cancer should take lots of vitamin D.

The problem is that not all studies have lent weight to this idea. We don't like to talk about the studies that don't support what we believe. If we acknowledge them at all, it is to find fault. When examined by Chandler et al, the expected impact of vitamin D supplements on PSA levels was not found.[16] Nor did Skaaby et al[17] or Holt et al[18] find associations between vitamin D levels and prostate cancer risk. Gupta et al reported no association between vitamin D levels in 125 newly diagnosed stage-4 prostate cancer patients and their survival times.[19] Nor did Sawada's 2017 case control study find vitamin D status associated with fatal prostate cancer.[20]

Some studies have reported a positive association between D status and prostate cancer risk. In 2014 Wong et al reported that in older men, lower vitamin D status was associated with lower risk of prostate cancer.[21] We should note clearly that in a 2014 meta-analysis, Xu et al reported a "… significant positive relationship between high level of 25-hydroxyvitamin D and increased risk of prostate cancer."[22] That is the opposite of what we expected to read. Meyer et al's report is similar, that high vitamin D was associated with greater cancer specific mortality in this same cohort.[23]

In the realm of nutrient supplementation, more is not necessarily better.

The conflicting outcomes with vitamin D may possibly be the result of a hormetic effect creating a U-shaped relationship making it difficult to determine the optimal dose range for vitamin D when it comes to prostate cancer prevention and control.

There's a 2014 paper by Kristal et al that is worth our attention because in their findings, "Both low and high vitamin D concentrations were associated with increased risk of prostate cancer, and more strongly for high-grade disease."[24] These findings were remarkably similar to the earlier 2004 report by Tuohimaa et al that suggested an optimal range for prostate cancer prevention between 40-60 nmol/l (16-24 ng.ml).[25] Of course these numbers are far below those often suggested by most practitioners.

Changing the topic slightly just, for a moment, we should note that a 2016 paper on vitamin D and heart disease reported a similar U-shaped curve in survival times with vitamin D, in which both low and high D levels were associated with an increased risk of death. Vitamin D levels <10 ng/ml or >30 ng/ml tripled risk of mortality during the study interval.[26]

Granted, there are ardent proponents of the idea that more is better when it comes to vitamin D who find counter explanations for these reported U-shaped D response curves,[27] but the striking contrast with what the research is suggesting and what many of us suggest to our patients, gives me pause. Until we have more certain data

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that our interventions don't actually cause harm, shouldn't we be more cautious? Is it good practice to dose every man with vitamin D?

If I decide to treat prostate cancer patients with vitamin D, it is because we have a suboptimal blood level reported on a lab test and my goal is to reach the top of the U-curve, a point that may vary over time as research is published.

I've wandered off topic; let me steer us back to the initial question on multivitamins. It's unclear at this point that men with prostate cancer or at risk for recurrence will benefit from folate supplementation. There are other vitamins contained in multis that also concern me.

Remember how antioxidant micronutrients, in particular vitamin E and vitamin C, were going to be the cure for most everything?[28] Some of you may be too young to recall this era. Well for any of you older folks who haven't been paying attention, randomized trials have done little to support this old notion.

Lippman et al reported in 2009 that in their "large, long-term trial of male physicians, neither vitamin E nor C supplementation reduced the risk of prostate or total cancer."[29] Nor by the way did similar doses of vitamin E decrease risk of heart disease in women.[30]

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The data on vitamin E in particular is no more straightforward than that on folate or vitamin D. Epidemiological studies and animal studies suggested that vitamin E would be protective against prostate cancer, but human studies have failed to confirm this. Several large-scale intervention trials have yielded such disappointing results that the authors of one 2016 study wrote, "Whether vitamin E prevents or promotes cancer is a serious concern."[31] This is clearly not a "might help, won't hurt" situation.

Wang et al reported in 2014 that in analyzing data from the Physicians' Health Study II that taking 400 IU of vitamin E every other day and 500 mg of vitamin C daily had no effect on risk for cancer and specifically for prostate cancer.[32]

Yet in a large-scale trial in which over 29,000 smokers received what we would consider a very low dose of vitamin E (about 75 IU/day), supplementation was associated with lower risk of prostate cancer in general but with some rather complex clarifications.

Impact varied with body mass index (BMI) of the participants. Relative risk dropped 13% in overweight men [0.87 (95% CI, 0.77-0.98)], but appeared to increase risk in obese men [1.25 (95% CI, 1.01-1.55)]. Taking low dose vitamin E was also associated with a lower risk of dying from prostate cancer after the trial was over (RR, 0.84; 95% CI, 0.70-0.99).[33]

But then we have the frightening results from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in which high dose vitamin E significantly increased risk of prostate cancer, and it looked as if vitamin E also increased the risk of high-grade disease. When Klein et al reported their results in 2011, men randomized to take vitamin E had a 17% greater risk of prostate cancer than those taking placebo. For those perhaps too young to remember this trial, it was quite large, with over 35,000 men randomized to take vitamin E, selenium, both or placebo, for an extended period.[34,35]

This is starting to sound like hormesis again. Low doses in the range of 75 IUs per day might provide benefit and slightly higher doses, 200 IU/day, did nothing and the 400 IU/day in the SELECT Trial were associated with trouble. We've been operating on the theory that more is better when it comes to E for a long time.

Now there are valid-seeming arguments that the particular form of vitamin E supplemented may make a difference but given the poor track record to date of predicting effects, I am becoming increasingly hesitant to bet on any particular theory until there is some compelling human evidence.

Let us assume that for many readers this sort of detailed study-by-study review gets tedious to read. (Certainly, writing this is proving to be something of a marathon.) So, let me skip over and simply say there is also good reason to believe that the effect of calcium on prostate cancer also varies with dose. And perhaps selenium.[36]

If this is the case, that many of the nutrients in multivitamins have hormetic action on prostate cancer, how do we know what the right dose should be? Too little could be a problem but so could too much. Could men already be getting adequate doses via their diet of these nutrients?

Let's back up a step further and wonder where we got the idea that treating cancer with nutrient supplementation is a good idea. Cancer in general is a disease of excess nutrition. Caloric restriction lowers cancer risk and obesity increases it. Isn't taking a

multi kind of like an excess in nutrition? Wouldn't it make more sense for cancer cells to go hungry than to force feed them with the nutrients needed to divide and grow? Why is it that we even believe that more nutrients the better?

This probably is left over from a time and a world where most people were both calorie-deprived and nutrient lacking. In that sort of world supplying missing vitamins and minerals could likely have near miraculous effect. Supplementation to those with deficiency historically has cured many diseases. Perhaps that era has passed us by. These days when major foods are fortified and most of our patient populations are amply fed, deficiency is not a common problem as it was in our profession's earlier years.

We could end the article here, but I would be remiss if I neglected to mention the recent study on vitamin supplements published in the *Annals of Internal Medicine* in May 2019, while I was ruminating on this prostate and multivitamin question.[37]

Fan Chen and a group of American researchers from Harvard and Tufts Universities evaluated the association among dietary supplement use, levels of nutrient intake from foods and supplements, and mortality among US adults. They followed a cohort of 30,899 US adults for a median of 6.1 years during which time there were 3613 deaths including 945 CVD deaths and 805 cancer deaths among the group. Adequate intake "… of vitamin A, vitamin K, magnesium, zinc, and copper was associated with reduced all-cause or CVD mortality, *but the associations were restricted to nutrient intake from foods.* Excess intake of calcium was associated with increased risk for cancer death…and the association seemed to be related to calcium intake from supplements…rather than foods."

The bottom line was that "Use of dietary supplements is not associated with mortality benefits among U.S. adults."[37] Taking a multi doesn't change your risk of dying. Well, duh, that didn't come our right. You are not going to live any longer if you take a multi. Taking a multivitamin didn't seem to make a difference. Eating well enough to get minimum RDAs does make a difference.

Admitting this change of thinking doesn't come easy, but at this point I'm not seeing a compelling argument for men with prostate cancer to take multis. I'm still hoping that someone will tell me why I'm wrong.

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Melatonin Prevents Delirium in Hospitalized ICU Patients

by Kelsey Asplin, ND

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We've been fascinated by the wide range of clinical uses that have been reported for the hormone melatonin. Initially we just thought of melatonin as an agent to improve sleep or help one get over jetlag faster. In the 1990s melatonin's anticancer effects were added to the list of possible uses. Over the years the list of applications has grown to include reflux disease (GERD), pancreatitis, anxiety, and others.

A paper published early in 2019 by Baumgartner et al, has added another possible use for melatonin, one that again catches us by surprise. Melatonin use has been demonstrated to lower risk of delirium in patients hospitalized in intensive care (ICU).

Delirium is a common complication among patients in intensive care units, but treatment options are limited and pose additional risks. It appears that melatonin, a simple and nontoxic intervention, may be an effective therapy for this condition.

By definition, patients in ICU are critically ill; and ideally any interventions one might choose to reach for to reduce the danger of developing delirium should have little or no added risk for side effects. Melatonin fits this requirement.

As most patients who develop the condition are critically ill, an ideal intervention would be one with a high rate of risk reduction, additional health-supportive actions, and little-to-no side effects.

Baumgartner's retrospective, observational cohort study included 232 adults (≥18 years of age): 117 patients in a melatonin group and 115 patients in a control group. Patients were admitted to medical or cardiac ICU between 2013-2017, and those given melatonin were compared to those who did not receive it. Exclusion criteria included use of antipsychotic or sleep medications prior to admission, primary neurologic condition or injury, hepatic encephalopathy, end-stage liver disease, active withdrawal from alcohol use, and any other conditions preventing delirium screening.

Development of delirium was determined by two consecutive positive scores on the Confusion Assessment Method for the ICU (CAM-ICU), within a 14-day period after inclusion. Participants in the study were assessed with the CAM-ICU every 12 hours.

The primary outcome measured was whether the patient developed delirium while in the ICU. Doses of melatonin administered were also tracked. A secondary outcome was also tracked, the number of delirium-free days in a 28-day period.

Patients who received melatonin were less likely to develop delirium. The patients taking melatonin had a significantly two-thirds lower rate of delirium compared to the control group (9 [7.7%] vs 28 [24.3%]; *P*=0.001).

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The findings remained consistently significant when assessed in statistical models that controlled for variables that included age, sex, history of hypertension, need for emergent surgery, Acute Physiology and Chronic Health Evaluation II scores, mechanical ventilation, length of stay in ICU, dexmedetomidine use, and benzodiazepine use.

In those who did develop delirium, there was no statistical significance in how long the delirium lasted. Those in the melatonin group experienced 19.9 delirium-free days, compared to 20.9 days in the control group (P=0.72).

Typical starting doses for melatonin were 3-6 mg nightly, and doses were titrated up to 9-10 mg as needed for sleep. In the patients who developed delirium, the average dose was 3 mg, with a range of 1-5 mg.[1]

Currently, there are no US Food and Drug Administration (FDA)-approved pharmacological therapies to treat or prevent ICU delirium. Management often relies on antipsychotic medications, which carry their own risk profile, including further neurological impairment and risk of death in older adults with dementia. Obviously older adults are the ones most likely to get delirium in the first place.

Several other, earlier publications have also suggested melatonin might be protective against delirium.

A paper published in March 2019 by Cuismano and colleagues at the Cleveland Clinic looked at factors that might predict which patients were most likely to experience a reduction in delirium risk from melatonin administration.[2] Martinez and colleagues in Australia announced their intention to run a similar clinical trial to this one back in 2017.[3] Clayton-Chubb also from Australia had also announced the same intention the year prior.[4] It seems that Baumgartner's team beat them to publication. A study done in Iran and published in 2018 failed to prove effectiveness of melatonin against delirium in surgical ICU patients and suggested that the benefit might be more likely seen in those hospitalized for medical reasons.[5] Sarah Joseph's 2018 article provides an excellent review and summary of this topic and provides a rationale for use.[6]

While not tracked in the current study, this simple and nontoxic intervention may impact overall outcome. The authors note that "Intensive care unit (ICU) delirium is an acute brain dysfunction that has been associated with increased mortality, prolonged ICU and hospital lengths of stay, and development of post-ICU cognitive impairment." This implies that further studies using melatonin in this patient population may show even more profound benefits.

Few patients who have endured a night in the hospital will tell you they slept well unless heavily medicated. Melatonin may offer benefit to many hospitalized patients by improving their sleep. This study suggests measurable benefits even in the critically ill.

Melatonin is a natural therapy with many other well-supported uses and generally mild side effects. It's not entirely clear if melatonin's usefulness in ICU delirium is grounded in its effects on circadian rhythm regulation (though this is likely one mechanism of action), or some other unknown mechanism. However, as sleep disparity is a concern and a plausible contributing factor in the development of delirium in critically ill patients, this, along with its proposed antioxidant, cardioprotective,[7] neuroprotective,[8] hepatoprotective,[9] and esophago-protective[10] properties (all potentially important actions in the population of chronically ill patients), makes melatonin a viable and encouraging therapy option.

While the study does not provide evidence regarding optimal dose, the data suggest that nightly doses of 3.5 mg or greater may be of more benefit.

But honestly, we can't think of any vendor that sells 3.5 mg doses of melatonin and so would just suggest using standard 3 mg capsules.

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Cannabidiol's Promising Role in Muscle and Visceral Pain

by Chris D. Meletis, ND, and Kimberly Wilkes

The endocannabinoid system within our bodies regulates many aspects of health, including pain control. This system is comprised of endocannabinoids produced within the body, including anandamide (arachi-donylethanolamide) and 2-arachidonylglycerol (2-AG), which are able to activate receptors in the endocannabinoid system. The presence of this system was an intriguing discovery, as it indicated our bodies produce substances similar to cannabis that are able to switch endocannabinoid receptors on and off.

Two important receptors in this system that are involved in pain management are cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2).[1] Activation of CB_2 receptors suppresses the pain response to thermal and mechanical stimuli,[2,3] thermal and tactile hypersensitivity produced by peripheral inflammation,[3-5] and neuropathic pain.[6] As with endocannabinoids produced in the body, phytocannabinoids such as Δ^9-tetrahydrocannabinol (THC), the psychoactive component of *Cannabis sativa* plant, and cannabidiol (CBD), a non-psychoactive component, are able to activate endocannabinoid receptors.

Endocannabinoids can indirectly work through the same receptors as opioid drugs to control pain. CB_2 receptors indirectly stimulate opioid receptors found in primary afferent pathways.[7] Furthermore, CB_1 expression is weak in the areas of the brain stem that regulate respiration. This suggests that respiratory depression, a potentially fatal adverse effect of opioid drugs, would not occur when using phytocannabinoids as painkillers.[1]

An extensive amount of evidence points to the endocannabinoid system's role in the management of pain caused by a wide spectrum of conditions. This article will focus exclusively on endocannabinoid and phytocannabinoid regulation of two common types of pain: muscle and visceral pain.

Musculoskeletal Pain, Fibromyalgia, and Temporomandibular Disorders

Chronic widespread musculoskeletal pain is a common disorder, occurring in approximately 10% of the population.[8] A subgroup of patients with this type of pain have fibromyalgia, which occurs in 3% to 5% of the population.[8] In women with musculoskeletal pain, levels of the endocannabinoids oleoylethanolamide and stearoylethanolamide were altered compared with healthy controls.[9]

Endocannabinoid alterations are thought to play a role in fibromyalgia and its frequent comorbidities such as migraines and irritable bowel syndrome.[10] A hallmark of fibromyalgia is sore muscles. The pain usually occurs in similar locations in different patients suffering from this disorder. Studies indicate there is an association between fibromyalgia and endocannabinoid deficiency and this deficiency may play a role in the sore muscles of this condition.[10-12] For this reason, cannabinoids are thought to be useful in chronic pain conditions such as myofascial pain syndrome and temporomandibular joint pain (TMJ).[10]

CBD has analgesic and anti-inflammatory effects that may prove beneficial in disorders that involve muscle pain.[13] CBD was first isolated in 1940, but it is only relatively recently that its full potential was realized due to studies showing its antioxidative, anti-inflammatory, and neuroprotective effects.[14] Some of these actions are independent of the CB_1 and CB_2 receptors.[15]

In studies using rodent models of inflammation, CBD reduces the migration and infiltration of inflammatory cells (neutrophils).[16] Cannabinoids are also thought to reduce inflammation by increasing the generation of eicosanoids, signaling molecules involved in regulating inflammation and pain.[17] In addition, CBD lowers production of the inflammatory cytokine TNFα and reduces fatty acid amidohydrolase (FAAH) activity, an enzyme that degrades the anti-inflammatory endocannabinoid anandamide.[17] CBD's reduction in FAAH causes a raise in anandamide production.[17] In animal and cell culture studies, CBD has demonstrated an anti-inflammatory effect that is several hundred times greater than aspirin.[13] CBD's analgesic properties are due to mechanisms that include acting as a lipoxygenase inhibitor, increasing the release of prostaglandin (PGE2) from synovial cells, and blocking production of leukotriene B4 in human polymorphonuclear cells.[13]

Other non-psychoactive phytocannabinoids such as cannabinol (CBN) and cannabigerol (CBG) also produce an analgesic effect, leading one group of researchers to conclude, "Therefore, there is potential for developing analgesic drugs based on these cannabinoids which do not have the psychoactive properties of THC."[13]

There are a paucity of human studies using cannabidiol in patients with fibromyalgia. Preclinical studies, however, suggest a promising role for this agent. For example, in a rodent model of myofascial pain, intramuscular injection of CBD alone, injection with another non-psychoactive phytocannabinoid (CBN), or the combination of the two reduced muscle pain.[18] The two phytocannabinoids combined appeared to have a synergistic effect, pointing to what is commonly called the entourage effect, the synergistic actions between the phytocannabinoids found in *Cannabis*. The researchers concluded, "These results suggest that peripheral application of these non-psychoactive cannabinoids may provide analgesic relief for chronic muscle pain disorders such as temporomandibular disorders and fibromyalgia without central side effects."

Multiple Sclerosis

Evidence indicates endocannabinoid system activation is beneficial in motor disorders associated with multiple sclerosis, including muscle spasticity. A large number of clinical studies show that a 1:1 combination of THC and CBD in an oral spray reduces muscle spasticity in multiple sclerosis patients. In one study of 50 multiple sclerosis patients, THC/CBD proved effective in 80% of participants at a median dose of 5 (2-10) inhalations/day.[19] Some of the patients experienced adverse effects such as dizziness (11 patients), sleepiness (6), muscle weakness (7), oral discomfort (2), diarrhea (3), dry mouth (2), blurred vision (2), agitation (1), nausea (1), and paranoid ideation (1).

In a double-blind, randomized, placebo-controlled study, a cannabis-based medicinal extract containing equal amounts of THC and CBD at a dose of 2.5-120 mg of each daily was given in divided doses to 160 patients with multiple sclerosis.[20] The participants suffered from at least one of the following symptoms: spasticity, spasms, bladder problems, tremor, or pain. The primary symptom score declined from mean 74.36 to 48.89 following THC/CBD and from 74.31 to 54.79 following placebo. Muscle spasticity scores significantly declined in the patients using THC/CBD compared with the placebo.

Cannabidiol (CBD) has strong anti-inflammatory and calming effects.

Because many patients are uncomfortable with the "high" feeling produced by THC, it is surprising that there are a lack of studies using CBD alone. Dr. Meletis has observed in his own clinical practice that CBD has an analgesic effect on muscle pain and that it is beneficial in patients.

Visceral Pain and Inflammatory Bowel Disease

Visceral pain is pain that affects the area around the stomach, rectum, bladder, or uterus. Abdominal pain that occurs during irritable bowel syndrome (IBS) is a type of visceral pain. Menstrual cramps and pelvic pain caused by bladder infections are also types of visceral pain. The endocannabinoid system modulates visceral hyperalgesia (increased sensitivity to pain) caused by chronic stress.[21,22] Alterations in this system may play a part in the association between chronic stress and irritable bowel disease(IBD)/IBS.[21,22] In rodent studies, early-life stress changes the endocannabinoid system, which leads to an increased vulnerability to IBS.[23]

As a key player in the regulation of visceral pain, the endocannabinoid system may play a role in the means by which psychological stress impairs GI function.[23] Chronic stress lowers concentrations of the endocannabinoid anandamide. At the same time, stress increases 2-AG in the brain and downregulates CB_1 receptors in sensory ganglia, which control visceral pain.[24] Chronic psychological stress changes CB_1 receptor activity by means of epigenetic pathways. This may be the reason why stress often triggers abdominal pain.[25] Epigenetics refers to the alteration of gene expression through pathways other than the genetic code. Epigenetic changes occur in our genes due to lifestyle or environmental factors. Through these epigenetic actions, chronic stress impacts the CB_1 gene promoter, resulting in reduced concentrations of CB_1 in sensory neurons in the colon and other pelvic organs.[26] In support of this concept, a substance that activated the CB_1 receptor reduced abdominal pain in mouse models that mimicked symptoms of functional GI disorders, such as stress-induced diarrhea.[27] The beneficial effects were thought to be due to activation of serotonin receptors.

