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May 2021
Issue #454
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Hypothyroidism: Looking Beyond TSH Levels

Marianne Marchese, ND

PLASTICS, PESTICIDES, AND OBESITY

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From the Publisher

When Are We Going to Stop the Rants About Masking Up?

I was recently sent, by an MD reader, the following email:

> Dr. Collin:
> A MASK?...***SERIOUSLY?!***
> You should be ashamed.

The first thing that came to mind was Hester Prynne in Nathaniel Hawthorne's novel, *The Scarlet Letter*. Having a baby out of wedlock was quite the sin in 1640's Puritan Massachusetts Bay Colony. Hester devotes much of her life thereafter seeking repentance, trying to reestablish her sense of dignity. Assuredly she experienced shame.

Was I guilty of a similar sin? Had I had an affair leaving some bereft woman to take care of a child alone?

I admit that I have had my share of questionable behavior, but I am quite certain that there has been no such scandalous misdeed.

So, what is it that I should be ashamed of? For abiding by recommendations subscribed to by all public health authorities

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Letter from the Publisher

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in the US and internationally? While mask wearing is hardly foolproof in preventing, acquiring, or spreading infection, it is a reasonable mandate for a pandemic. The idea that being required to wear a mask infringes on one's personal rights is an absurdity. We are required to come to a stop at a red light, pay sales tax when we purchase an item, desist from punching someone when we are offended. No one complains about these restraints.

Why is there such a hang-up about wearing a mask?

Yes, mask wearing is uncomfortable. That is about the sum of it: it's uncomfortable. All the rigmarole that it is harmful is largely bunk.

Early in March there was a small public demonstration of individuals huddled around a fire made in a large metal barrel gleefully burning their masks in front of the Idaho state capitol. Is this supposed to be comparable to burning the flag or burning books?

My question is why are some alternative practitioners so anti-establishment that they would decry those of us who mask as shameful? Our practices already extend beyond standard of care. Let's not position ourselves against common sense public health policy.

Ivermectin in the Prophylaxis and Treatment of COVID-19

Dr. Pierre Kory, MD, of the Frontline COVID-19 Critical Care Alliance together with nine other US and international physicians have reviewed the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19.[1] Multiple studies completed here and abroad have affirmed ivermectin's role in prevention as well as treatment of mild, moderate, and severe disease. A particularly striking study carried out last year in Peru revealed that widespread distribution of ivermectin in multiple locales dramatically reduced incidence, hospitalization, and death rate compared to within Lima where ivermectin was not distributed. While all drugs pose risk of adverse effects, ivermectin's risk profile is relatively low. The current conventional medical approach to early infection in the US is essentially no treatment except for usual supportive care for viral infection. The FLCCC Alliance protocol for prophylaxis and early disease includes the use of vitamin D3, vitamin C, zinc, melatonin, and quercetin. The addition of ivermectin to use on Day 1, Day 3, and then one dose every two weeks would provide a strong shield against developing severe symptomatic disease. Of course, this protocol does not have the consent of the CDC and is not considered standard of care. Nevertheless, it would seem much more prudent to initiate such a protocol rather than waiting for severe disease symptoms to manifest.

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Letter from the Publisher

➤ *continued from page 4*

A recently published randomized study in Colombia on the effect of ivermectin on mild COVID-19 published in *JAMA*, however, failed to demonstrate a significant benefit of ivermectin compared to placebo.[2] There was a non-significant reduction in time of return to asymptomatic status using ivermectin compared to placebo of two days. The authors note that the study population were generally younger individuals with few co-morbidities. This led to a relatively low rate of symptomatic deterioration of 3% in both treatment and placebo groups. Would the outcome have been different if older individuals with co-morbidities were studied instead?

Not the Season of the Flu

In my locale there have been zero deaths attributed to the flu this winter. Flu case numbers are down across the US. So, what happened to the flu? Assuredly the flu virus did not disappear. While some speculate that flu vaccinations really worked this season, it would be unreasonable to assume that the flu vaccine was more effective this year than the past.

Of course, COVID-19 case numbers exploded over the winter. For those who had mild to moderate symptomatic COVID-19, the illness resembled the seasonal flu. The one exception being that in some cases people temporarily lost their sense of smell, not a typical flu symptom.

So, how to explain the absence of the flu? Does the SARS-CoV-2 virus competitively inhibit an infection by the flu virus – does the COVID-19 virus prevent flu virus entry into our cells? After experiencing COVID-19 has one's immunity against flu virus been maximized to fend off flu infection?

Nobody has a good answer as to why the flu numbers are down – but its absence gives us something to cheer about in this season of misery.

Dr. McDaniel Has Something to Add to Your Knowledge About Hypothyroidism

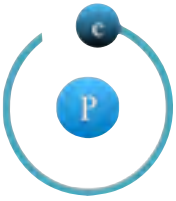
Like many other doctors practicing integrative and functional medicine, Dr. Alan McDaniel trained and practiced conventional medicine and surgery for much of his career. A graduate of Tulane, he trained in general surgery and emergency medicine before becoming board-certified in otolaryngology. He has sub-specialties in neurology and allergy. McDaniel has lectured at many professional societies, including the American Academy of Environmental Medicine where he has presented his two-day course on the "New Endocrinology." He authored the December 2016 cover story of the *Townsend Letter*: "The Clinical Importance of 5-Alpha-Reductase in Human Health and Pathology."[3]

continued on page 8 ➤

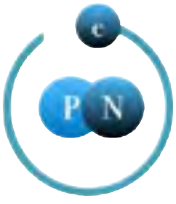
Deuterium in Water

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?

- *First* and foremost, regular consumption of deuterium depleted water (DDW). This healthy habit gradually flushes deuterium from your body.

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Letter from the Publisher

➤ *continued from page 6*

Here are four pearls Dr. McDaniel would like to offer for those treating hypothyroidism. First, thyroid prescriptions should be divided into two doses separated by 12 hours. Second, when measuring thyroid blood levels, the ideal time to draw blood is mid-way between the time of the am and pm dose of hormone treatment. Third, the best determination of how well the thyroid is functioning is not determined by TSH, free T4, or free T3. Instead, Dr. McDaniel asks us to measure the total T3 to "reverse" T3 ratio; if the ratio is low, the patient's thyroid treatment is inadequate. Fourth, in contrast to standard endocrinologist thinking, many individuals will require T3 hormone treatment in addition to T4 hormone to achieve best outcomes.

While most of us are already on board with using both T3 and T4 combination therapy, dividing thyroid treatment to every 12 hours and using total T3/reverse T3 ratio to guide our treatment are novel approaches to thyroid care. Dr. McDaniel's work is extensive and will be divided into three parts – read part 1 in this issue.

Cover: Dr. Marianne Marchese Considers Whether Chemicals are Making Us Fat

Townsend Letter readers are familiar with Dr. Marianne Marchese's column, "Environmental Medicine Update." Dr. Marchese graduated from Creighton University in 1990, training as an occupational therapist; she treated neurological and orthopedic patients for over 12 years. In 2002 she graduated from the National University of Naturopathic Medicine, acquiring her ND degree and then completed a two-year residency in integrative medicine. She is the author of the book, *8 Weeks to Women's Wellness.* Marchese has been named as a Top Doctor by *Phoenix Magazine* for four years.

In this issue Marianne makes the argument that environmental chemicals contribute significantly to obesity. Marchese labels the chemicals "obesogenic toxicants." The chief chemicals implicated in making us fat are bisphenol A (BPA), phthalates, polybrominated diphenyl ethers (PBDEs), polyfluoroalkyl chemicals (PFCs), organochlorine (OC) pesticides, and polychlorinated biphenyls (PCBs). The toxicants alter our glucose and lipid metabolism, modify our thyroid and sex hormones, interfere with the signaling proteins controlling leptins and related neuropeptides, and disrupt adipocyte cell metabolism.

Also, in this issue, Dr. Michelle Perro, MD, who writes the "Pediatric Pearls" column, tackles this same topic in kids; she also contends that chemicals are to blame for much of the obesity in children. Perro's list of endocrine-disrupting chemicals (EDCs) is extensive and deserves study. Both Marchese and Perro provide case studies for treatment of obesity.

When we treat obesity and metabolic syndrome, we need to move beyond calories and activity and begin to examine the patient's consumption of toxicants and endocrine-disrupting chemicals.

Jonathan Collin, MD

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3. McDaniel A., The Clinical Importance of 5-Alpha-Reductase in Human Health and Pathology. Townsend Letter. Dec. 2016: **401**, 53-61.
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No Deaths from Vitamins – Supplement Safety Yet Again Confirmed by America's Largest Database

by Andrew W. Saul, Editor, Orthomolecular Medicine News Service

The 37th annual report from the American Association of Poison Control Centers shows **zero deaths from any vitamin**. Supporting data is in Table 22B, p 1508-1518, at the very end of the report published in *Clinical Toxicology*.[1] It is interesting that it is so quietly placed way back there where nary a news reporter is likely to see it.

- Furthermore, there were no fatalities from amino acids, creatine, blue-green algae, glucosamine, or chondroitin.
- There were **no deaths from any homeopathic remedy**, Asian medicine, Hispanic medicine, or Ayurvedic medicine. None.
- There were **no deaths from herbs**. This means no deaths at all from blue cohosh, echinacea, *Ginkgo biloba*, *Citrus aurantium*, ginseng, kava kava, St. John's wort, valerian, yohimbe, ma huang/ephedra, guarana, kola nut, or yerba mate.

On page 1508, a single death is attributed to an unspecified "Other Single Ingredient Botanical." The obvious uncertainly of such a listing diminishes any claim of validity.

On the same page, a single fatality is attributed to an "Energy Product." The *Orthomolecular Medicine News Service* considers these items to be over-the-counter drugs. They are improperly classified as dietary supplements.

Throughout the entire year, coast to coast across the entire USA, there was not one single death from a vitamin. If vitamin supplements are allegedly so "dangerous," as the FDA, the news media, and even some physicians still claim, then ***where are the bodies***?

Andrew W. Saul is Editor-in-Chief of the Orthomolecular Medicine News Service, now in its 17th year of free publication. He is also a member of the Japanese College of Intravenous Therapy, the Orthomolecular Medicine Hall of Fame, and is author or coauthor of twelve books. He has no financial connection whatsoever to the supplement or health products industry.

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Shorts

briefed by Jule Klotter
jule@townsendletter.com

Arsenic and Type 2 Diabetes

Numerous epidemiological studies have linked inorganic arsenic (iAs) exposure from drinking water and some foods to type 2 diabetes. *In vivo* and *in vitro* studies, according to a commentary by Lindsey Konkel, indicate that arsenic can impair insulin secretion and signaling, contribute to glucose intolerance, and affect at least 16 genes involved with insulin resistance and type 2 diabetes.

Inorganic arsenic is found in Earth's crust. Some areas, such as Taiwan, Mexico, and Bangladesh, have very high levels (≥50 µg/L) in the groundwater. Grains, particularly rice, have increased uptake of arsenic from soil, making these foods another source of contamination. Arsenic is also used in cosmetics, wood preservatives, cotton desiccants, pesticides, and even some medical treatments.

