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Non-Allergic Rhinitis and Immunotherapy

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A Building Block for Coenzyme Q10 Production

Marc Grossman, OD, LAc
An Integrative Approach to Glaucoma

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From the Publisher

Congressional Report Finds All Commercial Baby Foods Contain Toxic Metals

A US Congressional report released on February 4 found that most commercial baby foods are contaminated with lead, arsenic, and cadmium[1]; the committee initiated its investigation in November 2019. Levels of lead, arsenic, and cadmium (mercury was not generally tested) were all found to exceed what the FDA considers acceptable for water or juice. Baby foods investigated included Nurture's Happy Baby, Gerber, Beech Nut, Hain Celestial, Earth's Best Organic, Campbell's Plum Organics, WalMart's Parent's Choice, and Organic Foods' Sprout; the three latter manufacturers refused to supply testing data and did not cooperate with the subcommittee.

Beech Nut used ingredients that sometimes tested over 900 ppb for arsenic. Happy Baby's testing revealed that more than 25% of their marketed baby foods contained over 100 ppb for arsenic. Hain baby foods used some ingredients that contained more than 300 ppb of lead with over 80 foods containing more

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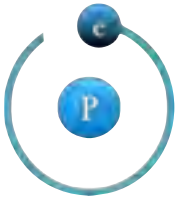
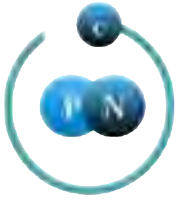
Deuterium in Water

The Explanation, the Risks, the Solutions

"Reducing the total body burden of deuterium may be the most significant health optimization, anti-aging, and longevity strategy known."

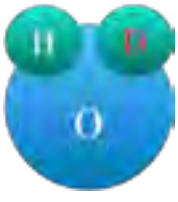


Light Hydrogen
Protium, "H"



Heavy Hydrogen
Deuterium, "D"

Light Water H_2O



Heavy Water HDO

It has been more than 60 years since the initial Russian discovery of the damaging biological effects of deuterium - found in ALL water sources on Earth and EVERY food we consume.

Mainstream health and medical professionals have been unaware of this health compromising phenomenon which has been hiding in plain sight.

Litewater Scientific is here to help you learn about this rapidly emerging health science which some refer to as the most profound biological discovery of our time. Shall we begin?

So, what is deuterium?

Designated as "D", it is one of the three isotopes of hydrogen - the simplest element. But "D" is *twice as heavy* as the more abundant common form, "H". This factor makes deuterium a biological toxin.

Both H and D combine with oxygen to form water molecules, predominantly H_2O and HDO. There are about 6 drops (150 ppm) of deuterium-containing water molecules in every liter of water on Earth.

Currently there are no hard and fast rules on characterizing deuterium ppm levels. However, water with less than 130 ppm typically qualifies as "deuterium depleted" or "light water".

Why is the deuterium in water and foods so damaging to living things?

Because of its high mass, deuterium routinely disables the most critical cellular functions - including ATP production and DNA replication. This occurs every moment from conception to death.

How can we avoid these life-long harmful health effects of endogenous deuterium?

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Letter from the Publisher

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than 20 ppb lead. Gerber's carrot baby food contained more than 5 ppb cadmium with some carrot products having more than 80 ppb. Sixty-five percent of Happy Baby foods had more than 5 ppb cadmium. Most companies did not test for mercury; Happy Baby's test revealed more than 10 ppb mercury. All of the levels cited above exceed greatly what the FDA accepts on water testing.

As the subcommittee report explains, baby food adulteration with toxic metals is extremely dangerous for a developing infant. The FDA has not established maximum safe levels for toxic elements in baby foods; manufacturers are free to decide whether their baby foods exceed acceptable limits for lead, cadmium, arsenic, and mercury. Of note, the Congressional investigation did not examine chemical levels found in baby foods; chemical contamination frequently correlates closely with toxic element levels.

While this report examined metals found in baby foods, it is entirely probable that such adulteration is found equally in processed foods eaten by older children and adults. It has been the experience of chelation physicians that upon provocation most individuals do show excretion of significant amounts of lead, mercury, and cadmium. The question often arises in patients as to what is the source of their high lead and mercury levels. We need not look much further than the food our patients eat to answer that question.

Diego Saporta, MD, Examines Allergy Desensitization's Role in Treating Asthma

Readers of the *Townsend Letter* are familiar with Dr. Saporta who has authored numerous articles on subcutaneous (SCIT) and sublingual immunotherapy (SLIT). (See his cover story for the April 2018 issue: "Management of the Allergic Patient: The Role of Different Diagnostic Tests."[2]) Dr. Saporta is board-certified in ENT, practicing in Elizabeth, New Jersey, in his clinic, Associates in ENT & Allergy. He is a fellow of the American Academy of Otolaryngologic Allergy and member of the American Academy of Environmental Medicine. As part of the teaching faculty of the Pan America Allergy Society, he directs the primary training in allergy.

In this issue Saporta examines the underappreciated role of allergy in patients with asthma. While it is understood that asthma has an allergic component, it is not uncommon for asthmatic patients to test negative on allergy testing. Saporta asserts that allergy testing depends on the immediate reactivity of IgE antibody to suspected allergens. However, asthmatic individuals may have non-IgE allergy reactivity, for example, allergy mediated by IgG antibody or mast cell reactivity. Once allergy sensitivity has been diagnosed in the asthmatic patient, allergic desensitization by injectable or oral immunotherapy

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Letter from the Publisher

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must be undertaken cautiously. An asthmatic individual is at high risk to destabilize when exposed to a known allergen. Undertaking a desensitization program may inadvertently trigger asthma and/or anaphylaxis – emergency support with injectable epinephrine, inhaled corticosteroids, and respiratory albuterol must be part of the patient's tool kit. Dr. Saporta argues for a greater awareness of diagnosing asthma in patients with allergic rhinitis as well as airway reactivity. While immunotherapy poses risks, asthmatic individuals will greatly benefit from properly administered SCIT and SLIT.

Trevor Cates, ND, Defines the Relationship Between Leaky Gut and Atopic Dermatitis

Last April Dr. Cates explored in the *Townsend Letter* not only how the appearance and condition of the skin reflect our internal health but also how healing a skin rash or acne requires cleaning up the body internally.[3] In this issue she compares the abnormal characteristics of leaky gut to a "leaky" skin condition. The disruption of the microbiome and the intestinal epithelial permeability and inflammation is comparable to cutaneous epithelial permeability, inflammation, and skin dysbiosis. Moreover, optimal acidic pH of the skin is characteristically alkalinized in atopic dermatitis. Treatment requires dietary management of leaky gut, herbal repair of intestinal inflammation, restoration of a balanced microbiome, and application of dermatologics to acidify and hydrate inflamed skin tissue.

Cates has designed her own line of creams to restore optimal skin pH and hydration. Many skin products do not effectively acidify and hydrate; Dr. Cates finds that a coconut oil base and vitamin E oil work best in normalizing the skin microbiome. She suggests testing the skin salve by applying it to the forearm and then covering with a Band-Aid for two days, watching for any allergic or inflammatory reaction before applying it broadly on the dermatitis. For Cates, the secret of managing skin conditions is always treating the patient internally and externally.

Cover Story: Dr. Marc Grossman on Glaucoma

Among the many things that have fallen to the wayside during the pandemic has been treatment of non-urgent medical conditions. In the first half of 2020, elective surgery and cardiology admissions dropped precipitously. For a brief period of time last summer and fall, COVID-19 hospitalizations dropped prompting more hip replacement surgery and dermatology exams. Despite the uptick now of emergency room and ICU treatment for COVID-19 patients, more individuals are seeking non-infection routine care. One of the conditions that has been neglected is glaucoma.

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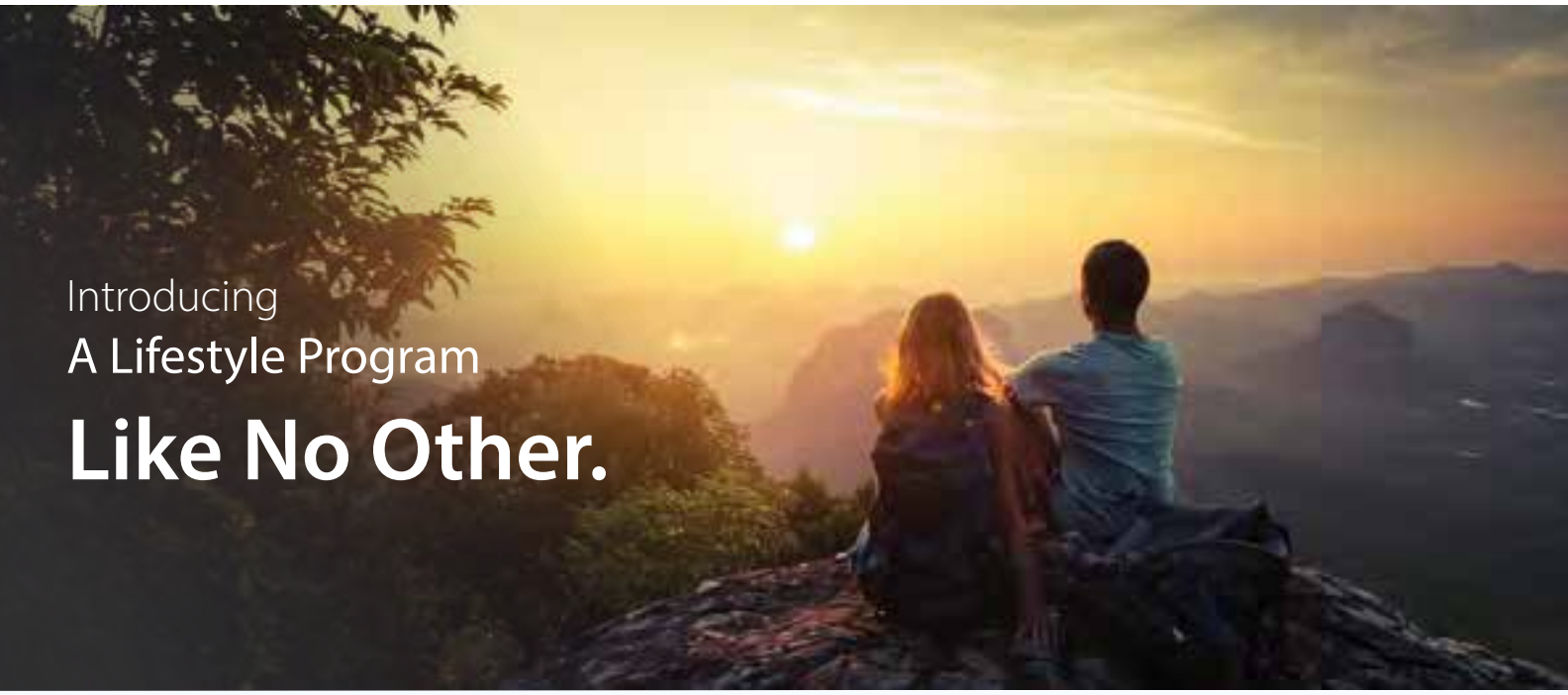

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Letter from the Publisher

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Like hypertension, it is "silent," meaning there is no pain, no discomfort, no physical impairment – nothing to alert one of its presence. The only clue that glaucoma is an issue appears during the eye doctor visit – an elevated intraocular pressure, defects in the visual field, an abnormal cupping of the optic nerve. Treatment of glaucoma is critical if one is to ensure preservation of one's vision. The question is whether it should only be managed with pharmaceutical drops and/or surgery or can it be managed by integrative medical approaches? Dr. Grossman would argue that nutritional supplementation, dietary and exercise changes, acupuncture, and stress management can play a major role in controlling glaucoma.

Primary nutrients advised for open-angle glaucoma include vitamin C, alpha-lipoic acid, and
Coleus forskohlii for reduction of eye pressure. Grossman's protocol for managing optic nerve health includes supplementation of taurine, bilberry, grapeseed extract, magnesium, B vitamins, N-acetyl cysteine, CoQ10, and omega-3 fatty acids. He suggests well formulated supplement formulas combining these nutraceuticals. Dr. Grossman's dietary recommendations advise reduction of coffee drinking, MSG-containing processed foods, and foods with artificial sweeteners. Foods thought to reduce intraocular pressure include garlic, onions, beans, spinach, celery, turnips, yellow and orange vegetables, green leafy vegetables, seaweed, apples, oranges, and tomatoes.

Dr. Grossman, a doctor of optometry and licensed acupuncturist, is a co-founder of Integral Health Associates in New Paltz, New York. He is the author of numerous books, including *Magic Eye Beyond 3D*: *Improve Your Vision;* also *Greater Vision – A Comprehensive Program for Physical, Emotional, and Spiritual Clarity.* Dr. Grossman founded the Rye Learning Center in 1980, a multidisciplinary institute for learning disorders. Grossman feels that vision can be improved without requiring stronger prescription lenses or surgery. To achieve such vision improvement requires a whole-body approach with lifestyle changes, eye exercises, as well as addressing emotional and spiritual well-being. *Townsend Letter* readers can read Dr. Grossman's article on "Integrated Approach to Macular Degeneration" in the April 2020 issue (available on our website: https://www.townsendletter.com.)

Jonathan Collin, MD

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Shorts

briefed by Jule Klotter
jule@townsendletter.com

Dry Eye Disease

Dry eye disease (DED), affecting up to 30% of the population, entails more than discomfort that can be relieved with eye drops. If untreated, DED can become a chronic, progressive condition that damages the cornea and leads to visual impairment and, possibly, blindness. Several factors can contribute to dry eye, including LASIK surgery, contact lens use, cosmetics, prescribed medications, and autoimmune disease. "Severe dry eye can be precipitated by several common autoimmune conditions [Sjögren's syndrome, lupus, rheumatoid arthritis, and thyroid diseases] in which inflammation plays a key role," explain Cynthia Matossian, MD, and colleagues. Women have a higher risk of DED (and autoimmune disease) than men.

The protective fluid that lubricates the eye's cornea and creates a smooth, refractive surface, enhancing vision, consists of more than the salty solution that we call tears. The outermost layer contains lipids, secreted by Meibomian glands (MGs) that line the upper and lower eyelids. These lipids act as a seal that inhibits evaporation of the watery-mucin tears, produced by the lacrimal glands. Beneath the tears and directly covering the cornea is a mucous layer, produced by Goblet cells and conjunctival epithelial cells. DED symptoms occur with insufficient tear production from the lacrimal glands and/or with increased tear evaporation, due to MG dysfunction and insufficient production of the protective lipid layer. As damage occurs to the eye's surface, inflammation ensues – leading to more damage.

Several prescribed medications can cause or aggravate dry eye, according to Matossian et al, including several antidepressants, antihistamines, antipsychotics, anxiolytics, and hormonal drugs. In addition, some topical eye medications contain active ingredients or preservatives that can destabilize the tear film, irritate the eye, and cause or aggravate DED. "The most widely used ocular administration preservative, BAK, has been shown to have cytotoxic and proinflammatory effects on the eye, and its detergent properties disrupt the tear film," they write.

Prolonged digital screen use is another factor in DED. Regular, daily use of visual digital terminals has been associated with Meibomian gland dysfunction and goblet cell dysfunction. Moreover, in vitro studies indicate that some wavelengths of light emitted from the screens may cause corneal damage. Numerous studies have also shown that blinking frequency is significantly less during digital screen use (7±7 blinks per minute), compared to reading print (10±6; $p = 0.001$), and relaxed conditions (22±9; $p<0.0001$). People also have more incomplete blinks when using a computer screen (median 13.5%) compared to reading a book (median 5%). Blinking less and incomplete blinking means less of the protective lipid layer, more tear evaporation, and more symptoms.

Limiting screen time and using blinking exercises can help reduce DED symptoms. For every two hours of computer use, the American Academy of Ophthalmology and the American Optometric Association recommend taking a 15-minute break. Another suggestion is to focus on an object 20 feet away for 20 seconds after every 20 minutes of digital screen use. Performing a quick blinking exercise every 20 minutes during waking hours (gently close eyes for 2 seconds, open eyes, again gently close eyes for two seconds, followed by squeezing eyes closed for 2 seconds) reduced symptoms in 41 people with DED. Computer users have also reported some relief of DED symptoms by using a desk humidifier; dry air can exacerbate symptoms.

Nutrition, of course, also plays a role in tear film homeostasis – although advice regarding DED seems limited at this point. Matossian et al report that vitamin A and "sufficient intake of protein" are important. A 2016 by S.H. Bae and colleagues reported that vitamin D reduced eye surface inflammation, promoted tear secretion, and reduced tear instability in people with DED (*Sci Rep.* 2016;6:33083). Omega-3 fatty acids have also shown benefits in some studies. However, the 12-month Dry Eye Assessment and Management (DREAM) study and the follow-up extension study showed no significant difference in conjunctival staining, corneal staining, tear break-up time, or Schirmer test (for tear production) between the omega-3 group and control.

In addition to modifying digital screen use and nutrition, other suggestions for mitigating DED symptoms include warm eye compresses to improve Meibomian gland secretion, ophthalmic gels, used at night to maintain moisture, and twice-daily use of artificial tear replacement (while avoiding products with ingredients that can further irritate the eye).

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Shorts

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Tinnitus and Oxidative Stress

Oxidative stress is a major factor underlying the ringing, roaring, or other annoying (even debilitating) sounds that characterize tinnitus. Those sounds can cause sleep disorders, depression, and impair social cohesion and quality of life. Cochlear degeneration is the main cause of tinnitus. Oxidative stress is known to produce cochlear degeneration and changes in auditory hair cells and nerve fibers. As Celik and Koyuncu explain in their 2018 article, "The sensorineural epithelial tissues of the cochlea are more susceptible to deleterious effects caused by free radicals than other tissues of the body."

Because of the known relationship between oxidative stress and tinnitus and because tinnitus patients have "higher plasma concentrations of oxidative stress biomarkers and lower antioxidant activity" than healthy people, a group of Greek researchers, led by Anna I. Petridou, decided to test the effects of supplementation on people with tinnitus. Their 2019 randomized, double-blind, placebo-controlled trial enrolled 70 people, between 25 and 75 years old. All participants had tinnitus in one or both ears for at least six months; the noise required at least 5 decibels of competing sound to mask it. Inclusion criteria also included a score of 4 or above on the Tinnitus Handicap Inventory (THI) questionnaire, which assesses the emotional and functional impacts of having tinnitus. Participants needed to have normal hearing or only moderate hearing loss. Exclusion criteria included Meniere's disease, otosclerosis, several chronic conditions and use of tinnitus-inducing medication (e.g., aminoglycosides, chemotherapeutics, loop diuretics, high doses of aspirin or quinine). Three participants (2 placebo group; 1 antioxidant group) discontinued the trial, due to unscheduled surgery; and four in the placebo group were lost to follow-up. Participants underwent a baseline assessment that included anthropometric, audiometric, and tinnitus psychoacoustic measures; tinnitus discomfort; psychological symptoms; physical activity; and dietary assessment as well as blood sample collection. Participants were re-assessed three months later, at study's end.

The treatment group took a commercially available multivitamin-multimineral supplement (Lamberts), which included 500 mg of standardized grape seed extract once a day with a meal. Grape seed extract is a rich source of phenolic compounds, such as epicatechin, resveratrol and procyanidin oligomers; "many experimental studies have proven the protective effect of polyphenols against cisplatin-induced ototoxicity and cochlear hair cell damage after intense noise exposure." Participants in the treatment group also took one tablet of alpha-lipoic acid (300 mg) twice a day on an empty stomach. Animal and human studies show that alpha-lipoic acid protects against noise-induced hearing loss. The placebo group took three placebo pills with similar shape and color to the supplements, made by a local manufacturing pharmacy. An investigator, uninvolved in the study, packaged the supplements and the placebos in identical containers and bags and labeled each with a participant's number.

At study's end, only participants in the supplement group had a significant reduction in tinnitus loudness from baseline, reflected in lower minimum masking levels ($p<0.001$). The supplement group also had a mean reduction in the Tinnitus Handicap Inventory of 6 points ("considered clinically relevant"). Also, the supplement group, unlike the placebo group, displayed "a significant decrease

in the auditory threshold at the frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 6000 Hz" – that is, their hearing improved. Blood serum changes in total antioxidant capacity, superoxide dismutase, and oxidized LDL were insignificant.

The authors note that the commercial multivitamin and mineral supplement used in this study contained only 150 mg of vitamin C and only 100 mg (150 iu) of vitamin E (dl-alpha tocopherol acetate), but they did not want to use isolated nutrients: "…our hypothesis was that an antioxidant combination might be more effective compared with single nutrients, since various antioxidants have a synergistic/complementary activity." Although the combination of vitamins, minerals, phytochemicals, and alpha lipoic acid reduced tinnitus intensity and patient discomfort, they would like to see further investigation on its possible effect on oxidative stress biomarkers.

Celik M, Koyuncu I. A Comprehensive Study of Oxidative Stress in Tinnitus Patients. *Indian J Otolaryngol Head Neck Surg.* Oct-Dec 2018;70(4):521-526.

Petridou Ai, et al. The Effect of Antioxidant Supplementation in Patients with Tinnitus and Normal Hearing or Hearing Loss: A Randomized, Double-Blind, Placebo Controlled Trial. *Nutrients.* December 12, 2019.

Coca's Pulse Test for Allergens

Can the pulse rate be used to identify allergens? Arthur F. Coca, MD (1875-1960), found evidence that it did. Dr. Coca was the founder of the peer-reviewed *Journal of Immunology* and served as the journal's first editor from 1916-1948. In addition to teaching at Cornell and Columbia University, he was medical director at Lederle Laboratories, a pharmaceutical company. Dr. Coca also held the title of Honorary President of the American Association of Immunologists from his retirement in 1949 until his death.

Coca first became aware of a connection between increased pulse rate and adverse reactions to foods and other allergens when his wife suffered a sudden attack of angina pectoris after receiving a morphine derivative. Instead of slowing down with the drug, her heart rate increased to over 180 beats a minute. Other episodes of tachycardia followed. She noticed that the attacks occurred after eating specific foods. Dr. Coca began using heart acceleration as a way to determine which foods were "injurious" and which were safe for her. As long as she refrained from eating the foods that caused heart rate acceleration, she remained pain free and was able to garden and do ordinary housework without becoming overtired. Moreover, conditions that had affected her for much of her life – migraines, colitis, attacks of dizziness and fainting, indigestion, and fatigue – disappeared.

Dr. Coca began investigating the use of pulse rate to identify and remove allergens from patients' diets. He eventually wrote a book for medical colleagues, *Familial Nonreaginic Food Allergy* (1943). Some doctors, like Milo G. Meyer, followed his lead. Dr. Meyer, an internist, wrote an article about his experience with the pulse test, which was published in *Annals of New York Academy of Sciences* (December 1949). For the most part, however, Dr. Coca's observations were censored and ignored. Patients urged him to write a book for nonmedical readers. The result, *The Pulse Test* (1956), is in public domain and available at www.soilandhealth.org. This 110-page manuscript explains how to conduct the pulse test and the benefits of avoiding foods that speed up the pulse, using patients' experiences as examples.

The test consists of taking the pulse before rising (while in the recumbent position); just before each meal and three times, at 30-minute intervals after each meal (sitting or standing); and before retiring (sitting or standing). The same posture should be used for each count. Coca recommends that people begin the test while following their usual diet for five to seven days: "If the *highest count* is the same each day, and if it is not over 84, you are most likely not allergic, and the range of your pulse from the lowest count (usually before rising) to the highest will be not more than 16 beats – probably much less." Counts over 84 beats/minute indicate "food allergy." Also, variation in the *maximal count* of more than two beats from day to day (ie, Monday 72, Tuesday 78, Wednesday 76, etc.) indicate an allergic reaction – if no infection is present. If the initial pulse test indicates an allergen is present, Coca explains how to identify the offender(s) by taking a day or two to test suspect allergens singly – eating a single food in small quantities at hourly intervals and taking the pulse at 30-minute intervals.

An array of conditions and symptoms disappeared in patients who refrained from consuming or using items that increased the pulse rate: gastrointestinal symptoms, such as constipation, indigestion, heartburn, abdominal and gallbladder pain, and colitis; recurrent headaches and migraines; hives; asthma; sinusitis; epilepsy; diabetes; heart pain (angina) and hypertension; fatigue; and emotional symptoms, such as nervousness, depression, and irritability. The symptoms returned when patients again consumed the offending foods.

I found Dr. Coca's chapter on high blood pressure and allergens particularly interesting. As an example, he wrote about a 60-year-old woman whose blood pressure was 198/120. "Sixteen days after avoidance of her major food-allergens the pressure was 112/78." When she resumed eating one of the allergens (wheat), the pressure gradually rose. She stopped eating wheat. Thirteen years later, her blood pressure was 124/70. He explained that part of the allergic reaction is a blockade of lymph vessels, producing internal pressure from edema. Compression of the kidneys was known to produce hypertension in animals. Coca postulated that "it is reasonable to surmise that allergy…produces [human hypertension] through the *internal pressure* of allergic edema affecting both kidneys."

Like elimination diets, the pulse test, in Dr. Coca's studies, found that wheat, cow's milk, and egg are typical allergens. Cane sugar, coffee, orange, pineapple, banana, and white potato also are on Coca's list. In addition, to foods, Coca found that some people were reacting to tobacco, aluminum cooking utensils, house dust, medicines, cosmetics, and paint fumes. The pulse test – for those with the ability and patience to follow Dr. Coca's instructions – might provide quicker and more specific feedback about suspected foods than an elimination diet.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Zinc for Children with Acute Diarrhea

Four thousand five hundred children (aged 6-59 months) in India or Tanzania who were experiencing acute diarrhea were randomly assigned to receive 5, 10, or 20 mg of zinc (as zinc sulfate) once a day for 14 days. The percentage of children who had diarrhea for more than 5 days was 6.5% with 20 mg, 7.7% with 10 mg, and 7.2% with 5 mg. The difference between groups was below the noninferiority margin of 4 percentage points. The mean number of diarrheal stools was 10.7 with 20 mg, 10.9 with 10 mg, and 10.8 with 5 mg. The difference between groups was below the noninferiority margin of 2 stools. Vomiting within 30 minutes after administration occurred in 19.3%, 15.6%, and 13.7% of patients after 20, 10, and 5 mg, respectively. The risk of vomiting was significantly lower by 19% with 10 mg than with 20 mg and significantly lower by 29% with 5 mg than with 20 mg. Lower zinc doses were also associated with less vomiting beyond 30 minutes after administration.

Comment: The World Health Organization recommends 20 mg per day of zinc for 10 to 14 days for children with acute diarrhea. In previous trials, this dosage improved diarrhea but increased vomiting. The results of the present study indicate that a lower dose of zinc (5 mg per day) was not significantly less effective than the currently recommended dose of 20 mg per day, and that the lower dose caused less vomiting. Based on these findings, the recommended zinc dosage for the treatment of children with acute diarrhea should be reevaluated.

Dhingra U, et al. Lower-dose zinc for childhood diarrhea – a randomized, multicenter trial. *N Engl J Med*. 2020;383:1231-1241.

Zinc-L-Carnosine for Binge Eating Disorder and Bulimia

Twenty-nine patients (aged 18-65 years) with binge eating disorder (n = 22) or bulimia (n = 7) who had been receiving a stable dose of an antidepressant for at least eight weeks were given, as add-on therapy, 75 mg per day of zinc-L-carnosine for four weeks, followed by 150 mg per day for 12 weeks. The higher dose provided daily 34 mg of zinc and 116 mg of L-carnosine. All but two of the patients had one or more psychiatric comorbidities, such as bipolar disorder, panic disorder, social anxiety disorder, borderline personality disorder, and attention deficit-hyperactivity disorder. In the patients with binge eating disorder, the mean number of binge-eating days per four-week period was significantly lower by 70% during the last four weeks of treatment compared with baseline ($p < 0.001$). In the patients with bulimia, the corresponding reduction compared to baseline was 35% ($p < 0.1$). Although the mean serum zinc concentration at baseline was in the normal range, all patients had at least three (mean, 6.5) of nine symptoms that can result from zinc deficiency: hair loss, dermatitis, acne, nail fragility, dysgeusia, stomatitis, glossitis, diarrhea, and dysphagia. Approximately 85% of these symptoms improved during treatment with zinc-L-carnosine.

Comment: Binge eating disorder is characterized by recurrent episodes of eating excessive amounts of food, and an associated sense of lack of control over what or how much one is eating. Approximately two-thirds of people with binge eating disorder are obese, and the condition is frequently associated with depression, bipolar disorder, anxiety, or substance abuse. Conventional treatment may include psychotherapy and medications such as lisdexamfetamine dimesylate (an amphetamine derivative) or antidepressants. Bulimia is a similar condition, characterized by extreme overeating followed by purging (self-induced vomiting). Zinc plays an important role in appetite regulation. L-Carnosine is an endogenous dipeptide, which may also regulate eating behavior through its histaminergic and anti-glutamatergic properties. The results of the present study suggest that zinc-L-carnosine is an effective treatment for binge eating disorder and possibly for bulimia, and that zinc deficiency may contribute to these conditions.

Sakae K, et al. Polaprezinc (zinc-L-carnosine complex) as an add-on therapy for binge eating disorder and bulimia nervosa, and the possible involvement of zinc deficiency in these conditions: a pilot study. *J Clin Psychopharmacol*. 2020;40:599-606.

Can Eating More in the Morning Help You Lose Weight?

Sixteen normal-weight male volunteers consumed, in random order, a low-calorie breakfast (11% of daily energy requirement)

and high-calorie dinner (69% of daily energy requirement) for 3 days, and a high-calorie breakfast and low-calorie dinner for another three days. Diet-induced thermogenesis was measured by indirect calorimetry. With identical calorie consumption, mean diet-induced thermogenesis was 2.5 times higher in the morning than in the evening after both high- and low-calorie meals ($p < 0.001$).

Comment: "Diet-induced thermogenesis" refers to the increase in energy expenditure that follows ingestion of a meal. This increase in energy expenditure is due mainly to the increased energy required to digest, absorb, distribute, and store the ingested nutrients. Additional energy is also expended as a result of diet-induced stimulation of brown adipose tissue. Diet-induced thermogenesis accounts for about 10% of total energy expenditure. In the present study, with respect to the high-calorie meal, the difference in diet-induced thermogenesis between breakfast and dinner was equivalent to about 2% of the energy content of the meal. While that difference is relatively small, long-term adherence to the old adage of Adelle Davis – Eat breakfast like a king, lunch like a prince, and dinner like a pauper – might help promote weight loss.

Richter J, et al. Twice as high diet-induced thermogenesis after breakfast vs dinner on high-calorie as well as low-calorie meals. *J Clin Endocrinol Metab*. 2020;105:dgz311.

High-Dose Thiamine for Fatigue Associated with Inflammatory Bowel Disease

Forty adults (mean age, 37 years) with quiescent Crohn's disease (n = 20) or ulcerative colitis (n = 20) and chronic fatigue with no other explanation for the fatigue were randomly assigned to receive, in double-blind fashion, high-dose thiamine or placebo for four weeks. After a four-week washout period, each patient received the alternate treatment for an additional four weeks. The dose of thiamine was based on body weight and ranged from 600 to 1,500 mg per day for women and 900 to 1,800 mg per day for men. The frequency and severity of fatigue was measured by the score on section 1 of the Inflammatory Bowel Disease-Fatigue questionnaire (IBF-F1). IBD-F1 is a 20-point scale, with higher numbers indicating worse fatigue. At baseline, the mean score in the group as a whole was 14.8. The mean improvement in fatigue was significantly greater with thiamine than with placebo ($p = 0.0003$). The proportion of patients who had an improvement of at least 3 points was higher during thiamine treatment than during placebo treatment (65% vs. 30%; p value not stated). At baseline, the plasma thiamine concentration was below normal in 30% of patients. The improvement in fatigue did not differ according to whether the baseline plasma thiamine level was low or normal. Side effects were uncommon and mild.

Comment: In this study, high-dose thiamine was an effective treatment for fatigue in adults with quiescent inflammatory bowel disease. The beneficial effect was probably not due to correcting a deficiency. A previous uncontrolled trial also found that high-dose thiamine was effective for fatigue in patients with quiescent inflammatory bowel disease.[1] While high-dose thiamine is relatively safe, it can cause sleep problems if taken at night. It has therefore been recommended that the last dose be taken before 5 p.m. In addition, in a previous study, one patient taking 1,200 mg per day experienced mild tachycardia, which resolved when the dose was reduced to 900 mg per day. Another concern with high-dose thiamine is its potential to cause imbalances with other nutrients, such as other B vitamins and magnesium. For that reason, I prefer in most cases to use lower doses of a wide range of nutrients, rather than a large dose of a single nutrient. However, if that approach is not successful, a trial of high-dose thiamine seems reasonable.

Bager P, et al. Randomised clinical trial: high-dose oral thiamine versus placebo for chronic fatigue in patients with quiescent inflammatory bowel disease. *Aliment Pharmacol Ther*. 2020 Nov 18 [Online ahead of print].

How Safe Is High-Dose Vitamin D?

The Calgary Vitamin D Study was a double-blind trial designed to examine the effect of different doses of vitamin D on the rate of bone loss. In this study, 373 healthy Canadian adults (aged 55 to 70 years) with a serum 25-hydroxyvitamin D level of 12-50 ng/ml (mean, 31.2 ng/ml) received 400, 4,000, or 10,000 IU per day of vitamin D for three years. A calcium supplement was given, if needed, to bring total calcium intake to approximately 1,200 mg per day. In the original study, the amount of bone loss at the radius and hip increased with increasing vitamin D doses.[2] The present study provided an additional safety analysis of the original study. The new analysis found that the incidence of hypercalcemia and hypercalciuria increased with increasing vitamin D doses. Mild hypercalcemia occurred in 0% of participants receiving 400 IU per day, 3% of those receiving 4,000 IU per day, and 9% of those receiving 10,000 IU per day (p for trend = 0.002). All cases of hypercalcemia resolved on repeat testing. Hypercalciuria occurred in 17% of participants receiving 400 IU per day, 22% of those receiving 4,000 IU per day, and 31% of those receiving 10,000 IU per day (p for trend = 0.01).