CBD exerts known anti-stress actions that may be beneficial in inhibiting stress-induced visceral pain. CBD positively impacts the hypothalamus-pituitary-adrenal axis in mice exposed to psychological stress.[28] These stress-shielding effects of CBD were due to activation of serotonin receptors.

A number of human studies also support CBD's calming effects. In a double-blind study, scientists investigated different doses of CBD and a placebo in 57 healthy male subjects undergoing a simulated public speaking test.[29] Before giving a speech, the men used oral CBD at doses of 150 mg, 300 mg, or 600 mg or a placebo. There was a pronounced reduction in anxiety during the speech in subjects taking 300 mg of CBD. The other CBD doses were ineffective, indicating there is a specific range in which CBD is effective. CBD's ability to have a calming effect indicates it may have a promising role to play in reducing visceral pain caused by stress.

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Conclusion

CBD exerts anti-inflammatory effects that are beneficial in patients with muscle pain, such as that caused by fibromyalgia or multiple sclerosis. This phytocannabinoid also has a calming effect that can play a role in inhibiting stress-induced visceral pain. Although studies investigating CBD and muscle and visceral pain did not report on whether CBD increased energy levels, it stands to reason that reduction in pain would also reduce fatigue. Alteration of the endocannabinoid system through the use of CBD holds great promise in supporting the health of patients with sore muscles and visceral pain. As optimal CBD absorption can be clinically challenging particularly in the cases of pain, enhancing absorption with tested delivery mechanisms such as VESIsorb® or other researched approaches can help achieve clinical therapeutic levels.

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Astaxanthin: A Lesser Known Carotenoid with Diverse Anti-Aging **Benefits**

by Carrie Decker, ND

Many healthcare practitioners can rattle off a handful of carotenoids along with a summary of their main benefits. A family of fat-soluble nutrients that range in color from dark yellow to red, carotenoids are most often derived from plants and algae, although because they bioaccumulate in the food chain we also may find substantial amounts in animal fat. Beta-carotene, lycopene, lutein, and zeaxanthin often are on top of the list when we think of those we use in clinical practice. However, there are far more carotenoids than this, as this family has more than 1,100 members.[1] Astaxanthin tends to be one of the lesser-known carotenoids, however it is backed by research that covers the body from head to toe, with documented benefits for the brain,[2] eyes,[3] heart,[4] joints,[5] skin,[6] immune and reproductive systems,[7,8] and more.

Natural astaxanthin is primarily derived from the microalgae *Haematococcus pluvialis*; however, it is a carotenoid that bioaccumulates with modest amounts being obtained in the diet from salmon, with wild-caught sockeye salmon providing 1 mg/ounce of flesh.[9] Interestingly, farmed salmon is fed a diet rich in synthetic or yeast-derived astaxanthin.[10,11] As the synthetic form has substantially lower antioxidant activity than naturally-occurring astaxanthin, this is one reason to consider the more natural choice.[12] Much like many other fat-soluble nutrients, astaxanthin has far greater absorption and retention (the area under the curve being more than double) if taken immediately after meals rather than away from food.[13]

The majority of carotenoids have vitamin A activity as they convert to retinol; however, the amount greatly varies. One microgram (mcg) of retinol has a retinol activity equivalent (RAE) of 1 mcg; however to obtain this same amount of retinol in the human body, it takes roughly 6 mcg of beta-carotene, or 12 mcg of alpha-carotene.[14] If bioconversion and absorption is poor, it may take even more than this.[15] Despite being a carotenoid, astaxanthin does not have any pro-vitamin A activity in mammals,[16] so there is not a risk of vitamin A toxicity with the higher milligram doses that often are used.

Clinical studies suggest this microalgae-derived carotenoid supports the health of the skin, eyes, brain, and male fertility.

Although many of the antiaging benefits derived from astaxanthin benefit both men and women, in the setting of reproductive health, we find a preponderance of evidence supporting its use to enhance male fertility, with only a few preclinical studies assessing female reproductive benefits. A summary of the antiaging benefits with a closer look at those pertaining to male fertility are discussed herein.

An Overview of Astaxanthin's Antiaging Benefits

Because astaxanthin easily passes through the blood-brain and blood-retinal barrier,[17,18] we shouldn't find great surprise in the fact that a substantial amount of research has focused on its central nervous system and ocular benefits.

Research suggests astaxanthin accumulates in the brain,[19] where it helps protect against numerous insults including aluminum,[20] a central nervous system toxin linked with the development of Alzheimer's disease,[21] tobacco smoke,[22] chemotherapy drugs,[23,24] as well as other toxic substances.[25,26] It induces proliferation of neural progenitor cells and promotes neurogenesis and neuroplasticity,[27,28] each of which decline with increasing age. It increases levels of brain-derived neurotrophic factor (BDNF),[29] a growth factor that is important for nerve growth in the brain and periphery.

Multiple randomized, double-blind, placebo-controlled trials (RDBPCTs) have assessed the impact of astaxanthin on cognitive function. At a dosage of 12 mg/day, CogHealth battery scores (a standardized test that assesses multiple domains of cognitive function) and maze learning rate improved in individuals 45 to 64 years of age with complaints of age-related forgetfulness.[30] In another study of individuals in this same age range (not having cognitive complaints), at a dose of 8 mg/day, word recall was

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significantly improved in individuals under the age of 55 in the astaxanthin group compared to placebo.[31] An additional RDBPCT found that the combination of 12 mg of astaxanthin (with 20 mg of tocotrienols) significantly reduced perceived mental and physical fatigue, improving number of errors, clarity of thinking, concentration, motivation, and mood compared to placebo (20 mg of tocotrienols) in healthy subjects undergoing mental and physical challenge tests.[32]

Astaxanthin also has an affinity for the eye, much like its sister carotenoids lutein and zeaxanthin, and it also accumulates here with ongoing supplementation.[33] Many of the age-related ocular health conditions are a result of ultraviolet (UV) exposure,[34,35] which astaxanthin has been shown to help protect against.[36] Animal studies have shown astaxanthin helps protect against photokeratitis,[37] cataract formation,[38] and retinal damage associated with increased intraocular pressure.[39] In humans, RDBPCTs have shown that astaxanthin at a dosage of 6 mg/day significantly reduces symptoms of eye fatigue, eye irritation, and complaints of blurred vision and improves visual accommodation and retinal capillary blood flow, another indicator of eye health.[40,41,42] At a dosage of 12 mg/day, far visual acuity and choroidal blood flow was also observed to significantly improve.[43,44]

Another tissue astaxanthin appears to accumulate in is the skin,[33] which also is greatly challenged by UV exposure. Cellular, animal, and human studies have shown astaxanthin helps reduce inflammation and/or cellular damage caused by UV light exposure.[45,46,47] The observed UV-protective effects along with astaxanthin's ability to increase immunosurveillance suggest astaxanthin may offer protection from malignancy as well.[6] In humans, a RDBPCT showed that supplementation of astaxanthin at a dosage of 4 mg/day for nine weeks increased the UV minimal erythema dose and decreased the amount of skin moisture loss in irradiated areas compared to placebo.[47] In the astaxanthin group, there also were subjective improvements of rough skin and texture in non-irradiated areas compared to placebo.

Astaxanthin also has been demonstrated to increase collagen production and the amount of growth factors in the skin,[48] which translates to enhanced wound healing (as seen in animals[49]) and improvement of age-related wrinkles and sagging. In numerous human studies, supplementation of astaxanthin at a dose of between 2 to 12 mg/day (most often 6 mg/day) reduced various wrinkle evaluation parameters, increasing skin elasticity and moisture content.[50] In one of the larger RDBPCTs, the impact of dosage was also investigated, finding that 12 mg was more effective than 6 mg in reducing inflammation; however, both doses significantly reduced wrinkle parameters and improved moisture content.[50] In an open-label, pilot trial, supplementation of astaxanthin at 6 mg/d also was also shown to improve age spot size and skin texture.[51]

Worthy of mention for athletes of all ages, data suggests astaxanthin may be a useful tool to support exercise performance and recovery,[52] decrease joint and muscle soreness after workouts,[53] and reduce normal age-related muscle loss.[54]

Male Reproductive Health Research

Several studies have investigated the impact of astaxanthin on male reproductive health. With age, oxidative stress becomes an increasing factor that affects spermatozoa quality and function.[55] With excessive oxidative stress, the plasma membrane of the sperm becomes damaged and fertilization cannot occur.[56] As a fat-soluble antioxidant, astaxanthin has an affinity for cellular membranes such as this,[57] leading to its consideration in several studies concerning male fertility.[58]

Multiple in vitro studies have shown that sperm capacitation is improved by incubation with astaxanthin.[59,60] Sperm capacitation refers to multiple physiological changes (including alteration of the sperm plasma membrane polarization and permeability) that are necessary for sperm to penetrate and fertilize an egg,[61] and often is a factor in idiopathic male infertility. Although a certain amount of oxidative stress is necessary for this to occur, *excessive* oxidative stress adversely affects this process as it causes lipid peroxidation, disrupting the membrane.[62] In addition to this aspect of sperm function, astaxanthin has been shown in animals to help protect against declines in fertility related to methotrexate-induced damage,[63] nicotine exposure,[64] and diabetes.[65] In the realm of animal breeding, studies have shown that astaxanthin can help improve sperm quality and function when it is contained within the liquid medium used for sperm storage.[66,67]

In one RDBPCT, 30 males with infertility for more than 12 months (having female partners with no demonstratable cause of infertility), receiving standard treatment per the guidelines of the World Health Organization, were given astaxanthin at a dosage of 16 mg/day or placebo for three months.[68] Of the biochemical and semen parameters evaluated, in the astaxanthin group, significant improvements were only seen in the level of reactive oxygen species (decreased) and sperm linear velocity (increased), while there were no significant changes in sperm motility and morphology or hormone levels. However, the per cycle and total

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pregnancy rates were significantly higher in those receiving astaxanthin, being 3.6% and 10.5% in the placebo group (total of two pregnancies, naturally conceived) and 23.1% and 54.5% in the astaxanthin group (total of six pregnancies, five naturally conceived and one with intrauterine insemination), respectively.

It is noteworthy that the natural pregnancy rate for males receiving the standard treatment guidelines at this clinic is between 3 to 4% each month, as was observed in the placebo group. As the effects of astaxanthin treatment were observed fairly rapidly, it is most likely attributable to improved functional capacity rather than changes in conventional sperm characteristics (motility, morphology, etc.).

Conclusion

Clinical studies clearly support the use of astaxanthin as an antiaging intervention. Additional research supports the use of astaxanthin as an agent to enhance detoxification,[69] cellular health and mitochondrial function,[70] immune system function,[71] and for general antioxidant protection[72] – each of which are important for individuals of all ages, but particularly important with aging as the body's inherent capacity to perform these functions declines in the later years of life.

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Pomegranates, Cholesterol, Hormones, and Cancer

by Dr. D. Lindsey Berkson

Pomegranates are as close to a miracle food as Mother Nature gets. Pomegranates protect your heart, safeguard your estrogens, "sensitize" insulin receptors better than many diabetic drugs without nasty side effects, slow down aging, and fight cancer. A pomegranate a day keeps the Mack truck of disease away!

My grandmother often said, in her very thick Russian accent, "If it sounds too good to be true, it usually is too good to be true." This does not seem to be the case with these juicy purple fruits and kernels (arils).

Pomegranates fight against lots of bad stuff: inflammation, oxidative stress, bad cholesterol, heart disease, kidney disease, cognitive disease, diabetes, obesity, and cancer.

Pomegranates support a lot of good actions: nitric oxide availability and levels, kidney health, blood vessel health, heart health, bone health, immune response, mitochondrial activity, and brain protection.

Pomegranates and Heart Health

I went for a thorough cardiac workup in October 2018, not because anything was wrong, but because my odometer was moving past the 200,000-mile marker and needed an under-the-hood checkup. My functional cardiologist, Mark Houston, MD, ran several days' worth of testing. Included was a thorough look-see at my genes that regulate every aspect of the human cardiovascular system.

Genetic glitches or variants of these genes, referred to as polymorphisms, are a contributor to heart disease. You can take a look at your heart-related genes and see if any of them are glitchy or twitchy, putting you at increased risk of something going wrong (in heart health, this usually means heart attack or stroke).

My genomic panel showed excessive levels of faulty ApoC-III genes.[1] This gene is a key regulator of triglycerides and sugar metabolism.[2] Elevated levels or impaired genes are associated with lipid issues and glucose metabolism issues no matter how you eat. And, by the way, for those with these glitches eating keto can be very troublesome, rather than healthy. ApoC-III mutations are associated with increased risk of heart disease and Type 2 diabetes.[3]

This gene also helps your good cholesterol do good things, such as pick up your peripheral cholesterol and take it, in "physiologic garbage trucks" so to speak, back to the liver for healthy processing.

I had good levels of my good cholesterol. But behind the scenes, because of this genetic glitch, my good cholesterol was actually bad. Thus, I was at risk for nasty stuff. All this created a terrain in which the ketogenic diet I'd been adhering to for the last year was actually working "against" me rather than "for" me.

Dr. Mark said, "You love food as medicine, right? So, I'm prescribing pomegranates." Dr. Mark said pomegranates are medical food that turn this bad gene "off" and boost the "good" functionality of the good cholesterol. Why? Pomegranates are a marvel food. But this benefit only happens if you consume them in an adequate dose on a regular basis, such as one-fourth to one-half cup most days of the week.

How Pomegranate is A Heart Helper

- Makes ApoC-III glitches work better, which improves triglycerides, lipids, cholesterol, and even blood glucose levels.
- Lowers bad cholesterol. High levels of circulating low-density lipoprotein (LDL) are the primary "initiating" events in the development of atherosclerosis (plaque in arteries, which is one hallmark of heart disease). Punicalagin, one of the main plant compounds in pomegranate, binds with a protein that surrounds LDL[4] and then helps move it out of the bloodstream. Both pomegranate juice and punicalagin remove LDL out of the bloodstream and then stimulate LDL to move into white blood cells, called macrophages, which "lowers" circulating bad cholesterol levels even more.[5]
- Lowers oxidized cholesterol. Fats that are oxidized are especially nasty acting and can damage the lining of blood vessels (endothelium), which leads to atherosclerosis (heart disease). Pomegranate juice is rich in antioxidants, which prevent LDL cholesterol from oxidizing and thus protects your precious endothelium and heart.[6]
- Makes cholesterol less dangerous and less sticky. Drinking or eating pomegranates fights heart disease. A scientific way of putting it is that pomegranates have "potent anti-atherogenic" effects. In human

studies, drinking pomegranate juice decreased bad cholesterol and made it less dangerous. How? Pomegranate compounds make bad cholesterol less likely to "stick together" in heart-dangerous, potentially clot-forming ways.[6]

- Boosts enzymes that keep blood fats healthier. Pomegranates up-regulate an enzyme called serum paraoxonase. This enzyme protects good cholesterol (HDL) from being oxidized (protects against lipid peroxidation, which is heart dangerous). This enzyme stops blood fats from releasing dangerous pro-oxidative compounds.[6]
- Reduces size of plaque (atherosclerotic lesions). In mice with heart disease (plaque in their arteries) given pomegranate juice, the size of their atherosclerotic lesions reduced by 44% compared with control mice given water instead.[6]
- Lowers blood pressure. A small pilot study out of Israel[7] (10 patients) found drinking one glass a day of pomegranate juice for one year (consistently) increased antioxidant blood activity by 130%, reversed plaque buildup in carotid arteries by 29%, increased the protective enzyme mentioned above by 89%, lowered blood pressure by 12%, and reduced cholesterol oxidation. They followed these participants for another two years, but the benefits stayed at the level achieved at the end of the first year.
- Blood clotting. A number of studies showed that pomegranates make platelets less sticky and less likely to clot, reducing stroke events in high-risk patients.[6,8,9]
- Increases nitric oxide. Several different studies have found that pomegranates boost nitric oxide protection, which keeps the lining of blood vessels (endothelium) more relaxed and healthy and less vulnerable to damage (initiating heart disease)[9] and reduces dangerous inflammation.[9] Pomegranates also improve nitric oxide "availability" by the body.[10]
- Treats angina. Five days of 7.5 ounces of pomegranate juice was given to ischemic heart patients in the hospital (100 patients randomized to experimental or control groups). Pomegranate juice caused significant reductions in the intensity, occurrence, and duration of angina pectoris in patients with unstable angina. Consistently, the test patients had significantly lower levels of serum troponin and malondialdehyde. The results of this study suggest "protective" effects of pomegranate juice against myocardial ischemia and reperfusion injury.[11]

Daily consumption of pomegranate supports health and protects against major diseases.

Researchers suggest that kidney patients (both with kidney disease not on dialysis as well as those on dialysis), all of whom are prone to heart disease complications, can minimize cardiac damage by regularly consuming pomegranates.[12] Giving pomegranates while on dialysis reduces inflammatory cardiac markers[13] and is suggested by a number of scientists at the conclusion of their research.

I was so excited to see the "benefits" of a regular menu of pomegranates for the heart, I sleuthed the literature to see what else pomegranates might provide for humans.

Diving into the pomegranate peer-review literature opened up a treasure chest.

It turns out that all parts of pomegranates contain healthy plant compounds. Healthy substances are found inside the reddish kernel (referred to as a pomegranate "aril") and inside the whitish seed core in the middle of the kernel where the distinct oil and fiber lives. Pomegranate juice contains all of these components, though it contains more available sugars then chewing the arils whole.

The pomegranate aril with all these plant compounds is one of the most potent antioxidants known to modern science.

The Many Ways Pomegranates Heal Us

Pomegranates contain a one-of-a-kind omega fatty acid. Arils contain seeds and the seeds contain oils. Most of the oil (80%) is made up of a unique omega-5 fatty acid. Omega-5 is the only known botanical form of conjugated linolenic acid (CLnA), also known as punicic acid. The term punicic acid comes from the fruit's official name *Punica granatum* L.

It's rather extraordinary that no other plant in the world contains omega-5 fatty acid. This oil is a gift to mankind from Mother Nature to help us stay well or fight off disease.

You can chew pomegranate arils mindfully to get the oil out of the seed (if your digestive enzymes are working optimally). Your stomach acid does not inactivate the healthy fatty acids in the seed oil.[14] When making pomegranate juice, the whole aril is juiced so the seed oils are present in the juice.

Punicic acid is rather magical, having anti-cancer, anti-diabetes, anti-obesity, antioxidant, and anti-inflammatory properties.[15] Pomegranates protect mitochondria (energy factories inside cells) from oxidative stress and other stressors and even from intense exercise adverse consequences.[16,17] Mitochondria make energy inside cells. Thus, pomegranates boost energy. Pomegranates protect the liver against oxidative damage.[18]

Pomegranates are type-2 diabetics best friend. Why? Pomegranates care-take the insulin receptor just like many diabetic drugs do, but without nasty side effects. Punicic acid (PA), the main ingredient of pomegranate seed oil, is a "peroxisome proliferator-activated receptor gamma" agonist. This means it signals insulin receptors. Yet, unlike synthetic insulin signalers, such as

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the diabetic family of drugs called thiazolidinediones, pomegranate oil has no nasty side effects.

Pomegranate signals "both" insulin receptors. Pomegranate is a dual activator of peroxisome proliferator-activated receptor (PPAR)-alpha and -gamma. Signaling these receptors improves hyperglycemia, hyperlipidemia (in humans), and reduces fatty and fibrotic heart tissue in diabetic animals.[19]

PA exerts anti-diabetic effects via various mechanisms, such as reducing inflammatory molecules (cytokines), helping achieve and maintain healthy blood glucose levels, and antioxidant properties. Pomegranate compounds can reboot damaged pancreatic cells (Islets of Langerhans), at least in rodents.[20] Healthy beta cells mean healthier insulin/glucose balance. Pomegranates are so helpful on so many levels where diabetes can cause issues, researchers suggest that pomegranate should be considered in the management of type 2 diabetes.[21] And pomegranates fight insulin resistance.[22]

Pomegranate protects breasts.[23] Pomegranates' omega-5 fatty acids act as a "selective estrogen receptor modulator" or (SERM). Punicic acid down-regulates (shuts up) estrogen receptor signals. Pomegranate tamps down the signals from estradiol. Thus, pomegranate is a "Food SERM"[24] acting like a gentle botanical tamoxifen.