"The toxicity of arsenic is influenced by its metabolism," write Maria Grau-Perez and colleagues. Inorganic arsenic can be metabolized into mono- and di-methylated arsenic compounds (MMA and DMA), depending upon genetic factors (e.g., *AS3MT* variants) and the availability of one-carbon metabolism nutrients, such as folate, choline, methionine, and vitamins B2, B6, and B12. Supplementation of these nutrients increases methylation, decreasing iAs% and increasing DMA% in urine. Less methylation is indicated by urine with higher MMA% and lower DMA%. Regardless of methylation, arsenic toxicity produces illness. Low methylation (higher MMA% and lower DMA%) increases the risks of illnesses that include cardiovascular disease, skin lesions and cancers, and bladder cancer. Higher methylation (lower MMA% and higher DMA%) is related to type 2 diabetes.

As part of the Strong Heart Family Study, Grau-Perez et al used the sum of inorganic arsenic, MMA, and DMA urine concentration as well as homeostasis model assessment for insulin resistance (HOMA2-IR) at baseline and follow-up to investigate the relationship between arsenic metabolism and type 2 diabetes. The Strong Heart Family Study is a prospective family-based cohort study designed to identify genetic and environmental factors for cardiovascular disease and risk factors in American Indians. The participants come from communities in Arizona, Oklahoma, North Dakota, and South Dakota. Arsenic levels in the participants' drinking water was below 50 µg/L (considered low-moderate exposure). In their conclusion, the authors write: "Among participants without baseline prediabetes, arsenic exposure was associated with incident diabetes. Low MMA% was cross-sectional and prospectively associated with higher HOMA2-IR. Research is need to confirm possible interactions of arsenic metabolism with B vitamins and *AS3MTi* variants on diabetes risk."

Arsenic exposure produces intracellular reactive oxygen species (ROS) that cause oxidative damage, alter signaling pathways, and affect gene expression. Yuxin Hu and colleagues, authors of a 2020 Chinese literature review, discuss the affected pathways – as known at this point – and the use of various antioxidants that might mitigate the damage. Animal studies indicate that a number of ROS scavengers may lessen arsenic toxicity, including grape seed proanthocyanidin extract, EGCG, flaxseed oil, pomegranate fruit extract (PFE), sulforaphane, vitamins C and E, lutein, and glutathione. "Natural antioxidants extracted from plants are more promising due to their rich sources, diversity, and few side effects," the authors write, "however, many studies on the role of plant extracts have not been systematically conducted." Oxidative enzyme inhibitors (grape seed extract and metformin) may also be helpful in combatting arsenic damage. Zinc and selenium, which are antioxidant enzyme cofactors, are also useful.

In addition to its enzyme functions, selenium sequesters arsenic (and cadmium) into biologically inert complexes, according to Iwona Zwolak. But too much selenium can lead to loss of hair and nails, skin disorders, poor dental health, and neurological problems. Zwolak says that the use of selenium in combination with plant-derived antioxidants have "enhanced protective activity": "For example, a combination of selenite with *Punica granatum* fruit extracts was more effective against As-induced hepatotoxicity in rats than selenite alone."

Nutrients clearly affect how a body responds to arsenic exposure; but is it enough to prevent diabetes? Perhaps, the first step, as Yuxin Hu et al advise, would be to reduce the

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amount of arsenic in the body by avoiding sources, whenever possible, and by safe chelation with DMPS and/or DMSA.

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Hydrogen Therapy

"Will the hydrogen therapy be approved shortly?" asks Shigeo Ohta, Department of Neurology Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan, in his 2020 editorial. The therapeutic benefits of hydrogen (H_2) – administered as a gas, in saline solution by intravenous or intraperitoneal injection, or consumed in water – came to the fore in 2007 with the publication of an article by I. Ohsawa and colleagues [*Nat Med.* 2007;13:688-94]; Ohta was senior author. The article reported that H_2 "acted as a preventive and therapeutic antioxidant through reducing highly reactive oxidants such as hydroxyl radical (.OH) and peroxynitrite (ONOO-) in cultured cells, and moreover that H_2 exhibited cytoprotective effects against strong oxidative stress in a model animal." Since 2007, researchers have learned that H_2 stimulates energy metabolism and has anti-inflammatory, anti-allergic, and anti-apoptotic effects. It also affects regulation of autophagy. H_2 readily crosses cell membranes and the blood-brain barrier, so it can protect all cells from cytotoxic reactive oxygen species.

Ohta's editorial focuses on a 2019 study by O. Malý et al [*Ann Transl Med.* 2019;7:774]. Malý et al showed that inhaling hydrogen gas prevented ischemia-reperfusion liver damage in 13 domestic pigs that underwent major liver resection. When blood supply to an organ is restricted (ischemia) and the blood supply and oxygen return (reperfusion), serious damage can occur due to oxidative stress. Ischemia-reperfusion damage is an issue in cardiac or cerebral infarction and cardiac arrest as well as liver resection and other surgeries. Ohta says that "[i]nhalation of H_2 gas of the range between 1-4% exhibits excellent efficacy and there is no risk of fire or explosion when the H_2 concentration is less than 4%." H_2 also has no cytotoxicity.

Hydrogen therapy may also be beneficial for people with metabolic syndrome. In a 24-week international study, hydrogen-rich water reportedly "significantly reduced blood cholesterol and glucose levels, attenuated serum hemoglobin A1c, and improved biomarkers of inflammation and redox homeostasis as compared to placebo." The randomized, double-blinded, placebo-controlled trial enrolled 30 men and 30 women of Indian ethnicity with metabolic syndrome who consumed one hydrogen-producing tablet (HRW Natural Health Products Inc., New Westminster BC, Canada), three times a day, in 250 mL of lukewarm water (12-18°C; 54-64°F). The participants were instructed to drink the water on an empty stomach as soon as the tablet dissolved. The authors note that their study leaves several unanswered questions: Is there a gender or age response difference? Does the effect differ if the tablet is taken with food? (Intestinal bacteria produce H_2 gas when digesting fiber.) How does drinking hydrogen-water compare to inhalation of H_2 gas? What are the effects of different doses and durations?

The Molecular Hydrogen Institute (https://www.molecularhydrogeninstitute.com/) promotes research and education about hydrogen's use in medicine. According to the group's website, about 40 human studies have been published so far; a few are double-blind, placebo-controlled trials. The literature suggests that drinking hydrogen-rich water may be beneficial for people with metabolic syndrome, diabetes, and hyperlipidemia – as well as other conditions, including Parkinson's disease, rheumatoid arthritis, and mitochondrial dysfunction. The website states: "…hydrogen gas, at orders of magnitude greater than what is needed for therapeutic use, is well-tolerated by the body with no chronic toxic effects. In some people, however, it is reported that hydrogen may result in loose stools, and in rare cases with diabetics, hypoglycemia, which is controlled by reducing the level of insulin administered."

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Glyphosate and GI Microbiota

A new rat study shows that glyphosate-based herbicides (GBHs) disrupt the gastrointestinal microbiota. Before the recent civil court cases filed by cancer patients, glyphosate was long publicized as being safe for humans because it kills plants by inhibiting the shikimate pathway – which is only found in plants and bacteria. When it was approved about 50 years ago, the vital health effects of commensal bacteria in the GI tract were largely unrecognized. Unfortunately, it is the beneficial commensal bacteria, not the pathogenic bacteria, that are

more likely to have glyphosate-sensitive enzymes – "thereby promoting dysbiosis," according to Jacqueline A. Barnett and Deanna L. Gibson.

A 2021 placebo-controlled rat study, led by Jianzhong Hu, showed that glyphosate and a glyphosate-based herbicide (Roundup) changed the composition of the gut microbiome and associated metabolites. The researchers gave female rats low doses of glyphosate (n=5) or Roundup (n=4) in their drinking water while the remainder acted as controls (n=5). Thirty offspring were exposed as embryos, during lactation, and then via drinking water for 90 days after weaning. The researchers measured urine metabolites and the composition of the gut microbiome using fecal samples. They found that male pups showed a significant increase in homocysteine, a risk factor for cardiovascular disease, that correlated to a decrease in *Prevotella*. Exposed female pups showed a similar trend that was not statistically significant. The authors say, "…it is plausible that the increased urine homocysteine we observed in male pups exposed to low-dosage GBHs [glyphosate-based herbicides] results from reduced production of folic acid by *Prevotella* bacteria, paralleling the increase in homocysteine in dietary vitamin deficiencies [i.e., vitamin B12, B6, and folic acid]." As shown in other research, the glyphosate-based herbicide was more toxic than glyphosate alone. In addition to homocysteine, methionine and N-methylglutamate (both involved in one carbon metabolism) were also affected.

Barnett and Gibson point out that Canada and the United States are among the top users of glyphosate-based herbicides – "with over 25 million kilograms purchased annually in Canada (Health Canada, 2012) and over 36 million kilograms applied annually in the United States (Benbrook, 2016)." While some of this use is due to genetically engineered seed, like Roundup soy that can withstand assaults from glyphosate-based herbicides, another factor is desiccation, in which the chemicals are applied shortly before harvest to promote harvest efficiency. The US and Canada permit glyphosate's use to desiccate wheat, other grains, and legume crops.

The Canadian non-profit group, Safe Food Matters, is challenging the use of glyphosate products for desiccation. The group's appeal to a federal court's 2020 dismissal of their lawsuit concerning safety issues is expected to be heard in 2021.

Barnett JA, Gibson DL. Separating the Empirical Wheat From the Pseudoscientific Chaff: A Critical Review of the Literature Surrounding Glyphosate, Dysbiosis and Wheat-Sensitivity. *Frontiers in Microbiology.* September 2020.
Jianzhong Hu, et al. Low-dose exposure of glyphosate-based herbicides disrupt the urine metabolome and its interaction with gut microbiota. *Scientific Reports.* 2021;11:3265.
Safe Food Matters. Backgrounder to Appeal. November 23, 2020.

HeartMath Training in Healthcare

A small survey study by Teresa M. Buchanan, MBA, RN, and Patricia M. Reilly, MSN, RN, assessed the effect of HeartMath resiliency classes, which were offered to all employees at an academic medical center. The eight-hour class informed participants about the physiology of coherent and incoherent states and about heart-focused techniques – such as intentional, heart-centered breathing and recognition and reflection of positive emotions – when experiencing stress. Those who volunteered to be part of the study completed the Personal and Organizational Quality Assessment-Revised 4 Scale (2016) before training and four-to-six weeks after training.

Twenty-six matched survey "pairs" showed significant decreases in physical stress, fatigue, and health symptoms. Moreover, participants reported improvements in sleep, hemoglobin A1c levels, and blood pressure in themselves or in family members to whom they taught the techniques. Several nurses also shared stories about using the HeartMath Quick Coherence Technique to relieve anxiety, pain, or sleeplessness in patients. Buchanan and Reilly say, "The technique is ideal for this purpose as it is simple to teach. It simply requires that the person focus his/her attention to his/her heart while imagining that he/she is taking deep, slow breaths through his/her heart. While doing this 'heart-focused' breathing, the person is directed to reexperience a positive emotion such as love, caring, or appreciation."

A May 2013 *Townsend Letter* interview with HeartMath Director of Research, Rollin McCraty, PhD, and Global Director of HeartMath Healthcare, Bruce Cryer, focused on the effects of HeartMath techniques on hypertension and metabolic syndrome. Bruce Cryer said, "When we saw the amount of improvement in diastolic and systolic blood pressures, we had one of our researchers do a meta-analysis of other interventions…. It was discovered that the HeartMath results were equivalent to a 40-pound weight loss. They were equivalent to about twice the impact of an exercise program and twice the impact of a sodium-restricted diet."