Comment: Over the past several years, I have presented evidence that high-dose vitamin D (such as more than 2,000 IU per day) is usually not more effective, and in some circumstances may be less effective, than moderate doses (such as 800 to 1,200 IU per day). The present study found that hypercalcemia and hypercalciuria are relatively common in patients receiving high-dose vitamin D, which raises concerns about the safety of such treatment. Hypercalciuria increases the risk of developing kidney stones, although that risk may be mitigated by supplementing with magnesium. While the hypercalcemia seen in this study was mild and transient, it may indicate that high-dose vitamin D creates "biochemical stress" in some people. The human body tightly regulates serum calcium levels by several different mechanisms, because both hypercalcemia and hypocalcemia can have severe consequences. Therefore, hypercalcemia probably only occurs after all calcium-regulating mechanisms have been overwhelmed. We still have a lot to learn about the long-term safety of high-dose vitamin D. Prudence suggests that it be used with caution, and previous evidence suggests that one cannot necessarily rely on the serum 25-hydroxyvitamin D level as an indicator of safety.

Billington EO, et al. Safety of high-dose vitamin D supplementation: secondary analysis of a randomized controlled trial. *J Clin Endocrinol Metab*. 2020;105:1261-1273.

Green Tea, Iron Absorption, and Thalassemia

Sixty-eight Iraqi patients (mean age, 13.5 years) with beta-thalassemia intermedia received usual treatment (deferasirox as an iron chelator and as-needed blood transfusions) and were randomly assigned to consume green tea (1 cup 3 times a day after meals) or to a control group for 12 months. Patients were also advised to consume a low-iron diet. Twenty-nine patients in the green tea group and 28 in the control group adhered to the program and were included in the analysis. The mean decrease in liver iron concentration was significantly greater in the green

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tea group than in the control group (-7.3 mg/g dry weight vs. -4.6 mg/g dry weight; p<0.05). The mean serum ferritin concentration also fell to a significantly greater extent in the green tea group than in the control group ($p < 0.05$).

Comment: Beta-thalassemia is an inherited disorder of hemoglobin synthesis that results in a decrease in the rate of synthesis of the beta chain of the globin molecule. The imbalance between the alpha and beta chains results in erythrocyte damage and hemolysis. People with the heterozygous form of the disease (thalassemia minor) are often asymptomatic or suffer from only mild anemia. Those with the homozygous form (thalassemia major) often develop severe anemia, which can lead to heart failure and death if not treated. Thalassemia intermedia is of intermediate severity and involves polygenic inheritance. Regular blood transfusions can prolong the life of patients with thalassemia. However, frequent transfusions also cause iron overload, which can result in damage to the heart and other organs. Iron-chelating agents are therefore used to remove excess iron. The results of the present study indicate that consumption of green tea can enhance the effect of deferesirox in treating iron overload in patients with thalassemia intermedia.

Al-Momen H, et al. Green tea influence on iron overload in thalassemia intermedia patients: a randomized controlled trial. *F1000Res*. 2020;9:1136.

Cinnamon for Migraines, or More Iranian Research Fraud?

Fifty Iranian patients with migraines were randomly assigned to receive, in double-blind fashion, 600 mg of cinnamon three times per day or placebo for 60 days. The mean frequency of migraine attacks fell by 80% in the cinnamon group and by 17% in the placebo group ($p < 0.001$ for the difference in the change between groups). The mean duration of attacks fell by 58% in the cinnamon group and by 33% in the placebo group ($p < 0.03$ for the difference in the change between groups). The mean severity of attacks fell by 56% in the cinnamon group and by 10% in the placebo group ($p < 0.001$ for the difference in the change between groups). Mean serum levels of the inflammatory markers, interleukin-6 and nitric oxide, fell significantly with cinnamon group compared with placebo, whereas there was no significant change in serum levels of calcitonin-gene-related peptide.

Comment: I have noted in previous issues of the *Townsend Letter* that a large proportion of the nutrition research coming from Iran appears to be fraudulent. Several issues in the present study raise concerns:

1. Unusually short recruitment period: A single neurologist assessed 114 patients for enrollment over a period of two months and six days.
2. Inefficient use of a specialist's time: A single neurologist collected all of the baseline data for the 50 enrolled patients. This data could easily have been collected by someone with less training or even by a questionnaire. Since the study was conducted by a graduate student as part of a masters' thesis, it would be reasonable to assume that the student would have been expected to collect the baseline data.
3. Funding issue: Double-blind studies are expensive, so it is difficult to believe that the funding source would have provided money for a randomized controlled trial when there had been no prior evidence from case reports or uncontrolled trials that cinnamon is beneficial for migraines. In addition, in a country with limited resources for research, it is difficult to believe that the funding source would have agreed to pay for laboratory tests that have little clinical significance (serum interleukin-6, nitric oxide, and calcitonin-gene-related peptide).
4. Unusually large effect size: The decrease in the frequency of attacks was greater than that seen with medications used for migraine prophylaxis. Considering that cinnamon is one of the most commonly used spices in the world, if cinnamon is even half as effective as reported in this study, it is difficult to believe that no one has previously observed a beneficial effect against migraines.

Zareie A, et al. Effect of cinnamon on migraine attacks and inflammatory markers: A randomized double-blind placebo-controlled trial. *Phytother Res*. 2020;34:2945-2952.

Vitamin D Effective for Chronic Urticaria, or Research Fraud from India?

One hundred twenty patients (aged 20-50 years) in Southern India who had chronic urticaria and a serum 25-hydroxyvitamin D level below 20 ng/ml were randomly assigned to receive, in double-blind fashion, 60,000 IU of vitamin D or placebo every two weeks for 12 weeks. The improvement in urticaria (as measured by the Urticaria Activity Score) was significantly greater in the vitamin D group than in the placebo group.

Comment: Several aspects of this study raise concerns:

1. Implausibly low dropout rate: All 120 patients completed the 12-week trial, yet the article stated that the patients could not be followed up at six weeks to assess disease severity because of "noncompliance." It is difficult to believe that there were no dropouts in a study of 120 patients in which many failed to show up for the six-week visit.
2. Implausible age distribution of the participants: To be included in the trial, patients had to be 20 to 50 years old. In the placebo group, the mean age was 38.8 years, with a standard deviation of 12.54 years. One can assume there was a normal (Gaussian) distribution of ages, because the authors stated that normally distributed data were presented as mean plus or minus standard deviation, whereas non-Gaussian data were presented as median with interquartile range. With a mean age of 38.8 years, a standard deviation of 12.54 years, and a normal distribution, approximately 16% of the patients in the placebo group would be older than 51.3 years. That would be impossible, since individuals over age 50 were excluded from the trial.
3. Other implausible baseline data: There were highly significant differences between the vitamin D and placebo groups for the baseline Urticaria Activity Score ($p < 0.0001$), number of antihistamine tablets being used ($p < 0.0001$), mean serum concentration of interleukin-6 ($p < 0.001$), and mean concentration of transforming growth factor-beta ($p = 0.01$). It is extremely unusual for a randomized trial to have so many highly significant differences in baseline data between groups.

Mony A, et al. Effect of vitamin D supplementation on clinical outcome and biochemical profile in South Indian population with vitamin D-deficient chronic urticarial - A randomized double-blind placebo controlled trial. *Clin Chim Acta*. 2020;504:1-6.

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1. Costantini A, Pala MI. Thiamine and fatigue in inflammatory bowel diseases: an open-label pilot study. *J Altern Complement Med*. 2013;19:704-708.
2. Burt LA, et al. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA*. 2019;322:736-745.

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Geranylgeraniol (GG) Boosts Endogenous Synthesis of Coenzyme Q10 (CoQ10) and Cell Essential Metabolites, Overcoming CoQ10 Supplementation Limitations

by Cristiana Paul, MS[1];
David M. Brady, ND, DC, CCN, DACBN, IFMCP, FACN[2]; and
Barrie Tan, PhD[3]

Introduction

There are inherent physiological challenges associated with oral supplementation with CoQ10, both in the ubiquinol and ubiquinone forms, which appear to limit the clinical efficacy and outcomes of this popular intervention. These challenges and limitations will be discussed in this article, along with a novel solution in the form of the molecule, likely new to many readers, geranylgeraniol (GG), now available as a nutritional ingredient commercially for the first time.

Main Takeaways

- Mitochondrial function and tissue content of CoQ10 start declining significantly in the middle-age adult. For individuals aged 60 years-of-age or older, CoQ10 contents of various tissues may be 17-83% lower than those in young adults. Supplementation with ubiquinol in combination with GG has the potential to improve mitochondrial function and raise intra-cellular levels of CoQ10 close to those observed at age 20.
- CoQ10 occurs in all body cells as ubiquinol and ubiquinone, which continuously interconvert into each other. Ubiquinol acts as an antioxidant, ubiquinone as an energy cofactor, while both affect gene expression, support DNA repair, may reduce DNA damage, as well as other functions (see Table 1a and 1b)
- Supplementation with 100-3000 mg CoQ10 was able to raise plasma CoQ10 levels as high as eight times, but intracellular content of CoQ10 was not increased enough to maximize its clinical potential. This is due to CoQ10's low GI absorption and limited transport inside cells and mitochondria.
- GG's molecular weight is one third of CoQ10's and therefore, diffuses easily inside cells and organelles. GG provides a promising approach to raising intracellular levels of CoQ10.
- GG supplementation boosts synthesis of essential cell signaling molecules not achieved by CoQ10 supplementation.
- Supplementation with CoQ10 and GG increase the rate of mitochondrial oxygen consumption and thermogenesis, which may boost energy expenditure and physiological performance.
- GG supplementation mitigates many of the side-effects of statins and bisphosphonates, which affect mitochondrial functions and cellular health. This is evidenced in muscle, brain, immune cells, reproductive organs, bone, and arteries.

Raising CoQ10 Levels

Raising intra-mitochondrial levels of CoQ10 may reverse aspects of age-related mitochondrial dysfunction. Age-related decline in health and function has been attributed, at least in part, to the progressive loss of mitochondrial function, and accumulation of DNA damage. Cumulative reactive oxygen species (ROS) exposure, inadequate antioxidant protection from low levels of intracellular CoQ10, and inefficient DNA

continued on page 22 ➤

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DuoQuinol™
Ubiquinol *Plus*

All the benefits of **Ubiquinol *Plus****:

- Supplemental Geranylgeraniol
- Activated natural CoQ10 production
- Enhanced cellular absorption
- Supported muscle function and strength
- Supported nutritional needs of statin users

DuoQuinol™ is a novel product with a patent-pending combination of the activated form of CoQ10 (ubiquinol) and geranylgeraniol (GG), a molecular component of CoQ10, often referred to as a building block of healthy aging. It is an endogenous nutrient which, like CoQ10, declines as we age.

The unique combination in DuoQuinol™ creates a complementary mechanism that supports heart function and cellular energy through well-evidenced ubiquinol. Coupled with the inclusion of GG, DuoQuinol™ provides additional benefits through the natural stimulation of CoQ10 production.*

DuoQuinol™'s composition gives it a distinctive advantage over ubiquinol when delivered in combination with statin drugs, as ubiquinol alone does not address the unwanted effects on muscles that often results from statin drug usage. Fortunately, research suggests that the GG in DuoQuinol™ works to support the unique nutritional requirements of statin users to promote healthy muscle function and strength.*

*These statements have not been evaluated by the Food and Drug Administration. These products do not intend to diagnose, treat, cure or prevent any diseases.

Geranylgeraniol

➤ *continued from page 20*

repair are some of the causes that lead to DNA mutations. These, in turn, are translated into mitochondrial proteins that may perform with lower efficiency, sometimes resulting in excess ROS. The additional ROS accelerates the rate of DNA damage, creating a vicious cycle of accelerated aging.[1,2] CoQ10's roles of antioxidant, cofactor in the mitochondrial production of ATP, and enhancement of DNA repair make it extremely relevant to anti-aging interventions.[2-8]

Mitochondrial dysfunction results in reduction of the rate of oxygen consumption (also called mitochondrial respiration) and increased levels of lactic acid. One study estimated the decline in oxygen consumption for every decade in skin fibroblasts at 10% (see fig 1a).[9] A second study observed a 22% decrease in mitochondrial membrane potential and a 17% increase in glucose diverted to lactic acid in skin cells from older subjects (61-73-year-olds) compared to younger ones (19-37-year-olds).[10] Both of these studies showed that supplementing cells with CoQ10 was able to partially correct markers of mitochondrial dysfunction. Figure 1b shows that in-vitro cell supplementation with 100 µmol CoQ10 in a solubilized form was able to bring up mitochondrial respiration level in cells from 40-80-year-old subjects close to those from individuals in their late 20s. This effect was observed in some but not all the subjects, pointing to other factors involved.[9]

In another study, a topical application of a 0.01% CoQ10 emulsified in a skin cream for seven days, resulted in an increase of 44% in mitochondrial membrane potential, thus more than counteracting the age-related decline of 22%.[10]

These studies suggest that part of the age-related mitochondrial dysfunction may be attributed to insufficient intracellular COQ10, which is corroborated by its known involvement as a critical component in the electron transport chain. They also showed that age-related decline in mitochondrial respiration and mitochondrial membrane potential may be completely reversed, at least in some of the subjects, with CoQ10 supplementation that ensures delivery inside cells.

However, these effects have not been obtained, to the same extent, with oral CoQ10 supplementation. Geranylgeraniol (GG), a naturally occurring compound, has the potential to complement and overcome oral CoQ10 supplementation limitations, as discussed below.

continued on page 25 ➤

Figure 1a. Mitochondrial respiration declines with aging in epithelial cells.[9] OCR = Oxygen consumption rate

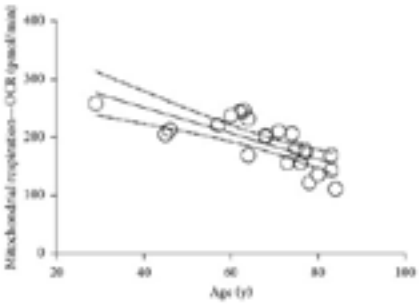


Figure 1b. Mitochondrial respiration increases in CoQ10 treated epithelial cells, close to younger levels.[9] OCR = Oxygen consumption rate

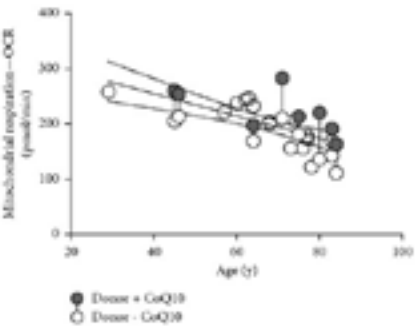
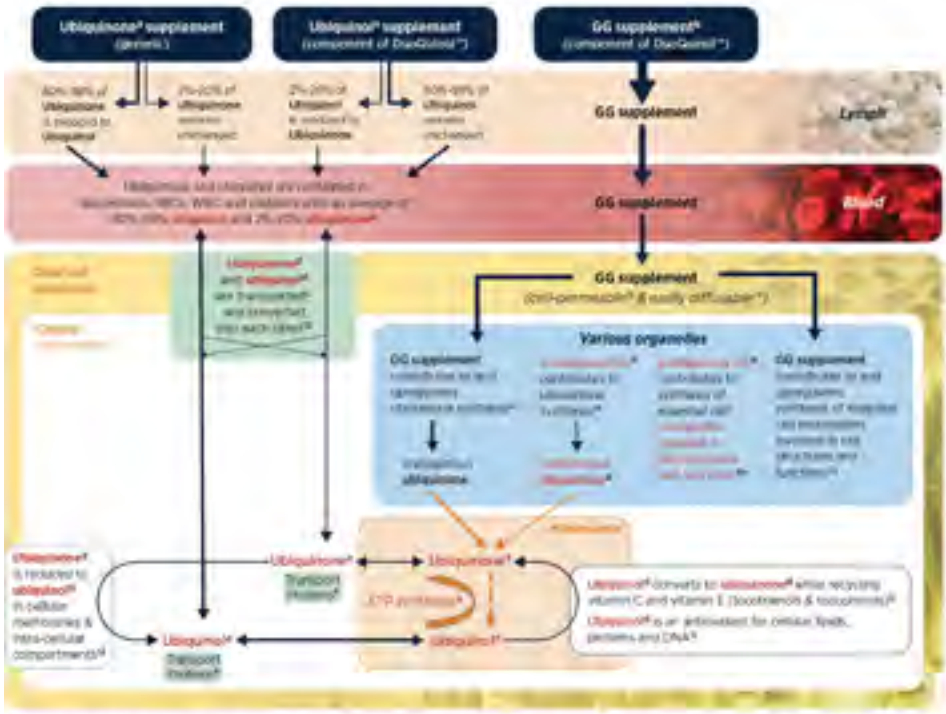


Figure 2. Complementary pathways of CoQ10 and geranylgeraniol in boosting intracellular levels of ubiquinone, ubiquinol and GG derivatives.



ATP = adenosine triphosphate; CoQ10 = coenzyme Q10; GI = gastrointestinal tract; GG = geranylgeraniol; RBCs = red blood cells; WBCs = white blood cells.

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Limitations of Oral Supplementation with CoQ10

Studies report a decline in organ tissue contents of CoQ10 observed at ages 77-81 versus age 19-21 as follows: pancreas (−83%), skin (−75%), heart (−58%), kidneys (−45%), adrenals (−50%), and liver (−17%).[11] This may be the result of reduced synthesis and/or increased degradation.[11] Deficiencies of CoQ10 tissue content were also found in individuals with diabetes (−65%), pancreatic cancer (−30%) and those treated with statins (−20% to −26%).[11] This may explain, at least in part, significant age-related decline in mitochondrial function occurring in most tissues, especially those with high energy demand such as brain, heart/skeletal muscle, kidneys and liver.

Endogenous synthesis of ubiquinone occurs in all tissues, estimated in one study at 500 mg/day (depending on body size), while CoQ10 intake from foods averages 5 mg/day.[12]

Ubiquinone and ubiquinol perform important cellular functions (see Table 1a) while interconverting into each other, as illustrated in Figure 2. Ubiquinol represents 80-98% of total COQ10 in the blood, with the rest occurring as ubiquinone. The % ubiquinone ranges from 24-100% in various tissues, and it is affected by aging, oxidative stress, and various conditions.[13,14] Studies with oral CoQ10 have shown the potential for numerous benefits (see Table 1b).

Supplemental ubiquinol or ubiquinone are absorbed from the GI tract and transported by triglyceride-rich chylomicrons to the liver, where they are repackaged into cholesterol-rich lipoproteins and carried back into the blood.[12] However, CoQ10 transport from blood to tissues and organs, and further inside the mitochondria, is inefficient.[12,15-17] CoQ10 is a large molecule, and its transfer is controlled by receptors and transporters not physiologically adapted to large quantities of exogenous CoQ10.[12,15-17] This is the opposite direction from how the body supplies endogenously synthesized CoQ10. The only modality utilized to date to overcome this hurdle has been to use increasingly higher doses of CoQ10 from 30 mg ➤

Geranylgeraniol

Table 1a. Biological Actions of CoQ10 in Human Physiology[2,3,12,26,27]

a. Ubiquinone is synthesized inside cells and converts back and forth to ubiquinol as follows:
Ubiquinone is reduced to ubiquinol:
(i) by oxidizing alpha-lipoic acid or glutathione
(ii) through participation in the mitochondrial electron transport chain, where 95% of the body's ATP is produced
(iii) via regulation of the cytosolic ratio of NAD+/NADH involved in the cell growth and differentiation. NAD+/NADP+reductase declines with aging.

b. Ubiquinol is an endogenous lipid-soluble antioxidant:
(i) It recycles vitamin E (tocotrienols, tocopherols) and vitamin C, while converting to ubiquinone.
(ii) It protects cellular lipids, proteins, nuclear & mitochondrial DNA.

c. Ubiquinone is required for the activation of mitochondrial uncoupling proteins, involved in thermogenesis and neuroprotection.

d. Ubiquinone regulates mitochondrial permeability transition pores. This affects apoptosis and DNA damage.

e. CoQ10 influences membrane fluidity of cells and organelles.

f. CoQ10 exerts anti-inflammatory effects.
It initiates the release of mediators from lymphocytes and monocytes into the blood, which stimulate anti-inflammatory genes in a variety of tissues.

g. CoQ10 affects more than a hundred genes, including those involved in mitochondrial biogenesis.
It stimulates SIRT1, SIRT3 and PGC-1alpha.

h. CoQ10 is involved in mitochondrial calcium homeostasis.

i. CoQ10 is involved in lysosomal pH maintenance.

j. CoQ10 may play a role in cancer risk reduction. It reduces oxidative stress and DNA damage.

Table 1b. Results from Supplementation with COQ10 in Human and Animal Studies[1-9,11,19,26-43]

CoQ10 supplementation raised blood CoQ10 levels in healthy and statin-treated individuals but not enough in various tissues such as muscle, brain, skin, etc.

a. Healthy aging:
- Reduced all-cause mortality
- Helped improve quality of life in the elderly
- Slowed senescence-specific cell processes
- Supported DNA repair
- Supported a healthy immune response

b. Brain health:
- Provided cognitive support, reduced mental fatigue
- Slowed progression of certain pathologies/symptoms of geriatric dementia, Alzheimer's, and Parkinson's disease
- Inhibited senescence in brain cells
- Reduced inflammatory response (CRP, IL-6, TNF-a)

c. Energy metabolism:
- Increased adenosine triphosphate (ATP) production and rate of mitochondrial oxygen consumption, which may improve metabolic rate
- Relieved mild fatigue in healthy individuals

d. Exercise performance:
- Reduced exercise-induced fatigue, oxidative stress, lactic acid levels and inflammatory markers (CRP, IL-6, TNF-a)
- Supported muscle contraction and glycogen storage in liver/muscle

e. Cardiovascular function:
- Improved left ventricular ejection fraction in patients with heart failure
- Reduced LDL oxidation
- Reduced fibrosis of the heart tissue
- Repaired damage after myocardial infarction
- Supported nitric oxide metabolism for healthy endothelial function

f. Glucose metabolism: Reduced HBA1c, advanced glycation end products and fasting glucose

g. Kidney health: Improved renal function in chronic kidney disease and for patients on dialysis

h. Bone loss: Mitigated oxidative stress in bone loss

i. Eye health: Improved visual function in patients with glaucoma and macular degeneration

j. Liver: Reduced inflammation in non-alcoholic liver disease

k. Skin health: Oral and topical application partially mitigated UV damage and reduced wrinkles

l. Fertility: Improved sperm motility and oocyte viability

➤

to 3,000 mg, in various emulsifying formulations.[18] The highest plasma levels of CoQ10 achieved with CoQ10 supplementation was eight times higher than the normal range.[18] Plasma CoQ10 concentration gradient forces intracellular transport of CoQ10, but not in adequate levels inside the mitochondria.[2,12,15-17,19,20-22] The insufficient intracellular delivery of CoQ10 in tissues, such as brain or muscle, may explain the limited clinical benefits obtained in conditions where mitochondrial dysfunction plays an important role, such as neurological or muscle degenerative diseases.[3,4,12,17,23]

Fortunately, GG supplementation could significantly overcome these hurdles, as a more effective and more economical means to increase intracellular levels of CoQ10 and of other essential cell metabolites, as discussed below. Besides, CoQ10 doses above 200-300 mg/day are not affordable by most individuals.

Geranylgeraniol (GG)

Geranylgeraniol (GG), a precursor for ubiquinone synthesis and an important molecule in human physiology, is ubiquitous in human physiology, as are ubiquinone and ubiquinol; and it occurs in the activated form of geranylgeraniol pyrophosphate (GGPP). GGPP is a precursor/building block in the synthesis of ubiquinone and other essential cell molecules.[24] This occurs downstream from mevalonate and the HMG-CoA reductase enzyme, on a parallel pathway to that of cholesterol synthesis. GG is a terpenoid naturally occurring in a variety of plants and a building block for carotenoids and many phytol-derived phytonutrients. The only supplemental form of GG available in the U.S. (manufactured by American River Nutrition, Hadley, MA) is derived from the annatto bean, native to tropical regions, which is used in South American cuisine and in food coloring in the US.

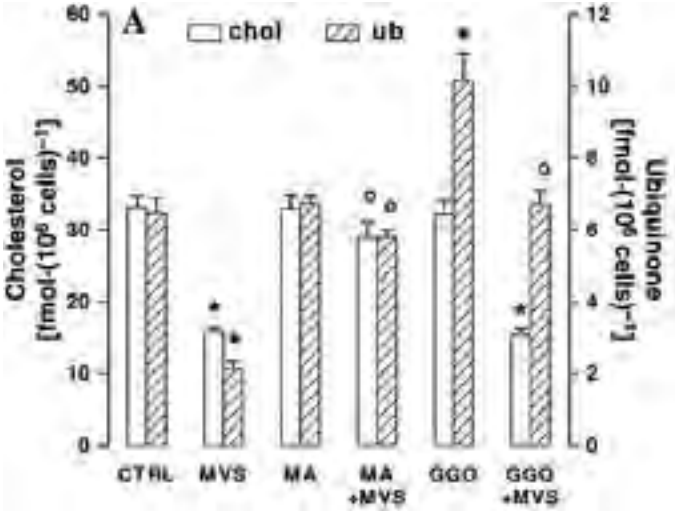
GG's molecular weight is one-third of CoQ10's, with a lipophilic hydrocarbon tail (see Fig. 3). GG is likely well absorbed in the GI tract since in vitro studies showed it diffuses inside cells with no need of adjuvants. This is in contrast with CoQ10, which needs to be solubilized and emulsified for absorption in the intestine, for skin topicals or inside cells in-vitro.

Table 2.a lists the main functions of GG in human physiology, while Table 2.b highlights results obtained from GG supplementation, in vitro or in animal models. GG easily diffuses inside organelles where it becomes the building block of ubiquinone synthesis (Fig. 3 & 4).[24] From there, the excess ubiquinone produced from supplemental GG is delivered to the mitochondria similarly to the basal endogenous ubiquinone, thus boosting mitochondrial function. This is a novel approach, since, to date, no other supplement has been shown to enhance endogenous CoQ10 synthesis.

Supplementation of cells with GG upregulates enzymatic reactions downstream from mevalonate, by mass action, resulting in increased synthesis of ubiquinone and other essential cell-signaling mediators (see Fig. 2).[24,25] Fortunately, the ubiquinone synthesis pathway is not tightly regulated, as is that of cholesterol, thus it can be upregulated by increased substrate concentration (Fig. 4). This opens the possibility to correct age-related decline in COQ10 and other metabolites derived from GG, in all tissues.

Figure 3. Structures of Geranylgeraniol (GG) and ubiquinone (CoQ10)

Figure 4. GG boosts CoQ10 levels above control. GG compensates for statin-induced reduction in CoQ10 synthesis, without affecting cholesterol levels.[24]



GG, Statins, and Bisphosphonates

GG can mitigate some of the side effects of statins and bisphosphonates, caused by the downregulation of synthesis of CoQ10 and other physiologically important metabolites. Some of the side effects of statins manifest as muscle pain/dysfunction, increased inflammation, cognitive problems, and liver toxicity.[70-74] Statin medication treatment lowers plasma and intracellular levels of CoQ10 and GG, leading to changes in mitochondrial functions, morphology and density and a lower rate of oxygen consumption.[75,76]

Supplementation with ubiquinol or ubiquinone was shown to mitigate the decline in plasma CoQ10 in statin-treated individuals but was not able to completely mitigate other adverse effects, particularly myopathy.[75-77] Metabolites reduced by statins or bisphosphonates are highlighted in red font in Figure 2. This illustrates why ubiquinol or ubiquinone supplementation cannot mitigate all side effects caused by these medications, as they reduce GG synthesis. Thus, only GG supplementation may replenish metabolites on pathways parallel with CoQ10 and cholesterol synthesis, all of which are essential in cell physiology.

For example, four weeks of statin treatment resulted in a drop in plasma CoQ10 from 773 mmol/L to 539 mmol/L.[76] Subsequent supplementation with 300 mg/day ubiquinol for four weeks, while continuing the statin, raised plasma CoQ10 higher than baseline at 2,305 mmol/L.[76] However, the mitochondrial dysfunction caused by the statin was only partially reversed by the ubiquinol treatment. This highlights the need for additional interventions, for which GG is a good candidate, as it was shown to mitigate mitochondrial damage in a cell model of mevalonate deficiency.[55] Furthermore, GG participates in a pathway parallel to those of CoQ10 and cholesterol synthesis. Another in-vitro study with human monocytes and hepatocytes showed that GG reversed mevastatin-induced reductions in a) ubiquinone synthesis, b) mitochondrial electron transport, and c) mitochondrial respiration without impeding the drug's cholesterol-lowering property, in a manner more effective than CoQ10 supplementation.[24]

Geranylgeraniol

CoQ10 and Aging

CoQ10 and GG supplementation mitigate central drivers of the aging process. GG supplementation complements CoQ10 due to its ability to easily penetrate cells, mitochondria and other organelles. GG increases ubiquinone synthesis, which results in higher levels of intracellular CoQ10 (both forms) and other essential cell signaling mediators. A boost in intracellular CoQ10 mitigates the aging processes due to the following: 1) Antioxidant protection of cellular proteins, lipids and nuclear/mitochondrial DNA, which may reduce risk of DNA mutations; 2) Improvement of mitochondrial function, which may increase physical and mental performance at any age; 3) Support of DNA repair; 4) Ability to decelerate senescence related processes; and 5) Support of immunity.

Since CoQ10 tissue levels decline significantly by middle age, well before any clinical signs of disease or impaired function could be observed, a dose of 100-300 mg CoQ10 and 60-150 mg GG should be adequate to support healthy aging,

➤

Table 2a. Biological Actions of GG Metabolites in Human Physiology

a. GGPP (GG pyrophosphate) is the active intracellular form of GG, a precursor and building block of
- ubiquinone[24]
- cell signaling molecules such as: Rho GTPase family (RhoA, Ras, Rap, Rac1, Cdc42), cytoskeletal proteins.[25]

b. GGPP metabolites coordinate
- cell function and communication
- cellular growth, survival, and apoptosis
- protein synthesis and modification intracellular protein placement.[24,25]

c. GGPP is involved in muscle metabolism.
- GGPP is involved in muscle cell metabolism and differentiation[25,44,45]
- GGPP protects against myotoxicity, myopathy.[25,45]
- deficient geranylgeranylation increases Atrogin-1, a muscle atrophy signal[46]

d. GGPP is involved in signals that support thermogenesis in white adipocytes.[47]

e. GGPP supports the immune system. Inhibition of protein geranylgeranylation interferes with B cell activation, resulting in a reduced capacity to induce T cell immunity.[48]

f. GGPP metabolites may protect against statin's effect on microglia.[49]

g. GG is a component of the MK-4 form of vitamin K2.
- GGPP contributes to the conversion of all forms of vitamin K ingested [K1, K2(MK-6), K2(MK-7), K2(MK-8), K2(MK-9)] to vitamin K2 (MK-4) for tissue storage.[50]
- Statins reduce synthesis of GGPP, thus reducing vit K2 (MK-4) deposition in various tissues, which may increase risk of osteoporosis and calcification in arteries, joints, and lung tissues.[51-53]

Table 2b. Results of GG Supplementation in Animal and In-Vitro Studies

a. GG added in-vitro increased synthesis of CoQ10 in control and statin-treated cells. This may compensate for age-related decline in tissue CoQ10 levels or due to treatment with statins or bisphosphonates.[24,25,54]
As a precursor and building block of CoQ10, supplemental GG may have similar benefits as those observed with CoQ10 supplements, as listed in Table 1b.

b. GG reduced inflammation.
- In-vitro addition of GG reduced inflammation related to the NLRP3 inflammasome.[55,56] GG supplementation in a rat study reduced IL-6 and NF-κB induced by lipopolysaccharides.[57]

c. GG reduced pain. GG's antinociceptive effects were found to be mediated through the vanilloid, glutamate and 5-HT3 receptors.[58,59]

d. GG increased synthesis of cell mediators essential to muscle function. GG mitigates the mitochondrial and muscle damage caused by statins.
- In an animal study GG improved muscle force production, skeletal muscle fatigue, cardiac muscle contraction/relaxation, and endothelium-dependent relaxation in arteries. This was shown, with and without, statin's negative impact. The equivalent human dose was 168 mg for 70 kg body weight.[60]
- May reduce statin-related muscle pain, by reducing muscle damage.
- In a rat study, GG was able to mitigate muscle degeneration caused by denervation (simulating muscle atrophy) by inhibiting atrogin-1.[61]
- An in-vitro study showed that GG can mitigate the effect of corticosteroids on muscle degeneration.[61]
- In-vitro treatment with a statin caused changes in mitochondrial respiration and its shape, which were mitigated by addition of GG.[24,55]
- In-vitro statin treatment reduced thermogenesis in white adipocytes, which was mitigated by addition of GG.[47]

e. Supports bone health
Based on animal and in-vitro studies, equivalent human doses of 30 mg to 160 mg GG may reduce bone resorption. In-vitro actions of GG are similar to vitamin K2(MK-4).[62-64]

f. GG helped alleviate some of the effects of bisphosphonate drugs on osteonecrosis of jaw, in an animal study.[65]

g. GG maximized synthesis of testosterone in studies with young male rats.[66,67]

h. GG mitigated the detrimental effects of statins on ovarian health and potentially on fertility. In-vitro addition of GG mitigates statin-induced ovarian cell apoptosis.[68]

i. GG mitigated MK-4 lowering by a statin or bisphosphonate treatment. In vitro addition of GG in the presence of a statin or a bisphosphonate restored the intracellular content of vitamin MK-4 closer to normal levels.[69]

➤

while more may be needed in cases of genetic polymorphisms and various chronic conditions. The supplementation with CoQ10 and GG early in the adult life is especially critical to reduce/delay DNA damage that cannot be reversed.