Pomegranate contains plant estrogens, which have estrogenic activities. Because of this some researchers have suggested that pomegranate is clinically helpful for menopausal women to improve depressive states and bone loss.[25] I doubt this since pomegranate's estrogenic activity is protective against estrogen growth signals and tamps down estrogenic signals, rather than increasing them. But it could be that pomegranates help these issues from other mechanisms, such as reducing inflammation and boosting mitochondria.

Some clinicians say that pomegranates are like an "adaptogenic food estrogen," increasing estrogen when more is needed and decreasing estrogen when less is needed. I have not seen this in the literature, but it's something to watch out for clinically and in peer review data.

You might wonder: if pomegranates contain estrogens, is this good or bad for cancer patients? Laboratory studies suggest pomegranate plant compounds don't raise estrogen levels in the blood and may even cause a slight decrease. In one study pomegranate juice consumption was tested for how it affected blood levels of estradiol, estrone, testosterone, androstenedione, and sex hormone binding globulin (SHBG).

Sixty-four healthy postmenopausal women[26] were randomly assigned to drink 8 ounces of either 100% commercial pomegranate juice (interventional group) or apple juice (control group) for three weeks. Women on the pomegranate juice had no change in hormones or their hormone binding protein. In a subgroup of 38 normal weight women, women drinking the pomegranate juice compared to a control group had a significant *decline* in estrone (the pro-carcinogenic estrogen) and testosterone levels.

Pomegranates are a breast and prostate cancer survivor's best friend. Pomegranate polyphenols (plant compounds) are inhibitory of metastatic processes in breast cancer and prostate cancer cells, suggesting they may prevent cancer progression in general.[27]

Pomegranate is a powerful tumor fighter[28] as shown in many studies. Pomegranate fruit, as well as its juice, extract, and oil, exert anti-inflammatory, anti-proliferative, and anti-tumorigenic properties by modulating multiple signaling pathways. Some scientists suggest pomegranates as promising chemo-preventive/chemotherapeutic agents in *both* the prevention and treatment of skin, breast, prostate, lung, and colon cancers.[28]

Surgery, radiation and even chemo mainly address "daughter" cancer cells. Yet it's "cancer stem cells" that cause cancer to recur. Cancer stem cells (CSCs) help make cancer cells self-renew, initiate tumors, and resist therapy. You want tools to fight cancer stem cells if you've had cancer and you want to "make remission your mission." Pomegranate extract has been found to do this.

Pomegranate compounds inhibits CSCs' ability to self-renew. Pomegranate compounds make cancer stem cells less active and more of what is called differentiated. Pomegranate also reduces cell migration, a major feature of traveling metastatic cancer. The ability of the magical stuff inside pomegranates to suppress CSCs can be used to both prevent and aid in the prevention of recurrence of cancers, such as breast cancer, according to top cancer centers of New York State.[29]

So, yes, pomegranate contain some plant estrogens; but like soy compounds, they help keep our estrogens healthier and help fight off cancer where it starts.

Pomegranates help control "growth-out-of-control" from estrogen signals (anti-proliferative and pro-apoptotic effects – good for protecting against cancer in the first place or with recurrence). When mice are exposed to a cancer-causing drug, DMBA, many of them get mammary tumors, but not if they are "pretreated" with pomegranate emulsion.[30] This suggests that taking pomegranates daily would protect from various future toxic exposures.

Pomegranate seed oil blocks proliferation (90% inhibition) of ER+ laboratory breast cancer cells (called MCF-7cells, first harvested from a nun and then cultured continually in experimental cancer labs all over the world), and cause 54% of cancer cell death in ER- breast cancer cells (MDA-MB-435).[31] This is why pomegranate seed oil is good to massage into breasts prophylactically or adjunctively. Run this by your own practitioner that knows your personal history. The use of juice, peel, and oil has also been shown to possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion and angiogenesis (getting food to the tumor so it can keep growing).[32]

Natural pomegranate peel extract has been found to inhibit

breast cancer progression.[33] The pomegranate peel acts by modulating the microenvironment of tumors. For you geeks, this refers to the matrix glycoproteins including MMP9 and fibronectin. These scientists put nasty aggressive triple negative breast cancer cells in with pomegranate peel extract, and these cancer cells died. These are some of the toughest breast cancer cells there are. The authors say that pomegranate peel extract helps stop metastases in these nasty breast cancer cells. Metastases, cells traveling from the primary tumor throughout the body, is how cancer kills.[33,34] But eating the bitter pomegranate peel is not like consuming the sweet arils, so one would have to do this in a concentrate in a capsule.

Blue, purple, reddish plant pigments contain plant anthocyanins. Anthocyanins are pigments that give plants these purple/blue/black colors. These pigments fight cancer cells, especially stem cancer cells, and cause them to "die." These pigments are found in high amounts in the skin and lesser amounts in the arils, or berries, of pomegranates. But they are cancer fighters.[35,36] I think if I were presently fighting breast cancer, I would be juicing the whole fruit pomegranates when in season. But I have never tried juiced pomegranate peel, and it might just be too bitter!

Pomegranates have anti-inflammatory effects.[32] Remember, most diseases are caused by excessive inflammation out of control at specific cellular levels.

Pomegranates have neuroprotective effects. They protect your brain. They are so brain protective that when given to rodents exposed to deadly prions, they postpone the brain damage.[37]

Kidney Effects

In both Chinese and Western medicine, the kidneys "drive" the health of the cardiovascular system. Often similar molecules demonstrate stress of both systems. Since the kidney and heart are so intertwined, it is not surprising that pomegranates, which are very heart protective, are also very kidney friendly.

Kidney disease patients are at higher risk of heart disease than the typical population. Pomegranates protect these patients in two ways:

- Pomegranates protect the kidney itself, and
- Pomegranates minimize downstream adverse cardiac consequences of kidney issues.

When animals are "pretreated" with nasty compounds that typically damage the kidneys, pomegranate protects the animals from the typical extent of renal (kidney) damage. Pretreatment with pomegranate blocks numerous toxic chemicals that would normally damage the kidney. Pretreatment with pomegranate compounds counteracts kidney inflammation, oxidative/ ➤

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nitrative stress, and apoptosis (kidney cell death). This has been shown in studies exposing mice to multiple kidney stressors, such as injections of nephrotoxic LPS (lipopolysaccharide)[38] and lead acetate.[39]

Adult mice given a shot of a substance that usually induces diabetes and diabetic tissue damage were not damaged in this manner if pretreatment was done with pomegranate compounds.[40]

Pomegranate pretreatment protects kidneys against chloride renal damage in rats.[41] Numerous studies show protection against kidney damage and, in fact, renal stabilization, when cancer drugs (chemotherapeutic drugs) are given after a prophylactic pretreatment of pomegranate juice.[42]

One study found that giving pomegranate along with the cancer drug cisplatin not only protected the kidney but also helped fight the cancer![43] The scientists recommended pomegranate supplements should be taken to accomplish all of the above, and more.

In fighting cancer, pomegranates are a food adjunctive tool to consider and run by your practitioners.

Dialysis patients have improved kidney and heart health when drinking pomegranate juice.[13]

Brain Effects

Decrease brain inflammation and boost brain protection[37] and plasticity. Pre-supplementing 4% pomegranate extract into standard chow and given to rats showed protection of brain neurons, decrease in neuroinflammation, and improvement in synaptic plasticity.

These neuroprotective effects were associated with less adverse brain changes in mice bred to have Alzheimer-like brain changes! These scientists suggest that long-term supplementation with pomegranates can slow down the progress of this cognitive disease.[44]

Where to Get Pomegranate Arils?

Most everywhere. Wal-Mart, Costco, Whole Foods, Trader Joes, and the list goes on. Go to the section that contains fruit in containers. You can use the juice if you have no issues with insulin resistance or blood sugar maintenance. Purchase as many containers of arils as you can and, like myself, fill your freezer and consume one-fourth to one-half cup/day.

As pomegranates go out of season, sometimes they have been frozen. Then they taste a bit alcoholic or fermented, but they still give huge benefits no matter the taste.

Contraindications: There is potential cross-reactivity with peaches. If you are allergic to peaches, you "may" have reactivity to pomegranates.[21] Tread lightly or don't eat daily.

May the pomegranate force be with you!

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Dr. Berkson wrote the first gut, mind, nutrition book published by Wiley (*Healthy Digestion the Natural Way*) and one of the first books on hormone-altering-chemicals (*Hormone Deception*. Dr. Berkson's newest book, *Sexy Brain,* presents the newest health issue (environmental castration) and how to protect our intimacy and brain.

Dr. Berkson consults around the world with patients and their docs. She has a very popular podcast, Dr. Berkson's Best Health Radio, along with Berkson Blog at DrLindseyBerkson.com.

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Microbiome-Disrupting Drugs

by Ross Pelton, RPh, PhD

During the past two decades, there has been an explosion of research into the human microbiome. From 2006 to 2010, there were 304 papers indexed in PubMed with the word "microbiome" in the title or abstract. However, from 2011 to 2017, the number of PubMed-indexed studies with "microbiome" in the title or abstract increased to 11,128.[1]

The massive increase in microbiome research is due to the emerging understanding that intestinal bacteria (i.e. our microbiome) play a critical role in the regulation of our health, behavior, and quality of life. This is ushering in a revolution in health and medicine as well as a new understanding of what it means to be human. We are a truly human-microbiome superorganism.[2]

In 2018, 5.8 billion prescriptions were dispensed in the United States, which means Americans are taking more medications than at any other time in history.[3] Last month I presented an overview of drug-induced nutrient depletions.

Drugs that disrupt the microbiome can also cause nutrient depletions because certain strains of probiotic bacteria synthesize B vitamins, vitamin K and various amino acids. If an individual's probiotic bacteria are depleted, there will likely be a decreased production of these essential nutrients.

In addition to nutrient depletions, disrupting the microbiome can cause intestinal inflammation and leaky gut or intestinal permeability. In addition to gastrointestinal diseases (IBD, IBS, Crohn's), leaky gut can also cause or contribute to the following extra-intestinal diseases: liver diseases (NAFLD, cirrhosis), metabolic syndrome, cardiovascular diseases, neurodegenerative diseases, asthma, allergies, obesity, autoimmune diseases, and mental health conditions such as depression, anxiety, autism and ADD/ADHD.[4,5]

The emerging understanding that the gut microbiome affects virtually all aspects of human health made me realize that I needed to create a new drug-induced nutrient depletion drug category that I refer to as microbiome-disrupting drugs. The following classes of drugs are known to have a detrimental impact on the microbiome. At the end of this article, I will offer suggestions on the fastest and most effective way to reestablish a healthy microbiome.

Antibiotics damage the microbiome because they do not discriminate between "good" and "bad" bacteria. In addition to the intestinal and extra-intestinal health problems mentioned above, antibiotics are increasingly enabling the development of antibiotic-resistant 'superbug' infections, which can cause death.

An alarming new article reported that antibiotic resistant "superbug" infections are killing more than 153,000 annually in the United States.[6] This means that antibiotic resistant 'Superbug' infections are killing two times more Americans than the combined number of men and women dying from prostate and breast cancers!

Acid-suppressing medications and antacids do not kill probiotic bacteria directly. However, suppressing acid creates a more alkaline microbiome ecosystem, which inhibits the growth of probiotic bacteria and promotes the growth of pathogens.[7]

The acid/base balance in the intestinal tract is a critical factor that regulates the health of the microbiome. Studies consistently show that the use of acid-suppressing drugs (antacids, H2 blockers and PPIs) enable the growth of pathological bacteria, which increases the possibility of developing gastrointestinal infections.[8,9]

In a healthy microbiome, probiotic bacteria digest and ferment dietary fibers, which results in the production of a range of postbiotic metabolites with weakly acidic properties such as short-chain fatty acids[10], organic acids[11], nucleic acids[12] and fulvic acids.[13] These weakly acidic postbiotic metabolites help create and maintain a slightly acidic pH in the intestinal tract, which prevents the growth of pathogenic bacteria and promotes the growth and proliferation of beneficial probiotic bacteria.[14]

Non-steroidal anti-inflammatory drugs (NSAIDs). Prostaglandins play a key role in the production of mucus, which becomes the all-important protective mucosal layer that lines the gastrointestinal tract.[15] Over 99% of an individual's microbiome consists of anaerobic strains of bacteria that reside in the mucosal layer of the large bowel and colon.[16] Thus, the thick colonic mucosal layer is the "home" where the majority of your probiotic bacteria live.

NSAIDs inhibit the synthesis of prostaglandins, which damages the integrity of the protective mucosal layer. Initially the maintenance of the mucosal integrity was attributed exclusively to

COX-1. However, it has subsequently been shown that both COX-1 and COX-2 contribute to mucosal defense.[17]

Thus, NSAIDs do not directly kill your probiotic bacteria, they destroy the "home" where they live. NSAIDs cause ulcerations, inhibit mucosal renewal, and cause mucosal inflammation.[18] These factors significantly change the composition of the intestinal microbiota resulting in dysbiosis.[19]

Statins are reportedly the most widely prescribed drug in the world.[20] Twenty-two percent of Americans 45 years and older take a statin drug, according to the most recent data from the National Health and Nutrition Examination Survey (NHANES).[21]

Statin-induced gastrointestinal side effects such as abdominal pain, bloating, diarrhea, and constipation are relatively common, which suggests that statins induce alterations of the gut microbiome.[22]

Human statin-microbiome clinical trials have not been conducted. However, results from a recently published study reported that statin therapy causes gut dysbiosis in mice. The authors of this study stated the following, "This study demonstrates that statin therapy drives a profound remodeling of the gut microbiota."[23]

Opioids. Opioid-induced gut dysbiosis can cause multiple GI symptoms such as constipation, bloating, nausea, vomiting, and intestinal permeability or leaky gut.[24,25] It is now becoming apparent that opioid-induced bowel dysfunction and gut barrier disruption are related to opioid-induced alterations in the gut microbiome.[26]

In addition to increased susceptibility to a variety of pathogens and a weakening of mucosal immune function, use of opioids is also associated with increased risk of developing *C. difficile* infections.[27]

Atypical antipsychotics. Studies in animals and humans have reported a connection between atypical antipsychotic drug-induced obesity and changes in the gut microbiome. These drugs are also referred to as second generation antipsychotics (SGAs).

Atypical antipsychotic medications cause significant weight gain in children, adolescents, and adults. Although there are several proposed mechanisms involved, there is increasing evidence that drug-induced alterations in the microbiome are complicit in these weight gain/obesity issues.[28]

What is alarming about this class of drugs is that they cause rapid weight gain that substantially increases patient's risks for metabolic syndrome, heart disease, obesity, and poor quality of life.[29] In my years of working in retail pharmacy, I observed numerous customers who gained from 30 to 50 pounds within six months of starting on one of the atypical antipsychotic medications. There are undoubtedly multiple mechanisms involved in weight gain associated with this class of medications, but drug-induced changes in the microbiome are strongly implicated as one of the primary mechanisms.[30]

Many commonly used drugs alter the GI environment so that beneficial bacteria cannot thrive.

Chemotherapy. Throughout the gastrointestinal tract, gut bacteria play a critical role in the regulation of intestinal function and integrity. Cancer patients who receive cytotoxic chemotherapy or radiation therapy develop significant changes in the composition of their microbiome.[31] Only a few studies have been published addressing chemotherapy-induced dysbiosis.[32,33] However, I think both radiation and chemotherapy-driven damage to the microbiome ecosystem are a primary source of cancer therapy side effects and a major impediment to healing.[34]

I have had a lot of experience working with cancer patients. From 1988-1994, I was hospital administrator of an alternative, non-toxic cancer hospital in Baja, Mexico. Many of our patients had previously received one or multiple courses of toxic chemotherapy and/or radiation before coming to our hospital for therapy. Since my time in Mexico, I've continued to consult with many cancer patients. I'm thoroughly convinced that healing the gastrointestinal tract and reestablishing a healthy microbiome must be a fundamental part of treatment protocols for cancer patients if successful healing and recovery is to occur. I will discuss how to successfully accomplish healing of the intestinal tract and the microbiome at the end of this article.

Metformin is the last microbiome-disrupting drug I will be discussing, and I've left it until last because it represents a very special situation and warrants a discussion that stands apart from the rest. Most of the data I have on microbiome-disrupting drugs produces a negative effect on the microbiome. However, metformin creates a different scenario, which I think has important implications. Metformin causes beneficial changes in the microbiome.

Metformin has been the #1 drug for the treatment of type 2 diabetes for decades and currently over 150 million people are taking metformin worldwide.

Metformin produces effects beyond lowering blood glucose. In recent years several studies have reported evidence suggesting that metformin provides benefits for patients with cardiovascular and neurological diseases, cancer, obesity, polycystic ovary disease, and as an anti-aging drug.[35] In fact, on January 28, 2017, I posted an article on my blog with the title "Metformin: A True Anti-Aging Drug." In my blog post I reported that in 2016, the FDA approved a study to examine the effect of metformin on "the biology of aging in humans." This study is titled "Targeting Aging with Metformin," or the TAME study.

The FDA's announcement about the TAME study was significant because it is the first time the FDA has ever approved a human clinical trial with a goal of establishing a drug's ability to protect against multiple diseases of aging. To read my blog post on metformin, go to naturalpharmacist.net/blog and click on metformin.

Some of metformin's benefits have been attributed to activation of adenosine monophosphate-activated

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protein kinase (AMPK) in the liver and skeletal muscle. AMPK is a cellular enzyme that reduces fat storage and promotes longevity. When AMPK is activated, it initiates the use of stored energy from fats. At the same time, it promotes the removal of sugar and fats from the blood, stimulates the production of new mitochondria, and reduces inflammation.[36]

However, metformin's effects are not reduced in AMPK knockout mice and also, IV metformin is less effective than oral administration. This raises the important possibility of metformin-microbiome interaction.[37]

Metagenome studies have reported that patients with type 2 diabetes have an unbalanced or deranged microbiome, or gut dysbiosis.[38] A couple of important microbiome alterations found include a decrease in the abundance of butyrate-producing probiotic bacteria and an increase in various strains of opportunistic pathogens. Butyrate, or butyric acid, which is classified as a short-chain fatty acid (SCFA) is an important postbiotic metabolite that is produced by certain strains of probiotic bacteria.

In addition to discovering that the microbiome of patients with type 2 diabetes is deficient in butyrate-producing strains of probiotic bacteria, studies with mice prone to developing type 2 diabetes have reported that butyrate supplementation slows the progression of type 2 diabetes and decreases blood HbA!c levels.[39]

Paradigm Shift

The metformin-diabetes "story" that is emerging is representative of a paradigm shift regarding our understanding of how many drugs work. Drugs such as metformin influence or change the microbiome, which results in the production of bacterial-produced postbiotic metabolites, which in turn exert biological effects. **Drug → Microbiome → Postbiotic Metabolites → Biological Effect**

Metformin alters the microbiome, resulting in higher concentrations of butyrate-producing strains of probiotic bacteria. Butyric acid is a postbiotic metabolite that reduces inflammation and improves both insulin sensitivity and energy metabolism.[40] Thus, the postbiotic metabolite butyrate is associated with important health benefits.

This is a great example that shows how a drug's effect can be due to the postbiotic metabolites that are produced as a result of a drug-induced change in the microbiome. This is what I emphasized in Part 1 of this two-part series: postbiotic metabolites are the new frontier in microbiome science.

Everything affects your microbiome. In my November 2019 *Townsend* article, I mentioned that there is no information available regarding drug-induced nutrient depletions for many drugs. The research simply has not been conducted. However, in the future, I believe we will learn that most drugs deplete one or more nutrients. This is due to the fact that numerous nutrients must be utilized in the process of detoxifying and eliminating foreign substances from the body.

A similar situation exists with microbiome-disrupting drugs. In most cases, no research had been conducted to determine what effect the drug(s) have on the microbiome. Since most drugs are xenobiotics, I expect that most drugs will eventually be found to exert a negative influence on the microbiome.

In a paper titled "Metformin Joins Forces with Microbes," author Filipe Cabreiro made the following statement: "Therefore, we can only truly understand the physiology of the host if we consider an organism and its microbiota as a combined metabolic entity, the holobiont."[41]

In considering the relationship between an individual and his or her microbiome, I suggest taking Cabreiro's statement one step farther. We can only truly understand the physiology, biology, and health of an individual when we consider the relationship between the host, their microbiome **and** the health-regulating postbiotic metabolites that are produced by the bacteria in their microbiome. Postbiotic metabolites are not only the new frontier in microbiome science, they are being increasingly understood as the new frontier in medicine and health.