While the small 2019 study has limitations, it offers another non-pharmacological tool for healthcare staff to reduce stress in themselves and their patients – and possibly improve health.

Buchanan Tm, Reilly PM. The Impact of HeartMath Resilience Training on Health Care Providers. *Dimensions of Critical Care Nursing.* 2019;38(6).
Faass N. HeartMath and Hypertension: A dialogue with Rollin McCraty, MD, and Bruce Cryer, PhD. *Townsend Letter.* May 2013;46-51.

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ON THE COVER: Marianne Marchese, ND – Plastics, Pesticides, and Obesity (pg. 26); Diabetes and Environmental Chemicals (pgs. 9, 26, 30, 40); Metabolic Syndrome and Lifestyle (pg. 40); Looking Beyond TSH Levels to Diagnose Hypothyroidism (pg. 44); Stress Reduction and Cardiovascular Disease (pgs. 9, 38)

If We Lose Compounded Bioidentical Hormone Replacement Therapy

As we look over the tools available to us, are there any more important than compounded bioidentical hormones? Imagine the day you would have to tell your patients that you can no longer prescribe these hormones to them. Imagine the impact on their lives, relationships, on careers, and to the health of our population as a whole. Devastating. And, NASEM[1] and the FDA threaten access to compounded bioidentical hormones for women, men, and health care professionals.

As so many of you know, back in the early 1980s, an American medical doctor searched for hormone alternatives to the few, widely utilized, FDA-approved, pharmaceutically manufactured hormone treatments of the time.[2] This physician pioneered the use of topical and bioidentical Bi-est, comprised of estriol and estradiol, a compounded hormone that is widely prescribed by health care practitioners to this day – and is available, along with many other formulations, only through compounding pharmacies.

Women and men vary enormously, individual to individual, as to their needs, sensitivities, balances, absorption, preferences, and so much more. Without our compounding brethren and sistren, there would simply be no way to personalize treatment programs for each patient. This customization is at the very core of sound hormone replenishment medicine!

As most of you know, hormone treatment of women radically changed when the Women's Health Initiative[3] (WHI) study was published in 2002. The WHI *incorrectly*[4] concluded that women in menopause who were treated with Prempro were subject to an increased risk for breast cancer, heart attack, and stroke. Even though the study, itself, did not back up this assertion of increased risk,[4] this report triggered an explosion of fear amongst women patients and prescribing health care professionals.

This fear generated by the WHI resulted in a precipitous decline in the number of women who were being treated with hormone replacement therapy (HRT). Prior to the WHI, 18 million American women – 40% of all those who were in menopause – were receiving HRT, and almost all of that being from Premarin and Prempro. After the WHI, women being treated declined to a fraction of this number.[5] The subsequent health consequences to women worldwide were monumental and egregious.

The loss of profits and market share to pharmaceutical manufacturers was also colossal. Before the WHI study, Premarin and its derivatives had been one of the most popular and profitable manufactured drugs of all time.

As an unintended consequence, however, the WHI study also inspired many women and physicians all across America and the world to seek safer and more effective alternatives; and they turned towards the use of compounded bioidentical hormones.

Of great note, that has gone almost entirely unnoticed: in 2017, the original WHI study group retracted its original assertion about a hormone-cancer link. They published, again in *JAMA*,[6] that "among postmenopausal women, hormone therapy with CEE (conjugated equine estrogens) plus MPA (medroxyprogesterone acetate: Prempro) was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years." Even though risk information has finally been corrected and thoroughly addressed (see reference[7]), the perception persists, both by the public and by healthcare professionals, that there is risk to women who are taking hormones.

Also of note: by 2016, approximately 5 million American menopausal women were using replacement hormones. Big difference: now, over half of these women are being treated with compounded bioidentical hormone replenishment therapies (cBHRT).[8,9]

Backing up in time, in 2008, the FDA launched its first concerted effort to restrict or even remove bioidentical hormones from the market. Overwhelming opposition from a public response – over 77,000 letters sent to the FDA and Congress, primarily by American women, during the public comment period – convinced Congress and the agency to temporarily suspend its ongoing quest to restrict women's health care choices.

As many of you know, fast forward, the FDA tasked NASEM with determining the safety and efficacy of compounded bioidentical hormones. The results of which are that NASEM has passed its findings[10] onto the FDA and the FDA has reported on them,[11] including suggesting that cBHRT could be classified on the "too difficult to compound" list.

This would be a catastrophe that would mean the end of hormone medicine as we know it and millions of women and men depend upon.

The Committee's "recommendations"[12] could have serious and disastrous consequences. Here are the most challenging issues that have emerged from this report:

The NASEM Report concluded that the FDA should:

1. *"Restrict the use of compounded bioidentical hormone therapy preparations.* Prescribers should restrict the use of bioidentical hormone preparations to the following situations:
   - documented allergy to an active pharmaceutical ingredient or excipient of an FDA-approved drug product, or a documented requirement for a different dosage form … "

This regulation directly has the FDA determining how a healthcare professional should practice medicine. This overreach goes beyond the mandate and authority of the FDA, and like violations have been successfully challenged in the past.

- "*Patient preference alone should not determine the use of bioidentical preparations."*

This overreaches into the freedom of women and men patients to freely and privately choose their healthcare providers, according to the modes of therapies and expertise offered.

2. *"Review select bioidentical hormone therapies and dosage forms as candidates for the US FDA Difficult to Compound List, [including]: estradiol, estrone, estradiol cypionate, estriol, pregnenolone, dehydroepiandrosterone (DHEA) progesterone, testosterone, testosterone cypionate, and testosterone propionate…"*

This recommendation is potentially devastating to providers and patients. No drug can be compounded, if it is on the *"Too Difficult to Compound List."*[13] If these bioidentical products are put on this list, that would be the immediate end of all bioidentical hormone therapy.

This regulation would destroy the present ability of physicians and patients even to access bioidentical hormone treatments, at all. Such undue limitation will impact millions of patients (both women and men) who are living fulfilling, productive lives, thanks to these currently legal bioidentical hormone treatments.

There are other alarming recommendations in the NASEM report:

3. *"A state-level certification program for providers seeking to start or continue to prescribe bioidentical hormones."*

Professional societies (which are often supported by money from the pharmaceutical industry) will promote "best practices" guidelines, stating when a provider should consider using a bioidentical hormone in lieu of an FDA-approved drug – essentially telling doctors when, how, and which formulations they could even think about using.

4. *"Additional federal and state-level oversight."*

This expansive recommendation includes new mandates, inspections, paperwork, reporting requirements, and other onerous restrictions on compounding pharmacies.

The Response

The robust response of cBHRT professionals and the public to these challenges has been inspiring. Coming forward are millions of American women, and many men, that are being treated with compounded bioidentical hormones. Along with them are thousands of physicians, nurse practitioners, and physician's assistants that are treating these women, as well as thousands of compounding pharmacies that are dispensing these hormones.

Memorandum to the FDA report. An immediate response to the FDA report came from Rachel Pontikes, an attorney with Reed-Smith, a prominent international law firm. Supported by several compounding pharmacies, she issued a profound legal memorandum to the FDA that has been published in the FDA docket.[14] (https://www.regulations.gov/comment/FDA-2015-N-0030-8335) It contains many points of contention:

- The FDA is overstepping its mandate and is interfering with the rights of women to choose which methods of treatment they want for their health care.
- The FDA is also exceeding its legal authority and is overreaching by dictating to medical professionals how to practice medicine. Again, the FDA has been successfully challenged on this issue, in the past.

In a recent follow-up Supplemental Report[15] to the FDA, Ms. Pontikes also pointed out the lack of credentialed legitimate authority of the members of the NASEM Committee, the interference of the FDA into the proceedings of the Committee, as well as the commercial conflicts of interest present in some of its members (https://a4pc.org/Common/Uploaded%20files/Advocacy/2021-03_cBHT-Supplemental-Comment-and-Exhibits.pdf).

APC: The Alliance for Pharmacy Compounding has mounted a phenomenal and multifaceted response. We recommend that you visit their website and participate in their calls to action (https://www.a4pc.org). Their commitment is prodigious and determined.

Coalition to Protect Compounded Bioidentical Hormone Replenishment Treatment (www.cbhrtcoalition.com). This is a coalition of numerous professionals and laypeople to address this coming threat to our health freedom. Members include physicians, nurse practitioners, attorneys, lobbyists, pharmacists, scientists, the strong presence of the APC, the Alliance for Natural Health (ANH), and excellent representation of women (www.WeTheWomen.com).

ANH – The Alliance for Natural Health (https://anh-usa.org) Always a major player in the protection of our healthcare rights.

We the Women (www.WeTheWomen.us). One of many organizations devoted to protecting the healthcare rights of women and deeply committed and involved in this bioidentical hormone challenge.

We invite all of you to join us (go to cbhrtcoalition.org). We are a central focus of much-needed synergy, energy, expertise, creativity, and co-ordination! Please send us your email and/or other contact information, so we can inform you about upcoming events, strategies, conference calls, campaigns, etc. and – also crucial – to be deployed at the best-coordinated timing. There are specific actions you can take to protect our personal and professional health care rights and freedoms. Join us.

Daved Rosensweet, MD

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11. https://www.fda.gov/drugs/human-drug-compounding/national-academies-science-engineering-and-medicine-nasem-study-clinical-utility-treating-patients
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13. See 21 US Code 353a(b)(3) and 353b for verification.
14. Reed, Smith: Rachel Pontikes https://www.regulations.gov/comment/FDA-2015-N-0030-8335
15. Supplemental Report from Reed, Smith: Rachel Pontikes. https://a4pc.org/Common/Uploaded%20files/Advocacy/2021-03_cBHT-Supplemental-Comment-and-Exhibits.pdf

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Literature Review & Commentary

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

Fish Oil and Heart Disease

Patients (n = 13,078; mean age, 62.5 years) from 22 countries who were at high risk for cardiovascular disease were randomly assigned to receive, in double-blind fashion, 4 g per day of EPANOVA (AstraZeneca) or placebo (corn oil). Each EPANOVA capsule contains 1 g of fish oil-derived free fatty acids, with at least 850 mg of polyunsaturated fatty acids (mostly eicosapentaenoic acid and docosahexaenoic acid). To be included in the study, the patients had to be receiving a statin drug, have a triglyceride level of 180-500 mg/dl, and have a low HDL-cholesterol level (<42 mg/dl for men, <47 mg/dl for women).

The trial was halted early, after a median duration of 3.5 years, because an interim analysis concluded there was a low probability the treatment would demonstrate a clinical benefit. The primary endpoint (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization) occurred in 12.0% of patients treated with omega-3 fatty acids and 12.2% of those given corn oil (p = 0.84). The mean triglyceride level in the fish oil group decreased from 239 mg/dl at baseline to 191 mg/dl after 12 months (19% decrease; p < 0.001 compared with the change in the placebo group). The authors concluded that these findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in high-risk patients.