Conclusions

CoQ10 is one of the most recognized and utilized nutritional supplements in use today and is widely recommended by health care providers for a diverse range of issues, but predominantly for fatigue, brain, and cardiovascular health. It is also commonly utilized in an attempt to counter the side effects of cholesterol-lowering statin and osteoporosis drugs. The predominant form of CoQ10 available is ubiquinone. The preferred reduced form, ubiquinol, has been available for several years as a nutritional supplement. Due to some potential difficulties in the efficient reduction of ubiquinone to ubiquinol in some individuals, more commonly in the elderly, this form is now preferred by many, and is generally substantially more expensive than ubiquinone. While the biochemistry of CoQ10, and its central role in energy metabolism, would suggest that it would be a highly effective therapy for those with fatigue and mitochondrial downregulation, it does not always produce the expected and desired clinical results. This is likely due to a multitude of reasons, including CoQ10's large molecular weight, poor absorbability in the GI tract, and its inefficient transfer from blood to tissues, organs, and then cellular organelles, especially mitochondria.

Geranylgeraniol (GG) is an endogenous precursor/building block in the synthesis of ubiquinone and other essential cell signaling molecules, and newly available as an ingredient in nutritional supplements. With a molecular weight one-third that of CoQ10's, and its lipophilic structure, GG offers a unique adjunct to overcome the inherent limitations of oral CoQ10 supplementation. GG is also a precursor to the synthesis of many other critical cell signaling molecules, which may be the missing elements in achieving the desired clinical outcomes in many oral CoQ10 therapeutic interventions. The use of oral GG, combined with reduced CoQ10 (ubiquinol), offers a unique and cost-effective 1-2 punch in the enhancement of cellular CoQ10 levels through both exogenous and endogenous pathways. It is hoped that this will greatly improve the nutritional support of a wide range of issues, including fatigue, mitochondrial disorders, cardiac disorders, cognition and brain health, and age-related changes, among others.

A scientifically designed product of an in-situ ubiquinol in the presence of GG is a functional solution to the inherent challenges of CoQ10 supplementation. This combination of ubiquinol and GG is commercially available in a stable and highly bioavailable nutritional ingredient under the patent-pending of DuoQuinol™ from American River Nutrition (Hadley, MA, USA).

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References and article are available online at www.townsendletter.com.

Cristiana Paul, MS, holds a Master's in Nutrition Science from Cal Poly Pomona, California, and has extensive experience in clinical practice and reviewing nutrition research. Cristiana is the author of peer-reviewed papers on topics such as the roles of inositol forms in insulin resistance/PCOS, new view of collagen protein in human nutrition, nutritional approaches to managing inflammation, and metabolism of B12 forms in the setting of various genetic polymorphisms. She wrote chapters on omega-3s and vitamins K forms, in the 2012 and 2020 editions of *Textbook of Natural Medicine* (edited by Joseph Pizzorno & Michael Murray). She has been a scientific consultant for Designs for Health for the past 20 years.

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Dr. Barrie Tan is hailed as a trailblazer and the world's foremost expert on vitamin E, credited with discovering tocotrienol in three major natural sources: palm, rice, and annatto. A scientist first and foremost, Dr. Tan earned his PhD in chemistry/biochemistry from the University of Otago, New Zealand, and spent several years as a professor at the University of Massachusetts. Today, his research focuses on lipid-soluble nutrients that reduce and slow chronic conditions.

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On the cover

Glaucoma: An Integrative Medical Approach

by Marc Grossman, OD, LAc

This article will help you make sensible, researched, and clinically based decisions to support optic nerve health with recommendations that include Western herbs, nutritional supplements, Chinese medicine, and additional therapies. You will learn about the underlying causes of glaucoma and be given tools and techniques to develop eye health strategies.

The primary goal of this article is to offer a practical approach, based on the underlying philosophy that emphasizes prevention and support. In doing so, we celebrate the healing power within all of us and the mind/body's inherent potential for self-healing.

What Is Glaucoma?

Glaucoma is a symptom-free condition that is thought to be caused by damage to the optic nerve, which robs the patient of peripheral vision and can cause blindness. It is often referred to as the "silent thief." More than three million people in the United States have glaucoma, 2.7 million people of whom have the most common form, open-angle glaucoma. The number is expected to increase to over four million by 2030. African Americans have the highest prevalence rate (3.4%), followed by other races (2.1%), whites (1.7%), and Hispanics (1.5%).[1]

Glaucoma can be difficult to detect without a regular eye exam until a significant amount of vision is lost. The reason it is so dangerous is that most people with glaucoma have no symptoms. Many feel no pain, and most have 20/20 visual acuity, although possibly only straight-ahead vision. But left untreated, glaucoma can slowly steal your peripheral vision until you think you are peering through a tunnel (at best) or until you go blind (at worst). Most frightening, 70% of the vision lost to glaucoma occurs before diagnosis. Glaucoma may be due to the result of the loss of retinal ganglion cells and axons (nerve cells that pass along information) in the optic nerve and retina.[2] Thinning of the optic nerve may occur as well.

Neurodegeneration

Researchers now view glaucoma as a disease of the brain (a neurodegenerative disease) rather than simply an eye disease. Recent research has shown that the complex connection between the eye and the brain is an important key to the disease. The retina and optic nerve are both made up of brain tissue and are part of the brain. Glaucoma shares a number of features with degenerative brain diseases such as Alzheimer's, Parkinson's, and Lou Gehrig's disease. In these diseases, age and family history are major risk factors, and specific areas of the brain are damaged over time.

In glaucoma, changes occur in the back of the eyes. The optic nerve continues to be a focus for researching the underlying causes of glaucoma. Whether due to mechanical trauma, decreased blood flow, or other causes, optic nerve axon injury causes changes in retinal ganglion cells, eventually resulting in cell death. Researchers have observed that specific areas of injured optic nerve axons and retinal ganglion cell loss match the peripheral vision damage from glaucoma.[3]

Neuroinflammation

Glaucoma, especially if acute, may be largely an inflammatory condition. Researchers believe that high intraocular pressure triggers an inflammatory response.[4] In experiments, inflammation occurs in the central nervous

system and at early stages of glaucoma. Inhibiting the process through which inflammation develops appears to protect the neurons from damage.[4] Investigations of the precise role of neuroinflammation in causing glaucoma are on-going. Cells known as microglia behave like sensors to damage the nervous system and play a role in the inflammatory response. The process contributes to beta-amyloid accumulations, implicated in Alzheimer's disease. Similarly, the eye, actually part of the brain, also accumulates beta-amyloid in the retina and optic nerve. Microglia activity and the inflammatory response are linked to protein clumping and nerve cell degeneration.[5]

Oxidative Stress

Increased oxidative stress is a risk factor. Antioxidant drugs and nutrients that reduce enzymes involved in oxidation are reported to be helpful in animals with glaucoma. Although targeting intraocular pressure has been a prime therapy, researchers are increasingly looking to antioxidants to target oxidative stress.[6] Damage to DNA in the tissue layers that regulate aqueous humor outflow is linked to oxidative damage, damage to neurons, and to the optic nerve.[7,8]

Causes and Risk Factors

Genetics. There is a strong genetic correlation related to the onset of glaucoma.[9-12]

High blood pressure. Although high blood pressure is not a direct cause of glaucoma, many studies have found it to be related.[10,13] In a 2011 study, researchers examined medical records of over two million people older than 40 who were enrolled in a US managed care network. Those with hypertension had a 17% increased risk.[14]

Hypertension may be implicated because high blood pressure can result from poor circulation. Poor circulation can also lead to a compromised delivery of nutrients to the eyes, possibly resulting in poor eye drainage, leading to an increase in ocular pressure. Poor circulation also can reduce the supply of critical nutrients to the optic nerve. Perhaps this is why glaucoma can result in vision loss at any level of eye pressure if the optic nerve is weak, due to poor circulation and lack of oxygen and essential nutrients.

Damage to blood vessels. Increased eye pressure can be caused by endothelial dysfunction and vascular structural changes. This can substantially alter blood flow within the tissues and elevate IOP, leading eventually to open-angle glaucoma.[15] Vascular changes, such as low blood pressure, and vascular obstruction (poor circulation), have been linked to glaucoma.[16,17]

Homocysteine. High homocysteine levels have been identified as a risk factor for open-angle glaucoma.[18,19] Other studies link high levels of homocysteine to the onset of pseudoexfoliation glaucoma.[20-22]

Diabetes. Research has shown that glaucoma is closely related to diabetes, indicating a link to circulation and possibly inflammation. Examination of medical records of over 2 million people older than 40 found a 35% increased risk for open-angle glaucoma in people with diabetes.[14]

Thyroid disease. According to the CDC's survey of 12,376 participants, an association has been drawn between thyroid disease and glaucoma. Researchers found that the prevalence of glaucoma was almost double in people with thyroid problems versus those without thyroid problems.[23]

Helicobacter pylori. Medical researchers believe that *H. pylori*, which is the cause of many cases of stomach ulcers, may be implicated in a number of non-digestive conditions. These conditions include cardiovascular disorders, cerebrovascular disorders (blood circulation in the brain), and vascular dysfunctions. This organism may be involved in the pathology of the eye, specifically glaucoma. Meta-analysis suggested a statistically significant association between *H. pylori* infection and open-angle glaucoma,[10] uveitis, and central serous maculopathy.

Oxidative stress and free radicals may play an important role in the onset of glaucoma.

Drugs and medications. Non-steroidal anti-inflammatory drugs (NSAIDs) may interfere with effectiveness of IOP-lowering medications such as latanoprost.[24] Ongoing use of corticosteroids such as prednisone to reduce inflammation could increase IOP.[25] Topiramate (Topamax) can increase IOP and cause acute glaucoma, as well as medications prescribed for depression, Parkinson's disease, and allergies. Such medications can cause the pupil to dilate, resulting in a smaller drainage angle of aqueous fluid.[26]

Allergies. One study showed allergic rhinitis is associated with open-angle glaucoma.[27]

Obesity. Health problems such as obesity can also increase risk of glaucoma.[28,29]

Integrative Medical Approach

Through nutrition, diet, and lifestyle modification we can help nourish and support the health of the optic nerve for those with glaucoma or at risk of developing glaucoma.

Oxidative stress and free radicals may play an important role in the onset of glaucoma by causing damage to the trabecular meshwork responsible for effective outflow of the aqueous fluid, and the retinal ganglion cells.[30-32] The optic nerve requires healthy circulation to the eyes and essential nutrients to maintain cell integrity and good vision. Research has shown that circulation to the optic nerve is poorer for those with glaucoma, particularly for normal or low-tension glaucoma.[10] Glaucoma is not just a matter of normal IOP but also of keeping the optic nerve properly nourished. There are numerous nutrients that have been well researched as supporting circulation to the optic nerve and being neuroprotective as well (see causes above). Antioxidants play many roles to help reduce oxidative stress and damage due to free radicals,[33] protect the trabecular meshwork,[31] and support healthy circulation to the optic nerve.

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Nutrients Related to Type of Glaucoma

Open-angle glaucoma. If you are already on eye medications for lowering eye pressure but would like to lower it further and lower it naturally, recommended nutrients include the following (any changes in medication should receive your eye doctor's approval and management):

- For circulation: *Ginkgo biloba* and/or vinpocetine. Also, a good Liver tonic such as Revision, which is based on the classic Chinese medical model, helps support healthy circulation and movement of energy in the eyes.
- For optic nerve health: *Coleus forskohlii*, taurine, bilberry, grapeseed extract, magnesium, folate, vitamin B6, vitamin B12, N-acetylcysteine, alpha-lipoic acid, CoQ10, omega-3 fatty acids, and vitamin C.
- For helping reduce eye pressure: *Coleus forskohlli*, vitamin C, and alpha-lipoic acid.

Narrow or closed-angle glaucoma. If surgery is not needed and the eye doctor is monitoring the condition, then the following nutrients can be helpful in supporting optic nerve health:

- For circulation: *Ginkgo biloba* and vinpocetine. Also, a good Liver tonic such as Revision, based on the classic Chinese medical model (this formula was based on "rambling powder" of *xiao yao san*), helps support healthy circulation and movement of energy.
- For optic nerve support: Taurine, bilberry, grapeseed extract, magnesium, vitamin B12, N-acetyl-cysteine, alpha-lipoic acid, CoQ10, pyrroloquinoline quinone (PQQ), omega-3 fatty acids, and vitamin C.
- Eyedrops: Cineraria homeopathic eyedrops and Pleo Muc homeopathic eyedrops can help support circulation in the outer layer of the eyes.

Low or normal-tension glaucoma (the appearance of glaucoma is present with normal IOP). Changes resulting in thinning of the cornea, damage due to poor circulation, and/or lack of available essential nutrients may be improved using the same nutrients as in chronic glaucoma, but without the nutrients that can help lower eye pressure.

- For circulation: *Ginkgo biloba* and/or vinpocetine.[34]
- Optic nerve support: Combination of *Ginkgo biloba* and bilberry,[35] as well as taurine, grapeseed extract, folate, vitamin B6, vitamin B12 (methylcobalamin), N-acetyl-cysteine, CoQ10, and pyrroloquinoline quinone (PQQ).[36]

Pseudoexfoliative glaucoma (PEX) is distinguished by clumps of amyloid protein that accumulate in the eye and ultimately end up blocking the outflow of aqueous humor by clogging the trabecular network. Recommended nutrients are those that are both natural anti-inflammatories and supporters of optic nerve health.

- Natural anti-inflammatories: These include omega-3 fatty acids, astaxanthin, vitamin D3, MSM, and herbs such as turmeric (curcumin), holy basil, resveratrol, ginger, digestive enzymes, and rutin.
- For optic nerve support: Taurine, bilberry, grapeseed extract, magnesium, vitamin B9, vitamin B12, N-acetylcysteine, alpha-lipoic acid, CoQ10, pyrroloquinoline quinone (PQQ), omega-3 fatty acids, vitamin C.
- Eyedrops: Pleo Muc homeopathic eyedrops, MSM drops (used as eyedrops), castor oil eyedrops, and Cineraria maritima homeopathic eyedrops.

Essential Individual Nutrients

Antioxidants. Oxidative free radicals and reactive oxygen species (ROS) appear to damage the trabecular network, a key cause of glaucoma. It is well established that antioxidants are effective in reducing the presence of these antagonists. Treatment with the antioxidants vitamin E or N-acetyl-cysteine induced decreased ROS production in glaucoma trabecular meshwork (GTM) cells.[31] We recommend 200 IU vitamin E or 600 mg N-acetyl-cysteine three times daily.

Alpha-lipoic acid. 150 mg–300 mg per day. Alpha-lipoic acid is the only antioxidant that is both fat and water soluble. Studies have shown that it benefits people with glaucoma by enhancing color vision, general vision sensitivity, and helps protect nerve cells from damage.[37] Alpha-lipoic acid is an ideal substance in the treatment of oxidative brain and neural disorders involving free radical processes. It is a powerful antioxidant and supports other antioxidants such as vitamin C and vitamin E. It helps to raise glutathione levels within cells.[38] It has also been found to reduce neuronal damage due to over-stimulation by cyanide, glutamate, and iron ions, and protects nerve tissue.[39]

Aminoguanidine. 75 mg, 3 times per day. This is an anti-glycating agent that inhibits the 'cross-linking' or glycosylation of proteins. Glycosylation may cause, or at least contribute to, many of the problems of old age, such as cataracts, glaucoma, and macular degeneration. In an animal study, aminoguanidine was shown to help protect the optic nerve from damage.[40]

Bilberry (Vaccinium myrtillus). 180 mg–240 mg per day. The anthocyanin antioxidants contained in bilberry have long been confirmed to benefit vision. The combination of bilberry and *Ginkgo biloba* was found to be very helpful in a study involving over 300 patients with normal tension glaucoma. Another study finds that a combination of bilberry and French maritime pine bark (pycnogenol) could lower IOP up to 24%.[41]

Ginkgo biloba. 120 mg per day. Found to improve the visual field in some patients with normal-tension glaucoma,[34] *Ginkgo biloba* supports vascular cell integrity, providing better delivery of antioxidants and nutrients to the optic nerve and related cell tissue.[42] Ginkgo stabilizes cell tissue on the mitochondrial level (where our cells'

energy is manufactured). The mitochondria play a major role in several diseases, particularly neurodegenerative diseases, including glaucoma.[43] Several studies have shown mitochondrial irregularities in glaucoma patients.[44] Finally, ginkgo supports microcirculation.[45]

Taurine. 500 mg-1,000 mg per day. Taurine is an amino acid that protects the eyes against neurotoxin damage. Nerve-damaging toxins include excessive levels of glutamate, which may be responsible for ganglion cell death and optic nerve damage seen in open-angle glaucoma.[46] It is recommended for glaucoma and retinal disease for its valuable antioxidant properties.[47]

Curcumin. 500 mg per day. Curcumin's antioxidative capacity provides good protection for the nervous system, due to its anti-inflammatory, antioxidant, and anti-protein-clumping capacity.[48]

Vitamin B1 (thiamine). 50 mg-100 mg per day. Glaucoma patients tend to have low levels of vitamin B1.[49]

Vitamin B6. 100 mg daily. A combination of B6, B9 and B12 helps to lower homocysteine levels that are linked to higher risk of developing glaucoma.[50] This is taken in divided dosages with food, often part of a vitamin B complex formulation.

Vitamin B9 (folate form). 800 mcg or more per day. Supplementing with folate may be helpful to those with the pseudoexfoliation (PEX) form of glaucoma.[51]

Vitamin B12 (methylcobalamin). 1,000 mcg per day (up to 1,000 mcg–1,500 mcg per day) may help protect vision in glaucoma patients.[52]

Vitamin C (buffered and ascorbated). 2,000 mg per day, divided amongst several meals. Whole fruit, natural vitamin C with bioflavonoids is preferred as opposed to vitamin C synthesized from corn. The eyes of open-angle glaucoma patients were found to have significantly lower vitamin C levels.[53] Several studies have determined that low vitamin C levels in blood and in the vitreous humor inside the eye can contribute to meshwork outflow blockage due to aging, and it can contribute to development of glaucoma.[54] Supplementation with large doses (10,000 mg daily) can significantly lower IOP by 10 points.[55] For some people, a lower dose is recommended if the larger dose causes loose stools.

In many parts of the world, vitamin C is routine for glaucoma patients because it has the capacity to both decrease aqueous fluid production and improve drainage. In addition, vitamin C supports collagen metabolism, which may be linked to glaucoma.

Vitamin E. 200 IU three times per day (d-alpha-tocopherol and preferably with tocotrienols and not synthetic dl-alpha-tocopherol). Vitamin E is also found in the vitreous humor and provides antioxidant capacity to the eyes. It is most effective when combined with vitamin C, which helps regenerate vitamin E.[56] One study showed that patients who supplement with 300 IU–600 IU of vitamin E per day, improved blood flow and reduced vision loss. Non-treated subjects showed a significant reduction in their visual field at 6 and 12 months.[57] The non-treated showed a statistically significant reduction in visual field (change in mean deviation) at 6 and 12 months.

Vitamin E combined with CoQ10 is also more effective than vitamin E alone; CoQ10 increases mitochondrial alpha-tocopherol concentration which improves mitochondrial-mediated neuroprotection and inhibits astrocyte activation (a biomarker for neuro-degenerative disease).[58]

CoQ10. 100 mg-200 mg per day. CoQ10 provided neuroprotection against mitochondrial DNA alterations in an animal model of pre-glaucoma. CoQ10 protected against retinal ganglion cell death, prevented upregulation of certain protein biomarkers, improved other biomarkers, and protected mitochondria and mitochondrial transcription factor A.[59]

Very Important Nutrients

DHA, B complex, and vitamin E. DHA 200 mg–400 mg per day, B complex, and vitamin E 400 IU. Another study showed that the fatty acid DHA (abundant in fish oil), along with B complex and vitamin E, were helpful in preventing or delaying vision loss associated with glaucoma.[60]

Essential fatty acids. 3,000 IU per day. Essential fatty acids can help reduce the chronic inflammatory processes associated with glaucoma. Fish and fish oils are rich in omega-3 fatty acids (as well as DHA and EPA). The best sources of omega-3 fatty acids are cold-water fish such as salmon, mackerel, sardines, anchovies, and codfish. Black currant seed oil and flaxseed oil are also good sources of essential fatty acids. One study showed patients with primary open-angle glaucoma had reduced levels of plasma DHA and EPA compared with healthy siblings. These findings may be significant since DHA and EPA could modulate impaired systemic micro-circulation, ocular blood flow, and optic neuropathy, the main changes associated with glaucoma.[61]

Magnesium. 500 mg per day. Magnesium improves micro-circulation in glaucoma patients and may protect the retinal ganglion cell against oxidative stress and cell death. Some studies conclude that magnesium improves peripheral circulation and improves the visual field in glaucoma patients with blood vessel constriction.[62,63]

Helpful Nutrients

Coleus forskohlii. 350 mg–500 mg per day. A clinical trial of a glaucoma supplement containing the active ingredient forskolin along with a form of taurine, carnosine, folic acid, B1, B2, B6, and magnesium found that it reduced IOP and improved nerve cell health in the retina.[64]

Green-leafy vegetables, carrots, and beets. Researchers found a 30 percent decline in glaucoma risk in diets that include green leafy vegetables, carrots, and beets. This group of participants also had a 40-50% reduced risk of developing a sub-type of the condition known as early paracentral visual field (VF) loss (peripheral/side vision), ➤

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which is linked to poor ability to maintain constant blood flow.[65]

Green tea extract. 725 mg per day. One study shows that antioxidants from green tea are absorbed in the lens, retina, and other eye tissue, and reduces oxidative stress in the eyes.[66]

Resveratrol. 125 mg-175 mg daily. The antioxidant resveratrol is able to cross the semi-permeable barriers in the eyes; it is bio-available to eye tissue to help combat oxidative stress in the eye.[67]

Quercetin. 250 mg–500 mg per day. Research indicates that supplementing with quercetin has direct effects on protecting the loss of retinal ganglion cells in glaucoma patients.[68]

Turmeric (curcumin). 500 mg per day. The antioxidant curcumin has possible benefit with respect to oxidative stress in the eyes.[69]

Melatonin. Intraocular pressure is usually lowest at night, which is also when natural levels of melatonin are near their high in the circadian cycle. IOP is highest in the morning when melatonin is low. There seems to be a correlation between IOP and melatonin; supplementing with melatonin may lower IOP.[70]

Glucosamine. Caution. A clinical study shows that taking glucosamine sulfate, 750 mg three times daily for three months, can increase intraocular pressure (IOP) in some people.[71]

Foods Known to Increase IOP

Coffee. Drinking just one cup of coffee can increase IOP by 1-4 mm Hg for at least 90 minutes.[72,73] Regular coffee drinkers have a higher average IOP (approximately 3 mm Hg).[74]

However, coffee beans also contain antioxidant compounds. These antioxidative effects and their possible neuro-protective implications need further research. One study concluded that oxidative stress can be a causative factor in glaucoma, and targeted nutrients can reduce oxidative stress at the level of mitochondria. This can be achieved by supplementing with *Ginkgo biloba* and liquids that contain polyphenolic compounds (such as tea, red wine, dark chocolate, or coffee), which all have anti-oxidative properties.[75]

Glutamate. Evidence also exists that glutamate contributes to glaucoma, so it is best to avoid any foods with monosodium glutamate (MSG). Glutamate that is not biochemically bound to other amino acids, causes our inherent glutamate levels to increase rapidly. These "free" forms of glutamate are found in nearly all processed or packaged foods. Genetic predisposition to glutamate sensitivity is being investigated.

Glutamate naturally found in some food is linked to amino acids and is slowly processed by the digestive system. Free glutamate passes through the digestive system rapidly and is quickly absorbed into the bloodstream. In some foods, such as aged or cured cheese or meats, soy sauce, mushrooms, tomatoes, broccoli, peas, walnuts, and gluten, glutamate exists in a free form.[76]

Glutamate is an essential nutrient for proper brain functioning, but excess glutamate results in "excitotoxicity" causing nerve cell death. Normally the brain is protected by the blood-brain barrier, but such protection can break down in cases such as head injury, stroke, or high blood pressure and as a by-product of aging. If the blood-brain barrier is compromised, then excess glutamate in the brain and nerve cell death can be the result.[77]

Artificial sweeteners. Avoid artificial sweeteners as studies indicate possible neurotoxicity. Though more research needs to be done on this, we recommend avoiding all artificial sweeteners.

Foods Known to Decrease IOP

Studies have shown that there are natural ways to reduce intraocular pressure naturally including the following: eating a healthy diet high in fruits and vegetables.[78] People with glaucoma can reduce their eye pressure by five to seven millimeters of mercury (mm/Hg) with an improved diet and supplement program—a reduction that is as good as, or better than, achieved with drugs. In general, a diet high in beta-carotene, vitamin C, vitamin E, and selenium is recommended. Foods containing those nutrients include garlic, onions, beans, spinach, celery, turnips, yellow and orange vegetables, green leafy vegetables, seaweed, apples, oranges, and tomatoes.

In addition, drinking lots of water helps maintain the flow of nutrients to the eye and drains metabolic wastes and toxins from eye tissues. Optimally, you should drink 16 four-ounce glasses of water per day, every half-hour. Our bloodstream can only handle being diluted by about four ounces at any one time. When you drink more than four ounces at a time, this means more work for the kidneys to filter water that hasn't had a chance to travel through the lymph system and clean body tissues.

Avoid carbonated, caffeinated, and alcoholic beverages since they can actually dehydrate eye tissues. Your optimal water intake depends upon your particular physiology, diet, climate, and physical activity. Too much water intake can reduce blood salt levels (hyponatremia) and cause cells to flood. A good way to gauge if you are properly hydrated is by the color of your urine. If it is dark yellow, then you are dehydrated and need to drink more water. If your urine is as clear as water, then you have over-hydrated and should cut back intake. Green tea is very beneficial for your health and body, but too much is dehydrating.

Lifestyle – Activities That Increase IOP

Excessive exercise. Exercise where the heart rate is at 80% maximum increases short-term IOP by 4.7 mm Hg.[79] Weight lifting can cause a temporary increase in IOP of approximately 4 mm Hg.[80]

Breath control. Playing a high-resistance wind instrument such as an oboe can double IOP during playing.[81] It returns to baseline after playing ceases.

Inverted yoga postures. An inverted posture where the eyes are below the heart can cause a doubling of IOP (returns back to baseline after 5 minutes). Certain yoga exercises such as Shirshasana leads to a two- to three-fold rise in IOP from baseline for a short duration.[82]

Tight neckties. These can increase IOP 2mm Hg (returns to baseline when loosened).[83,84]

Computer use. In a large study of programmers, software engineers, and gamers with a mean age of 43 years, one third were found to have glaucoma. Even more significant was that heavy computer users who were farsighted (presbyopia) or nearsighted (myopia) seemed to have a higher risk. Nearsightedness was found in 82% of those with glaucoma.[85]

The connection between computer use and glaucoma may be physical. Computer users tend to have a hunched over posture over their keyboard which makes it necessary for them to raise their head to see the screen. The head weighs on average 7-10% of body weight and its effective weight increases for every 1 cm (.393 inches) away from the spine. Over a period of time, the weight of keeping the head up causes the muscles of the neck to shorten (side and back), which compresses the nervous, vascular, and lymph systems of the neck, and compromises circulation to the brain (and eyes). This hunched posture eventually becomes habitual, so the person, even when standing, maintains the slouched posture. Additionally, the hunched posture collapses the lungs, which reduces the capacity of oxygen.

Note. To help reduce the effect of chronic computer use, take regular breaks, at least every hour, to relax the eyes, and do some eye exercises.

Alcohol and glaucoma. Intake of large quantities of beer or water increases IOP significantly because the kidneys cannot process large quantities of liquid quickly. However, a few studies did not report any association between alcohol intake and IOP.[86] Neuro-protective effects of red wine have also been reported. Although consuming one alcoholic drink per day may have some cardiovascular benefits, it also increases the risk of liver disease.

Both acute and chronic alcohol consumption have severe effects on the structure and function of the gastrointestinal tract.[87] The eyes rely on receiving significant amounts of essential nutrients from the food we eat to maintain healthy vision; compromises in absorption and gut health can severely affect eye health.

Activities That Lower IOP

Regular exercise. Studies have shown that people who exercise regularly and are more physically fit have a lower average IOP.[88-90] Regular exercise means exercise five days a week such as a brisk walk.[91] Other studies reinforce exercise as a way to lower eye pressure and reduce the risk of developing glaucoma.[92-94]

Hormone supplementation. Hormonal use in post-menopausal women reduced IOP and improved blood flow to the optic nerve.[95] The use of estrogen plus progesterone (but not estrogen alone) was associated with a 42% reduced risk of high tension POAG.[96] Women under 45 years of age entering menopause showed a 2.6% increase in risk of glaucoma.[97]

Above average stress has been shown to increase the risk for high eye pressure by almost three times.

Other health risks, however, are associated with hormone supplementation, including increased risks of endometrial cancer in women with an intact uterus, urinary incontinence, dementia, stroke, blood clots, heart attack, and breast cancer.[98]

Breathing. Breathing through the nose, versus breathing through the mouth, and a correctly aligned posture that expands the lung can increase oxygenation by at least 20% and release nitric oxide, a vasodilator.[99] It is the exhale stroke of breathing which pumps the most oxygen into the lungs. Reduced breathing occurs due to a hunched over posture, which compresses the lungs. Shallow breathing causes an imbalance in the oxygen and carbon dioxide ratio, reducing the ability of oxygen being transferred into tissues, and this causes stress through activation of the sympathetic nervous system.

Sleep position. One study reported that a low head position elevates IOP compared to lying on one's right side. Proper adjustment of the pillow height may help lessen ➤

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IOP elevations that result from lying with a low pillow or with no pillow.[100] Another study concluded that asymmetric sleep behavior is common. Right-sided sleep was preferred and correlated with a lower visual field index for those sleeping on their left side.[101]

Manage stress. Above average stress has been shown to increase the risk for high eye pressure by almost three times.[102,103] We recommend meditation, yoga, tai chi, qi gong, psychotherapy, or a combination of these to help with life stress.

Marijuana. This cannabinoid has been proposed as an IOP-lowering agent for a long time. The active ingredient in marijuana (delta-9-tetrahydrocannabinoid) reduces IOP by reducing aqueous humor production.[104-106] However, the IOP-lowering effect of marijuana is short term, and one would need to smoke marijuana every three hours for 24-hour IOP control. Note: The essential ingredient in marijuana is now available in CBD oil that can be ingested by mouth, without causing any effect of getting "high," or having the negative effects of inhaling smoke. We recommend this over smoking marijuana, though more research is needed.

Other Modalities

Chinese Medicine and Glaucoma. In Chinese medicine, the Liver "opens to the eyes" and is the primary meridian for supporting overall flow of energy and circulation through the eyes. The Kidney meridian nourishes the blood to the eyes. The Spleen meridian also nourishes the blood, while also helping to keep fluids from leaking from blood vessels and reducing dampness (build-up of fluids). Other meridians may be out of balance as well, and that can affect eye health. An evaluation by an acupuncturist can best determine where the out-of-balances are located, and then, offer the optimal treatment strategy. The following are patented formulas used for glaucoma:

- *Xiao yao san*. Rambling powder is a classic Liver tonic used in Chinese medicine. The Liver "opens to the eyes" and is the primary meridian (flow energy) that supports healthy circulation and the free flow of energy in the eyes and throughout the body.
- *Qi ju di huang wan*. Rehmannia 6 plus chrysanthemum and lycii nourishes Kidney and Liver blood and yin. *Qi ju di huang wan* is a classic adaptation of rehmannia 6 (*liu wei di huang wan*) with a special emphasis on the eyes, in particular dry eyes, redness, and heat caused by yin (fluid) deficiency.
- *Shu gan tang* regulates Liver qi.
- *Wen dan tang*. Warm the Gallbladder decoction nourishes Kidney and Liver yin and brightens the eyes. This is formulated for disharmony between Gallbladder and Stomach meridian systems.
- Medicinal mushrooms. Reishi, maitake, bitter tooth, and lion's mane are helpful for glaucoma as they are reported to have neurite outgrowth and neuronal health benefits.

Treatment strategies can vary based on the TCM practitioner's evaluation and intake.

Acupuncture. Combining acupuncture and eye drops is better than eye drops alone for primary open-angle glaucoma,[107] and regular acupuncture treatments improve intraocular pressure (IOP) and retrobulbar circulation (circulation behind the globe of the eye).[108]

Homeopathy. Glaucoma homeopathic pellets. 1–3 pellets dissolved in mouth 2–3 times per day, preferably before meals, or an hour or more after meals. You can keep taking these pellets for as long as you like, keeping in mind that regular check-ups from the eye doctor are essential.

Chelation Therapy. Calcium overload and dysregulation have been found in both trabecular meshwork[109] and lamina cribrosa[110] from human glaucomatous eyes.[111] Ethylenediaminetetraacetic acid (ETDA), particularly combined with MSM,[112] may help reduce excess calcium and zinc, as well as other metals, which in excess, may contribute to eye problems.

Hypnosis. Hypnosis may help lower IOP according to some researchers.[113]

Microcurrent stimulation. Daily use of microcurrent stimulation helps stimulate circulation in the back of eyes, and helps the eyes eliminate waste.[114] This is particularly relevant for those where circulation and nutrition are a factor in maintaining healthy optic nerve.

For more information on integrative medical protocols for vision conditions, visit www.naturaleyecare.com

Our goal is that the information shared here will help people keep their precious gift of sight. ◆

Marc Grossman, OD, LAc, is one of the few holistic optometrists and licensed acupuncturist in the world and has been in practice since 1980. Internationally respected, he has taught many hundreds of practitioners and physicians in his methods. Dr. Grossman is co-author of *Natural Eye Care, Your Guide to Healthy Vision and Healing*, an 800-page landmark guide written to empower readers of every age to support and preserve healthy vision through the health of the whole body. He is also the author of *Magic Eye: Beyond 3D* and *Greater Vision.* He lectures widely on topics such as natural vision improvement, vision, and nutrition, as well as Chinese medicine and vision care and has been interviewed by the *New York Times, Wall Street Journal*, and many other magazines and has appeared on local and national network television. His respected https://naturaleyecare.com/ website is the world's largest holistic eye care website in the world and followed by many millions. Dr. Grossman has offices in Somers and New Paltz, New York.

References and article are available online at www.townsendletter.com.