In 2016, a group of top doctors and scientific experts were asked to create a list of medical innovations that they expect to be major game changers in the near future. When this panel of experts announced their list of the Top 10 Medical Innovations that are most likely to transform healthcare in 2017 and beyond, topping the list as the #1 Game Changer expected to transform healthcare was *using the microbiome to prevent, diagnose and treat disease*.[42]

I believe most people can improve their health by improving their microbiome, and this is especially important for people who are taking microbiome-disrupting drugs.

Two factors that are critically important for a healthy microbiome are balance and diversity. When it comes to probiotics, many people have the mistaken belief that more is better. High-dose probiotics ("mine has 50 billion," "mine has 100 billion") do not promote microbiome balance, they actually work against it. It is better to have a smaller quantity of a wide range of probiotics rather than a high dose of just one or several strains.

Diversity refers to a wide range of different strains of bacteria. Taking probiotics that contain extremely high doses of one or several strains of bacteria also do not promote diversity. The most important factor related to creating and maintaining a healthy microbiome is the following: you must learn how to feed your probiotic bacteria well!!!

Different strains of probiotic bacteria require different kinds of fiber to support their growth and enable them to transform their unique and specific fibers into postbiotic metabolites. Consuming a more diverse range of dietary fiber-rich foods will promote the growth of a more diverse microbiome. This results in the production of a more diverse range of health-promoting postbiotic metabolites, which makes the immune system stronger, more adaptable, and

better able to respond challenges and perturbations.

How to Create a Healthy Microbiome

Diversity is critical to the health of all ecosystems, from the Amazon rainforest to each individual's intestinal microbiome. Conversely, loss of species diversity is associated with numerous diseases and lowered immunity.[43] The diversity of life in all of Earth's ecosystems is essential to human health. Similarly, diversity of bacteria in the gut microbiome is essential to an individual's health.

Scientists estimated that the human gut microbiome contains from 500 to 1,000 species and over 7,000 strains of bacteria.[44] Hence, you can see why taking a probiotic containing huge amounts of one or several strains really has minimal effects on increasing microbiome diversity.

There are two ways to increase the diversity and health of the gut microbiome: fiber-rich foods and consuming postbiotic metabolites.

Consuming a diverse range of *fiber-rich foods* is critically important for the development of a diverse microbiome. It has been reported that approximately 90% of children and adults in the US don't consume adequate amounts of fiber.[45] Unfortunately, for a number of reasons, diversity of dietary fiber has also declined over the past 50-70 years. It is not just quantity of fiber, a diverse range of different kinds of fiber is required to create and support a diverse microbiome.

The best way to *directly consume postbiotic metabolites* is to take Dr. Ohhira's Probiotics®. Dr. Ohhira's Probiotics Professional Formula is produced utilizing a five-year fermentation process, which allows the bacteria time to convert fiber-rich foods into postbiotic metabolites. Independent research has reported that Dr. Ohhira's Probiotics contain over 500 postbiotic metabolites.[46] When consumed, the postbiotic metabolites immediately begin to create improvements in the gastrointestinal tract and improve the overall health of the microbiome ecosystem.

For more information and free samples of Dr. Ohhira's Probiotics Professional Formula, call Essential Formulas at (800) 430-6180.

For a free copy of my Quick Reference Guide to Drug-Induced Nutrient Depletions, email your request to ross@naturalpharmacist.net.

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Microbiome-Disrupting Drugs

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Ross Pelton, RPh, PhD, CNN, graduated from the University of Wisconsin in 1966 with a degree in pharmacy and in 1984 he received his PhD in psychology and holistic health from the University for Humanistic Studies in San Diego, California. He is also a certified clinical nutritionist (CCN).

Ross is the author of 13 books. He is the world's leading authority on the topic of drug-induced nutrient depletions, and his book titled The Drug-Induced Nutrient Depletion Handbook (2nd edition, Lexi-Comp, 2001) is an important reference book that informs health professionals which nutrients are being depleted by the drugs people are taking.

In October 1999, Ross was named as one to the Top 50 Most Influential Pharmacists in America by American Druggist magazine for his work in natural medicine. From 1988 to 1994, Ross was the hospital administrator at Hospital Santa Monica in Baja, Mexico, which specialized in alternative, non-toxic cancer therapies.

Ross is a long-time member of the medical advisory board for the Life Extension Foundation, and he is deeply involved in life extension therapies and products. Pelton's website, bio and blog are at: www.naturalpharmacist.net. Ross is currently the scientific director for Essential Formulas, based in Dallas, Texas.

Letters to the Editor

Vitamin C and Kidney Stones: A Comment

Intravenous vitamin C (IVC) has been used for decades by many health care practitioners for a number of indications, particularly cancer and infections.[1] IVC has been shown to be effective at decreasing chemotherapy side-effects and improving overall patient quality of life.[2] IVC is generally considered to be safe with few adverse effects; however, it has been recommended that IVC be used with caution in patients with renal impairment or failure, or a history of renal oxalate stones.[1]

It has frequently been claimed that ingestion of large doses of vitamin C can increase the risk of calcium oxalate kidney stones because vitamin C is converted in part to oxalate. Oxalic acid is an end product of metabolic oxidation of vitamin C. Oxalate nephropathy has been reported after administration of intravenous vitamin C in subjects with renal dysfunction.[3,4] However, in people with normal renal function, only about 2% of large doses intravenous vitamin C (1.5 g/kg body weight) was found in the urine as oxalic acid six hours after infusion.[5]

The hyperoxaluria associated with the use of high-dose vitamin C has been found to be due primarily to a laboratory artifact, resulting from the conversion of vitamin C to oxalate ex vivo, i.e., after it has left the body while it is in the collection bottle.

If there is a small increase in urinary oxalate resulting from ingestion of large doses of vitamin C, that increase might be counterbalanced by other effects of the vitamin. For example, vitamin C binds calcium in the urine, potentially reducing the formation of calcium oxalate crystals; produces a small increase in urinary acidity, thereby increasing calcium oxalate solubility; and possibly decreases urinary stasis by promoting diuresis. Various studies have found either that vitamin C intake is not associated with kidney stone risk or that higher intake is associated with a lower incidence of kidney stones[6-12] and found no evidence of vitamin C increasing the risk of kidney stone formation.

Moreover, practitioners who have routinely used large doses of vitamin C have not observed kidney stones as a side effect. Despite the apparent safety of vitamin C for the general population with respect to kidney stone risk, there are rare cases in which high-dose vitamin C appeared to cause an increase in urinary oxalate levels. In this population, the risk of oxalate crystallization in the kidney was not increased, in particular since calcium oxalate stones develop over months to years. There is even some evidence that IVC may improve acute kidney injury in critically ill patients and also decrease renal toxicity in oncology patients receiving chemotherapy.[13,14]

Among the most important factors in kidney stones is dehydration, especially among the elderly. Ascorbate tends to bind with calcium leaving less calcium to bind with oxalate and, in effect, prevents the formation of calcium oxalate stone.[15]

Therefore, we conclude that the statement that high dose intravenous vitamin C causes kidney stones is unsubstantiated and that the concept that high-dose intravenous vitamin C may be contraindicated in people with renal dysfunction and a history of kidney stones should be reviewed.

Michael J Gonzalez,[1] Ron Hunninghake,[2] Thomas Levy,[2] Jose Olalde,[3] Jorge Duconge,[4] Miguel J. Berdiel,[5] Raul Morales Borges,[6] Ines Alfaro,[7] Victor Marcial,[8] Joseph Campos,[9] Roberto Rosso,[10] and Andrew Saul[11]

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Letter to the Edtior

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Re: Dr. Platt and Adrenal Fatigue

Recently I received an email from Dr. Jane Goldberg with some information written by Michael Platt, MD, as an introduction for his new book *Adrenal Dominance*, that I thought may be interesting for *Townsend Letter* readers. Dr. Goldberg writes Dr. Platt's research is fascinating and compelling. While he makes some interesting points, I disagree with his main premise that all adrenal problems are from too much cortisol and that adrenal fatigue is a "misdiagnosis."

He blames false salivary cortisol readings taken by naturopathic physicians for creating a disease that actually does not exist, namely adrenal fatigue. I would think that before anyone came to the conclusion that false salivary cortisol readings were responsible for a false reading, blood cortisol testing would be done at the same time. Also, it may be wise to do the classic 'blood pressure' test.

"Actually does not exist" is pretty conclusive although this is the position of many in mainstream medicine. However from experience over many years and taking into consideration Dr. Plechner's stellar work, there are, in fact, many cases of adrenal fatigue and even adrenal exhaustion.

Dr. Plechner was a veterinarian, and his work with animals (no placebo) and his correlation with humans would conclusively indicate that two-and-a-half to five mgs of prednisone and even better twenty to twenty-five mgs of hydrocortisone (Cortef) may be "lifesaving." Of course, too much cortisol can lead to Cushing's and too little to Addison's disease.

Also, according to Don Colbert, MD, in his excellent and informative book *Hormone Health Zone*, "excessive cortisol blocks the conversion of T4 to T3. Also increased rT3 production lowers testosterone and increases conversion of testosterone into estrogen." But Dr. Colbert asserts, "the overproduction of cortisol eventually wears the adrenal glands down, resulting in adrenal fatigue and even complete adrenal burnout"; "Cortisol levels plummet, which increases your risk for inflammatory and autoimmune diseases." Symptoms include low blood pressure, weight gain, brain fog, depression, memory issues, as well as constant fatigue.

I'm sure Dr. James L. Wilson would agree. His book *Adrenal Fatigue – The 21st Century Stress Syndrome* is described this way by Amazon: "This is an incredibly informative and reader friendly book about a common debilitating medical condition that very likely affects millions of people."

Also, Dr. Colbert says, "When your adrenals are tired, they produce less of the anti-aging hormone DHEA. Low levels can contribute to chronic infections, Alzheimer's, heart disease, Parkinson's, insomnia, lupus, cancers, accelerated aging, arthritis, wrinkles and sagging skin."

Dr. Norman Shealy knows about the consequences of low DHEA, and at 86 is a fine example of keeping DHEA levels up. He's written about it in his many books.

However, Dr. Platt does make a good point when he states; "It is important to have the understanding that the primary reason the body is releasing excess adrenaline is simply to raise glucose levels for the brain. However, by giving the brain the fuel it needs, there is a reduced need to use adrenaline. Adrenalin can create stress, stimulating the release of cortisol. Accordingly, there are two fuels the brain uses: glucose and ketones."

If this is true then obviously a ketogenic diet, where the brain runs on ketone bodies instead of glucose, would solve a myriad of health/medical problems. No doubt over-production of adrenaline/cortisol affects millions of people but likewise under-production also affects millions. Would a permanent ketogenic lifestyle largely solve this problem?

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A Look at Pattern Hair Loss

review by Carol Petersen, RPh, CNP – Women's International Pharmacy

Hair Like a Fox: A Bioenergetic View of Pattern Hair Loss by Danny Roddy
Available online (free) at https://www.dannyroddy.com/book and through Amazon
ISBN-13: 978-0615925363; 110 pp; 2013

Men and women alike have issues with hair loss. Is this natural? Is this normal? For Danny Roddy, author of *Hair like a Fox: A Bioenergetic View of Pattern Hair Loss*, fear of hair loss was imprinted in his childhood. At the age of 19, he made it a personal challenge to learn about hair loss and do all that he could to keep his hair. As he had feared, Roddy did begin losing hair despite his efforts. It was only by discovering the work of Dr. Ray Peat that Roddy finally found a new perspective on the underlying cause of hair loss and how it may be prevented.

Conventional Theories of Hair Loss

Let's examine the history first. In the 1940s, Dr. James B. Hamilton published his observations of 104 men without functioning testicles. He found these men did not mature sexually and had altered hormone levels. They also retained their scalp hair, had reduced oiliness of the scalp, and little to no dandruff.

Seeing this connection, Dr. Hamilton administered testosterone to men without functioning testicles who were not bald but who had a family history of baldness. Soon they experienced hair loss, which abated when the treatment stopped. When the testosterone was later resumed, balding proceeded again. Dr. Hamilton concluded that baldness was caused by androgens, specifically testosterone.

In the 1970s Dr. Julianne Imperato-McGinley studied a population in a remote area of the Dominican Republic who were born with ambiguous sexual features. From birth and throughout their childhood, these individuals appeared to be girls. At puberty, however, they developed male sex organs.

These men had no signs of baldness, had small prostate size, and normal testosterone levels. However, they lacked the enzyme needed to convert testosterone to its stronger metabolite, dihydrotestosterone (DHT). Dr. Imperato-McGinley became convinced that DHT – not testosterone – was responsible for male pattern baldness.

Merck scientists became aware of Dr. Imperato-McGinley's research and developed a drug that would block the production of DHT. The result was finasteride. Finasteride not only reduced symptoms and helped shrink the prostate in men with enlarged prostate glands but incidentally contributed to regrowth of hair as well.

According to Roddy, finasteride may have enough progesterone activity to help with hair loss–at least part of the time. This new treatment was not without drawbacks, however: Large numbers of men suffered side effects such as erectile dysfunction, lack of libido, depression, and suicide. In addition, finasteride was not the total answer for the hair problem, either, as it was only effective for about 40% of the men who took it.

Why do young men with the highest testosterone and DHT have the best hair? Why does balding occur when the hormone levels are dropping with age? Why do women experience "male" pattern baldness? Medical practitioners tend to cling to explanations involving DHT or genetics in spite of the holes in these theories.

Dr. Peat and the Hair Follicle as a Mini Organ

Dr. Ray Peat is a prolific writer and thinker and often challenges conventional thinking. Perhaps best known for his foundational research on progesterone, Dr. Peat's work directs one to consider the hair follicles as mini organs.

Like other organs in the body, hair follicles depend upon the energy of the cells in their structure, and this cellular energy is produced by mitochondria. With time, stressors may diminish the function of the cells; hair follicles become clogged with mucopolysaccharides (mucin), calcification, impaired blood flow leading to low available oxygen, oxidative stress and finally, impaired function of the mitochondria.

Mitochondria need glucose and oxygen to produce energy. We get glucose with carbohydrates, but our bodies can also convert it from protein. Even more than glucose, however, energy production relies upon oxygen sources. A byproduct of cell energy production is carbon dioxide, which helps move oxygen from the blood and into the tissues and cells.

Active thyroid hormone (T3) stimulates the use of oxygen in breaking down the carbohydrates, fats, and proteins. This, in turn, yields carbon dioxide, which improves the oxygen transport to the cell. In individuals with low thyroid levels, the body produces mucin, a gelatinous substance that solidifies in the spaces between cells. When mucin becomes calcified, it cuts off circulation to the scalp. Hairs become progressively wispier until the hair follicle is choked off entirely.

Graying and loss of hair are symptoms of declining mitochondria function and thus loss of cell energy. If proper cell metabolism is compromised, functioning in all parts of the body is slowed down. Declining cell energy may be linked to a wide variety of diseases:

- Alzheimer's
- Atherosclerosis
- Autism
- Cancer
- Chronic fatigue

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- Fibromyalgia
- Heart failure
- Epilepsy
- Hypertension
- Hypoglycemia
- Depression
- Infertility
- Migraines
- Non-alcoholic liver disease
- Obesity
- Sleep apnea
- Diabetes

Estrogen (and Other Hormones) Can Cause Hair Loss

Progesterone depends upon thyroid function. If estrogen is not balanced by plenty of progesterone, hair loss may result. During menopause, progesterone levels decline while estrogen activity soars. Relatively high levels of estrogen may, in turn, also inhibit progesterone production, creating a vicious cycle.

Hair is affected by other hormones as well. The pituitary hormone prolactin increases with age in men and may inhibit hair growth. Cortisol levels from the adrenal glands increase with aging and may contribute to hair loss.

As it happens, not only do men without functioning testicles have low testosterone levels, but they are also low in estrogen. Perhaps the lack of this hormone further inhibits hair loss for them.

Conclusion

Hair Like a Fox contains many more chapters discussing serotonin, essential fatty acids, types of carbohydrates, proteins, and fats that produce cellular energy and contribute to hair growth. Rather than the simple cause-and-effect theory of androgen-induced baldness, the real key to maintaining hair follicle structure may be to maintain mitochondrial health. Optimizing how the body can best produce cell energy applies to every cell in the body, not just the tiny hair follicle organ. This may be a remedy for not only defying hair loss but also resisting those diseases associated with aging.

If you are wondering how Danny Roddy and his hair are doing, check out his blog at www.dannyroddy.com. This website is rich with information, but Roddy feels the quest is not over yet and there is always more to learn.

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Shorts

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The Canadian, prospective, multicenter study used information from the Maternal-Infant Research on Environmental Chemicals cohort, which included children born between 2008 and 2012 in 10 cities across Canada. Forty-one percent of the mothers lived in communities with fluoridated water programs; most fluoride concentration measures were below the level considered optimal for caries prevention (0.7 mg/L). Fluoride is known to cross the placenta, and animal studies show that the mineral alters proteins and neurotransmitters in the central nervous system as well as accumulating in learning and memory centers of the brain.

This epidemiological study used data for 400 mother-child pairs that included maternal fluoride intake, using urinary samples averaged over three trimesters and self-reported water and beverage consumption. Children's IQ was tested between ages three and four. The researchers adjusted for "established factors associated with fluoride metabolism," socioeconomic factors, and quality of child's home environment. They also tested to see if the maternal urinary fluoride and IQ results were confounded by maternal blood concentrations of lead, mercury, manganese, perfluoro-octanoic acid, or urinary arsenic. Overall, the researchers found that "[a] 1-mg higher daily intake of fluoride among pregnant women was associated with a 3.66 lower IQ score (95% CI, -7.16 to -0.14) in boys and girls." There was no statistically significant association between fluoride consumption and IQ in girls, but boys had a 4.49 point lower IQ score for every 1 mg/L increase in maternal urinary fluoride.

Although this study cannot prove causation (being an epidemiological study), it joins over 50 other studies that found a correlation between fluoride exposure and lower IQ. Fluoride Action Network reports that the epidemiological studies are supported by over 400 animal and cell studies showing fluoride has neurotoxic effects.

In November 2016, Fluoride Action Network, along with a coalition of environmental and health groups and six parents, petitioned the US Environmental Protection Agency to ban the addition of fluoridation chemicals to public drinking water. According to the Toxic Substance Control Act, the agency has the authority to "prohibit the 'particular use' of a chemical that presents an unreasonable risk to the general public or susceptible subpopulations." About 60% of US communities have fluoridated water programs, compared to just 3% in Europe. Europeans rely on dental treatments and fortification of milk instead of water fluoridation.

EPA denied the petition, so the petitioners have sued. The Court denied EPA's motion to dismiss in December 2017. The fluoride lawsuit trial is set to commence on February 3, 2020 at the US District Court, Northern District of California, in San Francisco.

Fluoride Action Network. Criticisms of Recent JAMA fluoride/IQ Study Are Unfounded (press release). August 21, 2019.

Green R, et al. Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada. *JAMA Pediatr.* August 19, 2019.

The TSCA Lawsuit Timeline. www.fluoridealert.org

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Women's Health Update

by Tori Hudson, ND
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Two Nutrients for the Aging Brain

Botanicals and nutraceuticals could have a potential role in slowing progression of cognitive impairment and/or dementia, improving cognition and memory, and improving behavior in those with dementia, including Alzheimer's disease.

Alzheimer's disease accounts for 60-80% of all dementias and is one of the most frightening, life-altering, and deadly diseases of our time. Not all Alzheimer's disease is in the elderly; over 200,000 US adults have early onset (< 65 y.o.) disease. There is no cure at this time. Any role of botanical and nutraceuticals for risk reduction, prevention, and disease alteration must be considered.

Mild cognitive impairment involves problems with memory, language, thinking, and judgement and is at a stage that is greater than normal age-related changes but not as serious as dementia. Mild cognitive impairment may increase the risk of dementia, with approximately 10-15% going on to having some kind of dementia. While hypertension, sleep apnea, and depression should be addressed, as these conditions can affect memory as well, mild cognitive impairment should be taken seriously by including the use of dietary supplements that can improve memory and slow or prevent progression.

Acetyl-L-Carnitine

Acetyl-L-carnitine is derived from L-carnitine, an amino acid found naturally in the human body. L-carnitine is made in the brain, liver, and kidneys from lysine and methionine; and we convert the L-carnitine to acetyl-L-carnitine, and the reverse as well. The primary function of L-carnitine is to transfer long chain fatty acids in their ester form across the mitochondrial membrane prior to beta-oxidation. This process turns fat into energy. As a dietary supplement, until we know more, one should take L-carnitine when that is desired and acetyl-L-carnitine when that is desired as we do not know if we can supplement one for the other from a dietary supplement.