Comment: Many studies have investigated the effects of fish oil or the omega-3 fatty acids present in fish oil for the primary or secondary prevention of cardiovascular disease. Many studies have shown benefit, but many others (including the present study) did not. One possible reason for the negative results in the present study is that all of the patients were taking a statin drug and 71% were also taking a platelet inhibitor. These drugs mimic some of the effects of fish oil. Like statin drugs, fish oil has an anti-inflammatory effect and, like platelet inhibiting drugs, fish oil inhibits platelet aggregation. Therefore, the use of these drugs may have "stolen fish oil's thunder" (in a manner of speaking) and left little room for further improvement from omega-3 fatty acids.

Nicholls SJ, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. 2020;324:2268-2280.

Iron Deficiency and Heart Failure

One thousand one hundred ten patients (mean age 71 years) in Europe, South America, and Singapore, who were stabilized after being hospitalized for acute heart failure and who had iron deficiency, were randomly assigned to receive, in double-blind fashion, intravenous iron (ferric carboxymaltose) or placebo for up to 24 weeks, dosed according to the extent of iron deficiency. The patients were followed up for a total of 52 weeks. During the follow-up period, the proportion of patients who had to be readmitted to the hospital for heart failure was 24% lower in the iron group than in the placebo group (p = 0.013). The mortality rate did not differ between groups.

Comment: Iron deficiency is a common and often overlooked factor in patients with heart failure. Iron is a component of hemoglobin, which delivers oxygen to the tissues. In addition, iron is a cofactor for the enzyme cytochrome oxidase, which plays a role in mitochondrial ATP production via the electron-transport chain. ATP is essential for the pumping action of the heart; therefore, iron deficiency could exacerbate heart failure whether or not the patient is anemic. In previous studies, correction of iron deficiency improved functional status and decreased the frequency of hospitalizations in patients with heart failure. The present large-scale multicenter clinical trial confirmed the importance of identifying and treating iron deficiency in heart failure patients. As I have noted previously in the *Townsend Letter*, despite the growing body of evidence

continued on page 20 ➤

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Rebecca Harder is the author of "Gastra Girl: Saving America One Colon at a Time," and owner of an immaculate and highly esteemed clinic in Portland, OR. She offers this well-researched comprehensive resource guide of holistic health information on topics such as environmental toxicity, vaccines, EMF, autism, hyperbaric oxygen, ozone therapy, colon hydrotherapy, far infrared saunas and much more.

Rebecca had come across the Relax Sauna at professional conferences many times before she decided to finally try it. She had been committed to wooden infrared saunas for 10 years at her respected clinic. Immediately after trying the Relax Sauna, she experienced instant dramatic positive healing results. She was so impressed with it that she dedicates an entire 8 pages to the Relax Sauna in the chapter "Why infrared Sauna is an absolute necessity for Everyone." She enthusiastically recommends the Relax Sauna to her clients and lets them know that it is the best way to rid the body of toxins and feel good.

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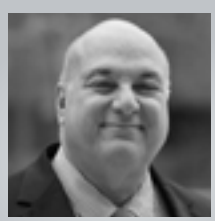

GEORGE L. BAKRIS, MD

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CHRISTIE M. BALLANTYNE, MD

Gaby's Literature Review

➤ *continued from page 16*

regarding iron and heart failure, most patients hospitalized for heart failure are still not being properly assessed or treated for iron deficiency.[1] Hopefully, the publication of this large-scale study in a major medical journal will help correct this epidemic of substandard medical care.

Ponikowski P, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;396:1895-1904.

Blueberries Improve Metabolic Parameters

Fifty-two male US veterans (mean age, 67 years; mean body mass index, 34 kg/m^2) with type 2 diabetes were randomly assigned to consume, in double-blind fashion, 11 g of freeze-dried blueberries or placebo twice a day (morning and evening with meals) for eight weeks. The total daily dose of freeze-dried blueberries was equivalent to 1 cup of blueberries. The placebo was matched with blueberries for energy and carbohydrate content. At the end of the treatment period, mean concentrations of hemoglobin A1c (7.1% vs. 7.5%; p = 0.03), fructosamine (276 vs. 292 µmol/L; p = 0.04), triglycerides (180 vs. 200 mg/dl; p = 0.03), aspartate aminotransferase (23 vs. 31 units/L; p = 0.02), and alanine aminotransferase (36 vs. 48 units/L; p = 0.0003) were significantly lower in the blueberry group than in the placebo group.

Comment: In this study, consumption of 22 g per day of freeze-dried blueberries improved glycemic control and certain measures of cardiovascular risk and liver function in men with type 2 diabetes. Certain compounds present in blueberries may also improve visual function, capillary integrity, and cognitive function. Blueberries are an excellent choice to include as part of a healthful diet. Blueberries are among the list of fruits and vegetables (along with apples, strawberries, grapes, and others) that may contain significant concentrations of pesticide residues, so it is preferable to consume organic blueberries.

Stote KS, et al. Effect of blueberry consumption on cardiometabolic health parameters in men with type 2 diabetes: an 8-week, double-blind, randomized, placebo-controlled trial. *Curr Dev Nutr*. 2020;4:nzaa030.

Eggs, Trimethylamine Oxide, and Cardiovascular Disease

Twenty overweight or obese postmenopausal women (aged 48-70 years) consumed an egg-free diet for two weeks and were then randomly assigned to consume two whole eggs per day at breakfast or the equivalent amount of yolk-free eggs for four weeks. After a four-week washout period with no egg consumption, each woman consumed the alternate diet for an additional four weeks. Morning blood samples were obtained after an overnight fast at the beginning and end of each intervention period. Compared with baseline, consumption of whole eggs significantly increased mean plasma choline and betaine concentrations, whereas consumption of yolk-free eggs had no significant effect on these levels. Neither diet had a significant effect on plasma trimethylamine N-oxide (TMAO) levels.

Comment: Dietary choline and betaine can be converted by intestinal bacteria to trimethylamine, which is then converted to TMAO in the liver. There is some evidence that TMAO is atherogenic, although other research suggests that TMAO is only a marker, rather than a cause, of increased cardiovascular disease risk. Because egg yolks contain relatively large amounts of choline, it has been hypothesized that eating eggs could increase TMAO levels. In the present study, consumption of 2 eggs per day increased plasma concentrations of choline and betaine (choline is converted in part to betaine), but it did not increase TMAO levels. In most observational studies, egg consumption was not associated with an increased risk of developing cardiovascular disease in non-diabetics, although it was associated with increased risk in diabetics. If eating eggs does increase heart disease risk to some extent, the mechanism is more likely related to the formation of atherogenic cholesterol oxides during cooking than to any effect on TMAO levels. Cholesterol oxides are less likely to form when the yolk remains intact during cooking (as in boiling or poaching of eggs).

Zhu C, et al. Whole egg consumption increases plasma choline and betaine without affecting TMAO levels or gut microbiome in overweight postmenopausal women. *Nutr Res*. 2020;78:36-41.

N-Acetylcysteine for Ulcerative Colitis, or More Iranian Research Fraud?

One hundred sixty-eight Iranian patients with severe acute ulcerative colitis, who had gone into remission after treatment with prednisolone (1 mg per kg of body weight per day) and oral mesalamine (4 g per day) for four weeks, were randomly assigned to receive, in double-blind fashion, 400 mg of N-acetylcysteine (NAC) twice a day or placebo for 16 weeks, and were then followed for an additional six weeks. At the start of NAC or placebo treatment, prednisolone was gradually tapered and discontinued. During 22 weeks of follow-up, 25 patients experienced a relapse: six in the NAC group and 19 in the placebo group. The relapse-free period was significantly longer (p = 0.007), and the proportion of patients who had an endoscopic relapse was significantly lower (p < 0.001) in the NAC group than in the placebo group.

Comment: As readers of the *Townsend Letter* know, I have been concerned that a large proportion of the nutrition research coming from Iran appears to be fraudulent. My reading of the present paper identified so many holes in it that (as the Beatles might have said) it could fill the Albert Hall.

1. Issue related to the submission date: According to the Iranian Registry of Clinical Trials document, patients were recruited from July 23, 2019, through April 20, 2020. The study included four weeks of high-dose prednisolone, followed by 16 weeks of NAC or placebo, followed by six weeks of observation. Thus, the earliest date the study could have been completed would have been October 19, 2020. Presumably, it would take at least several months for the data to be analyzed, the paper to be written, and the journal to accept and publish the paper. However, the paper appeared in print on October 14, 2020, even before it was possible to have completed the study.
2. The number of study subjects seems implausibly large: Patients were ineligible if they did not have pancolitis (which excludes about 80% of ulcerative colitis patients) or if they had been treated in the past six months with a tumor necrosis factor inhibitor or azathioprine (both of which are common treatments for ulcerative colitis). In addition, patients were eligible only

if they were treated with a specific drug regimen (high-dose prednisolone plus mesalamine) and if they went into clinical remission from that treatment. Moreover, eligible patients had to agree to visit the clinic every two weeks for 16 weeks to have their blood drawn and to donate a stool sample. It is likely that many patients would not be willing to enroll in such a tedious study. Considering these various obstacles to enrollment, the researchers would likely have had to treat many thousands of acute severe flare-ups at a single clinic over a nine-month period in order to enroll 168 patients.

3. Implausible diagnostic testing: The paper stated that pancolitis was verified endoscopically in all enrolled patients just before the study. However, the paper also stated that all patients had been diagnosed previously, based on standard diagnostic criteria including endoscopy. It is not plausible that every patient who presented with an acute flare-up of a previously diagnosed disease would immediately be given another colonoscopy.
4. Implausible treatment regimen: The paper stated that every patient was started on prednisolone at a dosage of 1 mg per kg of body weight per day for four weeks. Prednisolone was then tapered by 5 mg per day every week until a dosage of 20 mg per day was reached, after which the dosage was tapered by 2.5 mg per day every week until it was discontinued. For a 70-kg person, it would take 10 weeks to taper to 20 mg per day, and an additional four weeks to taper to 10 mg per day (a total of 14 weeks to reach 10 mg per day). However, the paper also stated that the dosage was reduced to less than 10 mg per day in the third month ("in," not "after" the third month). "In the third month" would be around weeks 9 to 13. It would be impossible to have decreased the dosage to less than 10 mg per day in weeks 9 to 13, if it took 14 weeks to taper to 10 mg per day.
5. Illogical diagnostic criterion: Clinical remission was defined in part as having at least three non-bloody stools per day. While cessation of bleeding is a logical criterion for remission, it is likely that many patients in remission would not have three or more bowel movements per day.
6. Ethical issue regarding the treatment: By the time the patients had tapered prednisolone to less than 10 mg per day, 13% had suffered a relapse. However, all patients were required to continue tapering prednisolone and then to discontinue it. Despite the risks of long-term glucocorticoid therapy, it would seem that at least some of the patients who suffered a relapse should have been advised to continue low-dose prednisolone for a longer period of time.
7. Funding issue: Double-blind studies are expensive, so it is unusual to conduct a double-blind study when there has been no prior evidence from case reports or uncontrolled trials that the treatment being tested is effective. This study was particularly expensive, because it included more than 300 colonoscopies and more than 6,000 laboratory tests. Conducting lab tests on every patient every two weeks for 16 weeks seems excessive and a waste of money. One wonders why anyone would have funded this study.
8. Issue related to the lead author: The lead author of this study published an earlier double-blind study of vitamin A supplementation for ulcerative colitis. I reviewed that paper in an editorial in the July 2019 issue of the *Townsend Letter*, and I pointed out many issues that raised concerns the research was fraudulent.