HYPERCOAGULATION

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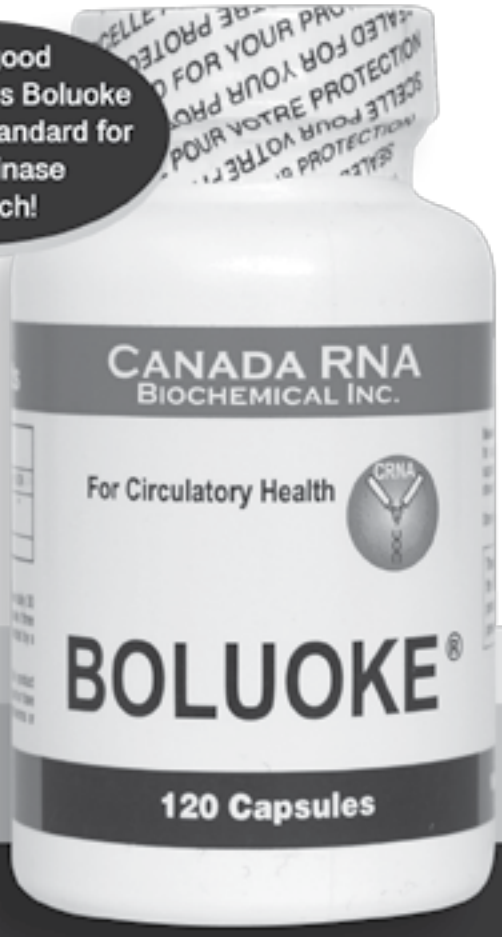

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Immunotherapy Management of the Allergic Patient with Asthma and Lower Airway Inflammation

by Diego Saporta, MD

Abstract

Administration of immunotherapy is rewarding but challenging. The reward is observing how a patient exhibits progressive symptom improvement while at the same time requiring less medication, even to the point of not requiring medications any more. The problem is the specter of a reaction to the immunotherapy injections. Even though the frequency of reactions to testing or immunotherapy administration is low, if a severe reaction were to develop it could have devastating consequences. The patient most at risk for this type of reaction is the asthmatic patient.

The purpose of this article is to bring awareness, both to patients and practitioners, that there are patients with allergy symptoms that are not considered to be allergic because their tests are negative; that there is a large group of patients that have evidence of inflammation of the lower airway but that usually are not identified as asthmatics. Their management should include the same precautions taken to manage the asthmatic patients. Lastly, perceptions of the significance of immunotherapy for the management of the allergic patient, mainly the asthmatic one, will be presented and a discussion about the management of such patient will follow.

Introduction

Allergy, a word derived from two Greek words meaning "different" (Allos) and "mechanism" (Ergos) describes the reactivity of an organism to the surrounding environment. Certainly, since the discovery of IgE in 1965,[1] the word "allergy" has been redefined as a phenomenon exclusively mediated by IgE even though Gell and Coombs had previously described four mechanisms by which the immunological system can react.[2]

Type I reactivity or hypersensitivity reaction is the mechanism that involves IgE. It is logical to think that the immunological system reacts as a whole, rather than with only one of its components. This common-sense thought is backed by multiple clinical observations of patients with clear symptoms of allergic disease but with negative RAST tests for IgE and/or negative prick tests. Is it possible that terms like "non-allergic rhinitis,"[3] described as a chronic nasal inflammation not caused by systemic IgE-dependent mechanisms, or Non-Allergic Rhinitis with Eosinophilia Syndrome (NARES) described as a syndrome consisting of allergic rhinitis (AR) symptoms with negative tests and nasal cytology showing greater than 20% eosinophils,[4] have been coined to describe these cases of clear allergic symptoms with a test that is negative?

Published evidence suggests that there is allergic reactivity not mediated by IgE. In this regard, IgG with its subclasses and IgA are currently being investigated for their role in allergic disease.[5] Allergic reactions induced by IgG, including anaphylaxis mediated by IgG, were studied in mice.[6] Mast cells and basophils can be activated in vitro independently of the presence of IgE, again suggesting that non-IgE pathways for hypersensitivity reactions exist.[7] Also, bronchial hyperreactivity and airway inflammation can develop via activation of mast cells without involving IgE.[8] The patient with inhalant allergies frequently develops reactivity to multiple foods. In this case the role of IgG is more significant.[9]

Mainstream medicine continues to define "allergy" as a phenomenon solely mediated by IgE. Sensitization is defined by the results of a positive test and the most common tests used for diagnosis are a blood test for IgE (usually known as "RAST'' test even though in most cases ELISA technology is used) or skin prick test. Often times these tests will be negative, either because the patient has reactivity that is not mediated by IgE, therefore the IgE-RAST will be non-reactive, or because the prick test lacks the sensitivity of an intradermal test.[10]

This produces an apparently contradictory situation: a patient with clear allergic symptoms and negative tests can be diagnosed as being non-allergic or having "non-allergic rhinitis" or similar. All this, despite evidence that in these "non-allergic" events there is inflammation[3] which is the hallmark of the allergic disease. Cases like NARES have an increase in eosinophils, cells that are always involved in the allergic response.

"Allergy" should be defined as the reactivity of the individual to the surrounding environment. This is a complex process that not only affects the whole body[11] but also involves one or

more of the immunological mechanisms described by Gell and Coombs. For management of the allergic patient, I rely mostly on the Intradermal Dilutional Test or IDT (previously known as Skin End Point Titration or SET) to determine which are the involved allergens. I evaluate not only the immediate skin response (ISR), but also the delayed skin response (DSR) that develops 24 or more hours after the injection of the allergen being tested.[12]

A skin response that occurs many hours after the injection of the allergen is, in all probability, not related to an IgE-dependent mechanism, rather to other immunological mechanisms. The papules of the DSRs are indurated, not well defined, often with significant erythema and they can persist for days and even weeks.[12] Delayed reactivity has clinical significance. For example, asthma can occur as a delayed response, and clinical improvement and decrease in the need for controlling medication can be attained if immunotherapy is administered.[13]

The ISR starts developing usually about 5-10 minutes after the prick or intradermal skin tests. The main allergy community defines these ISRs as being exclusively mediated by IgE. To be able to make that assertion would require histological studies of the papule developed after the skin test, for cellular and immuno-electrophoresis analysis. Otherwise, it cannot be asserted that the skin reactivity was mediated by one or another of the potential mechanisms by which the immunological system can respond to a stimulus.

Management of the Allergic Patient – The Role of Immunotherapy

Allergen Specific Immunotherapy (SIT) is the only treatment capable of modifying the inflammatory response[14] characteristic of the allergic conditions. Not only can it have a preventative effect on AR and asthma, but also can prevent further development of new sensitizations, progression of AR into asthma, and can even alter the natural history of asthma itself.[14-17] SIT was found to promote asthma resolution, and this effect was more pronounced with higher doses of allergen-immunotherapy.[18]

In the best of cases. immunotherapy administration can lead to a cure of the allergic condition affecting the whole body. In the worst of cases, it will produce an incomplete response. In general, it should be expected that some improvement will always occur when immunotherapy is administered.

Complications of Immunotherapy

Immunotherapy uses extracts of the same allergens responsible for patient's symptoms; therefore the extracts contain only natural proteins. This explains why immunotherapy has no side effects from the injected allergens themselves. This does not mean the patient cannot have an immunological reaction to the injected allergens. It is a fact that administration of allergens to which one is sensitized can trigger symptoms. Allergic disease is characterized by reactivity. Symptom development will follow exposure to the reactive allergens present in the environment. This "natural reactivity" triggers the usual allergy symptoms, which can be mild or severe. Occasionally, a serious reaction can develop. Example: the case of a cat-allergic patient that develops a bad asthma attack just by entering a home where there is a cat.

So, it is not surprising that when administering extracts from these allergens, symptoms can be triggered. In this case, these symptoms are called "reactions." When the administration is by injection, the reaction has the potential for severity. Most reactions develop at the injection site. They are known as local arm reactions, consisting of inflammation, swelling, and pain. They may alter the course of immunotherapy treatment, but usually they resolve without intervention. An injected allergen can also trigger systemic symptoms, which can be mild or severe. Severe systemic reactions are rare, but they can lead to anaphylaxis of which mortality, an infrequent outcome, is unfortunately a possibility. There are reports of mortality due to the administration of injectable immunotherapy (properly known as Subcutaneous Injection Immunotherapy or SCIT) or even during intradermal testing. It has been observed that severe reactions that required emergency intervention or that produced mortality occurred more frequently in asthmatic patients.[19-22] This is why it is of extreme importance for the allergy practitioner to become proficient in identifying and managing patients with potential inflammation of the lower airway. These severe reactions are rare; therefore, publishing a series as in the references above, requires reviewing reports in the literature over the span of several years.

"Allergy" should be defined as the reactivity of the individual to the surrounding environment.

Asthma

To recognize an asthmatic patient is not always straightforward. The National Asthma Education and Prevention Program, in the Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma[23] defines asthma (p.12) as a chronic disorder of the airways, characterized by an underlying inflammation. This produces bronchial hyperresponsiveness and, therefore, airflow obstruction, which are responsible for the characteristic symptoms including cough, chest tightness, shortness of breath (SOB), and wheezing. Cough, when present, is usually more significant at night. These symptoms usually respond to the administration of inhaled bronchodilators (Short Acting Broncho Agonists or SABA).[24] They are recurrent and can develop in any combination.

The term "cough variant asthma" (p.46) is used to describe cases of chronic cough that occur mainly in children. In these cases, cough is the principal or only manifestation. Response of this variant to usual asthma medications helps establish the diagnosis.

If the inflammatory condition becomes persistent over time, it may lead to permanent structural changes known as airway remodeling. It is important to understand that even without smoking or exposure to industrial chemicals or other irritants, an asthmatic patient can develop permanent damage of the lower airways. This airway remodeling is similar to the structural changes in emphysema. This process, the consequence of persistent airway inflammation, will not be prevented by currently available medical treatments.[25]

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Inflammation, the main defining aspect of asthma, is also the cause of the allergy symptoms. In other words, the allergic disease is an inflammatory disease that can affect any organ in the body: the nose and paranasal sinuses, the eyes, the ears – middle ear effusions[26] and other conditions – the upper and the lower airway, the skin, etc. When the lower airway is affected, the smooth muscle of the bronchi can "overreact," leading into bronchospasm and hyper production of mucous by the secretory cells. The bronchial hyperresponsiveness characteristic of the inflamed lower airway facilitates reactivity to a variety of allergic and non-allergic stimuli like exercise, cold air, tobacco smoke, and other irritants.[23] Airway hyperresponsiveness can be diagnosed by challenges with methacholine. In this type of evaluation, the patient inhales increasing doses of the irritant substance, attempting to demonstrate amongst others, a decrease in the functional values of the spirometry. This type of study is done only by pulmonologists under controlled circumstances.[23]

Table I. Symptoms and circumstances evaluated in any patient considered for IDT. (SOB: Shortness of breath).

Note: When patient is under treatment, the symptom scoring sheet will also include the PF value and information on medication use.

Cough
Chest tightness
SOB
Wheezing
Exercise induced symptoms
Exercise cough
Exercise chest tightness
Exercise SOB
Exercise wheezing
Waking at night with symptoms
Which symptom
History of bronchitis
Life time use of inhalers
Recent use of inhalers
Name if possible
When was it used last
Symptoms improved with it

At the present time it is thought that asthma and AR are better described as a continuum of inflammation involving one common airway,[14,27] with rhinitis often preceding asthma onset.[14] In other words, rather than considering AR and asthma as two different conditions, the evidence points to the fact that both are actually expressions of the same inflammatory disease, with different patients having more or less symptoms related to the upper or to the lower airways.

The prevalence of asthma and AR is increasing in the general population and a high proportion of new patients have coexisting upper and lower airway disease.[24,27]

My Personal Experience with Asthma Diagnosis

In the 2020 updates to the Asthma Management Guidelines, it is stated that the diagnosis of asthma is elusive, and depends on gathering information from history, clinical findings, tests, and repeated evaluations over time.[28]

This is why in our history taking, we ask the patient for the presence of asthma. If the answer is "no," we then ask, one by one, for the presence of symptoms or circumstances that could suggest the presence of inflammation of the lower airway (See Table I).

Because of the concept of "one airway-one disease," we incorporated the determination of the Peak Flow (PF) value in patients undergoing immunotherapy. We observed that with successful administration of immunotherapy the PF value improved. This observation prompted a chart review of 60 randomly selected patients[29] which confirmed that the PF exhibited a statistically significant increase when immunotherapy administration was successful. This improvement occurred in all patients even if not asthmatic. This finding strongly supports the concept of "one airway theory."[27]

One unexpected finding in that study was that 71.6% of the patients in this non-selected sample had one or more symptoms associated to inflammation of the lower airway. It became clear from that study that simply asking, "Do you have asthma?" was not enough to assess potential involvement of the lower airway. Self-reported asthma was present in 13/60 (21%) cases. When presence of symptoms suggestive of lower airway inflammation were considered, the percentage of affected patients increased to 71.6%.[29]

For children, the most common finding is cough during exercise, sometimes with SOB. Less frequently only SOB. When the mother denies this problem, if age allows, we also ask the child the same questions and we often find that the answer is affirmative, but the mother was not aware that her child had this problem. For the adult patient population, the most common symptom reported is SOB on exertion. For sedentary people, we ask for SOB when walking briskly or when going upstairs.

We have observed in the last few years that patients reporting symptoms of lower airway involvement are much more prevalent. Often the symptoms have developed from a few months to a few years prior to consultation. This could be related to the observed changes of skin sensitivity to intradermal testing after our geographical area was hit by two hurricanes in 2011 and 2012.[30,31] In these reviews, it became clear that after those hurricanes, the general population consulting at our office was more symptomatic, started to develop symptoms at an earlier age, had more involvement of the lower airway, and the number of children consulting for allergy management increased. Allergy testing in post-hurricane patients confirmed an increased sensitivity to tested allergens. These observations support the reports of increased incidence of allergic conditions worldwide[32-34] and of a dramatic increase in asthma prevalence in Westernized countries.[23,24,35]

Because severe reactions during administration of immunotherapy occur more frequently in patients with asthma and because asthma diagnosis is difficult and elusive, we think that isolated symptoms or circumstances pertaining to the lower airway (Table I) are potentially due to the presence of underlying inflammation characteristic of the allergic conditions. If administration of anti-inflammatory therapy, usually inhaled corticosteroids (ICS), leads to symptomatic improvement, we consider this patient to have an inflamed lower airway.

In our experience it is much more likely to find a patient with isolated

lower respiratory symptoms than a patient diagnosed with asthma. These patients do not conform to the usual asthma definition. They often have a normal spirometry, but the functional parameters (Functional Vital Capacity or FVC and Forced Expiratory Volume in the first second or FEV1) are both in the lower end of the range or just below the range, with normal FVC/FEV1 ratio. In these cases, in order to determine if the airway is inflamed, an ICS is used daily. On follow up we determine if the patient reports subjective improvement (for example: breathing better or being able to go upstairs without restriction). It is not unusual to observe a concomitant improvement in the predicted value of the functional parameters. If the patient does not improve, if there is a partial response or if the patient improves but the spirometric values do not, we increase the ICS dose and recheck both patient symptoms and spirometry in a few more weeks. The objective is to attain the best symptom control with the best spirometric value in preparation for intradermal testing in order to provide immunotherapy.

While diagnosing these patients with asthma could be considered controversial, assuming that these patients have an inflamed airway when there is a positive response to an ICS appears appropriate.

Reducing the Risk When Administering Injectable Subcutaneous Immunotherapy (SCIT)

As we discussed, allergen injections, either during testing or during immunotherapy, can trigger symptom provocation. Severe reactions, even though infrequent, can occur at any time during treatment, from the moment after the first injection of an intradermal allergy test to any time during dose escalation or maintenance (when immunotherapy dose does not change from week to week).

Sublingual immunotherapy (SLIT) can also trigger symptoms; but despite their relative frequency, symptoms are usually mild.[36]

That asthmatic patients have increased risk for severe reactions with increased risk of mortality should come as no surprise as the inflamed lower airway and hyperreactivity characteristic of these patients can trigger bronchospasm and mucous hypersecretion that can end with respiratory compromise and even death.[19-22]

Assuming that patients with one or more lower airway symptoms that exhibited improvement with ICS have lower airway inflammation and therefore potential lower airway hyperreactivity led us to implement the following precautionary measures when preparing these patients for intradermal testing (IDT) and subsequent immunotherapy administration:

- After clinical evaluation (Table I), an initial spirometry is obtained. Patient is treated with a daily ICS. Clinical and spirometric re-evaluation is done in 3-4 weeks. Once the best response and spirometric value have been ➤

established, the IDT is scheduled. The test will be done in several smaller sessions, challenging only a few allergens at a time. These tests always start with the weakest dilutions. The patient is kept on an ICS during the whole period of intradermal testing and also during the first few months of immunotherapy when dose is escalated, and symptoms come under control. All patients are trained on indications and use of an auto-injector of adrenaline. The patient needs to exhibit proficiency with a dummy device. At each encounter, for testing or treatment, patient needs to show the device to the allergy nurse, otherwise test or shot gets postponed.

- Patients with suspicion of airway reactivity (and those with asthma as well) have their allergy charts flagged. These patients are required to have a dedicated PF meter. Before treatment begins, an average of the PF value is determined. Before each shot, the PF value is measured. If it is not at 80% or more of the averaged value, the allergy shots will not be administered. If the PF is low, the allergy nurse will refer this patient back to the doctor.
- Attempt to discontinue the ICS is done when symptoms appear to be under control. The ICS dose will be lowered; and as long as symptoms do not relapse and spirometric values do not deteriorate, the ICS-weaning process continues. If appropriate, a rescue inhaler, to be carried at all times, is prescribed.

When dealing with asthmatic patients, we follow the same steps as above. Asthmatics are advised to carry the rescue inhaler at all times. It is important to verify that all patients with inflamed lower airway understand the difference between the maintenance and rescue inhalers and how to use them. Testing will not be done unless we have a certainty that the patient is stable.

When immunotherapy dose has been advanced and patient appears stable, the ICS dose will be reduced slowly, attempting to wean the patient from this medication. This requires patient re-evaluation every few months. Provided that the patient remains clinically stable and spirometric parameters do not deteriorate, weaning process continues. Eventually, when the ICS is discontinued, the patient is counselled again about the significance of a rescue inhaler and the need to carry it at all times, for at least a period of two-to-three years without having used it once.

It is our experience that after a few months of immunotherapy, many of the patients with asthma or symptoms of lower airway inflammation do not need inhalers any more and continue to be asymptomatic with improved or stable spirometry.

Role of Immunotherapy in the Management of the Asthmatic Patient

Asthma almost always has an allergic basis.[37] From all triggers (allergens, irritants and infections), allergens are the most important.[23] Immunotherapy is effective to treat asthma[14,17,38] and to prevent progression of AR into asthma.[15,16,38] It is accepted that immunotherapy is the only treatment able to modify the allergic disease and therefore able to alter the natural course of asthma,[14] but immunotherapy is frequently not offered to these patients. This is so despite the evidence that asthma incidence is increasing, knowing that anti-inflammatory medical therapy will not arrest the progression of the disease, knowing that some patients will develop airway remodeling, and knowing that there is a risk for exacerbation with potential mortality.

Because immunotherapy is riskier in the asthmatic patient, consideration of the severity level is important as asthma severity and poor medication control increase the likelihood of a severe attack.[39] But it has also been reported that 58% of the patients that died from asthma only had a mild or moderate disease,[40] which implies that the risk of mortality is not necessarily related to the severity of the disease. This is important, as patients and heath care professionals alike may think that having mild asthma, with minimal use of medications, perhaps affecting the individual only in a particular season or only when doing physical activity is a sign of safety, when this is not so. For example, sudden fatal asthma exacerbations have occurred in competitive and recreational athletes during exertion.[39] Also it is important to understand that ubiquitous allergens like molds, commonly present in indoor environments mainly if damp, can trigger asthma. Many cases of severe asthma with near fatal or fatal outcomes occurred in patients that were allergic to mold. In a report on 11 cases of respiratory arrest due to asthma, 10/11 cases had a positive skin test to Alternaria.[41]

From all this information, it should be expected that immunotherapy would play a predominant role in asthma management, but this is not so. The guidelines for asthma management from the National Asthma Education and Prevention Program[23] and the 2020 updates[28] state that the main objective of asthma management is to find the lowest dose of medication that will lead to symptom-control. Control is based on anti-inflammatory therapy, mostly ICS, but oral steroids are frequently used during exacerbations or when a loss of symptom control develops, knowing that medication use will not prevent disease progression. There is emphasis on environmental controls, considered one of the four cornerstones of asthma management.[23]

Modification of the sufferer's environment, by education on how to decrease exposure at home and/or at work, are obviously important interventions that will help decrease the level of reactivity and the need for controlling medication; but ultimately these interventions will not cure the patient nor arrest the progression of the disease. This can only be attained with immunotherapy.

SCIT is considered, in the asthma guidelines, as an adjunct treatment to standard pharmacotherapy if the patient cannot attain good control with medications, when it is suspected that the person reacts when exposed to a certain allergen and if sensitization to the allergen can be proven by a positive blood or skin test.[23,28] Sensitization is defined as the production of specific IgE, demonstrated in a positive blood or skin prick test. It is stated that SCIT is considered to provide only small benefits; therefore, the patient should consider the risks versus the potential benefits of this modality.[28]

In reference to sublingual immunotherapy (SLIT), there is a conditional recommendation against its use for asthma management[28] because the literature reviewed suggested that SLIT provided only a "trivial benefit" to prevent exacerbations, asthma control, and quality of life; and SLIT frequently produced reactions, either local reactions – in up to 80% of the cases – or systemic. It is acknowledged that no mortality cases were reported in the literature.

According to the asthma guidelines[28] SLIT can be administered as drops or as allergy tablets, emphasizing that the FDA has approved the use of allergy tablets for the treatment of allergic rhinitis and rhinoconjunctivitis but that SLIT as oral (sublingual) drops is not FDA approved.[28]

Allergy tablets are rapidly dissolving tablets that carry only one type of allergen, either grass, short ragweed, or a mixture of two types of dust mites.[42] To prescribe these tablets it is necessary to obtain a positive skin test or in vitro testing for IgE antibodies against the allergen being treated. The package information includes a black box warning stating that patients using allergy tablets should carry an auto injector of adrenaline in case a life-threatening allergic reaction such as anaphylaxis might develop.[42]

At the present time there is no effort in the main allergy community to distinguish between SLIT as the usual mixture of allergens according to the results of an allergy test, and SLIT referring to prescribing allergy tablets. SLIT is used liberally to describe either one of these completely different modalities.

The assumption that immunotherapy may not be very effective could be based on the following:

1. *Allergy test used for diagnosis.* The results of the allergy test are dependent on the type of test used for diagnosis.[10] The RAST-IgE will miss all reactivities that are not mediated by IgE but that still have clinical significance. Only a skin test can diagnose overall reactivity to the allergen mediated either by IgE or by one or more of the other immunological mechanisms. From the skin tests, the intradermal tests are much more sensitive than prick tests as with intradermal tests the allergen is injected in the dermis where the mast cells reside, rather than being applied over the epidermis as happens with the prick tests. Only an Intradermal Dilutional Test (IDT) can safely administer progressively stronger (more concentrated) dosages of the allergen being tested, increasing the possibility of finding a positive skin response. Not using an IDT will miss the majority of the positive skin tests.[31] For practitioners using the IDT, it is clear that most allergens react when a large amount of allergen is injected and injecting strong doses of allergens can be dangerous without knowing the reactivity of weaker allergen doses.[10] This explains the discordance between clinical history and test results, when a patient has clear reactivity to an allergen, but the skin test is negative. In this case, and according to the above guidelines, the patient will not receive immunotherapy. Example: the patient that develops asthma when exposed to cat, or nasal and ocular symptoms when exposed to dust but either the RAST or prick tests are negative.

2. *Concept of the allergy load.* By the concept of Total Body Load,[43] it is suggested that symptoms develop as a consequence of all the pollutants that are inside the body at one time. The more aggressors, the more symptoms. Any aspect of the load that can be removed will lead into some degree of improvement.

The same concept can be applied to allergies. All the allergens to which a patient is reactive determine the patient's "allergy load." Following this concept, removal of as many of the reactive allergens as the practitioner can treat, the better the clinical outcome. Certainly, some allergens will have more clinical relevance than others, but the overall results will be better if many or most of the involved allergens are treated.

Immunotherapy

The only test that enables the practitioner to diagnose most if not all of the reactive allergens is the IDT. If immunotherapy is implemented based on the results of tests of poor performance, only a small portion of the total allergy load will be "removed"; and the results of that immunotherapy will not be very significant.

The objective should be to desensitize the patient to as many of the reactive allergens as possible. Choosing the allergens to be incorporated in the vaccine based on clinical reactivity is not always easy. For example, it is a common finding to see a patient that may develop nasal obstruction and sinus pressure or pain upon going to bed or during wintertime who denies reactivity when exposed to dust. This patient should be suspected of being reactive to one or more of the allergens in the dust and dander panel. If the test proves such reactivity, desensitization to those positive allergens often leads to symptomatic improvement. This type of patient often has one or more chronic, persistent symptoms but lacks the typical symptom-fluctuation of seasonal allergies and may lack typical allergy symptoms like sneezing, itching of eyes, nose, and throat.

These patients frequently are not identified as allergic because the usual tests notoriously fail to demonstrate reactivity to common indoor allergens like molds or even dust mites, and clinical history is not the "typical allergic history." In these cases, immunotherapy

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will usually not be considered. The affected person will be condemned to having poor quality of life with chronic nasal obstruction at night and poor sleep. The significance of the IDT is again emphasized. If the concept of the total allergy load is not considered, many patients that could benefit fully from immunotherapy will not, as many of the allergens will not be diagnosed; or if diagnosed, they may not be deemed important as it is difficult to establish a clinical correlation and therefore those allergens will not be included in the allergy vaccine.

3. *Consideration of the Delayed Reaction.* Even the results of an IDT may be completely negative. In these cases, it is not uncommon to observe that at the site of the injection, a wheal develops many hours after the test. This is known as delayed reactivity. Delayed reactions are not considered of clinical significance by the main allergy community.[44] Despite evidence that they have clinical relevance,[13] few practitioners consider them for treatment.[12] Including the information provided by the delayed reaction improves the degree of improvement or response to immunotherapy treatment.

4. *Referring to SLIT specifically*. It should be imperative that the use of allergy tablets be clearly distinguished from the administration of a mixture of allergens usually (but not necessarily) mixed at the practitioner's office and provided as oral drops to be administered under the sublingual mucosa.

The fact that SLIT is not strongly recommended in the asthma guidelines[23] is probably related to poor results obtained by treating patients with one or just a few allergens. (Monotherapy for allergy tablets, oligotherapy for SLIT – oral drops – as diagnosed by prick or RAST tests).

Dr. Saporta completed his training in 1990 at Columbia Presbyterian Hospital in New York City. He is board certified in otolaryngology and has been a fellow of the American Academy of Otolaryngic Allergy (AAOA) since 2001. His private practice in Elizabeth, New Jersey, is heavily oriented to the management of allergic conditions. Interested in the use of oral vaccines since early in his practice, Dr. Saporta presented a protocol for sublingual immunotherapy at the 64th annual meeting of the AAOA that since then has been successfully used for the management of allergic rhinitis with or without asthma.

My Personal Experience with Immunotherapy

In my experience, immunotherapy is highly successful for the management of allergic conditions, including allergic rhinitis, allergic conjunctivitis, chronic sinusitis (even though some cases will require surgery despite intervention), some ear problems, asthma and even some cases of eczema or other types of skin rashes. SCIT and SLIT were found to be equally effective[45,46] as in both cases the full range of allergens diagnosed by an IDT was used.

SLIT has been reported to be effective for the management of children with asthma.[47-49] In my experience this is a correct statement supported by a report on the use of SLIT in a small group of children with asthma[50] and confirmed over the years by good clinical results when SLIT was administered to asthmatic patients, both children or adults.

When SLIT is mixed based on the results of an IDT, the results are the same as with SCIT[46] with the difference that SLIT is a much safer technique. There are no cases of mortality reported, related to the administration of sublingual immunotherapy.[28,51]

Our technique for SLIT administration[45] is based on daily administration with slow increment of the treatment dose. While some mild reactions can occur, we have never encountered a reaction that required administration of any parenteral medication (glucocorticoids, antihistamine or adrenaline).[36]

Therefore, poor results after immunotherapy are not related to the administration route of the allergy vaccine. It does not matter if the mixture of allergens responsible for a patient's symptoms is given as injections (SCIT) or oral drops (SLIT) rather to the factors above discussed. When only a few allergens are used, either because they are considered the most relevant or just because they are the only ones diagnosed with the allergy test, the clinical improvement will be commensurate with the number of allergens included in the vaccine from the total number of allergens that actually affect the allergy patient.

SLIT should be considered as the treatment of choice when treating the asthmatic patient or a child (with or without asthma) because of its excellent safety profile compared to the risk of a severe reaction when administering SCIT. Of note is that a few cases of severe reactions after SLIT administration have been reported. Review of those reports[36] showed that the patients that developed complications (asthma attacks sometimes requiring emergency room care) were mostly patients that did not tolerate shots – because of reactions – and therefore were switched to SLIT, often using a rush protocol. With this technique of SLIT administration, the dose is rapidly incremented until attaining a pre-established maintenance dose.

Using a protocol characterized by daily administration and slow advancement of the treatment dose, we never encountered a single severe reaction to SLIT (which does not mean this technique will not trigger reactions that require some intervention).[36] The concept of reaching the maintenance dose, for practitioners trained at the AAOA, AAEM or PAAS societies, is a clinical one. The maintenance dose is not a preset dose that needs to be attained, rather it is established by observing the response of the patient over time. Once attained, it is not a set dose, as it can be reassessed and changed if necessary.

Again, immunotherapy is a challenging therapy with potential for reactions, but it is important to underline that not all the administration techniques are the same. For example, and in contrast to the references cited above, a survey done by the AAOA[52] reported that there were no cases of mortality in the survey group and that the overall rate of reactions was 0.3%. Using the technique sponsored by the AAOA, AAEM or PAAS and applying the concepts here discussed provides for a safer way to administer immunotherapy.

Discussion

Immunotherapy should be considered the primary intervention for the management of the allergic patient as it is the only treatment modality that can lead to a resolution of the underlying inflammation present in allergic disease and asthma.

The management of a patient with asthma or with any isolated symptom suggestive of inflamed lower airway is complicated.

As the prevalence of lower airway involvement is rapidly increasing, the concepts here discussed become more relevant. The patient with asthma faces the following difficult situation: Either choosing immunotherapy because it is a treatment that realistically can lead into a cure or choosing to continue using inhalers and potentially other medications (even if only occasionally), knowing that pharmacotherapy will not alter the course of the disease, knowing there is always the specter of a sudden onset severe asthma attack (usually triggered by unexpected exposure to allergens or chemical irritants) regardless of asthma severity, knowing that there is a risk of developing airway remodeling with subsequent life-long impairment and finally knowing that, not frequently but realistically, there is a risk of developing a severe asthma attack with potential serious complications and even risk of mortality.

The conundrum is that the milder the disease, the smaller the risk for treatment complications and the more severe the disease, the higher that risk; but on the other hand, the more severe the disease the more important it should be to decrease and treat the underlying inflammation.

With experience, the allergy practitioner learns to recognize the patient that has an unstable lower airway. These patients should never be tested with any type of intradermal test until symptoms stabilize. To bring a patient under control implies acquiring proficiency in the use of inhaled corticosteroids as monotherapy or in association with long-acting bronchodilators and the use of rescue inhalers. It is also important to pay attention to patient's home and work environments and to patient's diet. Some cases are difficult to stabilize. In those cases, adequate vitamin and supplement support, optimization of thyroid function, and balancing other hormones when indicated are necessary interventions that have been and continue to be discussed in the *Townsend Letter*.

When the lower airway is inflamed, any stimulus can trigger reactivity leading to muscle spasm (bronchoconstriction) and mucus hyperproduction, which are responsible for the development of the usual lower airway symptoms in any combination. If immunotherapy administration is successful, it is often observed that the reactivity to many of those non-specific irritants will decrease and sometimes resolve. These are common observations for cold and exercise, not so common for cases of chemical reactivity.

A key question is why is the airway inflamed? If it is because of exposure to an irritant, removing the patient from the exposure should lead to a cure. Obviously, removing exposure to an irritant will lead to an improvement of patient's symptoms, but it is clinically observed that these interventions are not enough to lead to a cure. So, it is logical to assume that in these cases, the irritant behaves as an aggravating but not a causal factor.

Asthmatic patients, when receiving immunotherapy, should be treated with a slow dose advancement protocol. They should not be tested if they are not well controlled. When treating an asthmatic patient with SCIT, dose progression is often delayed or even reduced if the PF value decreases from expected, or if the patient has fever or any lower respiratory symptom, or if the patient skipped shots. Interrupting the treatment when an asthmatic patient is not controlled is not unusual. Safety is more important than expediency. The objective is to help decrease the inflammatory condition, which will bring symptom control rather than following a rigid protocol of dose advancement regardless of patient's clinical presentation.

The management of an asthmatic patient with SLIT is less troublesome than when using SCIT. Using our protocol,[45] SLIT dose advancement is, in general, uneventful.

Conclusion

To increase safety during immunotherapy administration, it is imperative to recognize the patient that has an inflamed lower airway as these patients are more at risk for reactions that potentially can be severe. This requires a high index of suspicion and the need for an in-depth history taking. This type of patient requires the same type of precautions as with the clearly asthmatic patients before considering testing in preparation for immunotherapy treatment.

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A Naturopathic Approach to Leaky Skin and Atopic Dermatitis

by Trevor Cates, ND

While leaky gut is now a common term, leaky skin is worthy of attention, especially during these times of widespread use of hand sanitizers and increased hand washing. Leaky skin (the external epithelium) is connected to leaky gut (the internal epithelium). Often times, leaky gut first presents as skin issues, and the most common example of this in clinical practice is atopic dermatitis (AD).

In a healthy state, our skin provides protection, temperature regulation, and maintains hydration. It is constantly renewing and regenerating itself with epidermal turnover. Genetic, immunologic, microbial and mechanical factors contribute to skin barrier function. When the skin's barrier is damaged or out of homeostasis, it no longer is able to function as designed, leading to leaky skin and appearance of a number of diseases, including acne, psoriasis, ichthyosis, and AD.