Acetyl-L-carnitine is used for a wide range of conditions, but the focus here is its use in Alzheimer's disease and age-related cognitive impairment. But there are many uses ranging from age-related fatigue and exercise performance to serious issues such as diabetic neuropathy, hepatic encephalopathy, and more.

Acetyl-L-carnitine might slow the rate of Alzheimer's disease (AD) progression as well as improve memory and improve measures of cognitive function and behavior in individuals with AD.

A 1996 double-blind, placebo-controlled, randomized, parallel-group study of one year compared acetyl-L-carnitine hydrochloride (ALCAR) with placebo in patients with probable AD.[1] Four hundred thirty-one patients, age 50 or older, who had probable mild to moderate AD were given 1 gm three times daily of ALCAR or placebo for 12 months; and 83% completed the one year of treatment. The Alzheimer's Disease Assessment Scale cognitive component and the Clinical Dementia Rating Scale were the primary outcome measures. At first glance, both ALCAR and placebo-treated patients declined at the same rate on all primary measures and most secondary measures. But when comparing early-onset patients (aged 65 years or younger at study entry) with late-onset patients (older than 66 at study entry), there was a trend for the early-onset patients on the acetyl-L-carnitine to decline slower than the early onset AD patients on placebo. In addition, in the placebo groups, early-onset patients tended to decline more rapidly than older patients; and late-onset AD patients on ALCAR tended to progress more rapidly than the ALCAR-treated early-onset patients. The study suggests AD patients aged 65 or younger may benefit from treatment with ALCAR whereas older individuals might do more poorly.

In a small pilot study of 30 mild to moderately demented patients with probable AD, acetyl levocarnitine hydrochloride at 2.5 g/day for three months followed by 3 g/day for three months was compared to placebo.[2] Tests of memory, attention, language, visuospatial and constructional abilities were administered along with measuring the spinal fluid for acetyl levocarnitine hydrochloride. At the end of six months,

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the treatment group had significantly less deterioration in several measurable tasks although no differences were found in any other neuropsychological test results. A small subgroup, with the lowest baseline scores and who received the supplement, had significantly less deterioration on the verbal memory test and a significant increase in the cerebrospinal fluid acetyl levocarnitine levels compared to placebo. Again, we may be seeing an ability of acetyl levocarnitine to retard the deterioration in some cognitive areas in patients with Alzheimer's disease.

In 130 patients with a clear diagnosis of AD, a double-blind, placebo-controlled, parallel-group, randomized clinical trial studied the efficacy of a year's oral treatment with acetyl-L-carnitine.[3] There were 14 outcome measures to assess functional and cognitive impairment. After one year, both the treatment group and the placebo group worsened, but there was a slower rate of deterioration in 13 of the 14 outcome measures in the treatment group and better scores in all outcome measures in the treatment group, including a statistical significance difference for the Blessed Dementia Scale, logical intelligence, ideomotor and buccofacial apraxia, and selective attention.

In another small but randomized, double-blind, placebo-controlled, parallel-group clinical trial, 36 individuals with AD were given either 1 g acetyl-L-carnitine twice daily and placebo for 24 weeks.[4] A total of 20 patients completed the full 24 weeks with seven in the active group and 13 in the placebo group. In the end, there was an apparent trend for more improvement in two short-term memory tests in the acetyl-L-carnitine. There was also a trend for less deterioration in reaction time in the active treatment group. Particularly in the area of short-term memory, this study suggests an improvement in the AD patients receiving this dose of acetyl-L-carnitine.

A meta-analysis of acetyl-L-carnitine in mild cognitive impairment (MCI) and mild early AD investigated only double-blind, placebo-controlled prospective, parallel group comparison studies of at least three months duration.[5] Studies ranged in duration from three to 12 months, and the daily dose varied in the studies with a range of 1.5-3.0 g/day. An overall summary effect was significantly better with the acetyl-L-carnitine compared to placebo, and the benefits were seen in clinical results and psychometric tests. These benefits were seen as soon as three months in all the studies.

A Cochrane review from 2003 identified 11 double blind randomized trials of people with AD and using acetyl-L-carnitine.[6] While there was evidence for benefit of ALC on clinical global impression, there was no evidence using objective assessments in any other area of outcome.

Dosages, Side Effects, Toxicity, Contraindications

For age-related cognitive impairment, oral acetyl-L-carnitine dosages range from 1500-2000 mg daily. For Alzheimer's disease, 1,500 mg-3,000 mg daily has been used.

Acetyl-L-carnitine is generally well tolerated, although it may cause nausea, vomiting, gastrointestinal upset, dry mouth, anorexia, agitation, headache, and insomnia. Less common reports include hiccups, abdominal distension, paresthesia, and pain. When acetyl-L-carnitine is taken orally in combination with alpha-lipoic acid, there are reports of rash, diarrhea, constipation, dyspepsia, and foul-smelling urine.

One major drug interaction should be avoided: Acenocoumarol, which is a shorter acting drug similar to warfarin. Caution is warranted with warfarin itself.

Using acetyl-L-carnitine may increase the risk of mania in those with bipolar disorder. It also may increase symptoms of neuropathy in those taking the supplement with taxane-based chemotherapy medications. It is also best to avoid acetyl-L-carnitine in those with hypothyroid as it seems to inhibit the activity of thyroid hormones in target tissues, and in those with seizure disorders; an increase has been reported when using acetyl-L-carnitine.

Phosphatidylserine

Phosphatidylserine is a phospholipid synthesized in the body and is a component of the phospholipid bilayer of the cell membrane. Phosphatidylserine is found in high quantities in the brain and particularly in myelin.

Phosphatidylserine has been used orally for dementias, including Alzheimer's disease, and in age-related cognitive decline. This will be our focus here in this report. But it has also been used to improve cognitive function in young people, attention deficit-hyperactivity disorder (ADHD) and depression with additional uses in preventing exercise-induced muscle soreness and improving athletic performance.

Several clinical studies show that phosphatidylserine improves attention, arousal, verbal fluency, and memory in aging people with cognitive deterioration.

One double-blind study assessed the efficacy and safety of oral phosphatidylserine (PS), 300 mg/day for six months, vs placebo in a group of elderly patients with cognitive impairment.[7] A total of 494 elderly men and women with moderate to severe cognitive decline and between the ages of 65 and 93 were recruited in clinical care units in Italy. Patients were examined at baseline, three, and six months. There were statistically significant improvements in the phosphatidylserine-treated group compared to placebo in both behavioral and cognitive parameters.

Another 149 patients with age-associated memory impairment (AAMI) were treated with 100 mg three times daily of phosphatidylserine or placebo for 12 weeks.[8] Patients treated with the PS improved compared to placebo in tasks of daily life, and those with the poorest initial performance at baseline were the best responders.

In patients who have a diagnosis of Alzheimer's disease, taking phosphatidylserine could increase cognitive function, improve global rating scales and behavioral rating scales.

Observations may be seen in 6-12 weeks although it may be most effective in those with less severe symptoms. One observation is that treatment effects may last only 16 weeks, and then the progression of the disease may dominate over any benefit of phosphatidylserine.[9-13]

Dosages, Side Effects, Toxicity, Contraindications

Sources of phosphatidylserine available are bovine or plant sourced and likely soy or cabbage derived. *Both* bovine- and plant-sourced phosphatidylserine, 100 mg three times daily for up to six months, have been used in age-related cognitive impairment. For Alzheimer's disease, bovine-sourced phosphatidylserine, 300-400 mg/day in divided doses, has been used.

Oral phosphatidylserine is usually well-tolerated although some patients may experience gastrointestinal upset, flatulence, nausea, headache, or insomnia – most likely to occur in higher doses such as 600 mg/day.

Moderate drug interactions include acetylcholinesterase inhibitors, anticholinergics, and cholinergics. Caution is warranted due to the theoretical possibility that phosphatidylserine might increase acetylcholine levels and potentially cause cholinergic effects.

Other nootropics agents not mentioned in this article can include bacopa, rhodiola, Ginkgo biloba, L-theanine, Panax ginseng, resveratrol, and even caffeine. Lifestyle factors must also be considered and one diet, the MIND diet (vegetables, fruits, nuts, fish and other brain healthy foods), has been able to slow brain aging and reduce the risk of Alzheimer's disease.

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Moldy Buildings, CIRS, Sick People, and Damaged Brains: 25 Years of Research Brought Us to the Cure Word, Part 5

by Ritchie C. Shoemaker, MD
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Editor's Note: Exposure to mold in water-damaged buildings (WDBs) causes a frustrating number of puzzling symptoms and eventually leads to chronic inflammatory response syndrome (CIRS), as explained in the first article of this five-part series, published in the July 2019 issue. In Parts 2, 3, and 4, the authors explained how to maintain the building envelope, CIRS diagnosis procedures, and a 12-step treatment protocol.

Transcriptomics

In the annals of medical history, there are advances that have changed both the art and science of the practice of medicine. A few we learned about in high school: Edward Jenner working to prevent smallpox with an inoculation with cowpox and sterilization from Joseph Lister come to mind. Louis Pasteur and the germ theory. Robert Koch and his proof of microbiologic causation, not to mention Semmelweis with his insights into prevention of child bed fever and maternal/fetal loss are revered (now) pioneers. Technical advances included use of radiation for x-ray machines, with CT and MRI scans to follow as the years went by. Certainly, automated blood chemistries, not to mention advances in development of antibiotics, beginning with penicillin and sulfa and extending to the modern armamentarium of effective oral and parenteral bacteria-killers, were great achievements. The new T-cell cancer therapies will soon be next (my opinion).

And yet, even these advances pale in terms of scientific discovery to the work done in the early 2000s in the Human Genome Project. While Watson and Crick get credit for discovery of DNA and working out some of the structures of DNA, it was the ability to identify individual genes that has heralded the advances that we see now in the 21st century. Who knew that there would only be 50,000 genes (20,000 protein-coding and 30,000 non protein-coding)? There is so much complexity of protein interaction, the diversity of diseases, all of which essentially end up having their roots in genes and gene activity. Fifty thousand seems like a small number to me.

The initial 3-5 billion dollars that were spent to sequence the human genome work seems like an overwhelming hurdle that practitioners would have to clear before bringing use of manipulation of gene activity to primary care. In just 10 years, however, automated sequencing devices brought next generation sequencing and RNA Seq to practice – with entire human genome sequencing now costing $5000 and not $5 billion. What an achievement!

It is with the Human Genome Project as a back drop for the work of transcriptomists, including Dr. James Ryan, that has helped us take the next step in not only identifying diagnostic features of illness but also identifying objective biomarkers that will let us follow the results of interventions as a basis for modern therapies. Use of transcriptomics, differential gene activation, permits us to truly see the miracle of monitoring DNA activity. We now know that environmental stimuli rapidly cause a targeted but diverse transcriptomic response. That response is rich in information!

When I use the term "transcriptomics," please recognize that this is a dynamic field of study with gene activity changing through a variety of mechanisms, including those regulated by non-coding RNA, by ribonuclear proteins, by microRNA, by methylation and demethylation, as well as acetylation and deacetylation. All these controlling elements lead to the function of transcription factors that are doing the work to initiate the copying of individual genes from our DNA, onto another nucleotide backbone, called messenger RNA (mRNA), as a cornerstone of adaptation of our genetic material to metabolic needs.

Transcription factors are not one to one; indeed, a quick read of www.genecards.org will show that for a given gene there can be literally a hundred or more transcription factors that can cause that gene to be activated. By focusing on gene activation, we can then compare gene activity to control patients and understand what "normal" is supposed

to be, with that insight also leading to the concept of what gene suppression is. Here we see less activity compared to controls. As an aside, we know that males and females have significant differences in gene activity more than seemingly would be based on reproductive functions alone, but we also see change in activity of genes through time of day and night. The more we learn, the more we don't know.

In the CIRS world, thanks to the work of Dr. Ryan, we were able to look at 50,000 genes in CIRS cases compared to controls with the discovery of approximately 2000 genes that showed significant differences between cases and controls, including both activation and suppression. For three years we used this 2000 gene registry to analyze complete human gene sequencing, looking at cases with CIRS and controls with RNA Seq.

This approach was unwieldy and used a long string of sample manipulations, increasing the likelihood of errors. By reducing the number of genes and using a simpler platform, we were able to create a diagnostic test called GENIE. GENIE involves less than 200 genes including some "housekeeping" genes designed to show stability of the test performance. The most important application in use of GENIE in CIRS patients as well as in other illnesses characterized by chronic fatigue had to do with Dr. Ryan's finding of "hypometabolism."

What we mean by hypometabolism is stunning in its evolutionary simplicity. Who knew that there were biological warfare elements that one-celled creatures used on other one-celled creatures 3 and 4 billion years ago? These biological warfare elements have different names such as mycotoxins, ribotoxins, ribosomal inhibitory proteins, endotoxins and others. As the names suggest, ribosomes, especially one structural element of the ribosome called the sarcin ricin loop, are attacked by ribotoxins disrupting cellular production of protein. Remember that ribosomes, found in the cytoplasm, can number in the low millions in a human cell. It's no wonder that ribosome production is one of the cells most energy intense operations. If a ribotoxin disrupts normal sarcin ricin loop functioning, which they do, the cost to a cell is such that it needs to suppress its metabolic rate to survive the attack.

All living creatures need to make protein; they all use ribosomal machinery to do so. There are two functional units that comprise the ribosome, called the large and small subunits, that wrap around a messenger RNA to then produce a protein by initiating and then elongating an amino acid chain that leads to a protein being created. *All known ribosomes of all creatures* carry the sarcin ricin loop, a structure that has been ultraconserved throughout evolution. Imagine, a vital piece of the mechanics of a cell not changing in 4 billion years.

Monitoring gene expression, using transcriptomics, can show the effects of medical interventions and give insights into a disease.

Ribosomes are also found in mitochondria, the power house of the cell. Here we have proteins made that are needed for mitochondrial function. Were these "mitoribosomes" attacked by ribotoxins? You bet!

I hope that you have seen that disruption of protein synthetic machinery is a common result of a biological attack. The cell, under attack, has multiple feedback systems built in to help the cell survive. The cost is chronic fatigue and multisystem, multi-symptom illness in humans. Without taking evasive action, the cell would otherwise die.

Energy production systems are also subject to attack. When thinking of mitochondrial function, we think about electron transport chains and production of 36 molecules of ATP for each molecule of glucose, but those thoughts end up being just a small bit of what is involved. Mitochondria, speculated to be free-living bacteria before they were engulfed and kept alive inside the engulfing cell, provide energy to the engulfer. Mitochondria had their own genome. Over time, and 4 billion years is a long time, the mitochondrial genes have migrated (or been migrated) to the nucleus leaving only 37 behind in the mitochondria.

Going back to the idea that everything that happens in disease and illness is controlled by DNA, the *control of mitochondrial function now comes from nuclear DNA*. This point cannot be underestimated in that many have felt that treatment of mitochondria with one nostrum or another made sense and yet they were firing at the wrong place. *The therapeutic target was in the nucleus and not in the mitochondria itself.*

As nature would have it, energy production and protein production are protected in the search for life. By suppressing both mitochondrial gene activity and ribosomal gene activity, the cell can almost "go into hibernation," or torpor or reduced activity – call it what you want – to "lay low and be still." This state of reduced metabolism or hypometabolism permits the cell to survive by downregulating its gene activity.

The role of glucose metabolism in this whole concept of reduced cellular metabolism is less well defined. Normally, glucose will be delivered with insulin to bind to the insulin receptor, making a complex on the outside of the cell. That complex will be internalized, surrounded by a cell membrane, in what is called an endosome, like a bubble. If there is insulin receptor substrate available, that bubble can be processed further, (1) releasing glucose to be used for fuel by mitochondria or (2) keeping glucose in cytoplasm where glycolysis, breakdown of sugar, provides a much smaller benefit of just two ATPs per glucose. It should not be a surprise that the role of sugar delivery becomes one of the feedback systems that guard against having too much sugar metabolism products present at a time since the mitochondria cannot handle sugar break-down products.

Said in a different way, instead of breaking down glucose into pyruvate, used for mitochondrial respiration, suppose that pyruvate *reduction* will help the cell survive biological attack. Remember that pyruvate is a three-carbon breakdown product of glycolysis; it can be converted to lactic acid, another three-carbon fragment, if pyruvate is not being taken up by the mitochondria. If

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mitochondria are being attacked and an endless supply of pyruvate supplied, there would be an endless supply of lactic acid made to either poison the cell or change pH-related activities in local tissue because glycolysis sent too much pyruvate towards the mitochondria. What the cell does is to reduce the impact of lactic acid production by preventing excessive amounts of pyruvate to be made in the cell. What an incredible feedback regulation system! Simply shut down glycolysis.

The complexity of these interactions of energy and protein are accentuated by mitochondrial translocases, proteins that are coded for by nuclear genes. These proteins provide a protein import system across the mitochondrial inner and outer membranes. If the translocase genes are suppressed, fewer necessary mitochondrial proteins will be transported into the mitochondria. By suppressing translocase activity, there is an additional mechanism to prevent excessive mitochondrial activation at a time of metabolic stress from external environmental attackers.

There are other modalities of feedback interaction that are remarkable. Some seem so simplistic now that Dr. Ryan has identified what they are for us based on his review of next generation sequencing and review of existing literature. As Dr. Ryan would say, "I didn't invent this, this was here, we have known all the time that these pathways were functioning in everyone's body."

Taking a step back, we see the complications that come from reduction of cellular metabolism. Where does chronic fatigue come from? Does this come from protein abnormalities or from energy abnormalities or both? Where does injury to grey matter nuclei that we see on NeuroQuant come from? Could there be a role for mitoribosomes in normal survival? What about in cardiac myositis? Could there be a role for reduction of activity of portions of cells that control contractility? You bet!

As Dr. Ryan expands his work, he has quietly set the stage for a massive rethinking of what chronic fatiguing illnesses are, what we do to diagnose them, and what we do to correct them. Dr. Ryan has shown what I would like to call a "CIRS curve," in which initial reductions of activity, gene suppression is a better term, for ribosomal RNA large and small subunits is evident. ATP synthesis (there are more new terms to come), mitoribosome large and small subunits, NAD-ubiquinone scaffolding for electronic transport chain systems inside mitochondria, together with translocase functions of inner and outer mitochondrial membranes all are involved in hypometabolism. When these are all suppressed, as we see in patients who have not been treated, i.e., they are "naïve to treatment," with use of the first of the 11 steps of the Shoemaker protocol, there will be correction of these evidences of suppression of gene activity. Indeed, there is an *overshoot* to exceed control values at the end of the first eleven steps. This overshoot is corrected by use of VIP, leading to the last step of the Shoemaker pathway which is one of restoration and normalcy. Over time, this restoration will stay constant and there will be no change when patients go off VIP.

What the CIRS curve means is that we can look at patients, whether they began with post-Lyme syndrome or CIRS-WDB or ciguatera or possibly traumatic brain injury or many others, that will predictably lead to identify metabolic abnormalities that let us not only establish the stage of therapy where people are but also what is left to be done.

These are exciting times for those in the chronic fatigue world because we finally have reached an objective, testable abnormality that defines the illness for the first time ever. If one thinks that we have finally reached the "Holy Grail" of disease management, maybe so. I do too. But the reality is that our knowledge is woefully incomplete. Yet our duty is to make the ***best use of the best data available to help our patients***. So, let us enjoy the Holy Grail idea for today. Tomorrow is another day.

What We Learn from GENIE

The key indication for GENIE is to verify whether a patient has hypometabolism. Taken together, all the elements of abnormalities of nuclear encoded mitochondrial genes are the keys to mitochondrial functioning that can't be evaluated by any mechanism other than transcriptomics.

We have an additional series of biomarkers that involve immune functions as well. The first are **CIRS biomarkers**. These are genes that have importance for CIRS patients. These markers are used as guides for diagnosis and monitoring sequential therapy as we are looking for transcriptomic cure. Here the word "cure" means that the biomarkers would be returned by therapies to equal levels seen in controls.

The vital importance of **apoptosis**, otherwise called programmed cell death, means that the cycle of cell life and death can go awry. When there is disruption of the enzymes that should be marking a cell to be killed by cytotoxic T-lymphocytes or natural killer cells, the cell is programmed to die but die safely. What can happen is that instead of dutifully packaging all of the intracellular contents before the cell is burst apart, when the cell enters *defective apoptosis* it will release into circulation free DNA as well as organelles such as Golgi body, endoplasmic reticulum, and mitochondria. These elements are intensely inflammatory, giving rise to the suggestion that defective apoptosis can be a form of ***endogenous inflammation added to exogenously induced inflammation in CIRS***. We need more data to support this idea but right now the hypothesis remains tantalizing.