Masnadi Shirazi K, et al. Effect of N-acetylcysteine on remission maintenance in patients with ulcerative colitis: A randomized, double-blind controlled clinical trial. *Clin Res Hepatol Gastroenterol*. 2020 Oct 14 [Online ahead of print].

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B Vitamins for Diabetic Foot Ulcers

A retrospective study was conducted on 29 US veterans with non-healing, early-stage diabetic foot ulcers who were treated daily with 5 mg of folic acid, 4 mg of cyanocobalamin, and 50 mg of pyridoxine for up to six months. Approximately 70% of the patients had hyperhomocysteinemia. Twenty-six of the patients (90%) had complete healing of the ulcer. Data were available for nine patients regarding the rate of wound healing in the four weeks before and the four weeks after B-vitamin therapy was started. The rate of healing was determined by calculating the absolute decrease in wound area (cm^2). In those nine patients, the mean reduction in wound area was significantly greater during B-vitamin treatment than before such treatment.

Comment: These results suggest that supplementing with folic acid, vitamin B12, and vitamin B6 can accelerate the healing of early-stage diabetic foot ulcers. Possible mechanisms of action include lowering homocysteine levels (hyperhomocysteinemia appears to be a risk factor for impaired healing of diabetic foot ulcers) and improvement of endothelial dysfunction. It should be noted that a previous study found that B-vitamin supplementation accelerated disease progression in patients with diabetic nephropathy. Circumstantial evidence suggests that this adverse effect may be preventable by supplementing with magnesium along with the B vitamins.[2]

Boykin JV Jr, et al. High-dose folic acid and its effect on early stage diabetic foot ulcer wound healing. *Wound Repair Regen*. 2020;28:517-525.

Gaby's Literature Review

Selenium, Cardiovascular Disease, and Mortality

A meta-analysis was conducted on 43 randomized controlled trials that examined the effect of selenium alone and antioxidant supplement mixtures (with or without selenium) on risk of cardiovascular disease and mortality. In the pooled analysis, neither selenium alone nor antioxidant mixtures had any significant effects. However, when selenium was included in the antioxidant mixture, there was a significant 23% decrease in cardiovascular disease mortality and a significant 10% decrease in all-cause mortality. In contrast, no reduction in risk was seen when selenium was not included in the antioxidant mixture.

Comment: In this meta-analysis of randomized controlled trials, selenium when given by itself, and antioxidant mixtures that did not contain selenium did not have a beneficial effect. In contrast, when selenium was included as part of an antioxidant mixture, reductions were seen in cardiovascular disease mortality and all-cause mortality. These findings should remind us that nutrients work in the body as a team, and that achieving the best results often requires the presence of adequate amounts of all nutrients.

Jenkins DJ, et al. Selenium, antioxidants, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2020;112:1642-1652.

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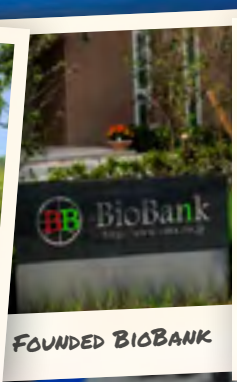

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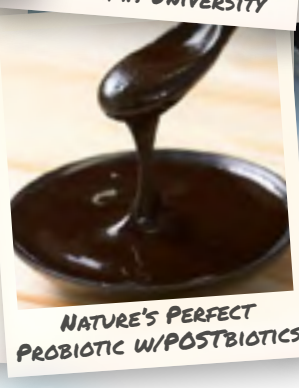

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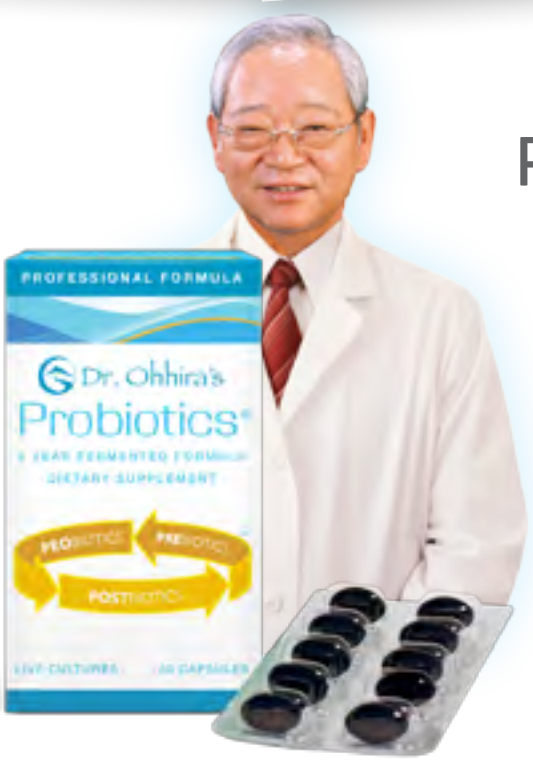

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➤ *continued from page 23*

Nitrate Supplementation for COPD

One hundred sixty-five patients (median age, 69 years) in the United Kingdom with chronic obstructive pulmonary disease (COPD) underwent a supervised exercise program twice a week for eight weeks. During this time they were also instructed in a home exercise program that included aerobic and strength training. The patients were randomly assigned to receive, in double-blind fashion, 140 ml of beetroot juice (containing 0.8 g of nitrate) or placebo (the same beverage that had been run through an ion exchange column to remove the nitrate). The beverages were consumed twice a week, three hours before each supervised exercise session. The primary outcome measure was the change in the incremental shuttle walk test (ISWT) distance. In this test, the subject walks at progressively increasing speed until they are either unable to continue or are unable to keep up with the required walking speed. Compared with baseline, the median ISWT distance increased by 60 meters in the beetroot juice group and by 30 meters in the placebo group ($p < 0.03$ for the difference in the change between groups). No serious adverse effects were reported.

Gaby's Literature Review

Comment: In this study, supplementation with nitrate in the form of beetroot juice was well tolerated and enhanced the beneficial effect of exercise training in patients with COPD. The beneficial effects of nitrate are thought to be due to its conversion to nitric oxide. Nitric oxide functions as a vasodilator (and thereby enhances blood flow) and improves mitochondrial efficiency by decreasing the amount of oxygen required to synthesize ATP.

Pavitt MJ, et al. Oral nitrate supplementation to enhance pulmonary rehabilitation in COPD: ON-EPIC a multicentre, double-blind, placebo-controlled, randomised parallel group study. *Thorax*. 2020;75:547-555.

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1. Mistry R, et al. Iron deficiency in heart failure, an underdiagnosed and undertreated condition during hospitalization. *Ann Hematol*. 2019;98:2293-2297.
2. Gaby AR. Diabetes. In Gaby AR. *Nutritional Medicine*, Second Edition, Concord, NH, 2017, doctorgaby.com, chapter 295.

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Townsend Letter
ISSN 1940-5434

Subscriptions • Editorial • Advertising

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24 Hr. Fax – 360/385-0699

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

On the cover

Do Chemicals Make You Fat? The Influence of Environmental Chemicals on Obesity

by Marianne Marchese, ND

Introduction

Obesity is a public health crisis in the United States. The CDC estimates that over 42% of adults and around 18% of children and adolescents are obese. Obesity is linked to cardiovascular disease, diabetes, cancers, gallbladder disease, pulmonary conditions, sleep apnea, arthritis, mental health problems, and premature death. There are numerous factors linked to obesity such as dietary patterns, level of physical activity, socioeconomics, genetics, family history, medications and more. One factor that is common yet often overlooked is chemicals in the environment. Some toxicants present in our food, water, air, and personal care and cleaning products are considered obesogenic. Obesogenic chemicals contribute to weight gain, obesity, and subsequent health problems. It is important that health care providers be on the lookout for exposure to these toxicants to prevent and treat obesity.

Obesogenic Toxicants: The Main Culprits

Evidence is mounting that chemicals we are exposed to at low levels daily are linked to obesity. These chemicals are called obesogens and can interfere with normal function of hormones and other cell signaling molecules. These chemicals can alter metabolism, thyroid function, and the formation of fat cells.[1-4] These processes can be triggered by chemical exposure prenatally, in-utero, through lactation, in early childhood, or as an adult. The effects can happen at any point in time and may be cumulative.

The main toxicants linked to obesity include the following:

- Bisphenol A (BPA)
- Phthalates
- Polybrominated diphenyl ethers (PBDEs)
- Polyfluoroalkyl chemicals (PFCs)
- Organochlorine (OC) pesticides
- Polychlorinated biphenyls (PCBs)[5]

There are several proposed mechanisms of action of these chemicals on the body, leading to obesity. These toxicants can disrupt homeostasis of energy metabolism, glucose and lipid metabolism, and control of adipogenesis.[5] They alter thyroid and sex steroid hormones; interfere with leptin, ghrelin, melanocyte-stimulating hormones, neuropeptide Y, and other key proteins; as well as through inhibiting aromatases as the P450 family members.[6] The toxicants may change nuclear receptor signaling pathways in preadipocytes, which would result in altered adipocyte differentiation and a tendency toward excess weight.[6]

Bisphenol A (BPA) is a chemical found in numerous household products, including hard plastic water bottles, plastic dishes, plastic cutlery, food packaging, canned food, paper sales receipts, and more. There are different classes of bisphenols with the most common one being bisphenol-A (BPA). Classes of bisphenols, BPS and BPF, which have replaced BPA in many BPA products, can have similar adverse health effects.[7] BPA is considered an obesogen because BPA exposure is linked with an increased risk of developing obesity. Studies clearly demonstrate that BPA promotes adipogenesis, cholesterol and glucose dysregulation, and adipose tissue inflammation, which contribute to obesity.[8]

Phthalates are a class of chemicals present in many consumer products. They are in products such as toys, vinyl flooring, mattress covers, vinyl shower curtains, detergents, and plastic food packaging such as storage containers and plastic food wrap. Phthalates are in personal care products such as nail polish, hairsprays, aftershave lotions, soaps, shampoos, and perfumes. Phthalates are also found in plastic beverage bottles such as water and soda bottles.[7]

Studies suggest that phthalates have significant effects on the development of obesity, especially prenatal exposure at low doses. Several proposed mechanisms of action include activation of peroxisome proliferator-activated receptors (PPARs), antithyroid effects, and epigenetic modulation. PPARs serve as metabolic sensors for lipophilic hormones, fatty acids, and fatty acid metabolites, which control adipocyte proliferation and differentiation.[9]

Polybrominated diphenyl ethers (PBDEs) are a class of chemicals that are added to products as flame retardants. They are in furniture, wire insulation, rugs, draperies, upholstery, plastic cabinets for televisions, personal computers, and small appliances. They get into the air, water, and soil and can leak from products that contain them. They accumulate up the food chain; food is the main source of exposure along with air pollution.[7] PBDEs contribute to adipogenesis and alter insulin metabolism, which are factors in developing obesity.[10]

Polyfluoroalkyl chemicals (PFCs) are man-made chemicals that have been used in non-stick cookware, water-repellent clothing, stain-resistant fabrics and carpets, cosmetics, firefighting foams, and products that resist grease, water, and oil. They are called 'forever chemicals' because they do not break down in the environment. In addition to being in products, they can accumulate up the food chain through air, soil, and water.[7] PFC can contribute to obesity as shown through studies looking at adults. Higher blood PFC levels are associated with increases in weight and hip girth over time.[11] The timing of exposure seems to be significant as childhood PFC concentrations were associated with higher adolescent body mass index and waist circumference.[11.]