Leaky gut and leaky skin share some key similarities that impact overall health. Leaky skin is not as efficient as healthy skin at keeping allergens out, so they cross the epithelial barrier and trigger a systemic immune response.[1] An impaired epidermal barrier also makes it more likely to absorb potentially hazardous chemicals, which might cause reactions in the skin (contact dermatitis) or systemic toxicity.[2]

Skin forms a protective barrier that limits external invasion and provides a natural habitat for a multitude of microbes (bacteria, fungi, viruses), called the skin microbiota. Microbes colonizing the skin support the skin's barrier function. There is diminished bacterial diversity in AD and elevated amounts of *Staphylococcus aureus* (*S. aureus*) are detectable on AD skin, which negatively impacts the skin barrier function.[3]

The skin's barrier function is dependent upon the structure and composition of the uppermost layer of the epidermis, the stratum corneum (SC). Lipid organization and lipid metabolism in the SC requires an acidic pH, and when this is out of balance it can contribute to the issues of skin barrier function seen in atopic dermatitis. And growth and virulence of S. *aureus* is pH dependent, which can further contribute to atopic dermatitis.[4]

Use of harsh alkaline detergents in skincare products may increase the skin's natural pH and trigger inflammation.[5] A leaky epidermal barrier, causing water loss from the skin and causing dry skin, further predisposes skin to microbial imbalances. Achieving a well-balanced skin microbiota protects skin from harmful pathogens and promotes the natural lipid barrier and skin's immune system. Ultimately, this function helps prevent AD and other skin conditions.

Conventional treatments for AD often miss addressing the underlying causes, and overzealous hygiene routines worsen the issue. Antibiotic prescriptions are common in dermatology, and excessive use of antibiotics has created an emergence of "superbugs."[6] With a naturopathic approach to AD, we want to support a healthy microbiome and restore the skin's hydration and pH to improve skin barrier function. The most effective approach occurs when we address these both internally and externally.

Internally

Improvements to the internal epithelium often lead to improvements on the external epithelium, so it's important to address leaky gut. The supplement that I have been using in clinical practice for twenty years to help support my patients with leaky gut is GI Revive (Designs For Health), which contains a combination that includes L-glutamine, N-acetyl-D-glucosamine, aloe vera extract, deglycyrrhizinated licorice, slippery elm, mucin, chamomile, marshmallow, MSM, and quercetin. I have found using this along with certain probiotic supplements plus addressing food allergies and intolerances are fundamental in supporting patients with AD.

Of course, there is more to treating leaky gut, depending upon the patient's individual needs. Testing can help determine specific dysbiosis issues, but overall probiotics have shown to be beneficial. Probiotics are known to enhance positive gut microbiota changes, and a great place to start is the diet, with fermented foods, such as kimchi, sauerkraut, pickled produce, yogurt, and kefir.[7] Fiber-rich and prebiotic foods can help promote the growth of probiotics – dandelion greens, garlic, onions, leeks, and chicory.

Probiotic supplementation has been shown to help prevent and treat AD.[8] In the research, species of Lactobacillus and Bifidobacterium are the probiotics showing the highest potential for the treatment of AD.[9] It is important to consider the strength, quality, and duration of probiotic supplementation and that an individualized approach works best.

Other supplements I often recommend to patients with AD that are also supported by the research include vitamin D3 and vitamin E. Vitamin D deficiency appears to be related to the severity of AD.[10] Vitamin E of up to 600 IU daily has been shown to be an effective adjunctive treatment for AD. [11]

Externally

With AD comes an impaired barrier and inflammation of the skin plus an increase in the pH of the epidermal surface. This elevated pH further triggers inflammatory cytokines and comprises the barrier function and increases the chances of infection. The mildly acidic normal SC (4.5–5) inhibits the growth of *S. aureus* and *Streptococcus pyogenes*, so that the normal flora can thrive, like *Staphylococcus epidermidis* and *Corynebacterium*.[12] So, the pH of routine skincare products as well as topical treatments should be in this 4.5 to 5 pH range. If you do not know the pH of a product, it can easily be tested with pH strips (unless it is 100% oil).

Restoring optimal pH helps support the skin's hydration. In addition, certain topical ingredients can help restore water loss. However, common moisturizers are known to worsen AD since the skin barrier is already compromised, and with leaky skin it is important to avoid toxic chemicals that can more easily find their way into the bloodstream.

What is applied to the skin can impact the skin microbiota, which is essential in addressing AD. Topicals commonly known to create imbalances include antibiotics and antimicrobial ingredients like triclosan. Occlusives (such as dimethicone, petrolatum or lanolin) are commonly used in AD, but since they are trapping moisture in, they do not allow the skin to breathe. The concern is that when moisture is trapped in, especially when the person perspires, it can potentially disrupt the skin microbiota.

Humectants (such as glycerin) pull water in from the surrounding area. These can be helpful, especially during dry winter months and after overzealous hygiene practices when AD typically flares. Ceramides in skincare are often more marketing hype than designed for efficacy. For these to be effective, there needs to be the correct physiologic lipids at an appropriate ratio, or the barrier function may deteriorate rather than improve.

Coconut oil is my favorite topical oil for AD and an excellent base for natural lotions and cleansers for people with AD. It contains lauric acid, which is known to have antimicrobial and anti-inflammatory effects, and it has been shown to positively impact the skin barrier. In a study of 117 children with mild to moderate AD, the topical application of 10 mL of virgin coconut oil for eight weeks was found to reduce the severity of AD by about 30% more than mineral oil.[13] I have, personally and with patients, experienced a reduction in leaky skin using the Daily Essentials Step 1 as a cleanser, which has virgin coconut oil as a primary ingredient. While it is designed for the face, I have found it helpful for hands and other irritated areas of skin on the body.

Topical use of sesame seed oil also shows some promise in reducing the need for children with AD to use topical corticosteroid treatment.[14] I recommend avoiding olive oil because it has been shown to worsen AD.[15] 5% vitamin E has been shown to help AD.[16] I would recommend adding vitamin E to a compounded formula or looking for it in the topical salves and lotions you may recommend.

Certain extracts of botanicals have shown some promising results in the research with topical applications, including St. John's wort, licorice extract, willow bark, gentian as well as topical use of evening primrose oil.[17] Topical use of manuka honey has been shown to inhibit *S. aureus* proliferation and reduce inflammation and shows promise in managing AD.[18] Any of these can be included in a topical made by a compounding pharmacy.

If you do not have experience with skincare, I would recommend finding a compounding pharmacy that specializes in topicals. Please remember to check pH and always recommend a skin patch test before applying to AD lesions and to the face in sensitive individuals. To do a skin patch test, apply a small amount of the product to the inside of the forearm, cover with a band-aid and watch for any reactions over the next 48 hours. If a product is being used on the face, I recommend doing a patch test on the skin just below the jawline.

Since probiotic supplements seem to help prevent and reduce AD severity from the inside, many people ask me about topical probiotics. There is a lot of buzz about this in the skincare industry right now, and many companies are starting to make probiotic skincare. Unfortunately, there is currently not enough clinical data to demonstrate that they are effective on a large enough scale.[19] I think there is a lot of opportunity here, so I am looking forward to seeing the research unfold.

As I continue to dig through the research on the skin microbiota, I have come across some interesting studies. Something I have not tried but have seen in the literature is topical ozone therapy, which has been shown to be effective for treatment for AD. According to one study, it can change the proportional ratio of Staphylococcus and Acinetobacter, thereby restoring AD lesions to a healthy microbiological diversity.[20]

Research is one thing, and helping patients is another since they can present so uniquely. To summarize a naturopathic approach, I want to stress the importance of addressing AD both internally and externally. Internally, we want to focus on healing leaky gut and addressing gut dysbiosis. We also want to address nutritional deficiencies common with leaky gut, such as vitamin D. Externally, our goal is to restore the skin's pH, microbiota, and lipid barrier in order to repair leaky skin. While AD typically takes time to heal, when you use this internal and external approach simultaneously, the healing will allow for not only short-term but also long-term results. ◆

References and article are available online at www.townsendletter.com.

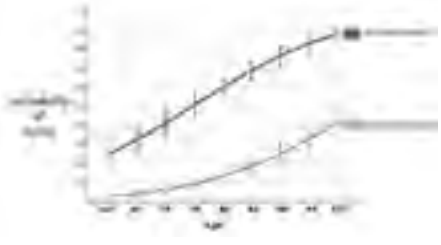
Dr. Trevor Cates graduated from the National University of Natural Medicine in 2000 and was the first woman licensed as a naturopathic doctor in the state of California, appointed by former Governor Arnold Schwarzenegger to California's Bureau of Naturopathic Medicine Advisory Council. Her book *Clean Skin from Within* is a *USA Today* bestseller and was an Amazon #1 bestseller in skin ailments following its release in 2017. She is host of the PBS Special *Younger Skin From Within*, *The Spa Dr. Podcast,* and *"Skin Stories*." Dr. Cates' *The Spa Dr.* skincare line is formulated with the ideal pH and plant-based organic ingredients, with the goal to achieve vibrantly healthy skin, even in individuals with sensitive skin. Website: TheSpaDr.com

The Life and Death Consequences of Low Plasmalogen Levels

by Chris D. Meletis, ND

Many doctors and patients are not addressing a critical factor involved in aging, Alzheimer's disease (AD), cancer, and heart health. That factor is low plasmalogen levels. Low or imbalanced levels of this special type of phospholipid may be the driving force behind age-related neurological problems such as AD and Parkinson's disease. In addition, virtually all cancers studied exhibit low blood plasmalogens. Put quite simply: If you are not detecting and addressing a patient's plasmalogen deficiency, you are leaving them open to a variety of health concerns. In this article, I will describe plasmalogens in detail and explain how and why they're so important to our health. I'll also address plasmalogen testing and the most effective way to raise levels of these important phospholipids.

Figure 1. Probability of dying in 5.3 years
Data from the Rush University Memory and Aging Project. Final dataset: 1262 participants, participants deceased since last visit = 557. Average age at enrollment = 81. Low plasmalogens = 5th percentile +/- 95% CI. High plasmalogens = 95th percentile +/- 95% CI.



Data from the Rush University Memory and Aging Project showed that a 95-year-old with high plasmalogen levels had the same chance of dying in five years as a 65-year-old with low plasmalogen levels. A 95-year-old with high levels had an almost 70 percent chance of living to their 100th birthday whereas a person the same age with low plasmalogen levels had a less than 20 percent chance of living to their 100th birthday[8]

What Are Plasmalogens?

Plasmalogens are phospholipids, lipids that contain a phosphate group. Plasmalogens are an important class of cellular lipids located in nearly all cellular membranes. They guard the cell against harmful agents such as excessive reactive oxygen species.[1] Low levels of plasmalogens leave the cell and its membranes more vulnerable to damage.[2]

In the human body, plasmalogen ethanolamines (PlsEtn) are the main form of these phospholipids; and in the brain, more than half of the ethanolamine phospholipids are plasmalogens.[3] The heart also contains high amounts of plasmalogens.[4] In addition, these phospholipids are abundant in the retina, leukocytes (immune cells), sperm, and skeletal muscle in mammals.[5] Plasmalogens are receptacles for oleic acid, arachidonic acid, and docosahexaenoic acid (DHA), all fatty acids that play important roles in health.[4] Plasmalogens have anti-inflammatory actions and are powerful antioxidants.[6]

Low Plasmalogen Levels Equal Greater Probability of Dying

Unfortunately, plasmalogen levels fall as we grow older. Plasmalogen concentrations rise up to 30 or 40 years of age then drop dramatically by the time a person reaches 70 years.[7] Data from the Rush University Memory and Aging Project show that having lower plasmalogen levels increases the probability of dying.[8] In fact, in this study, a 95-year-old who had high plasmalogen concentrations was as likely to die in five years as a 65-year-old with low plasmalogen levels. A 95-year-old person with high plasmalogen levels had a 70% chance of living to 100. Conversely, a person of the same age who had low plasmalogen concentrations had only a 20% chance of living to 100.

There's only one place in the body where plasmalogens are made: in the peroxisomes,[9] membrane-enclosed organelles that are similar to mitochondria in that they replicate by division.[10] During aging, peroxisomal function declines.[11] This, in turn, leads to less plasmalogen (PlsEtn) production and/or increased breakdown of plasmalogen, as well as less DHA-containing plasmalogen.[12,13]

Aging isn't the only factor that reduces plasmalogen levels. Peroxisome activity, and therefore plasmalogen production, is reduced by exposure to environmental toxins.[2] Neuroinflammation disorders such as autism and multiple sclerosis can cause local deficiencies and systemic plasmalogen imbalances.[14,15] Furthermore, inflammation causes oxidative stress, which may exacerbate plasmalogen decline.[16] This leads to a vicious cycle by triggering even more inflammation that weakens the anti-inflammatory and antioxidant defenses of brain tissues. Low plasmalogen levels are associated with a number of diseases (see table 1).

Table 1: Health Concerns Associated with Plasmalogen Deficiency

Aging
Alzheimer's disease
Parkinson's disease
Cancer
Coronary artery disease

Plasmalogen Deficiency and Alzheimer's

A lot of compelling evidence points to an association between low plasmalogen levels and Alzheimer's disease. First, plasmalogens are depleted in the brains and blood of people with AD.[3,17-19] In dementia patients, this decline starts years before the development of clinical symptoms.[17] Furthermore, in patients with AD, levels of brain plasmalogen ethanolamines (PlsEtn) are lower compared to age-matched controls.[3,19,20] This reduction in brain levels correlates with reduced serum concentrations.[20]

Further establishing the link between low plasmalogens and AD is the relationship between plasmalogen deficiency and dementia. Serum PlsEtn are associated with cognitive function in AD patients.[21] Additional evidence found that low serum levels of PlsEtn that contain arachidonic acid or DHA were associated with increased severity of cognitive dysfunction.[17]

Another group of researchers studied the relationship between plasmalogen deficiency and dementia.[22] They measured plasmalogen levels in cellular membranes of gray and white matter from brain regions of human subjects suffering from dementia of the Alzheimer's type. At a very early stage of AD, there was a pronounced decline in plasmalogen concentrations in the white matter of the patients' brains. In addition, the AD patients with the lowest gray matter plasmalogen levels had worse dementia. The participants who had mild dementia were only 10 mol% deficient. On the other hand, patients with severe dementia were 30 mol% deficient.

Finally, neurodegeneration of cholinergic neurons, the brain cells involved in cognition, is responsible for AD. These types of neurons are especially vulnerable to plasmalogen deficiency.[23,24] Low plasmalogen levels impair membrane fusion activity. This type of activity is needed for neurotransmitter release and uptake. When depleted plasmalogen concentrations weaken membrane fusion activity, this in turn reduces neurotransmitter function and cognition suffers.[23,24]

Plasmalogen Deficiency Linked to Amyloid Beta Buildup

The accumulation of β-amyloid (Aβ) plaques is one of the hallmarks of AD.[25] However, the buildup of these damaging plaques begins long before the diagnosis of AD. Although Aβ plaques become more common with age, they have been observed in healthy humans as young as 40 years old.[17] Plasmalogens can block the formation of Aβ plaques.[17] On the other hand, low serum PlsEtn levels are linked to the presence of Aβ plaques in the central nervous system (CNS).[17] Additionally, in humans, serum PlsEtn levels begin to fall at the same time Aβ begins to accumulate.[17]

Low plasmalogen levels are involved in the deposition of Aβ plaques and are not just a consequence of AD.[26] One group of researchers studied postmortem brains of humans who had AD.[26] The scientists found that plasmalogens were linked to weakened activity of γ-secretase, an enzyme involved in the production of Aβ. This enzyme synthesizes Aβ by regulating the body's processing of amyloid precursor protein (APP). Aβ lowers plasmalogen levels, leading to a rise in γ-secretase activity and synthesis of more Aβ plaques.

More support for the idea that plasmalogen deficiency is involved in Aβ plaque buildup has to do with the way the body metabolizes cholesterol. Higher membrane cholesterol levels result in the buildup of Aβ peptides by a process that involves amyloid precursor proteins.[17] Most APP is processed in a harmless way using the α-secretase enzyme.[17] However, APP is funneled into the β-secretase pathway, which results in the buildup of Aβ and possibly the development of AD.[17] Membranes containing phospholipids like plasmalogens are storehouses for the harmless α-secretase. Conversely, β-secretase is contained in cholesterol-rich membranes.[17] This indicates that plasmalogens can block Aβ accumulation by supporting levels of α-secretase rather than the more damaging β-secretase. Additionally, oxidative stress that leads to a drop in membrane plasmalogen levels also results in a rise in membrane cholesterol.[17,27]

APOE and Plasmalogens

Apolipoprotein E (APOE) is the primary lipoprotein in the brain.[28] The presence of the APOE epsilon 4 allele poses the most significant genetic risk factor for AD.[29] However, it's now becoming clear that high plasmalogen levels are needed to protect against increased risk of AD in persons carrying the APOE epsilon 4 allele. Dr. Dayan Goodenowe and his colleagues studied the possible connection between the APOE genotype and serum PlsEtn on cognition and dementia in 1,205 elderly individuals.[30] The extent to which the APOE genotype impaired cognition and increased the prevalence of dementia depended upon the subjects' plasmalogen levels. Independent of the APOE genotype, the probability of dementia neared zero when PlsEtn were higher. Participants who were older had a greater probability of dementia; but regardless of age, higher plasmalogen levels were linked to a near-zero probability of developing dementia. This indicates that higher PlsEtn concentrations are protective against dementia even in the presence of other risk factors.[30]

Plasmalogens are phospholipids in cell membranes that have anti-inflammatory and anti-oxidant effects.

Parkinson's Disease and Plasmalogens

Worldwide, Parkinson's disease (PD) is the second most common neurodegenerative disorder.[31] PD symptoms are caused by the degeneration of dopamine-producing neurons responsible for normal movement. Decreased brain and serum levels of ethanolamine plasmalogens occur in PD patients.[32] This plasmalogen decline may leave dopaminergic neurons more vulnerable to neurotoxins shown to cause PD in animals.

In animal models of PD, a DHA-containing PlsEtn precursor (PPI-1011) prevented the decrease in PlsEtn levels and was neuroprotective and anti-inflammatory.[31,32] This led a group of researchers to conclude that it has "potential utility as a treatment for both early and more advanced stages of PD."[31]

The conventional therapy for PD is the drug L-3,4-dihydroxyphenylalanine (L-DOPA). However, after years of treatment, most patients taking this drug develop erratic movements (dyskinesias). In a study using monkeys, researchers found that plasmalogen supplementation ➤

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together with L-DOPA reduced the number of dyskinesias caused by the drug.[33]

Plasmalogen's Role in Autism and Multiple Sclerosis

With these two conditions, it's not as simple as saying that plasmalogen levels are lower in these patients. In events leading up to MS and autism, mitochondrial insufficiency leads to fatty acids that are supposed to be metabolized by the mitochondria being metabolized by the peroxisome. This leads to higher omega-3 plasmalogens, elevated HDL, and higher triglycerides. However, the local need for omega-9 plasmalogens is much greater than the minor increase caused by the mitochondrial insufficiency.[34] Supplementing with omega-9 plasmalogens ensures that the surrounding glial cells can rebuild the white matter in the healthy cells as fast as the inflammation damages it. This results in a dramatic increase in glial cell recovery rate, which in turn results in a healthy inflammatory response and the inhibition of inflammation-mediated white matter loss. Inflammation can be reduced and mitochondrial health supported by delivering and keeping in reserve excess plasmalogen-building material.

Plasmalogens play an important role in supporting the health of MS patients through their effect on myelin. MS occurs due to the neurodegeneration of myelin, which insulates neurons. In fact, the highest levels of plasmalogens in the body are found in myelin. The activation of immune cells that occurs during inflammation can wreak havoc on the myelin. When this happens, additional omega-9 plasmalogens are required to repair the cells before the myelin dies.[35] Supplementing omega-9 plasmalogen concentrations stops demyelination by enhancing remyelination.[36,37]

In autism, low omega-9 plasmalogen levels are also directly linked to behavioral issues. In a mouse model of autism, plasmalogen deficiency resulted in a severe disturbance of neurotransmitter homeostasis and release as well as accompanying abnormal behavior, such as hyperactivity and poor socal interaction.[14]

Cancer

A cancer diagnosis can often seem to appear out of the blue. However, certain biochemical signs that a patient is more likely to develop cancer are present years before the development of the disease. Elevated levels of the diamines putrescine and cadaverine – amines containing two amino groups – have been observed in a number of unhealthy tissues, including cervical, colon, endometrial, oral cavity squamous cell, ovarian, pancreatic, and prostate.[38] At the same time, changes in plasmalogens and their fatty acid precursors occur in abnormal cells.[38] In fact, plasmalogen deficiency is thought to lead to cancer development.[38]

A study published in *Lipids in Health and Disease* investigated the effects of augmentation with a specific type of plasmalogen on cellular levels of diamines in Chinese hamster ovary (CHO) cells and NRel-4 cells, a CHO cell line with impaired plasmalogen synthesis.[38] The researchers found that plasmalogen supplementation reduced cellular diamine levels from both control and plasmalogen-deficient cells.

Plasmalogens and Heart Health

Clinically, a lipid profile is used to measure the risk of coronary artery disease (CAD). However, the conventional lipids measured in this profile – total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides – are not able to predict whether a person's coronary episode will present as stable or acute.[39] However, low plasmalogens are associated with the breaking off of coronary plaques from arteries.[39] This can lead to blood clots that can result in a heart attack. Researchers have found that measuring levels of phospholipids such as plasmalogens was a superior means of distinguishing acute coronary syndrome from stable CAD compared with conventional clinical risk factors like cholesterol.[39] Acute coronary syndrome refers to several conditions that can suddenly block blood flow to the heart, such as a heart attack. Plasmalogens were lower in the acute coronary syndrome group compared to the CAD group.

Evidence indicates plasmalogens protect against atherosclerosis plaque disruption and blood clots by reducing oxidation[40] and reducing the death of cells lining the blood vessels (endothelial cells).[41] Plasmalogens also are involved in cholesterol metabolism, another way in which they may protect the heart.[42]

In a preclinical study, raising plasmalogen levels reduced atherosclerosis by up to 70% in mice.[40]

Plasmalogen Testing

In my clinical practice, I have always operated under the philosophy, "Test, don't guess." This is especially true in regards to plasmalogens. A new test (ProdromeScan Blood Test) can measure levels of ethanolamine plasmalogens and choline plasmalogens as well as other phospholipids and biochemical markers. The test pinpoints specific underlying biochemical deficiencies that can lead to Alzheimer's, Parkinson's, heart disease, cancer, multiple sclerosis and autism, as well as aging itself. This test can be used to map out a protocol for patients at risk of – or currently diagnosed with – these conditions.

Plasmalogen Supplementation

Because plasmalogens are degraded in the gut, it is not possible to consume enough of them through the diet alone. Much of the research on raising plasmalogen levels in animals was conducted using the PPI-1011 plasmalogen drug. Dr. Dayan Goodenowe designed and invented this drug when he discovered there was a patent protecting the use of natural plasmalogens for dementia. However, that patent recently expired. Consequently, he developed a plasmalogen supplement (ProdromeNeuro™) that possesses the same activity as the PPI-1011 drug. Dr. Goodenowe's supplement survives the gut and bypasses peroxisomal production of plasmalogen so that even if peroxisomal activity is low, the body will continue to have access to this important phospholipid.

For age-related (AD, PD, cancer, heart disease) and neurological (bipolar, schizophrenia) diseases, it is critical to replenish plasmalogens with a supplement containing DHA at the 2-acyl position.[43] This has a number of benefits including dose dependently reducing cellular cholesterol levels by boosting cholesterol clearance.[43] In fact, this has been shown to be more effective at lowering cholesterol than statin-induced HMG-CoA inhibition.[43] Additionally, phospholipid-linked DHA is preferable because it contains plentiful levels of

plasmalogens.[44] This promotes memory and cognition, whereas triglyceride-linked DHA is much less effective.[44]

In November 2019, Dr. Goodenowe's synthetic, natural plasmalogen precursor was tested in humans for the first time.[45] The study included six adults who experienced a 50% increase in blood plasmalogen concentrations 12 hours after receiving the plasmalogen precursor. The rise in plasmalogen lasted for 24 hours in all the subjects.

Other trials are being conducted to determine dosing, demonstrate tissue concentrations, and safety. In 2020, a clinical trial funded by the Alzheimer's Association to investigate the use of Prodrome-Neuro™ Plasmalogen Oil began enrolling Alzheimer's patients. Goodenowe hopes to ultimately include Parkinson's disease and MS patients in the trial.

Conclusion

Plasmalogens are important phospholipids that decline with age. Low levels of plasmalogens are associated with an increased risk of dying. Furthermore, deficiency of these phospholipids is associated with Alzheimer's disease, cancer, multiple sclerosis, autism, heart disease, and Parkinson's. Testing for plasmalogen deficiency and replenishing plasmalogen levels can make a dramatic difference in a patient's health and possibly even lead to a longer lifespan.

As functional medicine clinicians we are always reviewing the scientific literature for new insights and clues as to how to best support the innate functions of the body. To access the latest ongoing research and educational videos on plasmalogens, healthcare providers can register for updates at www.Prodrome.com/65.

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An Old-But-New Treatment for Opioid Addiction

by Erica Zelfand, ND

Lucy's addiction to heroin began over 25 years ago. "It was a slow creep," she says, "and then all of a sudden I was doing an eight ball a day and living on the street."

Over the years, Lucy has tried to overcome opioid use disorder (OUD) through a variety of methods, including hospital detox and methadone maintenance. She is now taking frequent, high doses of buffered vitamin C to try and kick her addiction.

Lucy's curiosity in trying the vitamin C regimen was rooted in desperation. Even after enrolling in an outpatient injectable opioid agonist therapy (iOAT) program through which she received high doses of opiates twice a day, every day, Lucy was still plagued by drug cravings and breakthrough withdrawal symptoms. She controlled these symptoms with street drugs – about 300 mg a day of fentanyl, a synthetic opioid pain reliever 50 to 100 times more potent than morphine,[1] or "whatever I could get my hands on."

Lucy was flung into the throes of withdrawal, however, when she could no longer afford her $50 to $75-a-day fentanyl habit. "I was so sick I was blacking out – they wanted to call an ambulance," she says of the staff at the nearby health clinic. As a last-ditch attempt, a nurse suggested calling Trevor Millar, a local health advocate well versed in supporting those with opioid addiction.

Millar met Lucy that night with a bottle of sodium ascorbate, a buffered form of vitamin C, and instructed her to take 2 grams of the vitamin every two waking hours.

"The next morning, I woke up and I had no withdrawal symptoms," Lucy tells me. "I felt better than I had in years. Had I had to do that come down on my own, it would have killed me."

The Epidemic Rages On

Lucy isn't the only North American living with opioid use order (OUD). OUD refers to a problematic pattern of opioid drug use that leads to serious harm (or risk of harm) for a person. (The condition is also known simply as "opioid addiction.") While OUD used to be centered on heroin, the use of prescription opioids pain relievers – drugs like fentanyl, oxycodone (OxyContin®), hydrocodone (Vicodin®), codeine, and morphine – is now on the rise. Opioids are implicated in overdose deaths more than any other drug class, claiming more lives than guns, breast cancer, or car accidents.[2]

The prescribing practices of healthcare providers are implicated: opioid misuse often begins with a legally acquired prescription.[3]

OUD used to be associated with poor, inner-city neighborhoods. Since the 1980s, however, the epidemic has infiltrated all strata of society, including suburbanites and the upper class. OUD now affects more Caucasians than any other race, with women comprising the fastest growing demographic afflicted. This may be because women might be more sensitive to pain than men, and thus more susceptible to cravings and relapse.[4]

Simply put: OUD is the deadliest drug crisis in American history,[5] and it has only gotten worse since the onset of the COVID-19 global pandemic[6]: Opioid withdrawal-related emergencies and opioid-related deaths have increased since the SARS-CoV-2 virus erupted on the scene.[7] Lockdown has pushed more people into isolation and toward addictive behavior, and the closure of treatment facilities and the interruption of care has pushed those with OUD to the point of crisis.[8]

A Slow and Steady Taper

A good night's sleep after taking vitamin C was just the beginning of Lucy's recovery: Within a week of starting the vitamin C regimen, she was off all street drugs, save for a single dose in the morning. "That morning dose was really hard to kick," she explains, but within eight weeks she had successfully done so and has been entirely off of fentanyl ever since.

Fueled by her success in quitting fentanyl, Lucy continues taking vitamin C daily and working closely with her physician to steadily decrease her opioid usage. She has gradually dropped her iOAT dose of hydromorphone from 170 mL twice daily to 30 mL twice daily (the exact mg/mL potency of her preparation could not be confirmed). Her dose of morphine sulfate has likewise slid downward from 1,800 mg daily to now 30 mg daily – and she's still lowering her doses.

She attributes her drop in opioid dependency entirely to vitamin C. "I wish I could give the whole world vitamin C, it just works so well," she says, "I'm flabbergasted."

Millar is pleased with Lucy's progress as well, noting her absence of withdrawal symptoms despite the speediness of her taper. "And that's using nothing but sodium ascorbate in the poorest costal code in Canada," he says, pointing out that Lucy cannot afford to engage in psychotherapy, trigger avoidance, healthy eating, or other supportive services typically recommended to those battling substance use disorders.

But is Lucy's steady improvement on account of the vitamin C?

"I honestly cannot say," says her physician, who asked not to be named. The MD confirms that Lucy is, indeed, tapering down faster than is typically

seen at the clinic. The doctor points out, however, that Lucy has had to increase her dosages a couple of times during periods of acute stress – like when the pandemic began and Lucy feared contracting the viral respiratory illness on top of her pre-existing asthma and chronic obstructive pulmonary disease (COPD). Nevertheless, Lucy says the nurses at her iOAT program "can't believe I've pulled off the taper I have."

Lucy has some ground to cover before she's free of OUD. After several months of using vitamin C, she is still dependent upon opioids, albeit at much lower doses. Being spared withdrawal symptoms is not quite the same thing as overcoming a 25-year addiction or staying clean for the long haul, after all.

But even if Lucy never entirely stops using opioids, she has at least reeled in her drug use, saved taxpayers thousands of dollars, and significantly improved her quality of life since adding vitamin C into her treatment plan.

In addition to working with Lucy, Millar – who is also chair of the board for the Multidisciplinary Association for Psychedelic Studies (MAPS) Canada – has helped numerous other clients across North America successfully taper down their opioid use without having to suffer the horrific symptoms of opioid withdrawal. In fact, Millar says, "they feel pretty great."

Millar pulls out his phone and reads me a text sent by a client less than one day after starting vitamin C: "Dude I made it longer today with less stuff than I can remember." Millar explains that in fewer than three weeks this client dropped his daily buprenorphine (Subutex) use from 12 mg to 2 mg, without experiencing a single craving or side effect.

Millar also shares with me the success story of an Alaska couple who received his vitamin C protocol via e-mail: "Within three months they were both entirely off of all opioids and are still doing well."

What the Research Shows

Millar and Lucy's claims, as unusual as they may seem, are supported by research. The body of scientific evidence regarding vitamin C's efficacy in dampening opioid addiction is compelling – though somewhat patchy.

Much of the peer-reviewed data comes from animal studies, which may or may not translate into outcomes in humans. Nevertheless, the findings are consistent: Vitamin C supplementation makes animals take fewer "hits" of morphine and clearly mitigates opioid tolerance and dependency.[9-12] The vitamin has also been shown to reduce the number of opioid binding sites in the brains of guinea pigs.

Whereas most mammals synthesize vitamin C within their bodies, humans and other primates, bats, and guinea pigs are the exceptions to this rule. Vitamin C is thus an essential nutrient in humans – meaning we *must* take it in through the diet and/or supplements to ensure proper health, whether or not we suffer from substance use disorder.[13]

High doses of oral vitamin C have eased the symptoms of opiate withdrawal in at least a couple of human studies. A 2000 study by Evangelou et al,[14] for example, found that supplementation with vitamins C and E reduced opioid withdrawal symptoms in 57% of patients – compared to just 7% of those in the placebo group. Another study by Newmeyer et al.[15] found that just 1 to 3 grams of buffered vitamin C taken

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daily offset withdrawal symptoms for those in active detox as well as for those who had recently finished detoxing. The case reports of Schauss, Libby, and Stone (explained below) also support the case for using high dose vitamin C to abort opioid withdrawal symptoms.

I sent some of these studies over to Wesley Ryan, MD, a physician board-certified in both general and addiction psychiatry. "At first I thought it was probably ridiculous," Ryan admits, "but after skimming the studies, it seems like there's some real effect there."

Erick Turner, MD, a psychiatrist with Oregon Health and Science University, however, is not so easily convinced. "On the face of it, it doesn't seem biologically plausible," Turner writes to me in an email. "How/why would vitamin C affect opioid receptors? Even if there were some plausible sounding mechanism, that's no substitute for rigorous data."

There's no way around it: there aren't many – or even any – double blind, placebo-controlled clinical trials published in peer-reviewed medical journals assessing vitamin C's potential anti-addictive effect in humans.

There are, however, a number of studies and monographs in the literature postulating the mechanisms by which vitamin C may curb addiction. Many of these focus on vitamin C's antioxidant properties.

Free radicals – and the subsequent oxidative stress they cause – have been implicated in a number of mental illnesses, including opioid addiction. Antioxidants like vitamin C, however, have been shown to prevent that damage, thus easing the symptoms of opioid withdrawal and supporting mental health.[16-18]

Vitamin C's anti-inflammatory properties[19] may further protect the brain and nervous system against injury and stress.[20] The concentration of vitamin C (ascorbic acid) in the cerebrospinal fluid (CSF) that bathes the brain and spinal cord is two to four times higher than in the blood plasma.[21]

We now know that substance use disorders are incited and perpetuated at least in part by a dysfunctional response to stress.[22] Vitamin C may help, as it is essential for healthy recovery after stress exposure, helping bring the body back to homeostasis after the cortisol rush that accompanies stress and pain.[23,24]

The vitamin also has merit as a treatment for depression and anxiety. This could be because vitamin C supports the production of the feel-good neurotransmitters serotonin and dopamine.[25] (Dopamine is a particularly important chemical when it comes to addiction: We get addicted not merely to a substance itself, but to the dopamine hit that rewards us when we satisfy a craving.[26]) The vitamin has also been shown to protect the brain in neurodegenerative disorders like Alzheimer's and Parkinson's diseases.[27]

Vitamin C may also reduce opioid dependency by mitigating pain. Human studies have shown that giving vitamin C – in as low of a dose as 2 grams by mouth one hour before surgery – reduces the need for opioid analgesics post-op.[28-30] Vitamin C also has positive effects on collagen synthesis and wound healing, making it of further value in surgical settings.[31]

Vitamin C interacts positively with harder-hitting pain medications like morphine, yielding additive pain-relieving effects and thus allowing for lower doses of narcotics (in mice).[32] Considering that 75% of heroin users in treatment state that their opioid addiction began with a legal prescription[33] and that those undergoing even minor surgery (including outpatient and elective procedures) are at increased risk of persistent opioid use,[34] the potential positive impact of vitamin C is immense.