From ciguatera to mold to Lyme, **coagulation** abnormalities are routinely seen when transcriptomics are assessed. The coag abnormalities involve both suppression and activation of a series of genes that independently interact with platelet function together with coagulation pathways. We now know much more about coagulation problems in CIRS than just the well documented abnormalities in von Willebrand's profile. One of the observations for years has been the elevated levels of d-dimer in cases of CIRS as an unexplained finding in CIRS cases. I can't tell you in how many people I have chased after elevated d-dimer levels, looking for evidence of intravascular clotting, without finding a source.

Now that we have gene activity, we are looking at a different mechanism for this non-specific rise of d-dimer. At first glance, it seems odd that enhanced

clotting would lead to enhanced bleeding. Missing is the role of enhanced lysis of sub-clinical clots, hence the increased d-dimer. With correction of inflammation, the transcriptomic basis for d-dimer formation, namely enhanced clotting, resolves.

Defensins are substances made by white blood cells used non-specifically to combat ongoing bacterial or viral infection. With elevated defensins, there usually will be an infectious basis. Defensins are not activated without basis.

Granzymes are intimately involved with apoptosis. If granzymes are elevated, there will be activation of signaling for natural killer cells and cytotoxic T-lymphocytes to sort out and then kill the targeted cells. "No cell lives forever" is an old expression but has a lot to do with granzyme function.

For years, I have had wonderful Sunday afternoon discussions with clinicians regarding **methylation**. Methylation seems to be an active subject for discussion among many alternative providers. Epigenetics, anyone? The idea is that by putting a methyl group on a gene, there will be an effect on the gene activity. But that idea does not include the role of ***demethylation*** reversing the activation (or suppression) the methyl group could create. There is an additional role-modulating gene activity for a two-carbon chain attachment, that being ***acetylation*** and ***deacetylation***. This two-carbon subunit is more frequently attached to histones controlling the structure of the insulating proteins around DNA. We can't look at epigenetic change without thinking about methylation and demethylation – and acetylation and deacetylation. Some of these gene-changing properties of a single carbon group (or two-carbon group) can be long lasting, others are short lasting. It is another mechanism of regulation of gene activity.

Cytokine changes are very difficult to measure in blood. The reason for this oddity is that these pro-inflammatory humoral factors can be bound by the cell that makes them or by the adjacent cell. The only measure we see in blood test results is the so-called "endocrine" function of the cytokine floating unbound in blood. Assays, including the multiple cytokine assays, will tell us about the endocrine function of cytokines but not the autocrine or paracrine. Gene activity from GENIE tells us activity immediately, without concern about false elevation or false suppression of endocrine values.

In all the discussion about what an objective test for **Lyme disease** is, NeuroQuant rises to the top in that it shows a distinctive pattern whether the patient has had Lyme for six months or six years. Finally, thanks to the work of Bouquet, et al,[1] we also have an additional distinctive marker for Lyme, a transcriptomic series of genes that show us what occurs in Lyme before antibiotics and Lyme after antibiotics. We worked independently of Bouquet's group to now come up with a Post-CIRS marker for what we see in Lyme patients after antibiotics are done and CIRS therapy is initiated. These are exciting times for Lyme! ➤

Moldy Buildings

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As briefly mentioned previously, for years I have looked at HLA being the marker for who has increased relative risk for CIRS illness. The number 24% for total at-risk HLA in the US population has come up repeatedly both in my practice as well[2] as in practices of many other physicians. We know that HLA has a lot to do with antigen presentation and immune response based on its location of chromosome 6. The idea has been that if there is a problem with antigen presentation, represented by HLA, then there will be a defect in antibody formation. No antigen presentation, no antibody. No antibody, no protection for repeat illness with re-exposure.

Absence of protection from relapse with re-exposure is a cardinal finding in CIRS.

We now have an additional marker for defective antigen presentation, namely the gene abnormality seen in the **T-cell synapse** with antigen presenting cells. What this means is that when a pathogen is taken into an antigen presenting cell, the professional antigen presenting cell (1) breaks down the pathogen into small fragments in the lysosome; (2) is then processed through the endoplasmic reticulum; and (3) loaded onto a major histocompatibility (HLA) receptor; (4) which is then taken to the cell membrane, creating a signal that permits a naïve T-cell to home in and attach to this tasty morsel of this antigen ready for recognition and T-cell processing.

The first step for antigen presentation, after antigen processing, is formation of a synapse between the dendritic cell and the T-cell. The genes involved in this vitally important synapse are ones that are routinely found to be *suppressed* in untreated CIRS. Fortunately, treatment, especially with VIP, corrects the T-cell synapse abnormalities. The problem is not just HLA!

We know that the gene expression for **complement** remains important in many elements. By including a gene marker, we can look at the 33-member protein system in a different fashion compared to trying to make sense of changes in individual proteins. Complement interactions can be numbingly complicated!

In the world of **PTSD**, while we think we have identified a biomarker in NeuroQuant, we just don't have an adequate number of cases. There is a gene reported to be involved with ACTH and cortisol metabolism that has an association reported in the literature suggesting that it is important in recognition of PTSD. This gene is part of GENIE. Initial results are promising; data is in its infancy.

The **cytoskeleton** of a cell is based on microtubular formation. These microtubules are dependent on their genes called tubulins. If there are tubulin abnormalities, like what we see in genes found in plants where benomyl (an azole anti-fungal) had been used, abnormalities can tell us about microtubule problems in day-to-day life of the patient.

There are additional genes as part of GENIE, including those looking at insulin signaling; those looking at anti-inflammatory nuclear transcription factors; those looking at activation of MAP kinases as well as B-cell markers for the synapse between T-cells and B-cells.

Taken together, the information we glean from GENIE cannot be accessed by any diagnostic mechanism. GENIE, therefore, is providing us with information about abnormalities of physiology based on gene activation. CIRS remains the teacher for other illnesses to follow. We have identified the origins of abnormalities in transcriptomics, followed through with abnormalities of proteomics, followed through with hormonal disruption and multiple layers of dysregulation of proteomic activity.

All these changes can be shown to be related to *(1) dysregulation of (2) dysregulation of (3) gene regulation*. That's right; at least three layers of defective regulation of gene activity are found in illnesses such as CIRS.

From where I sit today, there is no limit to what questions we can ask of the transcriptomic findings accumulated to date. Sometimes the more important features of a new paradigm aren't simply what is newly found to be true, but what was incorrect about older ideas. We return to Aldous Huxley telling us, "The key to understanding is casting out false knowledge." We are "casting out" every day, it seems. Let us not forget that only a few ideas in sciences survive the passage of time.

Simple applications of the "casting out" from transcriptomics let us see that viral reactivation is not likely to be a root cause of CFS, despite antibody testing that appears significant. Another is the diagnosis of "mycotoxin illness," already been exposed as flawed earlier. With the ability to define the expected differential gene activation associated with mycotoxin exposure from the literature, we can flesh out what is likely associated with pathologic changes after mycotoxin exposure and what is not. Remember that in CIRS-WDB we see suspected endotoxin effects in over 50% of cases, closely followed in suspected incidence by actinomycetes. Mycotoxin findings are a distant third.

The enormity of importance of hypometabolism in assessment of a unified cause of fatigue and a transcriptomic mechanism to show correction of that cause brings hope to those searching for answers to fundamental questions, such as "When will I get my life back?" Or, "When can I walk into a new restaurant without fear that the restaurant was once a WDB from a prior flood indoors?" Or, "Are my children condemned to this kind of life due to my HLA?"

We must also consider the role of several compensatory metabolic mechanisms once hypometabolism has been initiated. If mitochondrial injury from a ribotoxin attack on mitochondrial ribosomes (mitoribosomes) is present, the cell won't be able to shuttle its normal amount of the fuel source pyruvate, created by glycolysis, into mitochondria. Excess pyruvate not taken into the mitochondria would otherwise be converted to lactic acid, an intracellular poison. How does the cell avoid dying from lactic acid? Simple, reduce glycolysis! Curiously, in the presence of interferon gamma, one of the enzymes that does the work in glycolysis (GAPDH) also interacts with ribosomal protein L13a and a transfer RNA (EPRS) to form a protein complex called GAIT. The GAIT complex will bind to a specific set of messenger RNA in the cell to curb inflammation. "Surviving hypometabolism" is getting complicated. And there is more.

We are building a database to attempt to show what role the insulin receptor has in hypometabolism. We have interesting

findings on insulin receptor substrate 2; the data show great promise.

The sustained finding of genes that predispose to defective apoptosis also holds great promise. We see one particular gene repeatedly in patients with abnormalities in the caspase-driven mechanism of programmed cell death. If the dying cell, programmed to be lysed by natural killer cells and cytotoxic T cells, fails to safely "package" its intracellular materials that are intensely inflammagenic before lysis, bad things will happen. Face it, if cellular contents, especially DNA, are released freely into circulation, we will have an endogenous source of inflammatory response. As Pogo would tell us, "We have found the enemy and he is us."

Upcoming investigations are focused on correlation of abnormal NeuroQuant findings with early dementia. By looking at tau in spinal fluid and simultaneous transcriptomics, we hope to bridge the gap between unknown gene activity in brain tissue and known activity in blood cells. We can't use brain tissue for gene expression studies, but we may have a biomarker in blood to correlate to NeuroQuant abnormalities and cognitive decline, as one of the genes on our GENIE, found overexpressed in CIRS patients, is also found in beta amyloid plaques.

The commonly found differential activation of coagulation genes that are responsive to VIP provides another reachable window for intervention. Stay tuned on this topic!

I would be remiss if I didn't mention treatment of dilated cardiomyopathy in a patient with at least four documented bouts with acute Lyme disease. As her ejection fraction by MUGA bottomed out at 11%, a referral to a cardiac transplant unit at the University of Maryland was made. RNA Seq using whole blood, not cardiac cells, showed a complex pattern of gene disruption, including adrenoceptors and those involved with the calcium/sodium pump, the basis for contractility. Addition of high dose VIP after antibiotics and CIRS RX resulted in correction of heart failure, reduction of LVIDD from 9.2 centimeters to 6.8 in less than one year. I was elated but Dr. Ryan quietly reminded me that a N=1 study, as this one is, must be shown in many others because we can't confirm that cardiac myocyte findings would parallel the WBC findings of correction of genes involved in contractility. My N=1 case success is one more than anything I have seen from the Lyme-dilated cardiomyopathy world.

Even still, the patient is fully active now, without symptoms of heart failure, off all meds. An unexpected spin off in this trial was confirmation of negative effects from carvedilol that followed a dose/response of adrenoceptors. This beta blocker is widely used in heart failure, sometimes with serious adverse effects. Transcriptomics showed us the way in this case; future titration of carvedilol dose to adrenoceptor expression makes sense if the WBC genes hold up as a model for cardiac myocytes.

Summary

The story of CIRS could fit into Thomas Kuhn's *Structure of a Scientific Revolution*. What began as an *anomaly,* an isolated observation of fish kills and human illness from exposure to *Pfiesteria*, a dinoflagellate, has expanded over the past twenty-three years to an integrated *paradigm* of an entirely new illness concept that for the first time provides a supported, evidence-based explanation for countless chronic fatiguing illnesses. It is possible that there is no "modern illness" paradigm that has *more supporting biomarkers* than CIRS. Beginning with exposure assessments, especially use of HERTSMI-2 for CIRS-WDB, cluster analysis of symptoms, and labs ranging to proteomics and transcriptomics, and including volumetric studies of brain injury, stress echocardiogram measurements and VO2 max, the diagnosis and treatment is buttressed by association studies, prospective re-exposure trials using a published protocol (SAIIE), and randomized clinical trials. Using published protocols, we have corrected proteomics, transcriptomics, and grey matter nuclear atrophy.

What this density of objective biomarkers provides is confirmation of diagnosis and treatment, backed by nearly 40 published papers and clinical use by thousands of physicians. As the research basis of CIRS continues to expand, we feel that CIRS will provide the basis to look for new approaches to inflammatory illnesses of our era, especially atherosclerosis, obesity, diabetes, and chronic pain.

And one parting thought: hope for cure is here. Hope now rests on hard clinical trials that show us the way to help those trapped by WDB, among other causes of CIRS. The answers to causes of chronic fatigue are apparent; effective gene-based therapies also are apparent.

In data we will find our answers for today's hope and tomorrow's standard of care.

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Ritchie C. Shoemaker, MD, remains active in the field of biotoxin-associated illnesses, the focus of his practice since 1997. At that time, an outbreak of unexplained human illness, associated with exposure to blooms of a dinoflagellate, *Pfiesteria piscicida*, attracted his attention and interest. Pfiesteria was the first example of an acute and then chronic biotoxin-associated illness recognized and published in peer-reviewed literature. Shoemaker's two papers on diagnosis and then treatment were the first in the world's literature on acquisition of illness from Pfiesteria in the wild. Since that time, other sources of biotoxin-associated illnesses have come forward including other dinoflagellates, cyanobacteria and, most importantly, organisms resident in water-damaged buildings.

Shoemaker has spent the last 22 years treating patients and conducting research that unveils the extraordinary complexity of these illnesses, now called chronic inflammatory response syndromes (CIRS). Starting with no biomarkers and now progressing to over 25, CIRS has been shown to have abnormalities in proteomics and transcriptomics with differential gene activation, the final ultimate pathway of disease production in the world of chronic fatigue.

His collaboration with Dr. James C Ryan, transcriptomist, has led to multiple publications that have application, not just to chronic fatiguing illnesses but to the inflammatory illnesses of the 21st century including atherosclerosis, diabetes, obesity, and autoimmune illness.

As Shoemaker's work has progressed on the complex problems of grey matter nuclear atrophy, a small but growing cohort of patients with multinuclear atrophy and cognitive impairment have led to improvements that may have application to illnesses such as Alzheimer's disease.

Porphyria: Beyond the Houses of Hanover and Stuart

by Diana Crumpler

Abstract

In 1966, Dr. Ida Macalpine and Dr. Richard Hunter demonstrated that the many health problems of George III were compatible with a diagnosis of porphyria. The porphyrias are a group of hereditary multi-system disorders involving abnormalities of porphyrin metabolism. They traced the disease through eight generations back to Mary, Queen of Scots, but made no attempt to delve further into the origins of the faulty gene. My hypothesis is that it was Margaret Tudor, sister of Henry VIII and wife of James IV of Scotland, who brought porphyria to the Royal House of Stuart. To this end, I have traced what appears to be a similar disorder back a further nine generations, through the French Houses of Valois and Bourbon.

Introduction

Porphyrins are cyclic tetrapyrole derivatives, found in all cells and fundamental to pigments such as hemoglobin. Porphyria involves a disturbance of the metabolism of porphyrins, sited either in the bone marrow (erythropoietic porphyria, caused by a recessive gene) or the liver (hepatic porphyria, caused by a dominant gene). Also known as Günther's disease, erythropoietic porphyria is hallmarked by unsightly pigmented scarring, hirsuteness and red-tinged teeth; it has been proposed as the origin of the werewolf legend.[1] The porphyrias highlighted in the following article are of the hepatic kind. My usual field of interest is multiple chemical sensitivity (MCS).[2-4] My interest in porphyria was sparked in 1994 when it was demonstrated that MCS and the related CFS (chronic fatigue syndrome) also involved a disorder of porphyrin metabolism.[5,6] It is now believed that this acquired porphyrinopathy is the upshot of interaction between nitric oxide and peroxynitrite and the regulatory mechanism governing the synthesis of porphyrin biosynthetic enzymes, both syndromes being underpinned by a vicious cycle predicated upon elevated nitric oxide and peroxynitrite (the $NO/ONOO^-$ cycle).[7]

In 1966, mother-and-son medical sleuths Dr. Ida Macalpine and Dr. Richard Hunter solved a two-centuries-old mystery. George III's numerous health problems, both physical and mental, were compatible with a diagnosis of porphyria. Sifting assiduously through archives, they traced the disease through eight generations back to Mary, Queen of Scots.[8] Thirty years later, Rohl, Warren, and Hunt extended the descent of porphyria to the Duke of Kent, who died in a plane crash in 1942. They also speculated that Queen Victoria and Princess Margaret may have been affected.[9]

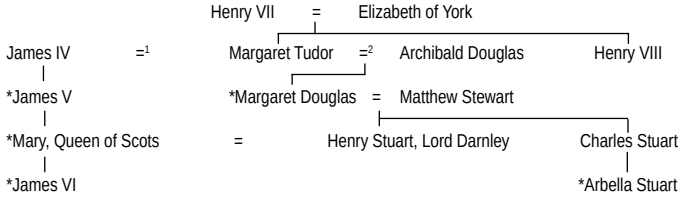
Rather than a single disease, the porphyrias are a group of related hereditary enzyme deficiency disorders involving the central, peripheral, and/or autonomic nervous systems. All involve abnormalities of porphyrin metabolism due to deficient enzyme activity; the type of porphyria depends on the specific defective enzyme (the affliction of the Royal Houses of Stuart and Hanover is now believed to have been variegate porphyria). As naturally occurring pigments, porphyrins are basic to life and all normal beings excrete small quantities. But if the processes governing porphyrin production and metabolism are disrupted, excess porphyrins may accumulate in organs and tissues, where they can produce toxic effects: the deposition of porphyrins in the skin, for instance, may result in acute sunlight sensitivity. In other words, a metabolic glitch allows porphyrins to accumulate to the point where they become toxic.

Symptoms may include acute abdominal pain, behavioral changes ranging from depression to frank psychosis, bowel and bladder problems, fatigue, fluctuations in blood pressure, menstrual exacerbation of symptoms, photosensitivity and skin lesions, paralysis (may be temporary and partial), fever, nausea, difficulty swallowing, headaches, paraesthesias, profuse sweating, tachycardia, and chest pain.

"Mary, Queen of Scots is one of the great invalids of history, not only the great tragic figure," commented Macalpine and Hunter. "So notorious were her colics that her son [James VI] who never lived with her knew of them and recognised his own affliction in hers." Royal physician Sir Theodore Turquet de Mayerne's meticulous record of James' symptoms – frequent bouts of colic, diarrhea, vomiting, palpitations, fast and irregular pulse, difficulty swallowing, rashes and skin lesions, pain and weakness in the limbs, bouts of melancholy, fits of unconsciousness, convulsions, and "water red like Alicante wine" – also allowed for a hindsight diagnosis of porphyria.[10] The latter was the clincher. Porphyrins, complexed with metals, are responsible for many of the brilliant colors of Nature, and the term *porphyria* (derived from *porphyra*, Greek for purple) refers to the discolored urine that may be present during an acute attack.

Mayerne's notes also enabled Macalpine and Hunter to identify porphyria as the cause of death for James' son, Henry, Prince of Wales. Henry died suddenly on 6 November 1612 at St James's Palace. He was only 18 and his death so violent and so sudden

Table 1: Relationship Between James VI, Arbella Stuart, and Margaret Tudor



*Clinical symptoms of porphyria

that poisoning was suspected. An energetic youth, fond of sport, and "of a good constitution," Henry had been stricken with acute abdominal pain and diarrhea, violent headaches, a rapid pulse, weakness, and buzzing in his ears. His breathing became labored, then came delirium ("alienation of braine, ravynge & idle speech out of purpose"), convulsions, and coma.[10] Henry had been buried with his grandmother, Mary, Queen of Scots, in Westminster Abbey. Three years later his cousin and friend, Arbella Stuart, was laid to rest in the same tomb. All three occupants had, during their tragic lifetimes, suffered from the same agonising and baffling symptoms.[11]

Macalpine and Hunter did not attempt to trace the origins of porphyria any further than Mary, Queen of Scots. The incidence of porphyria being relatively high among the Scots, Irish, and Scandinavians, the popular assumption appears to be that it was transmitted through the Stuarts, and Mary's father, James V, did indeed exhibit symptoms of the disorder. If, however, we factor the ancestry of Arbella Stuart into the equation it becomes apparent that the aberrant gene may have other origins (see Table 1).

Arbella, too, was severely afflicted, albeit with a greater tendency towards bouts of mental instability (Arbella had a better claim than James to the English throne, and except for this complication would most likely have been Elizabeth's successor.[1*])

It is not, however, a Stuart but Margaret Tudor, a sister to Henry VIII, that would appear to have been the ancestor-in-common who brought porphyria to the House of Stuart. Margaret had been married at the age of twelve to James IV of Scotland. After James IV was killed in battle in 1513, Margaret married Archibald Douglas, Earl of Angus; James VI was Margaret's great-grandson from her first marriage; Arbella, her great-granddaughter from the second marriage.