Organochlorine (OC) pesticides is the umbrella group for several pesticides, including DDT, eldrin, lindane, aldrin, chlordane, and heptaclor to name a few. They are and were used to treat pests and termites and used in agriculture on crops. Some of these are no longer in use in the US due to their adverse health effects but are still in our soil and water and used in other countries. We are exposed through air, water, and food.[7] Organochlorine pesticides are linked to metabolic syndrome and insulin resistance, which both contribute to obesity.[12]

Polychlorinated biphenyls (PCBs) are a group of chemicals that were used in manufacturing and in hundreds of industrial and commercial products. Although they were banned in 1979, they are in the soil and water and accumulate up the food chain. Meat, dairy, and farmed fish are a common way people are exposed to PCBS.[7] One study showed that PCB exposure, even in low doses, is linked to excess adiposity, dyslipidemia, and insulin resistance among study participants without diabetes. The mechanism appears to be through PCBs' influence on insulin and creating insulin resistance.[13]

Case Example

A 65-year-old female came to see me three years ago for help with her weight. She was motivated and ready to make some lifestyle changes as she admitted her diet was not great and she was sedentary. At the initial visit, her vitals were consistent with obesity and hypertension. Height is 5'5" and weight is 220 lbs., which is a BMI of 36.60. This meets the criteria for obesity. Her blood pressure was 150/80. She had hyperlipidemia and was on atorvastatin 20 mg. She takes a fish oil and vitamin D3 daily (2,000 IU). She is fatigued and gets winded easily. She sleeps well and last year had a sleep study, which was normal. She is managed by a cardiologist and recent cardiac testing was all normal. Her blood work from a month prior showed normal CBC, TSH 1.2, CMP normal except her fasting glucose was 102,

Obesogenic chemicals contribute to weight gain, obesity, and subsequent health problems.

HgA1C 5.4%, Vitamin D 54, and B12 897. Her lipids were not controlled, which is when her cardiologist increased the dose of her statin medication from 10 mg to 20 mg. She wants to lose weight and improve her health. She hates to exercise and knows this is an obstacle for her. She has tried several weight loss programs in the past, which did not help her lose weight or keep weight off. She has met with nutritionists and life coaches, and she has even tried counseling and hypnotherapy but could not keep her weight off consistently. She is looking for a wholistic approach.

Her environmental intake was significant for childhood and adolescent pesticide exposure. She grew up on an agricultural farm in Iowa. She currently uses regular conventional cleaning and personal care products. She eats non-organic meats and dairy and some farmed fish. She cooks with non-stick cook pans, uses plastic wrap on her foods, and stores food in plastic containers. She drinks bottled water that she buys in bulk from the store. She has a diet coke every day and does not exercise. Based on her exposure intake she clearly had exposure to organochlorine (OC) pesticides years prior, living on the farm in Iowa. She also has daily low dose exposure to BPA, phthalates, and PCBS. She declined toxicant testing and said she just wanted to focus on treatment.

Her plan began with educating her on avoidance of environmental obesogens, which included the following:

- Use cosmetics, lotions, and shampoos that are free of parabens or phthalates.
- Avoid using cleaning products with solvents and fragrances.
- Store and heat food in glass not plastic.
- Get rid of non-stick cooking pans.
- Stop buying plastic water bottles and instead install reverse osmosis filtration under the sink and use RO water for drinking and cooking.
- Buy in bulk to decrease plastic packaging.
- Store food in glass jars when you get it home.
- Carry groceries in cloth bags and reuse them instead of plastic bags.

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She agreed to go home and make changes in the products and plastics she uses in her home. Next, we addressed her diet and implemented a diet plan that would either eliminate toxicants in food or have her eat foods designed to help the liver metabolize hormones and toxicants.

- Buy only organic fruits and vegetables that are free of pesticide residues.
  - EWG.org list of the dirty dozen and clean fifteen.
- Choose USDA organic meats and dairy products.
- Avoid farmed fish.
- Buy fresh or frozen foods and avoid canned foods with BPA.
- Stop drinking diet soda and instead drink 100 ounces of filtered water a day.
- Avoid or minimize foods wrapped in plastic wrap.
- Eat wild-caught fish low in mercury (salmon, blue crab, flounder, haddock, pollack, trout).
- Add 2 Tbsp ground flax seeds/meal a day on food.
- Add 2 tsp a day of psyllium husk powder in water.
- Drink 3-4 cups of red rooibos tea or green tea.
- Increase legumes, fruits, veggies – organic only.
- Eat 3-4 servings of organic cruciferous veggies a day.
- No refined carbohydrates, white flour, or sugar.

Next, she was asked to do sauna therapy to help her metabolism and to mobilize obesogenic chemicals and eliminate them through perspiration. Sauna therapy instructions were to use infrared sauna therapy twice a week; start with 10 minutes in hot sauna, then do a 30-second cold shower rinse. Repeat this cycle five times and end on cold. She was asked to do this two times a week.

Three supplements were added as well. One is designed to provide vitamin and mineral co-factors for liver phase one and two metabolism. The cofactor support product contained vitamin A, vitamin D3, vitamin K1, vitamin B1, vitamin B2, vitamin B3, vitamin B5, vitamin B6, vitamin B12 (as methylcobalamine), vitamin C, vitamin E, biotin, folate (5-methyl-tetrahydrofolate), calcium, chromium, copper, iodine, magnesium, manganese, molybdenum, potassium, selenium, zinc, choline, inositol, boron, vanadium, green tea extract, and turmeric. The second was a liver herbal supplement with milk thistle, beet root, dandelion, burdock, and artichoke. The third was CoQ10, 200 mg.

The patient disappeared for four months and returned 30 pounds lighter. Her blood pressure at the follow up exam was 140/80 and her cardiologist had repeated her labs. Her fasting glucose lowered from 102 to 98 and her lipids were all within the normal range, but she was still on atorvastatin 20 mg. She said she followed the treatment plan to a T; and although it took a lot of work at home to make the changes to avoid obesogenic chemicals in products and plastics, she did slowly make the changes. I asked her to continue the avoidance recommendations and diet changes, stop the sauna therapy, and continue the supplements, and begin to exercise. We also lowered the atorvastatin to 10 mg.

Four months later she returned for another follow up and had lost another 20 pounds. She had started walking 30 minutes once a day and no longer felt winded or fatigued. She had done a great job sticking to the nutrition plan and avoiding toxicants. Now her height is 5'5", and she weighs 170 lbs., which is a BMI of 28.28. Her repeat lipid panel was normal, but she was still on atorvastatin 10 mg at this repeat lipid panel. Her blood pressure was 135/80 that day in the office, and we agreed she should start monitoring it at home in case it is high only at the doctor's office. At this appointment we decided to stop the liver cleanse supplement and atorvastatin and add in red yeast rice, 600 mg twice a day, and 350 mg magnesium. She is still on the CoQ10, vitamin D, fish oil, and cofactor support supplement. She said she was motivated and willing to continue her plan and agreed to try and increase exercise by adding in swimming.

Four months later she returned for a follow up, and four months off the statin drug her lipids were normal along with CBC, CMP, TSH. (I have patients repeat the labs the week before the follow up). She only lost another 10 pounds but is happy to be walking daily and swimming two times a week. She now weighs 160 and her BMI is 26.62. In one year, she lost 60 pounds and feels great and feels like she will keep the weight off. Her blood pressures at home averaged 130/78 and that day in the office was 132/80. Her cardiologist is on board with the plan and familiar with red yeast rice; and since she lost weight and her lipids improved, he is fine with her decision to stop the statin drug. I asked her why she felt like she had success with this approach in terms of her weight loss, and she said she felt that removing the chemicals from her home and diet really made the difference. She felt like it may have been the reason why she could not lose weight. She also felt the sauna therapy, done the first three months of the plan, made a big difference as well. To date, her weight fluctuates between 155-160; she did not achieve any further weight loss. Her lipids have remained normal, and she even stopped the red yeast

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rice supplement. She has continued to avoid obesogenic chemicals.

Summary

Obesity is a public health crisis in the US, and there are numerous factors contributing to this problem. One area that needs attention is the impact of toxicants considered obesogenic. These chemicals found in plastics, our food, personal care products, cookware, and water can contribute to obesity. When evaluating a patient or client for causes of obesity and cardiovascular disease, it is important to consider toxicants as a contributor. Educating patients on avoiding these chemicals is key to prevention and treatment of obesity. It begins with awareness and understanding of how chemicals in our environment affect our health.

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Pediatric Pearls

by Michelle Perro, MD

Obesity in Children: The ABCs of EDCs

I received a frantic call from a nurse/colleague, Liz, who just came back from her pediatrcian's office with a long list of questions concerning recent abnormal laboratory results for her five-year-old daughter, Sarah. Her physician had reviewed the lab results with her, but she wasn't satisfied with his answers. Sarah was being evaluated for obesity. Her height was calculated at the 50th percentile and her weight was above the 97th percentile on the growth chart, with a BMI of 27.1 (placing the BMI-for-age at greater than 99th percentile consistent with the diagnosis of obesity). Her lab results were remarkable for an elevated fasting blood glucose, concerning hemoglobin A1C of 6.1 and a lipid profile noted to have an elevated triglyceride level of 160. I was also concerned when the mom told me her ALT (liver function test) was 40 and her physician told her to "…Stop being a nervous Nelly!" and that it was "fine." (Clearly, he wasn't familiar with lab value recommendations for kids!)[1] Her MD's advice was to increase Sarah's exercise and put her on a Weight Watcher's diet along with Mom who was also overweight and trying to manage her Type II diabetes. Oy vey!

It was disheartening to learn that some of my colleagues had not moved out of the dated 1970s medical mantra that obese patients (even kids) overate and were lazy. I've been out of the mainstream medicine world so long that I forgot that pediatricians are undernourished with nutritional knowledge and overfed with drug information. Not to mention, there is a global lack of awareness of the myriad number of other factors that can contribute to obesity in kids. In the age of technology-driven learning/play and fast-food delivery services, indeed, getting kids to move and eat well are a big part of the conversation. However, let's talk about the elephant in the room.

The ABCs of EDCs

Substantial evidence has emerged over the last decades that exposure to endocrine-disrupting chemicals (EDCs) is connected to obesity and obesity-related metabolic diseases.[2] EDCs act as hormones, even in nano doses (which can cause larger or different effects than higher doses, called nonmonotonic dose responses). Childhood obesity is now epidemic, reported to affect 20% of US kids aged 2-19 years.[2] According to the Global Burden of Disease Obesity Collaborators, in 2015, a total of 107.7 million children and 603.7 million adults worldwide were obese.[3] Indeed, there is much written about the contribution of industrialized food and their associated pesticides as well as decreased nutrients in the food supply to account for this issue. However, environmental toxicity is playing an ever increasing and overlooked role in this obesity pandemic.