In addition, vitamin C supports the immune system and reduces the risk of infections.[35,36] It has also been shown to shorten the duration of ICU stays and the need for ventilation,[37] and is thus being investigated as a potential treatment for the serious complications of COVID-19. Considering that those with opioid addiction are at high risk for poor COVID-19 outcomes, vitamin C may serve a dual purpose for this population.[38]

These effects could be why Lucy tells me: "Vitamin C has saved me from a lot of pain and misery. I feel a lot better, a lot healthier in general."

High Doses in Harlem: Alexander Schauss, PhD

While Millar supports clients in slowly and gradually tapering down their opioid use, Alexander Schauss, PhD, advocates for a bolder approach: taking mega-doses of vitamin C and quitting cold turkey.

Intrigued by a paper by Becket and Casey arguing that vitamin C occupies opioid receptor sites in the brain,[39] Schauss conducted a study through the City University of New York in 1969. He instructed 20 study participants – all of whom were addicted to heroin and had unsuccessfully attempted cold turkey withdrawals prior to enrolling – to drink a mixture of diluted fruit juice and powdered sodium ascorbate throughout the day, for several days. Schauss reports that the cocktail aborted the signs and symptoms of opioid withdrawal in 100% of the participants.[40] (The full details of Schauss' dosing regimen, which includes dosages of 1 to 7.5 grams of sodium ascorbate taken every two hours, can be found in his 2012 paper in the *Journal of Orthomolecular Medicine*.)

Schauss tells me that his work caught the attention of two-time Nobel Laureate Linus Pauling, PhD, who developed a similar vitamin C protocol, to which he added niacin.

Schauss tells me that some participants in his study started using heroin again after discontinuing the vitamin C supplementation. "There were all these fights on the street about the heroin being fake and not working," he explains, "but the reason it wasn't working was because these people were saturated in vitamin C, which was blocking the effects of the heroin."

Have you used vitamin C to treat addiction?

I am compiling data from real people on their experiences using vitamin C (and other remedies) to treat addiction. Have you (or a patient, or a loved one) tried using mega doses of vitamin C to treat a drug or alcohol use disorder? If so, please tell me about it at: www.SimbaHealth.com/surveys

Are you an addiction researcher?

As mentioned in the article above, we need more modern-day case reports and studies on vitamin C's effects in those with opioid use disorder. I hope to address this gap in the research – and you can help. Please contact Research@SimbaHealth.com if you are willing to help fund research, if you are a researcher interested authoring (or co-authoring) a study, or if you can help in any other way.

His observations were echoed in the later work of Drs. Alfred F. Libby and Irwin Stone,[41] who, in their 1977 pilot study, supplemented heroin-addicted individuals with a whopping 25 to 85 grams of sodium ascorbate daily along with other nutrients in divided doses. (For comparison, most vitamin C supplements contain 0.5 gram per dose.) They report that 30 out of 30 (100%) of their patients were successfully treated with this regimen.

Like Schauss, Libby and Stone observed that heroin didn't seem to have much of an effect in patients who first took mega doses of vitamin C. They write this of a 24-year-old patient: "On a Sunday he first took 45 g of sodium ascorbate and then in the space of five hours he 'shot-up' $300-$400 worth of heroin, and he felt no effect from this large amount of heroin."

As compelling as these reports may seem, they are both old and anecdotal. Why haven't there been more studies on vitamin C's potential value in the treatment of opioid dependency since the 1970's?

"One thing that comes to mind," offers Ryan, "is that vitamin C has been around for a while. There's not as much financial incentive for a pharmaceutical company to research it. So it falls on governmental funding to pay for this kind of research, and getting that funding is a really competitive process."

In other words: Nobody stands to make money or look particularly flashy by conducting studies on a vitamin that is old, affordable, and widely available.

There's also an elephant in the room here: bias. When I asked Schauss why his 1969 study wasn't published until very recently, and why he didn't follow it up with more studies, he said, "Anybody doing this type of nutritional research was categorically getting rejected by medical journals." While thankfully most clinicians no longer believe that nutritional supplements just make expensive urine, allopathic medicine is still dismissive of orthomolecular therapies like vitamin C.

Current, Conventional Treatment of Opioid Use Disorder

"Nothing has been done for the addict in the 117 years since morphine was first introduced in the United States, except to substitute one addicting drug (like methadone) for another (like heroin)," said Dr. Alfred F. Libby In 1977.[42]

Thankfully, much has been done to better support those with OUD since Libby's time. We nevertheless have ways to go.

While opioid maintenance treatment can truly be helpful – over 100 randomized studies report benefits for those in treatment – the drugs used in the protocols are themselves opioids and thus come with the associated laundry list of serious and sometimes fatal side effects.[43] Unlike vitamin C, methadone and buprenorphine – the pharmaceuticals often used in conventional OUD treatment – do not confer any known health-promoting benefits.

As useful as it may be, the duration of treatment with a replacement opioid is unclear, furthermore. "There's research that suggests people who stay on suboxone longer have better outcomes," says Ryan. He explains that while some people are able to eventually taper off of their opioid replacement medications, many stay on them indefinitely.

Although opioid maintenance therapy is a worthwhile investment from a societal standpoint – it is cheaper to treat somebody with addiction than it is to incarcerate them, for example – the financial cost is nevertheless considerable. According to drugabuse.gov, the cost of methadone treatment is $126.00 per week, the cost of buprenorphine for a stable patient is $115.00 per week, and the cost of naltrexone is $1,176.50 per month (pre-COVID-19 statistics).[44] These medications must be administered by a licensed healthcare provider on a weekly or even daily basis.

Vitamin C, on the other hand, may be purchased over the counter at most pharmacies and supermarkets for a modest price. Lucy, for example, spends under $15 per week on sodium ascorbate.

Vitamin C mega-dosing is not without its risks, however. Although studies evaluating the claim that vitamin C causes kidney stones have yielded contradictory findings,[45] one analysis[46] reports an association between vitamin C intake and kidney stone risk in men – though not in women. The safety of vitamin C supplementation in the settings of hemochromatosis and other rare iron overload diseases is likewise a topic of debate.[47,48]

One Piece of the Puzzle

"Anything that can address withdrawal will help pull people in the right direction, but we can't view that as the whole puzzle," states Ryan.

Indeed, addiction is complicated and multi-factorial. No one agent can alone take the place of a multi-faceted treatment plan that includes counseling, exercise, rest, stress management, meaningful social connections, trauma integration, physical safety, and kinship with nature.

Nevertheless, medications and vitamins can have profound effects on the neurochemical aspects of addiction, and a substance that curbs opioid withdrawal symptoms can make or break a person's attempts to get clean.

That's why we need more clinical trials evaluating vitamin C's potential in the treatment of opiate use disorder. Ryan agrees: "This topic strikes me as meriting more investigation, particularly since vitamin C is so benign." But we both know that those trials are not likely to come any time soon, given the paucity of incentives for performing such research.

As a physician, I must weigh the risk-to-benefit of any treatment. When I consider the cost of opioid use disorder both to the individual and to society, along with the long list of vitamin C's proven health benefits,[49] sodium ascorbate strikes me as a rather low-stakes wager.

In the face of the opioid epidemic, which rages on with indiscriminate ferocity, I'm willing to take an educated guess and give vitamin C a chance. ◆

References and article are available online at www.townsendletter.com.

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Organic Germanium: A Natural Trace Element for Immune Enhancement and Cellular Protection

by Carrie Decker, ND

Of the many trace elements, germanium is one that we all naturally encounter each and every day; yet many healthcare practitioners have limited knowledge of it. Organic germanium is found at trace amounts in many foods, and the dietary intake of it has been estimated to be between 0.4 to 3.4 mg daily.[1] It is found at higher levels in substances like potato, carrot, cereals, meats, fish, shellfish, garlic, ginseng, and aloe vera.[2,3] Low levels of germanium have been shown to exist in the nails, hair, urine, and plasma of healthy humans,[4] at comparable levels to those of other trace elements such as strontium, manganese, and lithium.[1]

Organic germanium has a positive effect on health.

Much like these other trace or ultra-trace elements, organic germanium has been shown in numerous studies to have a positive effect on health, which will be reviewed herein. Germanium is found in mineral waters in Japan, Korea, and regions of Europe touted for their healing benefits; and certain "curative" natural springs are also high in germanium.[5] The first records of its use date back to the 1960s in Russia and Japan – documented in the writings of Mironov of Russia and Dr. Asai of Japan[6,7] – and we still see much research coming from these regions.

One item of crucial importance to note before further discussion of germanium's biological effects is the difference between organic germanium – also known as bis (2-carboxyethylgermanium) sesquioxide (CEGS), germanium sesquioxide, or Ge-132 – and inorganic germanium (typically germanium dioxide, but also existing as germanium citrate lactate).[8] While Ge-132 is extremely safe,[9] inorganic germanium compounds are not, and are highly toxic, particularly to the kidneys.[10] Numerous deaths due to renal failure have been reported with long-term ingestion of inorganic germanium compounds.[11] Additional symptoms that may occur with the consumption of inorganic germanium products are largely gastrointestinal and may include vomiting, anorexia, and weight loss.

The safety of organic germanium is highlighted in a 2020 publication that reviewed the outcomes of a battery of standardized toxicology tests.[9] Outcomes of many historic tests prior to these have been critiqued because the quality of organic germanium products were not verified, so low levels of inorganic germanium may have existed. Proper testing of organic germanium products is important to confirm that inorganic impurities do not exist.

The findings of the comprehensive 2020 review were that ≥99.6% pure Ge-132 with less than <50 ppm germanium dioxide was safe in rats when consumed for 90 days at a dose up to 2,000 mg/kg/day.[9] Additionally, genetic toxicology studies found that mutagenic, chromosomal, or *in vivo* genotoxic potential under the applied test systems was not seen up to the maximum recommended test concentrations or limit dose.

Immunoenhancer

One quality of Ge-132 leading to its clinical use is its action as an immunostimulant. Genetic assessment has shown that the greatest impact of Ge-132 is on immune activation, with the expression of more than 60 genes being affected by its intake.[12] Specifically, Ge-132 has been shown to augment the immune response by enhancing natural killer (NK) cell activity and increasing interferon (IFN)-γ.[13] Multiple studies have shown these effects, with a peak IFN-γ response occurring at 24 hours. Ge-132 has also been shown to attenuate immunosuppression due to physical stressors such as surgery or heat, enhancing IFN-γ and/or NK activity in these settings as well.[14,15] In animals subject to typically lethal viral infections, administration of Ge-132 increased the survival rate, prolonged survival time, and decreased viral titers and organ complications.[16]

Findings such as these have prompted investigations in settings of malignancy, where healthy immune surveillance and NK cell activity is paramount. In animals with malignancy, Ge-132 has also been shown to increase IFN-γ levels and NK activity.[17,18] Additionally, when given as an adjunctive to the chemotherapeutic agents 5-fluorouracil and bleomycin,

it enhanced their anti-tumor effects, increased animal survival, and decreased the treatment-related loss of weight.[19] Clinically, increased NK activity has also been seen with the use of Ge-132 at a dose of 1000 mg/day in patients with cancer, with an optimal response observed with intermittent (rather than daily) dosing.[20]

These immunostimulating effects have also led the study of germanium as an agent to improve the effectivity of vaccinations. In multiple animal studies, germanium was shown to increase the vaccine response.[21,22] Additionally, when it was applied as a monotherapy, it enhanced the immune response in a similar fashion.

A Panacea of Actions

The antioxidant effects of organic germanium have also been investigated in numerous cellular and animal models. In cell studies, Ge-132 has been shown to protect cells from oxidative stress induced by hydrogen peroxide;[23] in oocytes, it increases intracellular glutathione and reduces levels of reactive oxygen species;[24] and in animals, it decreases low-density lipoprotein oxidation,[25] increases α-tocopherol levels,[12] and protects the liver from chemically induced oxidative injury, enhancing levels of antioxidant enzymes.[26]

In vitro, Ge-132 has been shown to increase cellular ATP levels;[23] analysis of its effects on genetic expression also suggests this.[12] Positive outcomes seen with Ge-132 in patients with chronic fatigue syndrome have been attributed to its immune-enhancing effects[27]; however, this was prior to the more recent findings related to ATP.

Finally, interesting effects of germanium on calcification and wound healing have been seen. In hens, eggshell (primarily composed of $CaCO_3$) strength has been increased by the addition of germanium to the feed.[28] Germanium supplementation has been shown to increase bone strength in ovariectomized animals.[29,30] It is even being investigated as a material to alloy with magnesium for biodegradable orthopedic implants.[1] In cellular and *in vivo* wound-healing studies, treatment with Ge-132 has been shown to significantly improve the wound-healing rate, specifically increasing fibroblast proliferation and formation of collagen fibers, and decreasing edema.[31]

Clearly, Ge-132 is a mineral with interesting and varied biological effects whose reputation has been tarnished due to the adverse effects of its closely related peer, inorganic germanium.[8] With a higher level of scrutiny of the purity of Ge-132 – which scientific advancements since its discovery have enabled – we will undoubtedly continue to see an increasing interest in its research and use in human health.

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Treatment of Colds, Sinuses, and Allergies with Acupuncture, Essential Oils, and Simple Homemade Remedies for the Athlete

by Dr. Sabrina Brunner, DACM

Abstract
Acupuncture, essential oils, and homemade recipes are safe, organic, and healthier approaches to treating colds, allergies, and sinus issues that professional athletes are exposed to on a daily base. Acupuncture with a combination of certain points on the body has been proven to shorten the duration of a cold. Thieves essential oil diffused in a cold air diffuser has also been proven to shorten the duration of a cold when diffused for at least 10 minutes. Homemade recipes are quick and easy to make at home and have been used in homes for generations for treating colds, allergies, and sinuses.

Professional athletes are susceptible to catching colds from extreme heat, cold, and wind. Professional athletes travel six to nine months out of the year while catching planes and living in and out of hotels. When athletes from the Midwest are in a hot and windy environment such as being on an open field (e.g. Los Angeles) sweating with the sun out and wind whipping around, the heat and wind will get stuck in the muscle layer of the athlete because the pores of the skin are open from sweating. The wind, at high speeds, can carry viruses and bacteria that can enter through the skin and get trapped in the muscle. This causes a wind-heat cold and vice-versa wind-cold cold. Professional athletes who are conditioned to the warmer weather from the West coast's dry and sunny environment are more susceptible to catching a cold from the Midwest (e.g. Cincinnati) due to its cold, damp, and rainy nature. The opposite will happen to an athlete from the West coast who is on an open field sweating in the Midwest. When cold damp air whips around and goes through the skin's layer because the athlete is sweating, a wind-cold cold results. Once the game is over, the athletes are back on a plane with recycled air blowing on their faces, and they can easily pick up a virus or bacteria through their open pores. Most athletes continue to sweat through their face hours after they are showered and all cleaned up. Another way viruses and bacteria can spread is through direct body contact (e.g. sweating). Sweat can carry viruses and bacteria, too.

Essentials oils have many functions and can be used effectively in many different ways. Essential oils can positively impact an athlete's health. I use lemongrass essential oil with my cold air diffuser in my office waiting area and hallway. Lemongrass has an awakening property to promote psychic awareness and purification of the mind.[1]

Thieves essential oil, a combination of clove, lemon, cinnamon bark, eucalyptus radiata, and rosemary *essential oils*, has proven itself to be highly effective in treating the following symptoms: runny/stuffy nose, slight cough, itchy throat, and the body feeling slightly chilly or slightly warm due to sinus problems, allergies, or a common cold.

Clove essential oil is used for respiratory infections because its properties are antimicrobial, antiseptic, anti-inflammatory and even bactericidal.[2] Cinnamon bark essential oil is used for cough and respiratory infections because its properties are antimicrobial, anti-bacterial, anti-infectious, anti-fungal and anti-viral.[2] Eucalyptus radiata essential oil is used as an expectorant and for respiratory functions due to its anti-infection, antibacterial, and anti-viral properties (Young, 2013). Lemon essential oil is used for respiratory infections and sore throats with its anti-infectious, antibacterial, anti-viral, and antiseptic properties.[2] Rosemary essential oil is used to support the endocrine system and to treat respiratory and lung infections due to its antibacterial, anti-fungal, antiseptic, and antiparasitic properties.[2]

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Thieves is such a great blend of essential oils because of their different properties along with similar healing properties that are used to treat respiratory symptoms and infections related to colds, sinuses, and allergies. With the anti-viral, anti-fungal, anti-bacterial similarities, the essential oils vastly reinforce one another and really facilitate the healing properties of the oils. If one is allergic to any of the above listed essential oils, it is recommended that single essential oils be used in combination to make a personalized version of Thieves. Leave out the essential oil that causes the allergy or known sensitivity. Three to five drops of the non-allergic essential oils listed above will work well. Mix the non-allergic essential oils with one-quarter of a teaspoon of a carrier oil such as olive oil to place on bottoms of feet.

When distal acupuncture combination (Lu 7, Ki 6, Li 4 and 11, Lv 3) and local acupuncture points (bitong, St2, and yintang) are applied, place three drops of Thieves essential oil directly to the bottom of the feet and let the athlete rest for 20 minutes. Their symptoms will be reduced.

The aromatherapy cold air diffuser used with Thieves essential oil has shown that the cold, sinus, and allergy signs and symptoms were reduced by 75 percent. Webster State University discovered that after 10 minutes of using Thieves essential oil in a cold air diffuser there was a kill rate of 99.96 percent in regard to airborne bacteria.[1] This exact same protocol may have to be repeated in three days if the last 25 percent of the cold lingers. This has been a great discovery because my athletes love to use Thieves when they are coming down with a wind-heat cold or a wind-cold cold.

In addition to the use of essential oils, ginger tea or matcha latte are two recipes that I recommend for the athlete, depending on the cause of their symptoms: cold or sinuses (ginger tea), or allergies (matcha latte). These recipes follow.

Ginger Tea Recipe

- Three drops of Ginger Young Living Essential Oil or one root of organic ginger
- One tablespoon of honey
- Three cups of water

Slice the ginger root horizontally into five to seven pieces slender pieces (pieces should be longer than wider). Place in a pot with three cups water then boil for seven minutes. Drain the ginger water from the pot and add honey. If necessary, use three drops of ginger essential oil in place of the ginger root in hot water with honey and drink. If one is feeling slightly cold, drink it hot, if one is feeling slightly warm to hot, then drink room temperature or cool. Ginger is used for chills, respiratory infections, congestions, cough, sinusitis, and sore throats.[1,2] Honey is used for cough suppressant and is high in antioxidants.[4]

Matcha Latte Recipe

- One cup of coconut milk (milk of your choice)
- One quarter to one teaspoon of Organic Matcha Latte (whole leaf green tea)
- One quarter to one teaspoon of local bee pollen
- One tablespoon of local honey

Boil or steam milk in a pot for three minutes (do NOT microwave milk), stir in honey and bee pollen, then add matcha powder while stirring. The Nespresso-Aeroccino3 milk frother works best because one can use the heating option or cooling option for the milk. To make the recipe cold, place all ingredients in a shaker bottle with lid and add one cup of ice and shake ingredients.

Bee pollen has 22 amino acids, 27 minerals, many enzymes, and an entire range of vitamins.[5] Local bee pollen is great for providing natural allergy relief and is also found in local honey. Local honey is beneficial because the local bees use local plants, some of which may be causing allergy symptoms, to make honey. The honey is taken internally, which the body recognizes as safe, and provides a homeopathic remedy that helps alleviate allergens in the air. Matcha powder is used for boosting energy (10 times the amount of 10 cups of green tea) and is very high in antioxidants; it is very helpful in boosting the immune system by providing chromium, vitamin C, magnesium, selenium, and zinc.[6]

Acupuncture, essential oils, and these simple recipes have been proven to be safe, highly effective, and very practical in my practice in regard to colds, sinuses, and allergies.

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Wikipedia's Skeptical Assault on Botanical Medicine

by Richard Gale and Gary Null
Progressive Radio Network

Wikipedia's co-founder Jimmy Wales claims to hold high standards of objectivity and balance in the content of the online encyclopedia and the integrity of his volunteer army of editors. Indeed, this is largely true; except when it comes to the composition and editing of alternative medical systems and natural healthcare. A group of individuals and organizations, collectively known as Skeptics, who assert they represent "science-based medicine" now portend to be the final arbiters of what is and is not good medical science practice. However, it is our opinion the Skeptics are extremely biased towards erroneous, preconceived ideas and categorically refuse to accept an enormous volume of published medical research because it is contrary to Skepticism's narrow and limited understanding of medical science.

Among the many alternative health modalities that are targeted, criticized and debunked by the leaders and followers of Skepticism and Science Based Medicine (SBM) are the medicinal uses of botanical plants and herbs. Unfortunately, Wikipedia increasingly parrots Skepticism's biased attacks against medicinal herbs. As we reported in our earlier article "Wikipedia: Our New Technological McCarthyism," the Skeptic community has now hijacked the editorial functions on Wikipedia's entries dealing with alternative medical practices.

Of course, Skeptics do not claim to have any expertise in naturopathy, Chinese and Ayurvedic medicine, nor the medicinal use of herbs. Nor are they well-educated about botanical photochemistry and the use of botanical medicines for treating illnesses for centuries, even millennia, in traditional settings. Skeptics' claims against botanicals are specious; they ignore the well-known fact that approximately 40 percent of drugs prescribed by conventional medical physicians are derived from botanicals that have been used for centuries. Furthermore, most of the top 20 drugs sold in the US today, including aspirin, are based upon plant phytochemicals[1] – so are some common anti-cancer drugs such as Taxol (from a northwest pacific conifer/yew tree), often given as a first line of treatment for certain breast cancers, the anti-leukemia drug Vinblastine or Vincristine (from an African periwinkle), and the anti-tumor drug Lapachol (from the Hawaiian trumpet tree).[2]

The history of world civilizations and their societies' ability to persevere through lethal epidemics and disease is synonymous with the history of botanical medicine. One of the earliest findings to account for botanical medicine was found in a 60,000-year-old burial site of a Neanderthal man in northern Iraq.[3] Among the remains were eight plant species, seven of which are still recognized for their medicinal value today. Before the advent of modern drug-based medicine and a profit-driven pharmaceutical industry built upon patented molecules, humans have relied upon the plant kingdom to treat health conditions, fight parasites and infectious diseases, treat wounds and gastro-enterological conditions and much more with their knowledge about plants' healing properties. Our forbearing "doctors" had far keener insight into the biology of the human body than modern science grants them credit for. Through trial and error, certain plants were discovered to relieve adverse symptoms better than others, and over the course of centuries this became common traditional medical science. In the Skeptical utopia, however, thousands of years of human ingenuity and investigation into botanical medicine would be wiped clean and leave us only with drugs and their long lists of adverse effects and contraindications.

Nor should the research of the renowned pharmacognosist and internationally respected medicinal plant expert, Dr. Norman Farnsworth be forgotten for his pioneering work in validating numerous botanical plants' bioactive medical properties. From 1970 until his death in 2011, Farnsworth was head of the pharmacology department at the University of Illinois at Chicago. He brought together scientists and researchers from around the world to collaborate on drug discovery from medicinal plants. Many current plant-based pharmaceutical drugs are the fruits of his research. It is also largely on Farnsworth's account that high quality supplements are available today, having been part of Bill Clinton's commission to pass the Dietary Supplement Health and Education Act (DSHEA).[4]

Back in the 1990s, the small biotech startup Shaman Pharmaceuticals employed ethnobotanists and anthropologists to visit healers and shamans in their native settings, such as the Amazon and the Andean mountains, to learn which plants were used and for which conditions. For a short period of time the company was successful enough to go public and was traded on Wall Street. The hypothesis was that if a certain botanical herb had been used for centuries by traditional healers to treat a

certain health condition, in theory, a long historical clinical trial had already been conducted. This in turn would help the company's laboratory scientists to zoom in on the particular bio-molecules that were effective for a known disease. Traditional healers for centuries have followed a strategy of trial and error to identify plants or combinations thereof for treating numerous illnesses and infections. Some scientists understand this objectively, but not so the Skeptics who pride themselves today as the arbiters of medical truth.

According to a 2011 market report published by the University of Minnesota, the top botanical medicinal plants sold in the US include *Ginkgo biloba*, ginseng, echinacea, black cohosh, milk thistle, St John's wort, and saw palmetto.[5] Each of these hold an important place in traditional medical systems for treating specific health conditions. Since then, curcumin, the bioactive phytochemical in turmeric root and a medicinal herb used in every South Asian household, and resveratrol (a natural phenol found in the skins of grapes, blueberries and other berries) are now among the more popular botanicals recommended by naturopathists and increasingly among integrative physicians.

But if you were to search on Wikipedia to learn more about the medical benefits of these plants, you would come away severely shorthanded. In many cases the medicinal properties are altogether denied, the research ridiculed, and the positive scientific evidence ignored in the online encyclopedia. In addition, the SBM-Skeptic community is largely a monolithic Anglo-American movement, which regards legitimate and accurate medical science as the proprietary privilege of developed nations such as the US. Underpinning its prejudices is a denial that good, creditable science can be executed in developing nations such as India, China, Iran, Brazil, and elsewhere. On the other hand, these nations have a much higher respect for botanical medicine and are eager, and perhaps far more sincere, to investigate the medicinal properties of plants that have been part of their cultures' heritage for centuries. We have the same in the US among the Native Americans, yet the Skeptics attempts to colonize modern medicine has disregarded traditional Native American medicinal wisdom.

Therefore, we will look at a few of these more popular botanical herbs that have been used medicinally for centuries and show how Wikipedia is a source of gross misinformation and fabricated facts when it deals with botanical medicine.

Curcumin

Wikipedia states, "Although thoroughly studied in laboratory and clinical studies, curcumin has no confirmed medical uses."[6] Wikipedia also cites a 2017 review of over 120 studies that disclaims any of curcumin's therapeutic effects.[7]

Wikipedia increasingly parrots Skepticism's biased attacks against medicinal herbs.

For the moment we can ignore the 2017 review until we look later at the failures of the Cochrane Collaboration, the flagship medical review project of evidence-based medicine. However, the review only looked at 120 studies. In fact, there are over 11,800 entries for curcumin in the peer-reviewed literature found in the National Institutes' of Health (NIH) PubMed database. According to the nonprofit HerbMed site, which has been recognized by the *Wall Street Journal*, *Science* magazine, and the *Western Journal of Medicine*, there have been 375 human clinical trials and 499 animal studies, 74 observational case reports, 553 papers looking at curcumin's pharmacodynamic properties, and other studies investigating the plant's chemistry, genetics, and use in traditional societies.[8]

Contrary to the Cochrane review that only looked at 120 studies, a recent larger meta-analysis of curcumin's ability to lower plasma leptin concentrations was conducted by universities in the US (Weill Cornell Medical), Greece (Aristotle University of Thessaloniki), Italy (University of Pavia), and Iran (Mashhad University of Medical Science) and concluded that curcumin significantly decreased adverse leptin levels.[9]

A double blind randomized controlled study, with four-week monitoring, found that curcumin successfully improved all parameters of metabolic syndrome under investigation, including enhanced body-mass index, body-fat percent, blood pressure, lipid profile, and C-reactive protein.[10]

An Australian study conducted at the universities in Newcastle and Southern Queensland found curcumin sharply improved neurocognitive functioning and cerebral endothelial vasodilator function in elderly patients that may reduce dementia risks.[11]

To further reinforce the health benefits of curcumin and discredit Wikipedia's Skepticism, the federal government has provided $150 million in curcumin research through the National Center for Complementary and Integrative (CAM) Health. For a period of time, the MD Anderson Cancer Center had a separate laboratory conducting curcumin research. As we wrote in our previous article, Skeptics and SBM appear to abhor CAM medicine. However, as foolish as the US government is with ridiculous spending, we must also consider a sliver of wisdom's light in our federal health agency's recognition of curcumin's medicinal value.

Ginkgo biloba

Wikipedia states, "Although extracts of Ginkgo biloba leaf sold as dietary supplements may be marketed to improve cognitive function, there is no scientific evidence for effects on memory or attention in healthy people.... Systematic reviews of clinical trial results have shown there is no scientific evidence for effectiveness of ginkgo...."[12]

Ginkgo is a large Asian tree commonly found in China, Japan, and Korea. It is most often associated with improving memory disorders, including dementia and memory loss, and to enhance concentration. It has also been associated with improving blood flow, which may contribute to its cognitive benefits as well as treating sexual dysfunction.[13] Ginkgo has been utilized in Asian herbal medical systems for many centuries.

Wikipedia relies upon limited Cochrane Collaboration reviews to discredit ginkgo's medicinal properties. As with curcumin, it takes into account only a small percentage of the published scientific literature.

PubMed lists over 4,200 medical papers for ginkgo. According HerbMed, there have been 375 human clinical trials and 499 animal studies, 74 observational case reports, 553 research papers on the plant's pharmacodynamic properties, 81 studies on ginkgo's use in traditional cultures, and 290 additional peer-reviewed papers.[14]

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In 2016, researchers at the Technische University and Hannover Medical School in Germany conducted a randomized placebo-controlled double-blind study on 61 elderly patients to determine ginkgo's effects on memory. The study concluded that ginkgo indeed improved cognitive flexibility without changes in brain activation. The results were compatible with that associated with the prescription drug dopamine.[15]

There are many studies on ginkgo's cognitive and memory enhancement properties published in Chinese journals; unfortunately, many have not been translated. One multi-institutional meta-analysis conducted by researchers at Guangzhou Medical University in China, Australian universities, and Chinese University of Hong Kong found that ginkgo's antioxidant potential was an effective and safe treatment for tardive dyskinesia associated with schizophrenia.[16]

One growing health risk has been the epidemic of attention deficit and hyperactivity disorders. Conventionally, these are treated with pharmaceutical drugs with long litanies of potentially serious and even lethal adverse effects. An Isfahan University Medical School randomized, placebo-controlled study of children and adolescents diagnosed with ADHD treated with ginkgo found a 93% improvement compared to the placebo.[17]

Resveratrol

Wikipedia states, "Although it is used as a dietary supplement, there is no good evidence that consuming resveratrol affects life expectancy or human health."[18]

The NIH's PubMed database cites over 10,600 peer-reviewed studies on resveratrol. Most physicians acknowledge the cardiovascular benefits from drinking an occasional glass of red wine. This is because of the high resveratrol content in wine grapes. PubMed lists over 4,800 science papers referring to red wine.

Wikipedia's citation of the study to negate resveratrol's anticancer activity was limited solely to poorly designed pre-clinical trials. On the other hand, the lead Columbia University's authors state that resveratrol "is known to have potent anti-inflammatory and anti-oxidant effects and to inhibit platelet aggregation and the growth of a variety of cancer cells," and that "its potential chemo-preventive and chemotherapeutic activities have been demonstrated in all three stages of carcinogenesis (initiation, promotion, and progression), in both chemically and UVB-induced skin carcinogenesis in mice, as well as in various murine models of human cancers."[19] This is an example of a frequent, reoccurring problem with Skeptic edits on Wikipedia: distorting peer-reviewed medical research and twisting its content to serve their own biased dogma.

Wikipedia categorically denies resveratrol's benefits for heart disease, cancer, human metabolism, and its anti-aging properties. Among the more exciting laboratory investigations conducted on resveratrol's anticancer activities is a pharmacodynamic study performed at the

Nanjing University of Chinese Medicine in China. The study observed glioma tumor cell proliferation rates decreasing after resveratrol treatment.[20]

The accumulation of the science supporting resveratrol's medicinal properties – targeting breast and ovarian cancers, colorectal cancers, dementia and memory loss, cardiovascular protection from oxidation, safeguarding cells from ionizing radiation exposure that damages genomic integrity, etc. – has resulted in an increase in interest and attention to study the phytochemical more thoroughly. In an effort to better understand resveratrol's anti-atherosclerosis effects, the Chinese Research Center for Nutrition and Food Safety discovered that the phytochemical positively "remodeled" the gut's microbiota thereby inhibiting pathogenic bacteria known to be responsible for manufacturing trimethylamine-N-oxide (TMAO), which contributes to the development of atherosclerosis.[21]

Flaws and Biases

We have only referred to three of the more common botanical plants and phytochemicals, which have been shown to possess possible vital and important medicinal benefits for the health epidemics associated with our modern toxic lifestyles. To date, among the thousands of botanical plants with long histories of medical use, the FDA only recognizes two herbs that it claims have the scientific evidence to support their value and use: Veregen derived from green tea for treating genital warts, and Fulyzaq for treating HIV-associated diarrhea and derived from the South American croton tree. On the other hand, as of 2017, the federal agency has approved 868 synthetic molecules based on medicinal plant phytochemicals.[22] Of course, these are now patented "drugs." This statistic alone is indicative of the anti-botanical culture being promoted by the SBM Skeptics in order to protect the pharmaceutical industry's proprietary domination over the medicines.

In an earlier article in this series, it was noted that the Cochrane Collaborative project is one of evidence-based medicine's more important achievements. However, Cochrane is not without serious flaws and biases in its subjective criteria for evaluating clinical and observational research. For example, the *British Medical Journal* has challenged Cochrane for its erroneous evaluation and conclusions of systemic analysis of sodium cromoglycate, prescribed in the treatment of childhood asthma. A group of physicians and professors of asthma and allergy medicine from seven countries criticized Cochrane for scientific negligence in the manner it "discharges its responsibilities for the quality of reviews published."[23]

Another serious flaw in Cochrane's evaluation strategy is to discount trials, even if they are double-blinded and placebo controlled, if the participant enrollment is under their subjective recommendations of scientific rigor. For example, dozens of controlled trials may confirm the efficacy of ginkgo or any other botanical; however, if the number of people participating in the study is too small, it is tossed out as inconclusive or a failure. The Skeptics' Wikipedia entries ➤

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rely heavily upon Cochrane reviews to discredit the health benefits of botanical herbs. They also ignore Cochrane reviews they don't like.