How, then, could porphyria have infiltrated the House of Tudor? For a possible answer, we need firstly a nutshell history of the dynasty's rise to power. Henry V (1387-1422) was England's last great Plantagenet monarch. Charismatic and capable, he not only won back England's continental possessions lost by John but was named as successor to Charles VI, the French king. To seal this agreement, Henry was married to Charles' daughter, Katherine of Valois. Their son, Henry VI, was an infant of just eight months when Henry died on campaign in France in 1422. When young Henry came of age, he proved a weak and ineffectual ruler; like Charles VI, he was also subject to bouts of insanity. By 1450, the country was in a bad way: the king's advisors were corrupt; finances were chaotic; people marched on London in protest; and the French territories were again lost.

The upshot of this state of affairs was the civil war later dubbed the Wars of the Roses as Yorkist (white rose emblem) and Lancastrian (red rose) factions battled for supremacy. Both contenders were descendants of Edward III, the Yorkists through Edmund, Duke of York; Henry and the Lancastrians through John of Gaunt and Blanche of Lancaster. The Yorkists were ultimately triumphant and Edmund's great-grandson was crowned Edward IV in 1461. But still peace and stability proved ephemeral. Although Edward had been succeeded by his 12-year-old son Edward V, his brother, Richard of Gloucester, had Edward and his younger brother declared illegitimate and himself proclaimed king. Consigned to the Tower of London, the two little princes were never seen again.

Richard ruled by tyranny, and once again people looked to the House of Lancaster for salvation. But who was left of John of Gaunt's line? Henry VI had been murdered after his deposition and Edward, his only son, had been killed in 1471 at the Battle of Tewkesbury. The only suitable contender was Henry Tudor, John's great-great-grandson from his third marriage to Katherine Swynford. The forces of Henry Tudor and Richard III clashed at Bosworth Field on 22 August 1485. Richard was slain and there, on the battlefield, Henry proclaimed king. The Wars of the Roses were ended, and with them three centuries of Plantagenet rule. The House of Tudor now ruled England.

After Henry V's death, Katherine of Valois had either secretly married or formed a liaison with Owen Tudor, a Welsh squire descended from the olden princes of an independent Wales. History records as indisputable the fact that Katherine transmitted her father's mental illness to her son by Henry V. My hypothesis is that that illness was porphyria, and that it was also transmitted to her Tudor descendants (see Table 2).

The reign of Katherine's father, Charles VI, had started well. Governing wisely after a self-serving regency, he was soon known as *Charles the Beloved.* By the end of a reign blighted by bouts of psychosis, the sobriquet had become *Charles the Mad*. His first recorded attack occurred in 1392, when he was 24. From the start of a military campaign, Charles had appeared feverish, impatient, and rambling. One hot afternoon, as the army rested in a forest, a drowsy page dropped the king's lance. The noise as it clanged against a metal helmet sent Charles into a frenzy; by the time his chamberlain and soldiers were able to subdue him, several men lay dead. Charles then fell into a coma.

Later bouts left him at various times not knowing his name and unaware that he was king; unable to recognise his wife and children; claiming to be St. George; refusing to bathe or change his clothes; and running wildly through his palace. Pope Pius II recorded that one of Charles' delusions involved the belief that he was made of glass and would shatter if touched; to protect himself he had iron rods sewn into his clothes.

"It didn't come from my side of the family," Charles' supremely capable father could well have said. Where, then,

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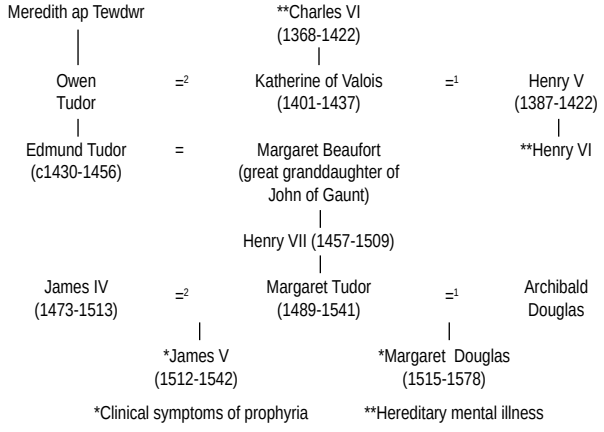
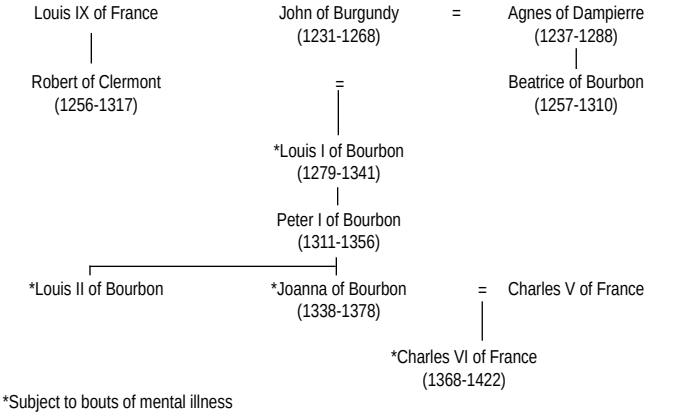
Table 2: Possible connection between hereditary mental illness in the House of Valois and porphyria in the House of Stuart.



1. *Porphyria has more than once determined the course of English history. Had Henry Stuart not succumbed to the disease in 1612, his younger brother of a different nature would not have come to the throne as Charles I. Had Princess Charlotte Augusta not died of an acute attack brought on by childbirth in 1817, there would have been no Victorian era – indeed, Victoria herself would not have been conceived as Charlotte's elderly uncles discarded their mistresses and took young brides of royal pedigree in the race to produce an heir to fill the succession vacuum created by Charlotte's death.

Table 3: Known descent of mental illness in the House of Bourbon



*Subject to bouts of mental illness

did it originate? With the Bourbons, his mother's people. The French House of Bourbon was founded in 1272 when Robert of Clermont, a younger son of Louis IX, married Beatrice of Bourbon. The daughter of John of Burgundy, Beatrice was heiress to the Bourbon estates through her mother, Agnes of Dampierre. Louis, Robert and Beatrice's eldest son, was then created the first Duke of Bourbon. (see Table 3)

Louis' legacy was, however, a blighted one. From some ancestor whose identity is now obscured by the mists of time, Louis had inherited mental illness, a trait that was transmitted to his grandson, Louis II (one of the incompetent regents during the minority of Charles VI); his granddaughter, Joanna of Bourbon; his great-grandson, Charles VI of France; his x 3 great-grandson, Henry VI of England and, if the Bourbon malady was indeed porphyria, through the Tudors and Stuarts to George III and beyond to the twentieth century. The chroniclers do not record whether the Bourbons also exhibited physical symptoms compatible with porphyria. Perhaps they did, but only the more dramatic, more politically disastrous mental manifestations were then considered worthy of mention; a colicky king does not pose the same threat to national stability as one periodically insane. Moreover, by Stuart times the zeitgeist had changed: de Mayerne was a medical man moved by the Renaissance spirit of scientific enquiry.

To return to the Tudors. If Margaret Tudor was the progenitor of porphyria in the House of Stuart, did she herself exhibit any symptoms of the disease? Of Margaret's medical history, we know only the cause of death: "palsy," a term not incompatible with porphyria. Margaret is reported to have "had a palsy on Friday and died the following Tuesday." That, believing she would recover, she failed to make a will suggests that she may have already suffered and survived similar attacks.

Of her daughter's health, we know more. Fourteen years before her death in 1578, Margaret Douglas had described to William Cecil symptoms of an affliction similar to that suffered by James V, Mary Queen of Scots, James VI, Prince Henry, and Arbella Stuart. In this letter "she acknowledges as constitutional the same malady which subsequently proved fatal to her, thus exonerating any accounts of poisoning her."[12] Margaret's precautions notwithstanding, Robert Dudley, Earl of Leicester, was later rumored to have poisoned her. In effect, Henry and Margaret *were* undoubtedly poisoned, not by political conspirators but by toxins produced within their own bodies.

Was Margaret Tudor's brother, Henry VIII, also affected? Food for thought perhaps.

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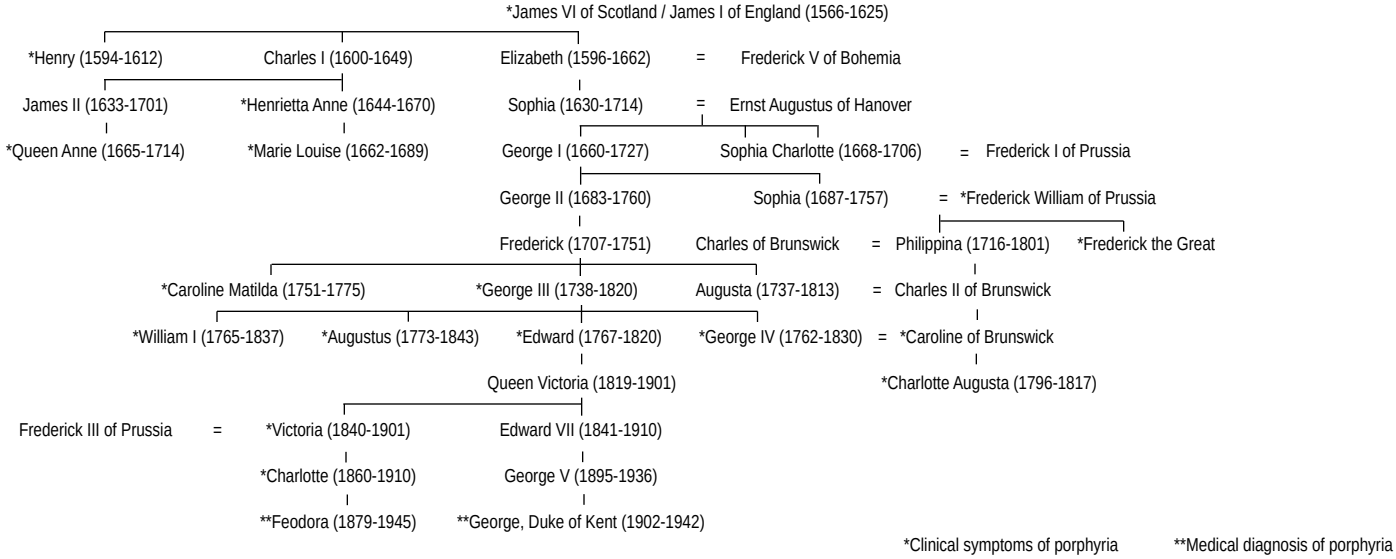
Table 4: Descent of porphyria through the Royal Houses of Stuart, Hanover, Prussia and Windsor



*Clinical symptoms of porphyria **Medical diagnosis of porphyria

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Rebecca Harder has one of the nicest looking, pristine Hydrotherapy clinics in Portland Oregon, which includes hyperbaric oxygen chambers, ozone therapy, massage, etc. She gives this extremely resourceful resource guide (GASTRA GIRL, Saving America One Colon at a time!) to many of her clients, which includes about 40 articles on environmental toxicity and natural solutions, written by some of the most famous individuals in the industry.

One of the articles is entitled, "Why Infrared Saunas are an absolute necessity for Everyone," (Rebecca had been promoting wooden far infrared saunas for 10 + years. She now recommends Relax Sauna.)

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Home heat stress training & Review of the Relax Sauna

"I made a post giving my thoughts on a more systematic way to evaluate saunas for home use and quantify heat stress training, citing some existing research."

I also noted that Both the $250 and $500 Amazon saunas I ordered were dismal failures. After my intense disappointment I started to research the more expensive but seemingly reputable brands in this category. I went with the Relax Sauna.

I was still skeptical of the Relax Sauna but as you'll see below, the results exceeded my expectations greatly. At 25 minutes my temp rose to 101.1F. Second, my heart rate went from 90bpm to 133bpm.

I'm thoroughly impressed with this unit and even more amazed as I write this up and am comparing my numbers to those in the studies on the benefits of Far Infrared Saunas.

I would recommend sauna training and The Relax sauna in particular to anyone (especially paired with cold showers). It seems to have such wide ranging benefits.

The Relax Sauna is probably the best and only realistic option to do hyperthermic heat stress training at home that can replicate (or actually exceed based on my results) the benefits found in studies (on the benefits of Far Infrared Saunas.) ... Do not waste your time with sub $500 units on Amazon.

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for the complete Relax Sauna Review.

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Pediatric Pearls

by Michelle Perro, MD

Men's Health, the Inner Child and ACEs

This topic could have gone down so many channels of funny quips and sarcastic bits, but the haunting of a lingering case of a dad I took care of called out to be shared. It is not unusual to see a child first, then their siblings, mom and occasionally dad and even grandma. I remember one child I cared for with gut issues that cleared up nicely. Ten years later his dad consulted with me regarding his cardiovascular health. Not a typical topic for a pediatrician, but considering I've cared for adults as well as kids for years, we began working together holistically.

SM is a 47-year-old dad of two healthy kids; he is a runner, vegetarian, and part-time stay-at-home dad. While running one day, SM developed acute onset of chest pain with typical myocardial infarction symptoms, including radiation of his pain down his left arm, diaphoresis, shortness of breath, and nausea. He was seen in the ER and diagnosed with a non-ST segment elevation MI. He went to the cath lab where he was found to have 100% occlusion of his LAD. He received a stent and was discharged on aspirin, betablockers, and a statin drug.

The dad was shocked and dismayed over his present status. He prided himself on his normal healthy weight and enviable cholesterol levels. We pursued all the possible triggers of his cardiac event. SM ate all organic food, used home-friendly cleaning and personal care products, shut his wifi off at night, and practiced yoga on a regular basis. He was a software engineer and could perform part of his job at home. He felt he was balanced and overall happy in his marriage as well as his career. This was a man to be cloned.

However, something was not right, and I knew we had not gotten to the root cause of his MI. Aha! Heavy metals! We know the link between heavy metals and CV disease, particularly mercury.[1] SM did have mercury amalgams removed in the past, and we pursued this lead.

However, a DMSA challenge via urine test revealed low levels of heavy metals and an unlikely culprit. We also explored other dental pathology sources such as root canals and cavitations, but SM received a clean bill of dental health.

I then inquired about SM's childhood and where he was raised. I was actually searching for genetic (or epigenetic) familial clues, thinking there might be a connection. There was a long pause and after a deep breath, SM revealed that he had a very chaotic childhood. After a "hmmm" to myself, we began to explore what was troubling from his youth.

SM reported that his mother was bipolar and very violent. He was removed from the home many times and placed in foster care where he was physically abused. His dad had been a drug user and he had very little relationship with him as a child. He witnessed other horrors that children should not experience and as he unraveled his story, I began to put together his history, which revealed a

high ACE (Adverse Childhood Experience) score of 7 and likely the root cause of his CV disease.

An ACE describes a traumatic experience in a person's live occurring before the age of 18 that the person recalls as an adult. Exposures to early adversity not only affects the developing brain (pleasure and reward center, often related to substance abuse), but the prefrontal cortex (impulse control, executive functioning, learning, etc.). We know short-term stressors are managed, but long-term chronic stress creates toxic vulnerabilities.

Much of our understanding of ACEs comes from the 1998 study by Dr. Felitti, et al, looking at 17,000 Kaiser members.[2] Ten historical factors, which are scored on a questionnaire, were broken down by the authors.[3] The list of physical health disorders are extensive with CV disease being prominent. Behavioral risks as well as life potential outcomes are also factored. The authors also reported a dose-response relationship between the ACE score and the corresponding negative health outcomes.

New data has also shown that accumulated ACEs in childhood predicted shorter telomeres later is life suggesting a pathway predicting adult disease.[4] Recent data has also shown relationships on how activation of the stress response can alter a patient's epigenetic process and expression of which genes get transcribed into proteins. Additionally, current data is now demonstrating how disturbances in early life may promote an inflammatory state that can lead to maladaptive changes in mood and behavior. Gut microbes, which play a major role in the gut-brain axis, are involved in this regulation.[5]

A treatment plan embraced cognitive behavioral therapy, hypnosis, cranial osteopathy, and a constitutional homeopathic remedy. Two years later, the patient had no further episodes of chest pain, however, he is being carefully monitored by his healing team.

Understanding the impact and sequelae of adversity during childhood should be a routine part of every clinical encounter and presents an opportunity to heal the child within.

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How Gluten, Casein, Meat Glue, and Colorants (aka a Fast-Food Cheeseburger) May Cause Autoimmunity

review by Jonathan Collin, MD

Food-Associated Autoimmunities: When Food Breaks Your Immune System by Aristo Vojdani, PhD, MSc, and Elroy Vojdani, MD
First Edition: Autoimmunity, Volume 1
A & G Press, A & G Wilshire, LLC., 822 S. Robertson Blvd, Suite 312, Los Angeles, California 90035
2019; Hardback; 432 pg.; $120.00

Recently a patient advised me of a diet that was being advocated not only for weight loss but also for health recovery. The individual promulgating the diet heartily proclaimed its simplicity and assured weight loss; he had lost 70 lbs. in the year he had been abiding by it. His daughter who had been suffering from a myriad of ailments not only lost weight but also became entirely asymptomatic. No testing was required before restricting food intake and there were no adverse effects over which one should be concerned. The diet: meat, salt, and water. Definitely not a diet for vegans or vegetarians. Certainly not a high fiber diet. A diet high in phytochemicals and anti-oxidants it is not. But it appears to have all the essential amino acids, fatty acids, vitamins, minerals and other nutrients sufficient for survival. Of course, this diet has not been tested and is not being advised by the book authors or this reviewer.

What is notable about the diet is what is missing, namely no grain, no dairy, no lectins, no nuts, no soy, no fish, no shellfish, no fowl, and no eggs. Yes, it is a very boring diet – no dressings, no condiments, no processed foods, no preservatives, no colorants, and no chemical additives. What the Vojdani authors, who are father and son, would tell you is that the diet removes offending foods from the gastrointestinal tract. With an elimination of sensitizing foods, the intestine's immune system would not continuously form antibodies to them. Such IgG, IgM, and IgA antibodies unfortunately not only have a high affinity for the respective food proteins but also diverse tissue receptors. In other words, the IgG antibody for gluten can have a strong cross-reactivity with myelin or neuron dendritic cells. It is the accumulation of antibodies formed by the intestine's mucosal immune system that sets the path for unimpeded cross-reactivity that leads to autoimmunity. Immune system antibodies rarely exist alone as individual immunoglobulins; much more frequently an antibody to food will complex with a tissue-based antibody and a complement component will cement the complex together. As one might imagine the body's ability to control such food-tissue complexes is limited, and the potential is high for major tissue damage to follow.

As the Vojdanis explain in this very well written and illustrated text, food ingestion plays a markedly important role in initiating and perpetuating autoimmune disease, a role that is nearly always ignored except in celiac disease. In fact, it is non-celiac gluten sensitivity, a condition that is rarely diagnosed by allergists or gastroenterologists, that is thought to be responsible for irritable bowel syndrome.

For most patients the "meat only" diet and other restrictive diets that eliminate grains and other foods would not be an acceptable option unless there was evidence provided why such a restriction would be required. Although an "elimination" diet would offer valuable information for the physician and patient, most individuals do not have the commitment and perseverance to wholly test the foods they are eating. An appropriate alternative would be to assess antibody levels to foods and food components. The Vojdanis discuss the need to measure blood antibody levels directly and avoid crude laboratory testing based on qualitative in-vitro assessment of cellular deformation following exposure to food antigens. From the authors' experience food testing needs to include antibody response to both cooked and raw foods – the reaction to a raw food is not necessarily the same as a cooked food. Individual protein components of grain and dairy need to be measured for similar reasons – one protein component may have a strong antibody response while a related component may not. The big one, nevertheless, is wheat, more specifically gluten. Missing a gluten sensitivity and finding reactivity to a fruit or vegetable would be a major oversight; once gluten sensitivity is confirmed or ruled out, determining other food reactivities would be helpful diagnostically.

A list of foods that have demonstrate elevated IgG antibody levels is a basis to ask a patient to undertake an elimination diet of the offending foods. But to what degree are these food reactivities damaging the body? Aristo Vojdani's work has demonstrated that cross-reactivity of food-based antibodies leads to tissue damage yielding tissue-damage based antibodies.