Going to the Source

One of the largest sources for EDCs are the effluents from sewage treatment plants (biosludge). (Want to watch a Friday night horror film? https://www.biosludged.com.) In 1986, when the US decided that the "solution to pollution was dilution" (ocean dumping) was no longer an option, we turned to using our wastewater filled with toxic chemicals as fertilizer. In addition, children can be exposed to EDCs via the placenta/breast milk, air pollution, toxic dust, personal care products, contaminated food (i.e., processed food container liners), cookware/household items, and environmental ingestions simply from hand-to-mouth behaviors when playing. Two classes of the biggest obesogens (a term now applied to certain EDCs) that are ubiquitous are bisphenols and phthalates, but there are many toxic endocrine mimics.

The chemical soup of EDCs, to which many of us are already familiar, includes the following:

- Polychlorinated and polybrominated biphenyls (PCBs and PBBs)
- Bisphenols (BPA from plastics, Bisphenol S [BPA substitute], BPF and BPAF)
- Phthalates (DEHP, DINP, DOP, DIDP, DINCH)
- Perfluorooctanoic acid (PFAS/Teflon: 'Forever Chemicals' found in 99% of Americans)
- Parabens (preservatives; look for words ending with -parabens)

- Triclosan/Triclocarban (Hand sanitizers)
- Dioxin (high in animal products)
- Dichlorodiphenyltrichloroethane (DDT)
- Pesticides (organophosphates, atrazine)
- Vinclozolin (Fungicides)
- Perchlorate (found in baby formula!)
- Polybrominated diphenyl ethers (PBDEs: Fire retardants – 100% of people are positive in the state of California)
- Pharmaceutical chemicals
- Heavy metals (lead, mercury, arsenic)
- Solvents
- Fragrances – complex combinations of EDC chemicals (phthalates in 100% of tested fragrances)

The intent of this article is not an academic review of EDCs, but to raise awareness regarding these ubiquitous chemicals that have been invading children's bodies for decades and offer evaluation and treatment solutions. For an in-depth review of the subject, I refer you to an excellent medical toxicology text, *Clinical Environmental Medicine* (Crinnion/ Pizzorno, 2018). This is also a great segue into a pitch to join the National Association of Environmental Medicine (NAEM) which has abundant resources on EDCs and other toxicants.[4]

Are EDCs Causative for Sarah's Obesity and Obesity-Related Issues?

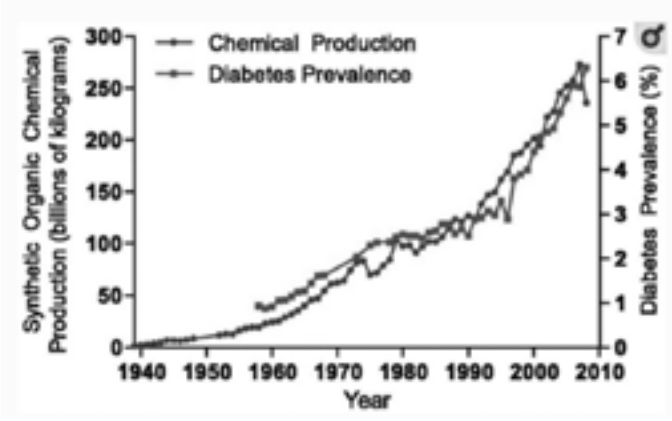
As reported in so many *'Pearls'* prior, the first place I start is the history. I had Sarah and Liz come into the office for a second opinion and sought out our usual root cause assessment for obesity/metabolic dysregulation, Type II diabetes, hypertriglyceridemia and mild hepatitis. The list of potential obesogens and triggers were long, including a stressed-out single mom who ate a lot of junk food (no organics) during pregnancy, had regular manicures, used a vast number of personal care products, including hair dyes and make-up and worked in a hospital setting with significant exposures to hand sanitizers and plastics, guzzling down iced decaf coffee sweetened with Splenda®. Sarah was bottle-fed with non-organic formula, ate a lot of microwaved frozen pizza, drank tap water, lived in an apartment where Mom used fragrant candles and roach sprays and attended a newly remodeled primary school: An unfortunate portrait of the modern American family.

Trying to reeducate parents that are entrenched in Western medical thinking can present a real challenge. Treating children with obesity from whatever causes can be difficult since you are not only treating the child, but the parents' deeply held beliefs regarding food. There is no quick fix! When I explained that the environmental factors were the likely culprits for Sarah's issues, Mom was not only dubious but wanted to know why she's never heard this before. Sigh. That could have taken a few days to explain. I decided to show her some of the chemicals bathing Sarah's body and ordered an environmental pollutants panel. Funds were limited, so I only ordered one test from US Biotek (and urine samples are a great way to go in kids).[5] Since there are many testing challenges, such as short half-lives and incomplete testing of some of the toxicants, I utilize it more as a tool for nay-sayers to overcome mental hurdles (in particular, mainstream medical professionals). Some individuals also are not good excreters of toxicants, so 'normal' results may not mean that there aren't significant exposures. For Sarah's sake, I was hoping it would show what I thought it would in order to persuade Mom to make some needed changes.

Of the 14 metabolites reported, Sarah was off the charts for all but three of the reported chemicals. She had significant benzene, trimethylbenzene, styrene, phthalate and paraben exposures. I recommended to Liz that she read the classic book *Our Stolen Future* (Colborn, et al., 1996) and gave her references (www.madesafe.org) to assist her understanding in the health:toxicology interface. Eventually, most of our patients will know more about toxicology than their primary care physicians once they get on board. While many people are aware of the adverse role of plastics on health, other chemical toxicants do not have the same celebrity status. I explained that there are reports in the literature dating back to 1997 that showed solvents (which were very high in Sarah), were also EDCs, so there were many chemical groups causing metabolic disruption to consider.[6] And we know very little about the health effects of the many-ingredient toxicant soup to which we are all exposed.

What really convinced Mom to trust a different approach was she really didn't want Sarah to follow in her diabetic footsteps. This graph below showing correlation between organic pollutants and diabetes was helpful in our discussion; and since parents don't necessarily come with PhDs in environmental health, I use a lot of diagrams, graphs, and summaries to go home with.[7]

The Diabetes Epidemic Correlates with Release of POPs into the Environment.



Sarah was a hot, toxic mess.

A Treatable Condition

I begin treatment with my favorite cliché, "This is a marathon, not a sprint." My treatment protocol, which occurred over two years, is enumerated below. This was developed with the knowledge that Mom had a limited budget and time, so we worked together within those parameters.

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Phase I consisted of reducing the toxic load in order to give her detox pathways a little breathing room to do their job:

1. Organic diet – no take-out
2. Eliminate all processed foods – no cans, packaged foods
3. Filtered water only
4. Eliminate plastics in food preparation
5. Toss the microwave
6. Ban the Teflon
7. No fragrances!
8. Make friends with insects
9. Regular activity daily with Mom
10. Limit screen time, especially before bedtime
11. Shut the wifi at night
12. Switch to non-toxic cleaning products and hand sanitizer

Phase II consisted of healing intestinal permeability/dysbiosis since the majority of kids I see with chronic diseases have both. I test when feasible.

1. German Biologic Medicine for gut healing
2. Removal of inflammatory foods (dairy and gluten)
3. Introduction of fermented foods/probiotics
4. Bolster antioxidants (Vitamins C, D, A and E which also protect against solvent exposures)
5. Omega 3s – I like algae omegas in kids

Phase III consisted of detoxification strategies. (Homeopathics are the core of my go-tos):

1. Homeopathic detox focused on liver, kidney, and lymph drainage
2. N-Acetyl cysteine (NAC)
3. Alkalization with lemon water and increased greens/herbs in smoothies
4. Sauna three times/week
5. Curcumin (for everything)!

Sarah did not lose any weight, nor did she gain any more weight over the next two years. I met with her monthly to check in and give Mom support. However, all of her abnormal lab values returned to better than normal over six months. What was most interesting is that Sarah's body habitus changed. Prior to our treatment, she was very rounded in her chest and had evidence of early puberty. Her torso elongated, puberty arrested, and she grew in height. Mom lost 40 lbs. following the same protocol, and her Type II diabetes was history.

Recognizing, diagnosing, and treating children for environmental toxicity should be the focus of pediatric education; and it behooves any practitioner that works with families to include environmental health analyses in their child encounters.

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(For an excellent review for patients, download the PDF at Environmental Working Group: https://static.ewg.org/pdf/kab_dirty_dozen_endocrine_disruptors.pdf?_ga=2.53040298.305740248.1611525098-709861240.1611525086)

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The Coenzyme Q10 Quagmire

by Dr. Douglas Lobay, BSc, ND

It was a hot, dry afternoon in the summer of 2019 in the middle of an herb farm in the North Okanagan. Acres of colorful herbs, including echinacea, chamomile and calendula, adorned the rolling landscape and swayed in the gentle wind. I was attending a seminar in a modified barn with one of the preeminent naturopathic lecturers in North America. The talk was on mitochondria and cellular aging. During the question-and-answer section of the presentation, the talk diverted to the subject of coenzyme Q10 or more specifically, what type of Q10 was preferred? Simply put, which was better ubiquinone or ubiquinol? The esteemed doctor gave an honest and forthright answer and said he simply wasn't sure. The group of about fifty individuals included naturopaths, dentists, medical doctors, chiropractors, and other allied health professionals. Some opinions were offered and were loosely based on personal experience and conjecture. They seemed to lack scientific merit and the support of evidence-based medicine. One other doctor emphatically contested that ubiquinol was by far better and this was based on the idea that it had superior absorption. Still others said ubiquinone was just as good. The seminar concluded without a general consensus, and we all left without closure about whether ubiquinone or ubiquinol was better – or was there even a difference?

The answer to the question nagged the back of my brain when I had time to think about it. I ruminated about what I seemed to know about coenzyme Q10. Q10 was certainly one of my top ten most important supplements that I recommended. It was good for mitochondrial function and the generation of energy inside cells. It was supposed to be a good antioxidant. It appeared to be very safe. I recommended it to almost every patient who took a statin medicine to lower cholesterol. I recommended it to improve brain function, skin support, chronic fatigue, periodontal disease, and maybe to help improve kidney function. I knew it was fat soluble and had a poor absorption profile. I knew that ubiquinol was a more expensive form of Q10 and was told that it was supposed to have superior absorption and perhaps worked better. I used both forms of Q10 at different, random times without much forethought. The major difference I knew for sure was that ubiquinone was a bright orange or yellow color and ubiquinol was milky white in appearance. Beyond that, I realized I didn't know much.

Ubiquinol and ubiquinone are continuously inter-converted from one type to the other.

Coenzyme Q10 is a naturally occurring benzoquinone compound that is important in electron transport in mitochondrial membranes. Coenzyme Q10 has a ubiquinone ring structure and has a side chain of 10 isoprenoid units. The name Q10 is derived from its chemical structure. The Q refers to the quinone benzene ring group, and 10 is related to the number of isoprenoid subunits in its tail. The atomic weight of Q10 is 863.3 grams/mole. Its melting point is between 50 to 52 degrees Celsius. The active site of electron transfer and binding are two double-bonded oxygen molecules on the quinone ring structure. Uncoupling of one of the oxygen bonds to the ring structure creates a negative charge that attracts an unpaired positive hydrogen atom for binding. The oxidized form of Q10 is known as ubiquinone and is displayed by two opposite oxygen molecules with a double bond to the quinone ring structure. The reduced form of Q10 is known as ubiquinol and is displayed by two opposite OH or hydroxyl groups bond to the quinone ring structure. Ubiquinone and ubiquinol are inter-converted into each other depending on the redox reaction and the necessity to accept or donate electrons. Both are necessary and both are considered active, albeit with different redox states.[1]

Mantle and Dybring provided an excellent overview of the absorption process and subsequent metabolism of coenzyme Q10. They acknowledged that some manufacturers made incorrect claims regarding the bioavailability of Q10 supplements based on the current research.