Skeptics and SBM followers also criticize Cochrane reviews whenever their conclusions are contrary to their ideological mission to stamp out alternative medicine. Our own experience has included a backlash from Mark Crislip on the SBM blog after the lead author of a Cochrane review confirming the influenza vaccine's ineffectiveness, Dr. Thomas Jefferson, appeared on my broadcast.[24] The SBM community and Skeptics are staunchly pro-vaccine and categorically deny any research that puts a light on vaccinations' dark side.

After sharing Crislip's denouncement of Dr. Jefferson for appearing on my radio program, Jefferson wrote back about the Skeptics, "My only comment is that they should read our reviews before writing their thoughts on paper. I have been subjected to this kind of thing before, and in my experience, it is not worth answering."[25]

When a Cochrane analysis concluded the efficacy of acupuncture for treating migraine headaches, Skeptics went on the attack.[26] On the other hand, the Skeptics are correct in stating that the Cochrane Collaboration is "not an infallible guide and should be considered within the context of all the available evidence regarding treatment." In another blog article, Mark Crislip remarks, "Just because something is labelled as a systematic review does not mean it is any good..... Even a review with a Cochrane label does not make it true."[27] We concur wholeheartedly, especially concerning herbs for treating many health conditions and diseases. Cochrane has also come under criticism more recently for conflicts of interests in some of its reviews and kowtowing to the private interests of the medical establishment and pharmaceutical companies.[28]

Conclusion

Fortunately, the Skeptics have yet to mangle and misrepresent all of Wikipedia's botanical entries. In most cases, a plant's medical properties are largely ignored or only mentioned as an afterthought. Regardless of the Skeptics' attempts to silence plants' medical value, research continues and at a higher pace than ever. Scientists at the USDA-funded Western Human Research Center in Davis, California, are collaborating with university medical research labs to identify promising phytochemicals in herbs and foods to fight cancer. The center's state of the art laboratory has already been able to identify half a dozen plant molecules to destroy cells in childhood acute lymphoblastic leukemia. These include carnosol in rosemary, curcumin, resveratrol in grapes, and ellagic acid and kaempferol in strawberries.[29] And hundreds of other universities and laboratories throughout the world continue to explore the wonders and secrets of the plant kingdom that have yet to discovered. If we were to believe the Skeptics that these plants have no medicinal value, then they have a lot more convincing to do.

With healthcare costs increasingly rising beyond the reach of the average American, and with every indication this will continue into the future, botanical plants remain a valuable line of defense in the prevention and treatment of disease. Finally, please do not take our word for anything out of blind faith. Instead visit reliable websites with databases of the peer-reviewed medical literature such as PubMed and HerbMed. Investigate the facts supporting botanical medicine. Then ask yourself, why is Jimmy Wales permitting the Skeptics to rule Wikipedia?

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LDN and Gut Health: Mast Cell Activation Syndrome

by Leonard B. Weinstock, MD, FACG

The following excerpt is from *The LDN Book, Volume 2: The Latest Research on How Low Dose Naltrexone Could Revolutionize Treatment for PTSD, PAIN, IBD, Lyme Disease, Dermatologic Conditions, and More* (Chelsea Green Publishing, October 2020), edited by Linda Elsegood and is reprinted with permission from the publisher.

There are several gastrointestinal (GI) diseases and disorders for which low dose naltrexone has been applied as a therapeutic agent. The pathological factors that allow for the use of LDN in gut disorders and diseases include uncontrolled inflammation, abnormal immunity, increased intestinal permeability, increased visceral hypersensitivity, abnormal motility, and unregulated cellular growth.

The potential use of LDN or endorphins to treat motility disorders is not well known by clinicians. If LDN does lead to improved motility, then it could be used to treat constipation, abnormal small intestinal motility, small intestinal bacterial overgrowth, and gastroparesis. Reducing the overactive immune system by reducing T cells can help Mast Cell Activation Syndrome (MCAS), sarcoidosis, and mesenteric panniculitis. Direct toll-like receptor blockade by naltrexone could help reduce neuroinflammatory processes such as visceral hypersensitivity in IBS.

The following is a review of the medical literature that illustrates the effect of LDN on Mast Cell Activation Syndrome.

Mast Cell Activation Syndrome (MCAS)

Mast cell activation syndrome is a common disorder involving uncontrolled mast cell (MC) activation with multisystemic inflammatory and allergic symptoms.[46] A study of a German control group estimated the prevalence of MCAS in this population to be 17 percent.[47] Of the patients in the study, 74 percent reported similar symptoms in one or more first-degree relatives. The indirect prevalence estimate for MCAS in Americans is 1 percent.[48] Although MCAS is technically an immune disorder with a mutation in the MC control gene, the GI tract is a common site of MC deposition, and activation of these cells produces symptoms both in the gut and systemically. The most common symptoms reported by 50 percent or more of the 413 patients were fatigue, myalgia, conjunctivitis, rhinitis, tinnitus, hives, itching, nausea, heartburn, dyspnea, near syncope, headache, chills, and edema.[49] Virtually all organ systems can be involved in MCAS.[50]

GI symptoms are commonly reported by MCAS patients and often mistaken by physicians for symptoms of functional syndromes, especially in the cases where the term *IBS* is assigned to the patient.[51] In IBS patients, local and systemic effects of mediators released by MCs can account for constipation, diarrhea, and pain.[52] In a study of IBS patients' colon tissue, histamine and tryptase levels were shown to correlate with pain, as was proximity of the MCs to the submucosal nerves.[53] Interestingly, constipation has been linked to the local release of MC mediators near glial cells and filaments.[54] Thus, MC-induced neuropathy may explain reduced peristalsis of the large intestine. GI symptoms can include tingling or burning, aphthous ulcers, globus, heartburn, dysphagia, chest pain, nausea, altered bowels, bloating, and abdominal pain.[55] Dyspepsia may be due to mediator-induced nociception.[56] Gastritis, in the absence of *Helicobacter pylori* and/ or non-steroidal anti-inflammatory medications, could be explained by MC-mediator-induced inflammation.[57] Chronic and acute peritoneal pain has been reported in the setting of epiploic appendagitis, where local increased MC deposition was identified.[58] Studies that demonstrate success with MC-directed therapy in some patients who were labeled with an IBS diagnosis are suggestive of a pathophysiological role of the aberrant MC.[59] SIBO was recently shown to be common in MCAS.[60] Bacterial overgrowth, as determined by an abnormal breath test, was present in 30.9 percent of 139 MCAS subjects versus 10.0 percent of 30 controls.

MCAS is often associated with hypermobile Ehlers-Danlos syndrome (hEDS) and postural orthostatic tachycardia syndrome (POTS), both of which also have extensive GI system involvement.[61] MCAS, both alone and in association with these other disorders, results in significant GI morbidity.[62] MCAS patients pose considerable management challenges due to their pathophysiologic heterogeneity, numerous systemic symptoms and triggers, comorbid conditions, and varied response to therapy. Triggers for MC activation include stress, food, alcohol, excipients in medications, infections, altered microbiome, environmental stimuli (including heat, chemicals, atmospheric changes, electrical changes, and odors), and mold exposure.[63]

The first publication to demonstrate the efficacy of LDN in MCAS looked at a patient who also had POTS and SIBO. In addition to receiving antibiotic therapy for SIBO, the patient received LDN and immunotherapy with intravenous immunoglobulin (IVIg). A dramatic and sustained response in more than 40 severe symptoms of POTS, MCAS, and SIBO was documented. The utility of IVIg in autoimmune neuromuscular diseases has been established, but clinical experience with POTS is relatively unreported, and data on IVIg in POTS and MCAS had not been previously reported. In this case study the patient found significant benefit from IVIg and rifaximin, but it was not until she escalated the dose of LDN from 2 mg to 4.5 mg that she attained complete improvement. Other early experience in our clinic was also discussed in this publication. We looked at 27 patients with POTS, 11 of whom were

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administered LDN. Seven of the 11 experienced improvement in GI symptoms, and five experienced improvements in MCAS and POTS. Out of 15 patients who were administered antibiotics for SIBO, this therapy helped GI symptoms in 10 and POTS symptoms in four. We did not use an improvement scale.[64] This has been observed in additional POTS patients in our clinic as well.

Owing to the numerous MC mediators and receptors, no single medication currently available will control all symptoms of MCAS. It is a common approach to offer first-line therapy with efforts to identify and avoid triggers and then to prescribe antihistamines, vitamin C, vitamin D, and montelukast. A number of MCAS physicians have seen that LDN helped some of their patients. In a review of a cohort of my own MCAS patients, I found clinical evidence of LDN's efficacy in treating the condition. Out of the 116 MCAS patients who were given daily 4.5 mg LDN, 60 percent reported improvements, 28 percent saw no benefit, and 22 percent had to stop LDN owing to side effects.

Symptoms Relieved in MCAS Patients Taking LDN

- Depression
- Anxiety
- Insomnia
- Rash
- Allergies
- Edema
- Fatigue
- Dizziness
- Diarrhea
- Bloating
- Brain fog
- Nausea
- Hives
- Itch
- Dyspnea
- Erythromelalgia
- Headache
- Abdominal pain
- Constipation
- Pain (joint, nerve, and muscle)

Although worthy, it would be difficult to have this data accepted for publication given that the patients involved simultaneously altered their diets and used several medications. Patients in this series could tell that the LDN treatment was effective due to the clinical response they noted as they increased their doses to 4.5 mg. Others noticed the therapeutic impact when they ran out of LDN, or after they had stopped and then restarted the medication.

LDN has the potential to restore gut health in several GI disorders and diseases, including inflammatory bowel disease, constipation, gastroparesis, irritable bowel syndrome (IBS), MCAS, sarcoidosis, and mesenteric panniculitis. High-quality research using randomized, double-blind, placebo-controlled studies is the ideal. However, until funding is available for such trials, continued clinical use and reports of case series will benefit many patients.

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Linda Elsegood is the founder of the LDN Research Trust, which was set up in the U.K. as a registered charity in 2004, and is the editor of *The LDN Book, Volume 1* and *2*. Diagnosed with multiple sclerosis in August of 2000, she started LDN therapy in December of 2003, and now has a better quality of life and hope for the future. Through the Trust, she has connected thousands of patients, doctors, and pharmacists around the world with information, articles, and patient stories about LDN, and helped organize conferences, seminars, and the Trust's *LDN Radio Show*.

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Do Viruses Cause Disease?

review by Ira L. Goodman, MD, FACS

The Contagion Myth – Why Viruses Are Not the Cause of Disease by Thomas Cowan, MD, and Sally Fallon Morell
Skyhorse Publishing, ISBN -13 9781510764620; c. 2020; 216 pages. $24.99 (hardcover)

When I first looked at this book's cover, title, subtitle, and blurb that states the current coronavirus pandemic is not actually from a virus but from widespread 5G, I, like so many of my colleagues, dismissed it as absurd.

Then I read the book.

I must admit the arguments were convincing, the research was thorough, and the historical vignettes were enlightening. I came away wondering if this could actually be true.

This book is consistent with the counterintuitive ideas that Dr. Cowan has written about in his past books, including *Human Heart, Cosmic Heart*, in which he claims the heart is really not the pump it is made out to be; *Cancer and the New Biology of Water*, in which he claims that the true cause of cancer is a specific kind of water; and others. I found all of these books very intriguing, so I immediately purchased his current book.

It was his best.

I was especially curious when I discovered it was banned on Amazon.com. That made me want to read it more, given the unprecedented censorship that exists today. The first amendment is apparently dead. I wish Amazon would list all the books they banned; those books are likely to have some good information. You can still get most of them from other sellers.

Cowan weaves the argument that viruses have never fulfilled Koch's postulates, which are the following:

1. The infective agent should be found in all ill people or animals infected.
2. The infective agent should be isolated from all infected.
3. The infected agents should be cultured.
4. The agent should be re-isolated from others given the agent from the culture.

These postulates were modified by Rivers in 1937 to account for viruses, but neither Koch's nor River's postulates have been fulfilled for viruses to date. Modern virologists conveniently claim they are obsolete.

Even Louis Pasteur admitted on his deathbed and through his notes that it is the terrain and not the infective agent that is the most important. He admitted that he was never able to infect anyone with anything even though he tried frequently. Attempts

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to infect normal people with the influenza virus of 1918 from the secretions of ill people failed. Yes, this was done, according to Cowan.

Cowan goes on to claim that the main cause of the COVID syndrome we are all witnessing is the introduction of 5G radiation combined with other environmental toxins and toxicants. There is a very interesting summary of many past pandemics dating back to the Black Plague and explanations for each one based on environmental factors, including 5G and other widespread electrical smog like radar, electricity use, cell phones, and other electrical events like sunspots. He points out that there was a massive 5g rollout in Wuhan in September of 2019 right before the "COVID" epidemic. Coincidence?

Also the new cruise ships that had epidemics of COVID were loaded with newly installed 5G and advertised as such. There are many unknowns about 5G and RFK, Jr, just filed a comprehensive lawsuit with 11,000 pages of supporting information against the FCC that has a hearing set for 1/25/21. 5G and the COVID vaccines are giant experiments as far as I can tell. They will both have dramatic consequences. Whether these consequences are good or bad remains to be seen.

It would be impossible for me to list every interesting story, association, and conclusions drawn in this book that argued against the prevailing and accepted theory about the microbial causes of multiple diseases. Cowan claims that the so-called viral particles seen on electron microscopy are actually exosomes, that TB is not an infectious disease since there was never a successful attempt to infect a normal person with TB from a sick person's secretions. As I said this book is counterintuitive. The theory that polio is actually caused by DDT, that rabies is not caused by dog bites, of course that AIDS is not caused by HIV are all described. There are numerous anecdotes and historical facts (like Germany's 2016 court ruling that there is no evidence for the existence of the measles virus) that make the reader question long-held tenets of medicine, infectious disease, and what is actually going on now.

There are many holes in Cowan's arguments, and I cannot say I agree with all of it; but it's certainly worth thinking about and should not be censored. I hope he is wrong since if 5G is really the main cause of COVID-19 we are all doomed given the widespread future use of it. I would rather it be the virus, frankly. It would be easy enough to prove by shutting off all 5G in a city to see what this does to the case load. Good luck with getting anyone to cooperate and agree this is worth trying.

No, we would rather vaccinate every person on the planet, including pregnant women with an experimental vaccine, made with a method that has never been used, in warp speed. Cowan has a section on the COVID vaccines that, as expected, pans all of them. There has never been a successful vaccine against any of the other six coronaviruses, against HIV, Dengue fever, SARS, MERS, the Asian flu, or the Swine flu although attempts were made. I guess the current vaccines could be the first, but I would not bet on it. The efficacy of the annual flu vaccine is highly questionable, according to the Cochrane Collaboration. I would love to know what the manufacturers mean by "90% effective." Effective in what way? Antibody production? Clinical disease? What about long-term side effects? What will it do to the fetus? All unknowns currently. According to a recent article posted on mercola.com, there are many serious side effects from the COVID vaccines and that the overall side effect rate is 2.79% and counting. The press release from Pfizer touting 95% effective rates is in terms of relative risk, not the absolute risk which is the most clinically significant. The absolute risk reduction of the vaccine is actually 1%, and even the relative risk reduction is 19-29%, not 95%. The choice to get the COVID vaccine appears to be governed by hope and fear – both emotions driven by the limbic system as opposed to the frontal lobe that governs rational thought.

Talking about the studies that "prove" COVID-19 is caused by the coronavirus, Cowan states:

> These papers never show that all the people with COVID-19 had the same set of symptoms, they never purify any virus from the sick people; they never demonstrate the absence of the virus from normal people, and that they never show that the transmission of purified virus could make well people become sick. This is scientific fraud of the first order.

He goes on to say: "In short, no study has proven that coronavirus, or indeed any virus is contagious, nor has any study proven anything except that virologists are dangerous, misguided people and that hamster and monkey kidney rights people are not doing their jobs."

There is a chapter on the testing scam, the perverse financial incentives to prove caseloads and death numbers. The PCR test with 40x amplification would likely be positive much more than clinically indicated, and he quotes Endelbrecht et al: "the COVID PCR tests are scientifically meaningless." According to Cowen, "even the FDA and CDC admit that the PCR test cannot be used for diagnosis."

When hospitals, and vaccine manufacturers get paid more for every death called COVID-related, these numbers can be suspicious. If someone comes into the hospital today in heart failure, for example, and dies, his death is likely recorded as a COVID death if the PCR test is positive with 40x amplification sometime during his long hospital stay. Yes, many people are dying of something every year (about 3.5 million/y all causes in the USA). Sometimes what is put on the death certificate is subjective. Could these numbers be influenced by the vaccine push? There is no doubt there are many deaths from the COVID syndrome. What Cowan is questioning is the cause.

The assertions made in this book are based on scientific studies, not Cowan's own theories. If I were willing to read each and every one of the hundreds of references cited, I might be able to figure out if Cowan is correct. There are many holes in his arguments since COVID appears obviously infectious; however, his conclusions that the real cause of this syndrome is a combination of bad water, bad food, environmental pollution, 5G, and emotions resonate with me as a functional medicine practitioner. I do think there is a real problem with animal viruses that migrate to humans as a result of large-scale factory farming (see Michael Greger's book *How to Survive a Pandemic*); and unless this is resolved, I think we will see more frequent pandemics of every kind. The 1918 flu pandemic was exquisitely described by Barry in his book *The Great Influenza*, and its association with WW1 and the widespread use of radar and communication towers is noteworthy.

In summary, I think Cowan is worth listening to. Is he a visionary or something else? Read his book and decide for yourself.

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CALENDAR

Please visit www.TownsendLetter.com for the complete calendar

MARCH 26: SOUTHWEST CONFERENCE ON BOTANICAL MEDICINE begins streaming online. Pre-conference intensive on managing the side effects of pharmaceuticals, plus 24 other lectures. 40 hours of continuing education for ND, DO, MD, RN, FNP, LAc and others. CONTACT: 541-482-3016 or www.botanicalmedicine.org

APRIL 5: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE SPRING MEETING – Mold, Mycotoxins, and Human Health Online. CONTACT: http://aaemconference.com/

APRIL 14-17: ENVIRONMENTAL HEALTH SYMPOSIUM 2021 In Tucson, Arizona. Toxic metal effects, diagnosis, and treatment. Building immune resilience. CONTACT: https://www.environmentalhealthsymposium.com/about-ehs

APRIL 17-18: LOW-DOSE LITHIUM – The Mineral as Medicine Online. This international, online symposium will review the evidence-based use of low-dose lithium for treatment of psychiatric and neurological disorders. CONTACT: www.LithiumSymposium.com.

APRIL 22-25: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING with Simon Yu, MD, in St. Louis, Missouri. Also, **AUGUST 26-29.** CONTACT: 314-432-7802; http://www.preventionandhealing.com/

APRIL 23-25: 16th ANNUAL JOINT HOMEOPATHIC CONFERENCE Online. CONTACT: https://www.jahc.info/

MAY 13-14: INFLAMMATORY BRAIN DISORDERS CONFERENCE Online. CONTACT: https://www.neuroimmune.org/inflammatory-brain-disorders-conference/

MAY 21-23: ADVANCED INFECTIOUS DISEASE MANAGEMENT in Scottsdale, Arizona, and Live Online. CMEs available. CONTACT: Sharon Phillips, phone 954-540-1896; Email: sharon@aampconferences.com; https://aampconferences.com/

MAY 28-29: 50th ANNUAL INTERNATIONAL ORTHOMOLECULAR MEDICINE TODAY CONFERENCE Online. CONTACT: https://isom.ca/event/50th-conference/

MAY 28-JUNE 1: 12th INTERNATIONAL CONGRESS ON AUTOIMMUNITY in Athens, Greece. Special session on diet and autoimmunity, chaired by Dr. Aristo Vojdani. CONTACT: https://autoimmunity.kenes.com/

JUNE 3-6: SASKATCHEWAN ASSOCATION OF NATUROPATHIC DOCTORS HEALING SKIES CONFERENCE in Saskatoon, Saskatchewan. CONTACT: http://www.sanp.ca/index.html

JUNE 4: MEDICINES FROM THE EARTH HERB SYMPOSIUM begins streaming online. Intensive: Targeting the Biological Terrain in Collaborative Oncology, plus over 25 other lectures. Over 40 hours of continuing education for ND, DO, MD, RN, FNP, LAc and others. CONTACT: 541-482-3016 or www.botanicalmedicine.org

JUNE 4-6: LDN RESEARCH TRUST 2021 CONFERENCE livestream online. CMEs available. CONTACT: https://www.ldnrtevents.com/pages/ldn-2021

AUGUST 26-29: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING For Doctors, Dentists & Health Professionals: Detecting Parasites, Dental & Fungal with Simon Yu, MD, in St. Louis, Missouri. CONTACT: **www.preventionandhealing.com;** 314-432-7802**.**

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Ivermectin, COVID, and Censorship

At the December 8, 2020, US Senate Homeland Security and Government Affairs Committee hearing, pulmonologist and critical care specialist Pierre Kory presented studies and other documentation showing that the anti-parasitic drug ivermectin "basically obliterates transmission of this virus. If you take it, you will not get sick." In addition, mortality rates decreased in hospitalized COVID patients who received the drug. Dr. Kory is president of Frontline COVID-19 Critical Care Alliance (FLCCC: https://covid19criticalcare.com/), a group of highly published physicians, led by Professor Paul E. Marik. This group published the MATH+ integrative protocol for COVID in March 2020.

In response to the scientific literature presented by Dr. Kory, summarized on page 71, the National Institutes of Health removed its barrier to using ivermectin for prevention and treatment of COVID-19 on January 14, 2020. Instead of being "against" use, NIH upgraded its status to "neither for nor against."

Instead of publicizing ivermectin effectiveness, YouTube and corporate media are ignoring or outright censoring the information. In early February, FLCCC reported that YouTube removed Dr. Kory's Senate committee testimony, which had been posted by the committee's chair. FOX NewsNow also removed Dr. Kory's testimony from its YouTube channel.

As the summary on page 71 explains, "…widespread use of ivermectin resulted in a significant reduction in cases and mortality rates that approached pre-pandemic levels" in areas that initiated ivermectin distribution programs. This information needs to widely shared – particularly because ivermectin inhibits the replication of many viruses, including SARS-CoV-2 and influenza.

For more information, go to www.flccc.net.

Jule Klotter

One Page Summary of the Clinical Trials Evidence for Ivermectin in COVID-19

Ivermectin, an anti-parasitic medicine whose discovery won the Nobel Prize in 2015, has proven, highly potent, anti-viral and anti-inflammatory properties in laboratory studies. In the past 4 months, numerous, controlled clinical trials from multiple centers and countries worldwide are reporting consistent, large improvements in COVID-19 patient outcomes when treated with ivermectin. Our comprehensive scientific review of these referenced trials can be found on the Open Science Foundation pre-print server here: https://osf.io/ws3zn/.

Properties of Ivermectin

1) Ivermectin inhibits the replication of many viruses, including SARS-CoV-2, influenza, and others;
2) Ivermectin has potent anti-inflammatory properties with multiple mechanisms of inhibition;
3) Ivermectin diminishes viral load and protects against organ damage in animal models;
4) Ivermectin prevents transmission of COVID-19 when taken either pre- or post-exposure;
5) Ivermectin hastens recovery and decreases hospitalization and mortality in patients with COVID-19;
6) Ivermectin leads to far lower case-fatality rates in regions with widespread use.

Evidence Base Supporting the Efficacy of Ivermectin in COVID-19

as of January 11, 2021

(RCT's = randomized controlled trials, OCT's = observational controlled trials). Every clinical trial shows a benefit, with RCT's and OCT's reporting the same direction and magnitude; nearly all are statistically significant.

Controlled trials studying the prevention of COVID-19 (8 trials completed)

- 3 RCT's with large statistically significant reductions in transmission rates, a total of 774 patients
- 5 OCT's with large statistically significant reductions in transmission rates, a total of 2,052 patients

Controlled trials in the treatment of both early and hospitalized COVID-19 patients (19 trials completed)

- 5 RCT's with large, significant reductions in time to recovery or hospital length of stay, a total of 774 patients
- 1 RCT with a large, statistically significant reduction in rate of deterioration/hospitalization, total of 363 patients
- 2 RCT's with significant decreases in viral load, days of anosmia, cough, or time to recovery, a total of 85 patients
- 3 RCT's with large, significant reductions in mortality, a total of 695 patients
- 3 OCT's with large, statistically significant reductions in mortality, a total of 1,688 patients

Number of Studies and Patients Among the Existing Clinical Trials of Ivermectin in COVID-19

- 27 controlled trials, including a total of 6,612 patients have been completed using well-matched control groups
- 16 trials, including over 2,500 patients, are prospective, randomized, controlled studies
- 11 of the 27 trials have been published in peer-reviewed journals, 3,900 patients, remainder are in pre-print

Front Line COVID-19 Critical Care Alliance – Recommendation on Ivermectin in COVID-19

Even restricting analysis to just the 16 randomized controlled trials (totaling over 2,500 patients), the majority report a statistically significant reduction in transmission or disease progression or mortality. Further, a meta-analysis recently performed by an independent research consortium calculated the chances that ivermectin is ineffective in COVID-19 to be 1 in 67 million.[1]

The FLCCC Alliance, based on the totality of the existing evidence, supports an A-I recommendation (NIH rating scheme: strong level, high quality evidence) for the use of ivermectin in both the prophylaxis and treatment of all phases of COVID-19.

Furthermore, we encourage all regulatory agencies to review our manuscript detailing these studies above as well as the multiple population-wide "natural experiments" that occurred in numerous cities and regions after the initiation of ivermectin distribution programs.[2] The widespread use of ivermectin resulted in a significant reduction in cases and mortality rates that approached pre-pandemic levels in these areas. As evidenced by what occurred in these regions, ivermectin is clearly an essential and vital treatment component in achieving control of the pandemic.

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[1] c19ivmmeta.com

[2] Kory P, Meduri GU, Iglesias J, Varon J et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. *Open Science Foundation*. https://osf.io/ws3zn/

Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, MSW
www.healthyhomeopathy.com

Homeopathy for Stir-Crazy Kids During the Pandemic

A New Reality for Parents and Children

It's been nine months since COVID-19 changed our lives dramatically. Our routines, plans, social interactions, work and play lives, travels, health care, family gatherings, shopping…. just about everything has been altered dramatically with no clear end in sight. And this is for individuals who are healthy, much less those who have contracted COVID-19, or have lost family members to the virus. These dramatic changes have affected families, parents and children, those living alone or in health care facilities, workplaces, businesses of all kinds. I think it is safe to say that little, in many places on our planet, has remained unchanged since the onset of the pandemic. This is definitely true of families. Kids staying home and learning virtually. Initially no in-person schools, extracurricular activities, graduations…. Then, beginning this fall, a changing scenario of virtual learning and limited or rotating in-classroom education. This in addition to many parents working from home, curricula being hit and miss initially, and job cuts resulting in diminished income for many families. And much more dire implications for some worldwide.

I treat many children in my practice, which has been completely virtual since the onset of the pandemic – kids and families across the US and Canada, and in various other countries. They have been affected universally by the COVID-19 pandemic, though only a small number in my practice have contracted the virus. I am also treating many kids on the autism spectrum, who typically require far more parental supervision than kids with ADHD and related problems.

What the Parents Are Telling Me About Their Kids These Days

- Starving for social contact
- Climbing the walls during lockdowns
- More hyper than ever, given the decrease in extracurricular sports
- "We're working at home and can't monitor him all day long."
- "On his devices all day long and now for class, too."
- Withdrawn, socially challenged kids have no socialization
- Scattered, unfocused, drifty, all over the map
- Out of control. Screaming. Breaking things. Hurting siblings.
- "Wants my attention all day long and I have to work, too!"
- "All of the progress we were making before has been lost."
- "I don't know how long I can go on like this with the kid(s) at home."

What the Kids Say

- "I'm dying of boredom."
- "I'm not learning anything."
- "I just want to go back to school!"
- "How long will this last?"
- "I miss my friends!"
- "I hate math/reading."
- "I can't even see my grandparents!"
- "When will this ever end?"

Case 1. Cory: An Eight-Year-Old Boy Diagnosed with ADD and LD (Learning disabilities)

This was the grandson of a long-time patient of mine whose sons (now fathers) I had treated decades ago for attention, behavior, and learning problems. He was first brought to see me in person by the grandma, pre-pandemic, because the mom was working. But it is a fascinating case with an unusual remedy, and he has continued to progress beautifully during the pandemic. "All of a sudden, two years ago, Cory started getting

angry in school. They called us after he got into a confrontation with another little boy. He is the oldest of three and is extremely protective of his younger siblings. He acts like a parent to them. He'll tell them, 'Okay girls, what is the #1 rule? We stay together.' Cory is very nurturing. All the kids sleep together in a big bed with mom… Cory is the last to eat. He serves his sisters first…. He is a hugger and a kisser and a toucher. He just can't keep his hands to himself. He's just so sweet and nurturing.

"Cory hates school. He especially struggles with spelling. But you can ask him about any animal, and he can tell you all about it. Like how the keratin in rhinoceros horns resembles human fingernails…. There are times when he can't sit still. You cannot calm him down. When he gets mad, he crosses his arms over his chest and you just can't reason with him. Then he comes out of it as if it never happened, and he plays by himself or with the animals. Cory is particularly fascinated by zoo animals. But he really loves farm animals and figurines, too. He can tell you about any dinosaur, penguin, or zebra. He loves to watch the zebras head butt… When we had our big family get-together, Cory dragged out his laundry basket full of toy animals…. He helps his dad feed the cows, goats, chickens and pigs. He names every single farm animal except our goats, because we have too many.

"Cory can be loud. And a teaser. But he shuts down in school. Spelling and math are especially hard for him. He was diagnosed with Learning Disabilities. But, if they start talking about animals, he'll participate more. He'll have the whole class doing a safari or going through the jungle."

Then I engaged Cory. When I asked about his favorite thing to do, he replied: "Go to the zoo. See the Komodo dragon and the elks. They have two antlers. In the spring they grow a new pair. I love giraffes and dinosaurs. I know everything about animals. Some live in Africa, some in Asia, the Arctic, the Antarctic… different species." Cory was very animated as he shared all of this with me about this favorite subject. "I have toy animals. They have parts to protect themselves. Like hooves, horns, scales, quills, and antlers. Quills belong to the porcupine, claws to lions and tigers. Pangolins have scales and live in a zoo. They have scales so the lions can't get through to them with their sharp jaws."

I inquired, "Do you ever feel like an animal yourself?" Cory: "I love tigers… I like wild animals and farm animals. A donkey. They have long ears. They're a type of horse but with no fur on their tails. A baby donkey is called a foal like a baby horse." I asked Cory if he was afraid of anything. He told me, "My sisters might fall and get hurt." Then I asked if he could be an animal, what would he be. "A donkey. Long ears. Be like a horse. Have a little foal. A little donkey." Then I asked why a donkey. "They are incredible animals. They have big ears like mama goats." Finally, I inquired about any fears: "Monsters. Predators that like to eat meat. Carnivores. Wildebeests, gazelles, warthogs, giraffes, Cape buffalo."

Though I had never before prescribed the remedy, it was clear that Cory needed *Lac asinum* (Donkey's milk), which has been prepared as a homeopathic remedy and proven. From the proving: "Jesting; delusion he is stupid; dreams of being abused or being too weak to defend himself; imitation/mimicry; ailments from mental work." Additional information from the proving: "Donkeys have a great sense of self-preservation, so they will not do anything that puts them in danger. This has resulted in them being called stubborn, but that is a misinterpretation. Themes: Humility and kindness. A little foolish but obedient. Innocence, passivity." It turns out that donkeys have a keen sense of curiosity. A 2013 study at the *Donkey Sanctuary* in the UK found that they can learn and problem-solve at the same pace as dolphins and dogs (www.thedonkeysanctuary.org.uk).

I gave Cory *Lac-asinum* 1M (4 doses) and LM8.

Six weeks later: The subsequent appointments and feedback are from his mom. "He is calmer. You can communicate with him better. He is more able to listen and pay attention. He shares more easily with his sisters, and does better playing by himself." He continued *Lac-as* LM8 daily.

Three months: The school conference went very well. He is still doing a lot better in math and he loves his reading class now. Cory is doing much better in the intermediate school. All the kids want to help him. The teachers are horrified that we put him on the bus by himself, but he's fantastic with it. He is more able to focus on conversations.

Four and a half months: Doing great. Attitude is good. Doing really well in math. Terrified of his grandma's cows.

Seven months: Doing great. Started Lacrosse. The mom requested another high dose, so I gave 4 doses of *Lac-as* 1M.

Nine months (two months into the pandemic): Some highs and lows. Talks about being a zookeeper. Goofy. I changed the potency to *Lac-as* 1M plussed 1-2 times a week.

One year: He is doing great. Taking the remedy twice a week is working great. A lot calmer. Loves cows but would keep his distance till yesterday when he was right out there with them. His fears are better, too. We are going back to all classes online.

Fourteen and a half months: Starting school half days in the afternoons. Doing fantastic. Takes *Lac-as* 1M every 3-4 days.

Sixteen months: Doing extremely well. "Two bus drivers told me that he is the sweetest, nicest boy they had ever met. That he takes such good care of his sisters and the neighbor girl to make sure they are securely in their seats before the bus pulls out. When he gets off the bus, he's the only one to tell them, 'Thanks for the ride.' He's beginning to love to cook and is doing a great job."

This was a fascinating case for me – partly because patients needing animal remedies are typically fun, entertaining, engaging. And because it was a remedy that I had never before given. I was reminded that a couple of years ago Bob and I went to visit a donkey sanctuary in Southern Spain, rather than spending the afternoon at a busy beach in Málaga. There was a story posted about the history of each donkey (some 20+ years old), how he or she had arrived, and about their health and personalities. Some were quite aged. It was fascinating, as was the information from the sanctuary in the UK about their high level of intelligence!