Laboratory assessment of antibody reactivity can be measured of the mucosal epithelium providing an assessment of intestinal permeability. Similarly, antibody reactivity of neuronal epithelium and its associated immune system provides a means to assess blood brain barrier function and central nervous system immunity. Indeed, much of the body tissues can be evaluated to determine if there is pathologic tissue reactivity providing a novel means to determine if there

continued on page 84 ➤

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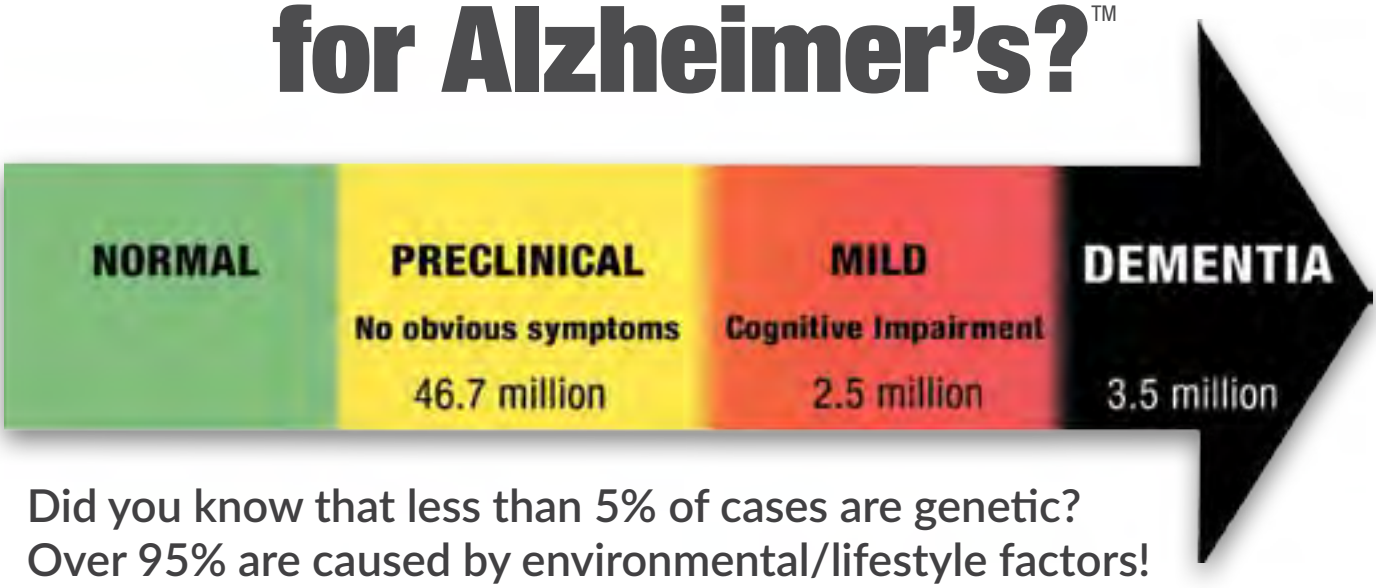

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➤ *continued from page 82*

is autoimmunity developing in connective tissue, muscle, bone, skin, thyroid, liver, and other organ tissues. If there is a relationship between food reactivity and tissue reactivity, theoretically one could modify one's diet and observe symptomatic changes while monitoring changes in antibody levels.

Dr. Aristo Vojdani is the head of Immunosciences Laboratory where he has developed the methodology for assessment of food reactivity and tissue reactivity. Lab testing utilizing Dr. Vojdani's technology is available through Cyrex Laboratory in Phoenix, Arizona. Laboratory testing is organized in arrays that address pathological concerns such as "Wheat/Gluten Proteome Reactivity & Autoimmunity" and "Multiple Autoimmune Reactivity Screen." While some patients who have immune system deficiency will not show any food reactivity, most patients with autoimmunity will have significant food reactivity. Hence, complex, symptomatic patients deserve to undergo food reactivity testing.

Returning to the "meat only" diet discussed earlier, meat has been documented in the past few years to be a cause of food reactivity. People who have been bitten by the Lone Star tick have developed an IgG allergic reaction to beef and pork. Such individuals manifest severe allergic reactions whenever they eat meat. Moreover, the Vojdanis discuss the mechanism by which digestion of red meat can lead to formation of xeno-antigens that bind to tissue and form xeno-autoantibodies, which threaten development of autoimmunity and cancer. Hence, the "meat-only" diet could cause autoimmunity. Furthermore, salt, itself, can help drive autoimmunity, according to the Vojdanis because high salt can alter the microbiota inducing an increased production of T_H17 cells, the helper-T cells that can initiate autoimmunity. Finally, meat glue is used by the food industry to glue meat together. Unfortunately, as the Vojdanis discuss in their well-referenced, encyclopedic text, meat glue and meat proteins contribute significantly to autoimmunities. ◆

CALENDAR

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CALL FOR ABSTRACTS for the **12th INTERNATIONAL CONGRESS ON AUTOIMMUNITY** (May 2020 in Greece). Abstract deadline: **DECEMBER 3.** CONTACT: https://autoimmunity.kenes.com/abstract-submission/

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MARCH 3-7: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE SPRING MEETING – The Roots of Toxicity in Dallas, Texas. CONTACT: http://aaemconference.com/

MARCH 26-28: THE FORUM FOR INTEGRATIVE MEDICINE – "Solutions for Complex Illness: Putting The Pieces Together" in Seattle, Washington. CONTACT: https://forumforintegrativemedicine.org/

MARCH 27-29: FLORIDA HOMEOPATHIC SOCIETY ANNUAL CONFERENCE – The Microbiome and Homeopathic Bowel Nosodes with Hilery Dorrian, LicAc, LCH in Orlando, Florida. CONTACT: https://www.floridahomeopathicsociety.org/

APRIL 2-4: 17th INTEGRATIVE MEDICAL CONFERENCE FOR CANCER AND CHRONIC DISEASE in Grapevine (Dallas), Texas. Pre-conference training. CONTACT: https://bestanswerforcancer.org/

APRIL 3-5: ENVIRONMENTAL HEALTH SYMPOSIUM 2020 – Immunotoxicity: The Intersection Between Toxic Exposure, Infectious Disease, and Autoimmunity in Scottsdale, Arizona. CONTACT: https://environmentalhealthsymposium.com/

APRIL 3-5: SIBOCON2020 – Clinical Applications in San Diego, California. CONTACT: https://www.synergycmegroup.com/sibocon2020

MAY 15-17: 15th ANNUAL JOINT AMERICAN HOMEOPATHIC CONFERENCE – Homeopathy in Pain Management in Orlando, Florida. CONTACT: https://www.homeopathycenter.org/2020-joint-american-homeopathic-conference

MAY 20-24: 12th INTERNATIONAL CONGRESS ON AUTOIMMUNITY in Athens, Greece. Special session on diet and autoimmunity, chaired by Dr. Aristo Vojdani. CONTACT: https://autoimmunity.kenes.com/

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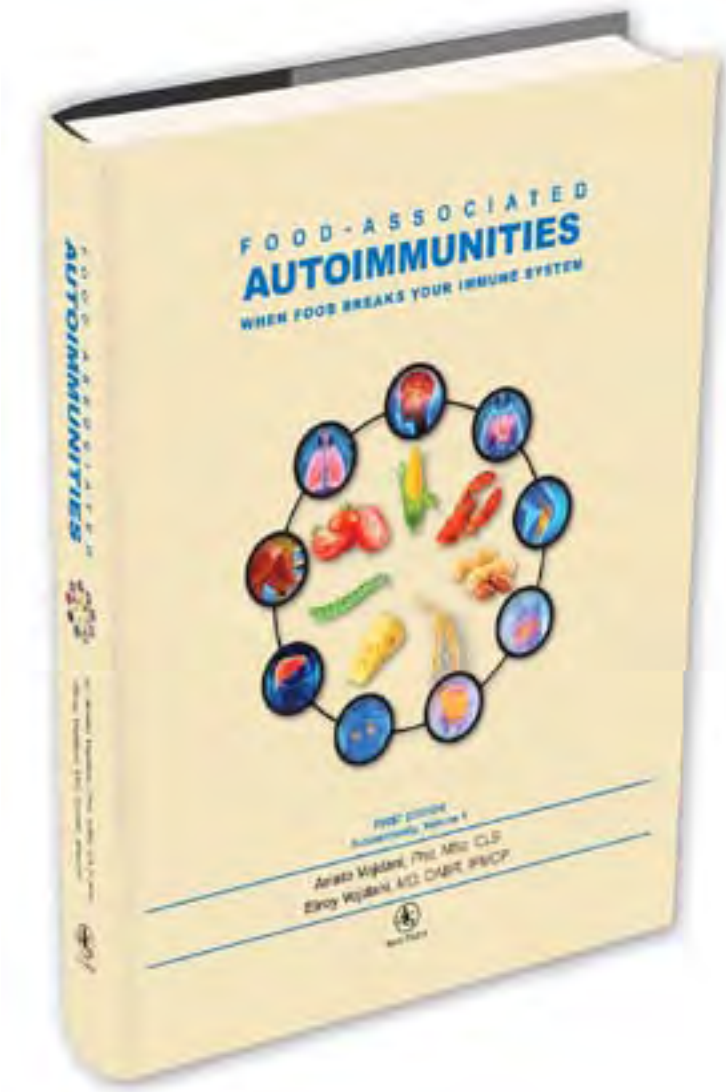

The original inventor of food IgG testing breaks decades of silence regarding the prevalence of innacurate food testing and reporting in many laboratories.

This ground-breaking book redefines the standards for reliable reporting of food antibody test results.

In this book, the father and son team of Aristo Vojdani, PhD, MSc, CLS and Elroy Vojdani, MD, DABR, IFMCP, reveal new discoveries and information regarding the relationship between food proteins and autoimmune disorders.

The growing scientific interest in the interaction between diet and autoimmune disorders has created the new field called immunodietica, which is the subject of this book.

Ask Dr. J

by Jim Cross, ND, LAc
thias1020@yahoo.com

Does the Dose Really Make the Poison?

Was Paracelsus correct with his statement above from the 16th century[1]? Making sense of this statement goes a long way into helping us understand how we can effectively deal clinically with the garbage bag of chemicals and heavy metals that we are assaulted with in the 21st century plus what is still present from the 20th century.

Cat Stevens' wonderful song, "On the Road to Find Out," contains a line that has always helped me make sense of seemingly disparate, contradictory options: "I found my head one day when I wasn't even trying." Like most readers and practitioners of the *Townsend*, I have gone through multiple health incarnations in this lifetime: taking large doses of multivitamins/minerals because the soil is depleted, being a vegetarian because meat is too acidic for our bodies, taking tons of antioxidants because the environment is just too toxic, etc., etc. Fortunately, I am not satisfied with the status quo and continue to read, attend seminars, and learn from my patients. Because of this, I continually modify what I eat and take as supplements and also adjust what I recommend to my patients. I, no longer a vegetarian, buy fresh, local mostly organic fruits and veggies which, I feel, provide me with more than adequate nutrition. I have also begun to question "the world is just too toxic" argument and thus we need to consume tons of antioxidants. Fortunately, as the line from the song above so elegantly states, I keep moving in new directions even though I don't necessarily push myself to. My drive for perfection makes sure that these opportunities keep appearing in my life, and my being is open enough to recognize the importance of these new directions.

Our cells generate supposed dastardly molecules called reactive oxygen species/ROS naturally during mitochondrial oxidative metabolism but also in response to molecular invaders from our environment such as heavy metals, pesticides, volatile organic compounds, etc. If these ROS are not neutralized, they have the ability to overwhelm cellular defense strategies and initiate cellular damage that can lead to various disease states like coronary artery disease, cancer, neurodegenerative diseases, and just plain old aging. Conflicting studies are beginning to show that these same evil ROS molecules can actually serve as critical signaling molecules for healthy cell survival through regulating proliferative and apoptotic pathways.[2]

So, what path is one to follow: spend hundreds of dollars on effective ROS quenchers or walk down a San Francisco street and deeply breath the polluted air that exists there? As my father so astutely taught me, the answer always appears to lie in the middle of the road. I know this is hard to swallow for Trump/Hillary supporters because unfortunately the squeaky wheel always seems to get the grease. I do think, though, my father had the right idea: be quiet and observe what is really happening and don't let anyone dissuade you from your path.

Although some data suggests that high levels of ROS contribute to insulin resistance, there are other datasets that suggest the complete opposite might be true. For instance, there is some evidence that mitochondrial oxidants are required for the glucose-induced insulin secretion by pancreatic beta cells.[3] Furthermore, like many other growth factors, insulin binding to its cell surface receptor stimulates production of hydrogen peroxide.[4]

In addition, ROS species have been increasingly implicated in the physiological regulation of crucial embryological processes such as the differentiation of cardiomyocytes during fetal development and the emergence of embryonic stem cells.[5,6] So, maybe the old adage is correct: no one or no thing is completely evil.

Now, let's move in the antithetical direction and observe where ROS can become problematic: insulin resistance pathogenesis. One study found high plasma glucose levels, as can occur in insulin resistance, alters the morphology of mitochondria and causes them to fragment.[7] Another study established that increased ROS levels are an important trigger for insulin resistance in numerous cellular model settings.[8] The source of this ROS appears to be in the mitochondria where increased amounts of the ROS hydrogen peroxide are produced.[9] These mitochondrial metabolic defects have at least partially been reversed by pharmacological or genetic strategies that increase mitochondrial antioxidant levels.[10]

Another area where ROS can initiate bodily disease lies in cardiovascular disease/CVD. ROS have been shown to be a primary or secondary cause of many cardiovascular events.[11]

ROS mainly act as a trigger for damage to the vascular endothelium, which leads to endothelial inflammation. Macrophages are then recruited to the area, which leads to ROS generation in the area of the plaque. Next, circulating LDL is oxidized by the ROS leading to foam cell formation and lipid accumulation and eventually the formation of atherosclerotic plaque. Both in vivo and ex vivo studies provide evidence supporting the role of ROS in atherosclerosis formation.[12-15]

Cat Stevens' song has one more fantastic line: "the answer lies within." For me, "within" here means inside our cells. With regards to ROS, I like to think that our lives will hopefully resemble a neutral teeter totter where both sides are suspended equally in the air. Hopefully, the ROS we generate ourselves and are generated from the outside world will be neutralized by our internal cleansing system. Here is an instance where the status quo needs to be maintained. If we have patients who exist at a neutral teeter totter state, then all we need to do is attempt to help them remain there: tweak their diets a bit, point out where they could be exposed less to whatever environmental toxins are present in their life, identify genetic emunctory weaknesses they have inherited and attempt to strengthen them, etc.

If we have patients where the teeter totter is depressed so that they are not effectively eliminating the ROS, then we must become very good game show contestants. Instead of having to guess which door, 1/2/3, the new car sits behind, we need to become effective sleuths and figure what aspect(s) of their internal cleansing system is not effectively performing their tasks. This requires looking at more than three possible doors and up to 10 or so. We also need to decide which door to open and deal with first. For e.g., a person comes to you with what they say is Lyme's disease. That seems like an easy fix. Unfortunately, they may just now be expressing the Lyme's because they moved into a house filled with mold which pushed the teeter totter into an unstable direction that caused a TILT/Toxin Induced Loss of Tolerance. This TILT then allowed the Lyme to express itself. TILT will also be a topic for a future column, as it basically indicates that people have become intolerant to their chemical environment.

Our patients are becoming more complex. This requires us to also become better lateral thinkers and expand our clinical boxes so that we can effectively deal with patients in a manner that actually identifies the cause(s) of their maladies and sets them on a course that will steer their bodies back to a more homeostatic balance.

Like my father, walk the middle of the road with regards to ROS and the antioxidant system. Also, increase your cognitive dexterity so that you can constructively wade through the mine field that science has become and make solid, clinical choices that benefit you, your family, and your patients.

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The Value of Patience

A few weeks ago, I was taking a road trip on which there was a 28-mile stretch with one lane in each direction. The traffic flow was relatively slow – at or slightly below the speed limit. Often, when confronted with slow-moving traffic, I stay close enough to the car in front of me to be able to pass during one of those occasional times when the solid yellow line changes to a broken yellow line. On this day, however, I was not in a hurry, so I took a different approach.

The conventional wisdom is that a driver should stay at least two seconds (and preferably 3 seconds) behind the car in front of him, in order to be able to stop safely in an emergency situation. On this day, however, I chose to maintain an even larger distance – around six or seven seconds behind the car in front of me. While I was still traveling at the same speed as the cars in front of me, maintaining the additional distance shielded me from the compressions and rarefactions that are an inevitable part of driving in traffic. When the car in front of me slowed down, I simply took my foot off the accelerator and gradually decelerated as I moved closer to the other car. Using this method, I never came so close to the car in front of me that I had to apply the brakes. In fact, during more than 30 minutes of driving on that road, I did not have to press the brake pedal even once.

In contrast, the driver in front of me was following the car in front of him quite closely, and his brake lights were frequently going on and off. Similarly, the driver behind me was tailgating, apparently annoyed that I would not move a few seconds closer to the next car. Eventually, the car behind me passed me, accomplishing the questionable feat of promoting himself from ninth to eighth in the caravan.

It occurred to me that there are a number of advantages of maintaining a greater-than-usual distance behind the next car. First, it decreases the amount of wear and tear on the brakes. Second, avoiding repeated cycles of braking followed by accelerating probably decreases the amount gasoline used, which is good for both the environment and the pocketbook. And third, cruising along at a comfortable distance is easier on the nerves, although that ease is mitigated to some extent by the perception of being followed by an annoyed tailgater.

This leisurely road trip was a lesson in the value of being patient. And it reminded me of how that lesson applies to my professional life. Forty-six years ago, I decided that my life's work would be to learn all I could about nutritional medicine and to teach others what I learned. Early on in this journey, I was frequently frustrated and angry at the unwillingness of the medical establishment to take a serious look at nutritional medicine or other alternative therapies. I was anxious to help start a revolution in healthcare and to get it going sooner rather than later. After a while, however, it became clear that any progress that was going to be made was more likely to be evolutionary than revolutionary. The entrenched powers that had shaped modern medicine's world view (such as the medical schools, the medical journals, and the pharmaceutical industry) had built up too much inertia (i.e., resistance against change) to be overcome easily or quickly.

I came to realize that I had a choice between being angry at the slow pace of progress or being appreciative of the fact that things were moving in the right direction (albeit slowly). Those of you who have followed my writings in the *Townsend Letter* over the past 36 years may have guessed that I have shifted to some extent from the former to the latter. One of the laws of physics is that force x time equals mass x velocity. That is, the longer that we keep pushing, the greater will be the speed at which we can get from where we are to where we want to be (of course, the speed also depends on how hard we push, but that is a discussion for another day).

We can be encouraged by the fact that the acceptance of natural/integrative/holistic/alternative medicine has been accelerating over the past decade or so. The number of schools teaching alternative therapies, the number of practitioners using these types of treatments, and the interest among the general public are all increasing rapidly. Patience in the pursuit of a goal is being rewarded, and continued patient pursuit will continue to be rewarded. To paraphrase the Jewish text, *Pirkei Avot* (Ethics of our Fathers), we are not obligated to complete the work, but neither are we free to abandon it.

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Clinical Study #1 (1999)

In a study of 319 women visiting three medical clinics, most women's normal vaginal bacterial residents included *L. crispatus* (32%), followed by *L. jensenii* (23%), *L.* 1086V (15%), *L. gasseri* (5%), *L. fermentum* (0.3%), *L. oris* (0.3%), *L. reuteri* (0.3%), *L. ruminis* (0.3%), and *L. vaginalis* (0.3%).*

Antonio MAD, *et al. Journal of Infectious Diseases* 1999;180:1950–6.

Clinical Study #2 (2007)

In another study involving 126 healthy pregnant women, *L. crispatus* and *L. gasseri* were the most dominant species found, followed by *L. jensenii* and *L. rhamnosus.**

Kiss H, *et al. BJOG: An International Journal of Obstetrics & Gynaecology* 2007;114: 1402-1407.

Clinical Study #3 (2014)

In a double-blind, randomized placebo-controlled trial, 1-week of oral supplementation with the four Astarte strains significantly enriched *Lactobacilli* in the vaginal tract and reduced Nugent score in the neo-vagina of post-operative transsexual women, an environment typically resistant to colonization by *Lactobacilli.*

Kaufmann U, *et al. Eur J Obstet Gynecol Reprod Biol.* 2014 Jan;172:102-5.

Clinical Study #4 (2016)

In immunosuppressed pregnant women with herpes infection, oral supplementation with the four Astarte strains significantly reduced undesirable microbes in the intestines and vagina, and simultaneously increased vaginal *Lactobacilli* 3-fold compared to placebo.* This was accompanied by reduced incidence of placental insufficiency, pre-eclampsia and fetal distress in the probiotic supplemented women.

Anoshina TM, *et al. Perinatologiya I Pediatriya* 2016;4(68):22-25.

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