Case 2: Jillian: A Really Tough Cookie!

Though I see more boys with behavioral and learning problems, girls can be super challenging as well, as you will see in this case. Jillian was six. Her mom had seen me during her pregnancy, and she was helped significantly with homeopathic

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Sepia (cuttlefish). The mom contacted me out of desperation to help Jillian just at the beginning of the pandemic nine months ago. "Jillian gets very, very angry. She makes mad faces and tells everyone how much she hates them and wishes they would die! She was such a happy baby… always laughing. Now we're all walking on pins and needles around her. Nobody else in the family has this anger. She has to be in charge, the leader. Otherwise, she starts crying, and becomes emotional and dramatic. I think she has lots of friends at school, but she insists that nobody likes her. Jillian gets so angry with me that she grabs me and wants to hurt me. 'Stupid mom… I hate you!' I can't tell her anything or she'll lunge at me.

"Jillian is very jealous of her younger sisters. Like she's walking around with a chip on her shoulder. 'You like Callie better than me.' She'll throw a Barbie at her sisters, pinch them, slap her little sister in the face. She's just plain mean! It's her way or the highway. We always have to go where she wants to go, play what she wants to play. Or she says she wants to kill us, then storms off. She's such a sweet, little girl. Then, all of a sudden, it's like she's possessed…. She always has to have things her way. And tells me I'm mean and stupid. No matter how much attention I give her, it's never enough." Jillian wasn't in the mood to talk to me.

It took me two tries to get the right remedy for Jillian. Six weeks after the initial appointment (I first gave her *Lac leoninum* or Lion's milk), she was pretty much the same. Six weeks later: "She still wants control. If we're watching TV and one of her sisters talks, she insists that we start the video over from the beginning. She can do that seven times. 'I hate all of you. You're all stupid.' She pinches, slaps. Dr. Jeckyll and Mr. Hyde. One day so sweet and helpful. The next she says everyone hates her and that she is a dumb kid. She wants to be the boss of every situation. She can throw a chair across the room because she didn't get a pretzel!" Again, Jillian refused to talk to me.

Seven and a Half Months of Follow-up: I used the rubrics: "Mood, changeable; dictatorial, repulsive mood, reproaches himself, malicious, mood alternating and irritability in children." It was notable that, as foul-tempered, pushy, and even violent she was, she called herself dumb and insisted that no one liked her. The remedy I gave her was a very common one: *Lycopodium* (club moss). Kids needing this remedy need to be in charge and push around their younger siblings, but they have a deep insecurity and sense of inadequacy. Their worst fear is to fail in front of others. The other remedy that I strongly considered was *Anacardium* (Marking nut), which has the feeling of an angel on one shoulder and a devil on the other.

Six weeks after Lycopodium 1M (4 doses) and LM8 daily: Jillian's mom reported that she had been behaving a lot better. No more hitting nor throwing furniture. "She still wants to hit, but she stops herself. She can regulate her emotions. She still needs a lot of attention and seems to have an angry heart. She still says she's dumb and that everybody in the house hates her." She hadn't hit her mom during that six weeks. We were on the right track, so I suggested that she be given the *Lycopodium* up to once a day in a plussed form.

Four months after starting the Lycopodium: "Jillian is a lot better. Not throwing things nor pinching. I'd say maybe 80% better. Not as many emotional highs and lows. She is just who she is. Much happier. It was a whole family affair when she would get upset like that. She still wants to be in charge, but she's not nearly as intense…. Jillian doesn't furrow her brow in anger like before. Not saying she wishes we would die. It feels like a different person…. I felt like we were at a point before seeing you that I could have put her on medication…. She is no longer grabbing or wanting to be physical with me. She stopped saying, 'Stupid mom, I hate you.' It was like she was possessed before…. like she really wanted to hurt someone." She continued the *Lycopodium* 1M plussed as needed up to every two days.

Five and a half months: "She likes school and is doing well, but she seems to be backsliding. She gets very shy and nervous around people, but she is aggressive at times. She thinks she is my equal. She started pinching again." I raised the potency of the *Lycopodium* to 10M and gave four doses along with LM10 daily.

Seven months: "She is doing well again. More reasonable to talk to and it is easier to bring her back. Jillian is back in school in the afternoon with half the kids and the morning classes are remote. Her Halloween costume got caught in the washing machine. Normally she would have thrown a huge fit. But she was flexible enough to change her mask and costume at the last minute. She had to mask, of course. I think she pinched once, but she's not pushing or throwing things as much nor hoarding stuff. Overall, I would say she is much more manageable, and where you would expect a seven-year-old to be. I'd say she's 85%-90% better than when we started." I still couldn't get Jillian to talk to me.

I will continue to watch Jillian closely. The *Lycopodium* has made a huge difference, but I really want to talk to Jillian and make sure the remedy is exactly right. There are elements of *Anacardium* that may become more prominent over time, even though she is doing extremely well at this point. Talking to the child, as you could see with Cory, is essential and makes for a much deeper and richer understanding of the child.

Homeopathy During the Pandemic

So, as families struggle to navigate these uncharted waters of the pandemic, you can see how remarkable homeopathy can be for the well-being, health, and sanity of all family members. There are now 8000 (!) individual homeopathic remedies. The key is understanding the uniqueness of the child on a deep level and finding just the right remedy that matches most closely.

Dr. Reichenberg-Ullman is the author of *Whole Woman Homeopathy*, and co-author with Dr. Robert Ullman, of eight books: *Ritalin-Free Kids, Homeopathic Self Care, The Savvy Traveler's Guide to Homeopathy and Natural Medicine, Whole Woman Homeopathy, A Drug-Free Approach to Asperger Syndrome and Autism, The Homeopathic Treatment of Depression, Anxiety, and Bipolar Disorder*, and *Rage-Free Kids* as well as *Mystics, Masters, Saints and Sages – Stories of Enlightenment.* They have been columnists for the *Townsend Letter* since the early 90s, and taught internationally. They live on Whidbey Island Washington, and in Pucón, Chile.

Please visit www.healthyhomeopathy.com (where you will find a wealth of articles, blogs, and more) and Facebook at Healthy Homeopathy. Dr. Reichenberg-Ullman can be reached at drreichenberg@gmail.com.

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Ask Dr. J

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

Weight Loss Hits and Semi-Misses

As Peter Tosh so eloquently sings in his song "Equal Rights" from his egalitarian album *Equal Rights*: "Everybody wants to go to heaven, but nobody wants to die." Everybody wants to lose weight, but very few people understand where the solution to lasting weight loss truthfully lies. One pound of fat contains 3,500 calories, so to lose 1lb in a week you need a deficit of 500 calories a day. Is the secret to slimming down really that simple? The people at Jenny Craig, South Beach, Nutrisystem, etc. all seem to think so. People have been guilt tripped to think that they have been lazy and overly greedy with calories. An alternative, logical conclusion might be that our current dietary advice doesn't really work and might actually be one cause of our obesity epidemic, which it was supposed to cure. The effects of chronic societal stress on our bodies is one other potential door that needs to be cracked open much wider, so we can peer into and understand its important effects.

Over the years I have had a plethora of patients seeking my nutritional wisdom to hopefully facilitate some sort of weight loss. Let's take a look at some hits and semi-misses of mine. A quick hit was a 44-year-old woman who wanted to lose 100 pounds. She claimed a history of major depression and self-abuse, and of course she had no health insurance. Any lab work wasn't going to fit into her diagnostic picture. At the time, I was utilizing the blood type diet along with a questionnaire that very generally ascertains if you are a slow/fast/medium oxidizer. Basically, a fast oxidizer is someone whose metabolism is super quick and the opposite for a slow oxidizer. Fast oxidizers do better with higher amounts of fat and lower amounts of carbs and vice versa for slow oxidizers. She tested out Blood Type O and a fast oxidizer. Her present diet consisted almost exclusively of fast carbs: chips, cookies, donuts, bagels, etc. I explained to her that she was basically from Venus but eating a diet suitable for Martians. She liked that metaphor and attempted to make a complete diet reversal: now lots of meat, dairy, cheesecake, avocadoes, etc.

Getting back to the Peter Tosh song above, her heart was in the correct space, but her brain was unfortunately problematic. Two weeks later she returned and sheepishly said she could go a day without carbs, but then she would break out in a cold sweat and would literally shake until she ate some quick carbs. Fortuitously I had just returned from a seminar where they had talked about casomorphins from dairy products and gluteomorphins from carbs. Some people, myself included, actually produce morphine-like molecules when they eat certain products like wheat and dairy products. They, in truth, enter a mini detox if their bodies don't ingest the products that produce these feel-good molecules.

So, now, what to do with her. She's basically a food addict with no money. I had learned a treatment modality called EFT or Emotional Freedom Technique. I have used it in many clinical situations but never with someone who is addicted to a substance. Basically, with EFT you tap a specific sequence of acupuncture points and repeat a mantra that says you are a beautiful human being and that you want to change this specific situation in your life. Figuring out the phrase is the hardest part of the treatment because you're working on some deep psychological issues, not just the specific addiction. I also want the person to come up with the phrase, so we talk and I kind of guide them to a specific event in their life. For her, it was the fact that her father would have violent outbursts consistently when she was growing up and her mother would mollify her with sweet carbs. She utilized the EFT with her personal phrase and came back two weeks later extremely excited because she had completely changed her diet successfully and had already lost 6 lbs.

Two weeks later she came back completely dejected because the EFT had stopped working, and now she was feasting on carbs again. Emotional insults to our bodies are usually multiple and can lie deep in the cerebral cortex somewhere, waiting to escape. It took us five more specialized mantras before she was able to consistently keep carbs out of her diet. A year and a half later she had lost the 100 pounds, but more importantly her major depression had completely vaporized, plus she wasn't harming herself anymore.

Next is a semi-miss, Rhonda. When she first came to me, she was 48 and wanted to lose 150 lbs. Rhonda is part of what I call the working poor: she had a low paying job with no health insurance (this was back in 2010 before we were coerced into obtaining health insurance). She had a work history of exposure to multiple chemicals and heavy metals. She also had a palpable goiter. Her energy was extremely low, and she had to drag herself out of bed in the morning.

In a case, like this where do you start, or do you just punt the ball? Fortunately, I'm a person who would always go for it on fourth down and a half yard to go. I started with acupuncture, which increased her energy levels but had no effect on weight and

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the goiter. I muscle tested her for food allergies and found several. She avoided all of them meticulously for three months, but there was still no change in weight or the goiter. I then had her remove all chemicals from her home and place of work and begin cleaning with baking powder and vinegar. three months later brought no change again. She also has no excess money for supplements.

We kept doing acupuncture every two weeks for two years which gave her a temporary reprieve with her energy levels. Then I magically read an article stating that bone broth is a good fix for leaky gut which can be the initiating factor for many autoimmune diseases, including Hashimoto's, which I suspected she already had. I told her this might be the ticket to ride for her. I asked her to fast on homemade broth for three days and then drink a pint a day while only eating two meals per day. I went away for a few weeks and then didn't see her for a number of weeks after that. It had been almost two months, and she finally came in for a visit. Miraculously the goiter is completely gone! She is slowly starting to consistently lose weight and didn't realize how tight her anterior cervical region had been. All this from incorporating bone broth into her diet! Rhonda is fortunately and unfortunately why we practice medicine: great results but her situation also shows the economic disparities that exist in our society.

Ann is a lovely 44-year-old woman who came to me initially for fatigue and sleep issues. She is 5 foot 4 inches and was 290 pounds. After our initial consultation I convinced her that, if we focused on her weight as the root cause, the fatigue and sleep matters would more than likely improve dramatically. She had attempted multiple different systems at losing weight, which had steadily climbed since the birth of her second child when she was 28. None had had more than a mild, short term effect. Her diet was veritably quite exemplary. All her family's meals were cooked from scratch with many ingredients coming from her local farmer's market. She didn't drink alcohol and had cut dairy and wheat products completely from her diet. She in fact taught me a few hidden places where wheat and dairy lurk in the modern US food system: vodka and gin for wheat/canned tuna fish for dairy!

She said that no matter what she ate or how much she exercised she just couldn't drop more than a few pounds without them coming right back on plus even more. She commented she was reaching the end of her rope. With that comment, my frontal lobe lit up, and we started talking about stress in her life. First, she is a single mother of a 17-year-old female and a 15-year-old male with no financial or emotional support from their father. She works 50-70 hours/week, mostly at home, as the head of human resources for some internet company. Now I was getting somewhere.

I had her fill out my questionnaire that lists hypothyroid symptoms in several different categories. She circled 30 of 36 possibilities. I asked if she had brought her lab results. She had. Her TSH was 4.58 which falls within the normal lab limits in my area of 0.3 – 5.5. This brought me to explain my duck analogy to her: if it looks like a duck, walks like a duck, and quacks like a duck, it's a duck. In her case, no one would prescribe thyroid hormone because of her high TSH even though she clinically fit the bill of hypothyroidism.

I have been lucky to read Alan McDaniel's chapter on thyroid hormone in his forthcoming book on Endocrinology and to pry some incredible tidbits from him. One is the use of Thyroid Panel Complete from www.directlabs.com, which also has the best price. This is what the panel tests and what her results were:

Free T4: 0.98 ng/dL	**Reference Range:** 0.78 ng/dL - 2.19 ng/dL
Free T3: 1.8 pg/mL	**Reference Range:** 2.0-4.4
TSH: 4.28 mcIntlUnit/mL	**Reference Range:** 0.47 mcIntlUnit/mL - 4.68 mcIntlUnit/mL
Total T3: 66 ng/dL	**Reference Range:** 71-180
rT3: 18.5 ng/dL	**Reference Range:** 9.2-24.1

As you can see her Free T4 was at the low end of normal, her Free T3 and Total T3 were below normal, TSH is theoretically within normal, and her rT3 or Reverse T3 is towards high normal.

Alan also taught me most importantly to look at the ratio of Total T3 to rT3 which, for him, optimally lies in the range of 10-14 in a healthy individual. Her ratio is extremely low, 3.57, which can signify peripheral conversion issues of T4 to the active form of thyroid hormone, T3. Stress is a significant inhibitor of this conversion which made sense 1,000 years ago when there wasn't abundant calorie-rich food year-round. Back then, a bad harvest meant a long, stressful, low-calorie winter. You would want a poor ratio meaning less active T3 and more rT3 to bind to thyroid receptors and render them less active. In other words, rT3 inhibits thyroid function, which would lower people's metabolism and allow them to burn whatever calories they had built up for the winter at a slower rate: win/win scenario. In modern, nutrient-poor, calorie-rich America, this is a recipe for disastrous weight gain: lose/lose scenario.

She started on 2.5 mcg bid of Cytomel. Miraculously her fatigue and sleep immediately improved. A month later, she still hadn't started losing any weight. I upped her Cytomel to 5 mcg bid. A month later she said she still hadn't lost any weight. I thought about upping her Cytomel, but I asked her again regarding her seemingly excellent diet instead. She confessed to sneaking one to two pints of Ben and Jerry's Cherry Garcia slowly over the course of every day. We both made a pact to not eat any more Ben and Jerry's Cherry Garcia. It has been six months since Ben and Jerry's stock started to drop, and she has dropped 40 pounds. She is ecstatic and feels like this is only the beginning of a long, strange Ben and Jerry-less trip of continual weight loss.

Unfortunately, more people seem to be unsuccessful in their weight loss journey than are successful. For them to reach a fruitful conclusion regarding their weight loss, we need to individualize each person's treatment regimen to some degree. Otherwise they are just cogs in revenue-producing, dietary programs that offer poor long-term success. Finding the key that unlocks their specific weight loss door is our job. Too often it is an extremely arduous journey that the doctor and/or the client can't complete. Thus, I use my Peter Tosh heaven line very often. Sometimes, it even works! ◆

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Circle the Wagons: Antioxidants Are Being Attacked

Back in 2019, data from two noteworthy trials on the impact of taking antioxidant and vitamin supplements during cancer treatment were published. Their results are important to us. They provide additional data that may help inform our thinking. Unfortunately, they contradict our long-held belief that such supplements are safe to use. Our reaction is to immediately criticize the research looking to find fault in the methodology.

The question of whether antioxidant supplements will aid or hinder cancer treatment has become highly divisive over the years with sharply contrasting opinions and little room for a middle ground. The standard medical wisdom adhered to by a majority of oncologists is that because many medical interventions, especially radiotherapy and traditional forms of chemotherapy, work by increasing reactive oxygen levels in tumor cells and eventually triggering apoptosis, that taking antioxidants will quench these free radicals neutralizing the expected benefits of therapy. Thus, their general opinion has been that cancer patients should avoid antioxidant supplements like the plague.

On the other hand, most practitioners of a naturopathic persuasion have not taken this view, pointing out the lack of incriminating evidence that taking antioxidants is harmful and suggesting that antioxidants may offer systemic protection against harm secondary to treatment. They cite specific examples of individual supplements that appear to be associated with improved outcome.

This debate has gone on for years without adequate published data to help anyone reach a definitive resolution. It is with this backdrop in mind that two studies crossed our virtual desktops in 2019 that both bear examination.

The first, written by AY Jung et al was published January 1, 2019, in the *American Journal of Clinical Nutrition*. Acknowledging the paucity of information both on supplement use by breast cancer patients and that few studies had looked at the impact dietary supplements, particularly antioxidants, have on breast cancer prognosis, the authors undertook an investigation of supplement use in postmenopausal breast cancer survivors in Germany – specifically looking at postdiagnosis use of antioxidants and other supplements and associations with breast cancer mortality and recurrence free survival in women who were treated with chemotherapy and radiation therapy. Data from 2,223 postmenopausal women diagnosed with nonmetastatic breast cancer from the Mamma Carcinoma Risk Factor Investigation (MARIE) study were used. Women were interviewed at recruitment in 2002-2005 and again in 2009 and followed through June 2015. Multivariate Cox regression analysis was used to estimate Hazard Ratios (HRs) and corresponding 95% Confidence Intervals (Cis).

Before diagnosis 36% of the women reported they took supplements. This increased to 45% after diagnosis. By 2015, 240 of the initial 2,223 women had died, (134 from breast cancer) and 200 had their breast cancer recur. After adjusting for relevant confounders, using antioxidants during chemotherapy or radiation therapy was associated with increased risk of total mortality (HR: 1.64; 95% CI: 1.01, 2.66) and worsened recurrence-free survival (HR: 1.84; 95% CI: 1.26, 2.68). Supplement use in general was not associated with breast cancer prognosis. Only the antioxidants were.[1]

The second paper of interest was written by Christine Ambrosone, from Roswell Park, and colleagues from across the US and Canada and published in the *Journal of Clinical Oncology* almost 12 months later, in December 2019. They too hoped to determine if an association exists between dietary supplement use during chemotherapy and outcomes for patients with breast cancer.

This was a prospective observational study, which used questionnaires to assess supplement use in patients with breast cancer enrolled in a phase III chemotherapy clinical trial. The questionnaires were administered twice, initially prior to beginning chemotherapy and then after completion of chemotherapy. A total of 1,134 patients completed both questionnaires. Among these patients, there were 251 recurrences and 181 deaths. Far fewer

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patients in this study reported taking supplements than we would have expected based on earlier studies, especially in comparison to the study by Jung et al just mentioned. Whereas in the Jung study supplement use increased dramatically during treatment in Ambrosone's patients use dropped during treatment. This difference may reflect differing attitudes of German vs. American oncologists.

> … prevalence of supplement use, particularly antioxidants, was low compared with reports in the literature of use by patients with cancer and tended to decrease during treatment. For example, vitamin C was used by 20.5% of patients before treatment but only 12.2% during therapy. Vitamins E and A were taken during treatment by 10% of patients. Use of any antioxidant during treatment (vitamins C, A, and E; carotenoids; or coenzyme Q10) was observed among 17.5% of patients, whereas 44% of patients took multivitamins during chemotherapy. [Ambrosone]

Because so few patients reported supplement use, many of the statistical tests lacked power and did not reach statistical significance. However, many of the trends suggested by the data did suggest unwanted effects.

Use of any antioxidants (vitamin A, vitamin C, vitamin E, carotenoids, and CoQ10) *both* before and during chemotherapy was **non-significantly** associated with an increased risk of cancer recurrence (adjusted hazard ratio [adjHR], 1.41; 95% CI, 0.98 to 2.04; *P* = .06) and death (adjHR, 1.40; 95% CI, 0.90 to 2.18; *P* = .14. The key word here is "non-significant" and that distinction was lost in the news stories that reported these results wherein these non-significant associations were reported as fact. For example, Forbes headlined: "Taking Supplements During Breast Cancer Treatment Increases Risk Of Death And Relapse"[2]

As my dear friend Ian Beirs, ND, enjoys reminding me, non-significant numbers are non-significant and should not be suggested to mean anything. The fact that they might be 'almost significant' does not count.

But let's be honest. Over the years some of us may have, on occasion, cited a paper or two to patients in which the findings did not reach statistical significance. One in particular comes to mind, a paper published in 2012 on metformin use by 63 diabetic patients with triple negative breast cancer against 67 who weren't taking metformin. After a bit more than five years, the diabetic patients not taking metformin had a 63% greater risk of having had a distant metastasis than those who took metformin (hazard ratio [HR], 1.63; 95% confidence interval [95% CI], 0.87-3.06 [P = .13]).[3] Obviously the confidence intervals reveal that this number wasn't statistically significant. Thus, the study accurately concluded that taking metformin didn't make any difference, but that didn't stop me from asking patients, "Imagine there are two teams here, and the one not taking metformin is maybe 63% more likely to be diagnosed with cancer recurrence. Which team do you want to be on?"

We should never do this. We should stick with one set of rules; we can't have it both ways. We should not ignore significance or lack of it to support something we want our patients to do and then ignore a study whose outcome says something we don't like. We should ignore much of what Ambrosone reported because it wasn't significant, but we should pay attention to Jung.

Ambrosone did detect several associations with supplement use that were significant and that we should take note of. First, vitamin B-12 use both before and during chemotherapy was significantly associated with poorer disease-free survival. Vitamin B-12 takers were 83% more likely to have the cancer return and twice as likely to die during the study period (disease free survival: adjHR, 1.83; 95% CI, 1.15 to 2.92; *P* < .01 and overall survival adjHR, 2.04; 95% CI, 1.22 to 3.40; *P* < .01).

Likewise, the use of iron during chemotherapy was significantly associated with recurrence (adjHR, 1.79; 95% CI, 1.20 to 2.67; *P* < .01). Results were similar for overall survival.

I've written in the past about my concern regarding vitamin B-12. Recall that high levels are significantly associated with cancer occurrence and also associated with lower short-term survival. Johan Arendt reported in 2013 that cancer incidence in people with elevated B-12 levels (>1084 ng/ml) was more than six-fold higher than for people with normal levels.[4] Arendt went on to report in 2016 that for patients diagnosed with cancer, one-year survival for those with similarly elevated B-12 levels was about half of what it was for patients with moderate levels.[5]

Many practitioners have used vitamin B-12 to prevent and treat neuropathy secondary to cancer chemotherapy. This practice may need to be reconsidered. The relationship between vitamin B-12 status and development of chemotherapy-induced neuropathy may be better predicted by methylmalonic acid levels (MMA) than by serum B-12 status. There is much that we don't understand about B-12.[6]

The association with iron supplementation is also a concern. It seems to be common practice by many of our local oncology offices to suggest patients take iron "because they are anemic." Our response to this suggestion has always been to encourage testing ferritin levels in the hope of differentiating anemia of malignancy from frank iron deficiency. The negative association between iron and prognosis seen in Ambrosone's data should lend further weight to our hesitation to supplement with iron.

In the course of conversations with multiple colleagues, I have heard a multitude of reasons why Ambrosone's study results should be discounted for methodological reasons. This issue makes me want to rephrase that line from Hamlet to, "My colleague doth protest too much, methinks." We want to continue believing that cancer patients should take high doses of antioxidant vitamins before, during, and after treatment. We believe that doing so will be beneficial. Any information that may contradict our belief must be wrong.

Jung's study showed statistically significantly poorer outcomes associated with taking antioxidants. Ambrosone's results, probably because fewer patients took vitamins than in the German study, did not have the statistical power to reach significance. We can quickly get lost arguing over whether this is really a bad idea or not, whether we are harming patients or not.

The main thing though is that neither study showed benefit from taking antioxidants; this argues against our long-held assumptions that taking antioxidants is a good idea. If doing so doesn't help, then why do it at all? We have other interventions that we might invest patient energy and time into adopting that perhaps may have a positive influence on outcome. What comes to mind as I write this? Exercise, weight loss, dietary shifts in macronutrients, meal timing, caloric restriction, fasting and

so on. Of course, there has always been a financial incentive to sell vitamin supplements to our patients. If we profited from these other interventions perhaps, we would be more eager to encourage such behavioral changes with the same zeal as we've sold antioxidants?

This topic brings to mind a detail from Kurt Vonnegut's 1963 book, *Cat's Cradle.* In his story, Vonnegut describes a fictional religion called Bokononism. Part of this religion's beliefs entails the concept of a granfalloon, defined as a "false karass." A granfalloon in Vonnegut's thinking was a group of people who affected a shared identity or purpose but whose mutual association is meaningless. I recall, even after all these years, that Vonnegut used "Hoosiers" as an example to illustrate his idea. This idea of a granfalloon comes to mind when this debate about antioxidants comes up. We may have grouped too large a group of chemicals together into a shared identity where in reality their mutual association has become meaningless. We are trying to predict the behavior of a diverse group of materials based on a single trait and contrasting that action with the equally broad group of things lumped together as oxidants. Put simply, a blueberry may have more going on inside itself than the vitamin C it happens to contain. Biology is not this black and white. [reading through this many months after my initial draft, this last line wants me to take this a step further than 'black and white.' Our segregating the world into oxidants vs, antioxidants may have as much predictive value as trying to judge a person based on skin color. Of course, as absurd a practice as this is, there are no shortage of people who think this is a valid practice.] Our minds are attracted to binary

Attack on Antioxidants

segregation, but the world itself isn't. This habit of putting value on anything labeled antioxidant may no longer be appropriate.

When deciding which supplements may be beneficial during cancer treatment, we should not slip into the granfalloon of calling them antioxidants to justify their use. Rather we must do the hard work and ask what happens when a specific nutrient, phytochemical, or I suppose, food is used in conjunction with the specific chemo drugs against a specific cancer type. Does the total combination increase reactive oxygen species in the cancer, does it increase apoptosis? Even being this persnickety may not be adequate to predict long-term outcomes, in particular overall survival (that was for you, Ian); but at least it will be a step in the right direction. Our past strategy of assuming all antioxidants fight cancer is fast becoming outdated.

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who had an increase of at least 2 points.[5] Another study found that when patients with celiac disease went on a GFD, 66% of those who were underweight gained weight. In contrast, among those who were obese, 47% lost weight and only 18% gained weight. Among those who were overweight, 54% lost weight and 40% gained weight.[6]

If various headache specialists are wrong about issues related to gluten and migraines, and if they provide a somewhat unbalanced view of the effect of GFDs on BMI, why are they considered experts in these areas? As a first step in trying to answer that troubling philosophical question, I looked up the word "expert" in the dictionary. I learned that an expert is "a person who has a comprehensive and authoritative knowledge of or skill in a particular area." So, then I looked up "authoritative," which means "able to be trusted as being accurate or true." Which begs the question: why should someone who went through a specialty training that likely ignored the role of food allergy in migraines, and then practiced that specialty while continuing to ignore the role of food allergy in migraines, be considered an expert on the role of food allergy in migraines?

Modern medicine has a long history of equating credentials with expertise, but these things are not synonymous. This is especially true with respect to food allergy. While hidden food allergy is an important contributing factor to many symptoms and diseases in the fields of gastroenterology, cardiology, dermatology, psychiatry, rheumatology, nephrology, neurology, and otolaryngology, few specialists in these fields consider hidden food allergy in their differential diagnosis or know how to identify it.

Editorial

If having credentials does not necessarily guarantee expertise, how can we know whom to trust as experts? In my 47 years in the field of nutritional medicine, I have tended to view most "expert opinions" with some degree of skepticism. If I have questions about whether the information is being presented accurately, I look up the reference citations and try to come to my own conclusions. With time, one learns that certain writers, thinkers, and researchers are quite reliable, and that their works are less likely to require fact-checking. These individuals typically undertake a comprehensive, balanced, and detailed review and analysis of the evidence; are free of obvious biases and conflicts of interest; understand the limitations of the evidence and do not over-interpret the data; and are not afraid to admit when they don't know something.

I realize that many of us do not have the time or the training to investigate each scientific question for ourselves. By necessity, much of what we learn will come from teachers and other experts. However, it is important to maintain a healthy degree of skepticism in all areas of inquiry, and to remember that credentials and university affiliations do not automatically endow someone with the truth.

Alan R. Gaby, MD

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What Makes an Expert an Expert?

An article recently appeared in the journal *Headache*, under the title, "Expert Opinions: Gluten-free diet and migraine."[1] The article presented a case report of a woman with migraines and alternating constipation and diarrhea. Testing for celiac disease was negative, and the woman was diagnosed with irritable bowel syndrome. After reading about gluten and migraines on social media, she went on a gluten-free diet (GFD) and reported that her migraines were less frequent. The article went on to pose several questions to a panel of "experts": Is there an association between celiac disease and migraine? Does migraine improve after going on a GFD? Does a GFD improve migraine in people who do not have celiac disease? Is there any harm to a GFD? Two of the four experts are neurologists and the directors of headache clinics. Another expert is also a neurologist specializing in headaches, and the fourth expert is a research coordinator.

These experts cited literature demonstrating that migraine is more frequent in patients with celiac disease than in controls, and that migraines usually improve in celiac patients after they go on a GFD. With regard to migraine patients who do not have celiac disease, they stated that there is little research on the subject, and that it is unclear whether a GFD is beneficial. In the "Conclusion" section of the article, they were somewhat more negative, stating that . . . "a GFD is only significantly beneficial to patients diagnosed with CD [celiac disease]." They further argued that a GFD is potentially harmful because it can lead to weight gain, which may exacerbate migraines and increase the risk of various diseases associated with obesity.

I am certain that few, if any, headache specialists would consider me an expert on migraines. However, I am nearly as certain that the experts who wrote this report are incorrect in asserting that there is little or no evidence a GFD can prevent migraines in non-celiac patients. It is difficult to ignore the many patients I saw over the years who were firmly convinced that wheat (the major gluten grain) was a trigger for their migraines. And the observations of my patients are supported by a number of published studies. In Grant's landmark 1979 paper in *Lancet*, 60 patients with a long history of frequent migraines underwent an elimination diet followed by individual food challenges. Seventy-eight percent of the patients were found to react to wheat. When all symptom-evoking foods were removed from the diet, 85% of the patients became headache-free, and the total number of headaches per month in the group as a whole fell by 98.5%.[2] In a 1983 study of 88 children with severe frequent migraines, an elimination diet resulted in complete resolution of migraines (n = 78) or marked improvement (n = 4) in 93% of cases. Of the 82 children who had a positive response to the diet, 21 (25.6%) reacted to wheat.[3] In a 1955 report, of 45 patients with migraines, nine (20%) found on elimination-and-rechallenge testing that wheat triggered attacks.[4]

For two reasons, I suspect that the experts who wrote the report in *Headache* have little or no experience with elimination diets. First, based on the medical literature, as well as my clinical experience and that of many other nutrition-oriented practitioners, it seems implausible that anyone who routinely investigates food allergies and sensitivities could come to the conclusion that the role of wheat as a trigger is "unclear." Second, the experts implied in the article that people who suspect gluten sensitivity is contributing to their migraines should consult a nutritionist.

In addition, the experts' statement that GFDs cause weight gain is open to debate. They did not provide a reference for that statement, but they did mention that the study included 679 patients with celiac disease. A search of PubMed revealed only one study that enrolled 679 patients and assessed the effect of a GFD on body mass index (BMI) in people with celiac disease. Mean BMI did increase to a small extent (from 24.0 kg/m^2 to 24.6 kg/m^2) over a mean follow-up period of 39.5 months, after the patients went on a GFD. However, celiac disease is associated with malabsorption, which can cause some patients to be underweight or have a low-normal BMI. In those people an increase in BMI is probably a good thing. When considering only those people in the study who were overweight or obese at baseline, the number who had a BMI decrease of at least 2 points was similar to the number

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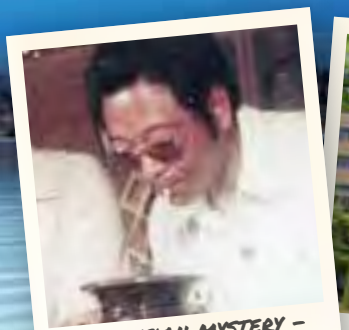
Dr. Iichiroh Ohhira: A Pioneering Genius in Probiotic Science



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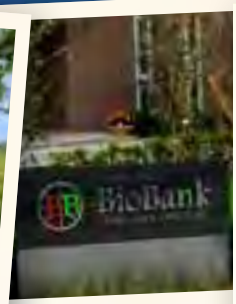

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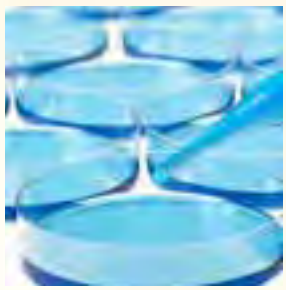

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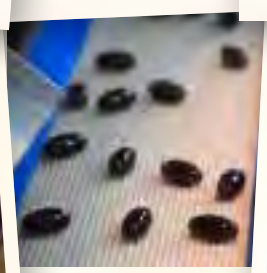

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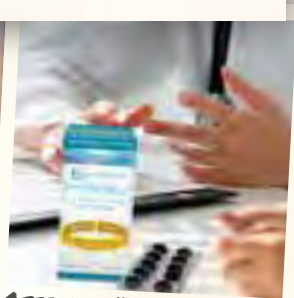

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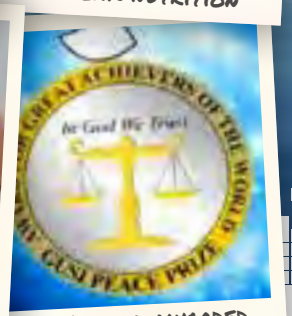

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