Contrary to some manufacturers claim, ubiquinol is not the active form of Q10. Both forms are continuously inter-converted from one type to the other. Most Q10 studies found on medical databases are with the ubiquinone form. Two landmark studies about Q10 in congestive heart failure (CHF) both used ubiquinone. The 2014 Q-Symbio study involved 420 CHF patients in a placebo-controlled trial who were administered the ubiquinone form of Q10. A significant improvement in heart function was observed in the Q10-treated group. The 2013 Kisel-10 study was conducted with 443 heart patients in Sweden and showed significant improvement with the group that received 200 milligrams of ubiquinone per day. Mantle and Dybring further stated that coenzyme Q10 is being constantly regenerated. Q10 influences several hundred genes in the human body. And at least five different enzymes are believed to be involved in the conversion of ubiquinone to ubiquinol. There appears to be a wide variability in individual absorption capacity.[2]

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Ingested levels of coenzyme Q10 from daily food intake are estimated to be up to 5 milligrams per day. Total daily requirements of Q10 in the body are estimated to be 500 milligrams per day. Total body stores of Q10 are estimated to be 2 milligrams. Therefore, ingested sources and body stores of Q10 are being constantly regenerated to meet daily requirements and demands. These numbers seem to justify the recommended daily dose of 300 milligrams of Q10 in congestive heart failure patients to meet therapeutic plasma levels. Optimal biosynthesis of Q10 occurs in the mid-twenties and decreases with age. Q10 was originally purified from bovine heart tissue in the 1950s. Q10 exists in cis and trans isomeric forms based on the isoprenoid side chain stereochemistry. The trans form of Q10 was identified as the only active form utilized in the human body. It is only absorbed as an unbound molecule. It is transported as ubiquinol in the plasma bound LDL and VLDL molecules in the blood irrespective of what form that is initially ingested. Some manufacturers claim that ubiquinol is better absorbed.[2]

The concept of superior absorption promulgated on the internet originated from comparisons between bioavailability data take from earlier published studies that did not provide the form of Q10 used, provided no direct comparison between the different forms and did not use thermal dispersion techniques to enhance the absorption of ubiquinone. Newer research shows lipid carriers such as soy or palm oil seem to enhance the intestinal absorption of Q10. The transit time from stomach to duodenum is about 60 to 90 minutes. Most ingested ubiquinol will be oxidized to ubiquinone during this time. The transit time from stomach to intestines to lymph is between 5 to 8 hours. Q10 is generally acknowledged to have poor water solubility and is incorporated in fat micelles for transport and absorption. Absorption is via passive facilitated diffusion across enterocytes. Nashimoto and others discovered a mechanism of intestinal Q10 absorption involving Niemann-Pick C1 like (NPC1LI) transporter protein. This protein spans the cellular membrane of enterocytes and hepatocytes and is involved in absorption of fat soluble molecules and cholesterol. Transport of Q10 was dramatically increased by genetic over-expression of this protein transporter in animal experimental models. Singh and others showed that the administration of 2 capsules of 100 milligrams of Q10 at different times increased absorption better than the 2 capsules administered at the same time. They concluded that there was a limit to the intestinal absorption capacity of Q10.[2-4]

Once inside enterocytes Q10 is incorporated into chylomicrons and released via exocytosis and then transferred to lymph and blood. Q10 in the blood is mainly in the reduced form as ubiquinol. Dietary or supplementary Q10 in the oxidized form as ubiquinone is rapidly converted to the reduced form as ubiquinol in the enterocytes and lymph. Q10 is mainly protein bound in the blood and very little is in free form. Chylomicrons containing Q10 in the form of LDL and VLDL then go to the liver for processing. Cmax or maximum concentration in the blood occurs 6 hours after initial ingestion of Q10. The half life of Q10 in the blood is about 33 hours. Plasma levels vary from person to person and can range from 0.5 to 1.5 micrograms/milliliter. Twice per day dosing resulted in increased plasma levels from 0.90 to 3.25 micrograms/milliliter.

Q10 is found in all cells and is dispersed to all tissues of the body. Generally, the higher the level of cellular metabolic activity, the higher the concentration of Q10 of intracellular Q10. Heart tissue has the highest concentration in the entire body. Q10 is not considered a vitamin per se, because all cells in the body can make it, except for red blood cells. Besides mitochondria, Q10 is also found in the endoplasmic reticulum, Golgi apparatus, lysosomes, and peroxisomes.[2]

Kaikkonen and others summarized the main determinants and absorption of plasma Q10 in the form of ubiquinone in a blinded, placebo-controlled trial. A dose of 30 milligrams had only a marginal effect on plasma Q10 levels in a group of non-Q10 deficient subjects. However, a dose of 200 milligrams increased plasma Q10 levels by 6.1 times.[2,5]

Bhagavan and Chopra showed that both total and plasma Q10 levels increased above baseline in a gradual manner with increased doses of Q10. Plasma Q10 levels hit a plateau at 2,400 milligrams of Q10 per dose. Ninety-five percent of all circulating Q10 was in the form of ubiquinol in plasma and blood. Solubilized forms of Q10 have superior bioavailability as evidenced by the increased Q10 dose response.[2,6]

Bhagavan and Chopra discussed Q10 absorption, tissue uptake, metabolism, and pharmacokinetics. They acknowledged that Q10 is hydrophobic, has large molecular weight, and has a rather slow and limited absorption profile. The time to reach maximum concentration in the blood is up to 6 hours after initial ingestion. The elimination half life is up to 33 hours. The accepted plasma reference range was between 0.40 to 1.91 micromoles/liter in healthy adults. There is a correlation between increased plasma Q10 levels and ingested dose to a certain point. Animal studies showed that Q10 in large doses is taken up by all tissues, including heart and brain. They also noted that Q10 has an excellent safety profile.[2,7]

Barakat and others analyzed the fraction absorbed of different coenzyme Q10 formulations in human and animal models. The purpose of their review was to assess different drug delivery systems that might improve the problems of low solubility and low absorption of Q10. Different drug delivery systems that might enhance Q10 bioavailability ranged from simple oil dispersions to emulsions and nanotechnology. The results were given as fraction of the original amount absorbed and measured in the bloodstream. In humans the fraction absorbed of different formulations ranged from 1.53 to 12.48%. The highest fraction absorbed was measured in a formulation that had a self-emulsified drug delivery system or sedds. It was generally agreed upon that coenzyme Q10 has a poor absorption profile because of its hydrophobicity and large molecular weight size. And it was further agreed, that technological enhancements in formulations and delivery system are necessary to improve its profile and utility as a supplement in humans.[8]

Lopez-Lluch and others assessed the bioavailability of seven different forms of Q10 supplements administered as a single 100-milligram dose to 14 young, healthy volunteers. Bioavailability was measured 48 hours after consuming a single dose of different Q10 supplements followed by a washout period of four weeks, then followed with another measurement after consuming a different formulation. They

analyzed the area under the curve (AUC) that represented the percentage of Q10 that entered blood circulation. They also analyzed the peak plasma concentration of Q10 following intestinal absorption. The failure to subject crystalline Q10 in the ubiquinone form to thermal crystal dispersion resulted in a 75% decrease of absorption and a subsequent decrease in plasma levels. Ubiquinol is not bound in a crystal lattice and does not require crystal dispersion to enhance absorption. Different Q10 matrix affected different absorption rates. The two best responses were an oxidized Q10 in capsule and reduced Q10 in a soft gel.[2,9]

In one crossover study by Vitetta and others, 150 milligrams of either ubiquinone, ubiquinol or ubiquinone liposome were administered to a group of subjects at different times. Significant intra-subject variability of Q10 absorption was observed and persisted throughout the duration of the study irrespective of what form of Q10 was used. They concluded that Q10 absorption rates varied significantly between individual subjects. No significant difference between the type of Q10 and absorption was noted.[2,10]

A study by Miles and others looked at nine healthy subjects who were given 100 milligrams of ubiquinone and 100 milligrams of ubiquinol at different times. No significant difference in plasma Q10 levels was observed. In contrast, some other studies showed a significant improvement in bioavailability of ubiquinol versus ubiquinone, particularly in older subjects.[2,11]

In a 2009 study by Evans and others, a 100-milligram single dose of ubiquinone and ubiquinol was given to 10 healthy volunteers over the 60 years. The plasma level of Q10 was significantly higher when ubiquinol was consumed compared to ubiquinone.[2,12]

In 2018 Zhang and others performed a double-blind randomized crossover trial involving 10 adult males who were 55 years or older. Respondents consumed a specific form of 200 milligrams of Q10 per day for two weeks, followed by a two-week washout period, then consumed 200 milligrams of a different form of Q10 for two weeks. Four different blood samples were taken at different times. Plasma Q10 levels were significantly higher when the subjects took ubiquinol. Ubiquinol significantly increased plasma ubiquinone levels from 0.2 to 0.6 micromoles/deciliter and total serum Q10 levels from 1.3 to 3.4 micromoles/deciliter. Ubiquinone did not significantly increase plasma levels. Of the 10 subjects, six responded better to ubiquinol and two responded better to ubiquinone supplementation.[2,13]

In a 2014 study, Langsjoen and Langsjoen compared ubiquinol versus ubiquinone in a crossover study where 12 healthy volunteers consumed 200 milligrams of a form of Q10 for four weeks, followed by a four-week washout, then consumed 200 milligrams of the other form of Q10 for four weeks. The ubiquinol-treated timeline resulted in significantly higher levels of plasma Q10. Plasma Q10 levels increased from 0.9 to 2.5 micrograms/milliliter after four weeks when ubiquinone was administered. Plasma Q10 levels increased from 0.9 ➤

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to 4.3 micrograms/milliliter after four weeks when ubiquinol was administered. It was noted that the crystal ubiquinone was not subject to thermal dispersion before encapsulation. No side effects were observed and either Q10 was well tolerated.[2,14]

Pravst and others assessed the bioavailability of different formulations of coenzyme Q10 in a randomized, three period, crossover study involving 21 older adults between the ages of 65 to 74 years. The treatment was a single dose of 100 milligrams of Q10 in the form of ubiquinone, ubiquinol, and water-soluble Q10 syrup at separate times. Ubiquinol increased plasma levels 1.2 times above baseline compared to ubiquinone. The water-soluble syrup increased plasma levels 2.4 times above baseline compared to ubiquinone. No difference in redox status was observed between the different formulations. The absorbed Q10 observed in the blood was in the form of ubiquinol for all different formulations.[15]

Petrangolini and others revealed that the phytosomal form of Q10 improved absorption by three times. One capsule improved plasma Q10 levels to 0.864 +/- 0.120 micrograms/milliliter. This represented an increase of 41% above unbound Q10. Two capsules improved plasma Q10 levels to 1.321 +/- 0.400 micrograms/milliliter. This represented an increase of 116% above unbound Q10. This was compared to a baseline of one capsule of unbound Q10 giving a plasma level of 0.614 +/- 0.120 micrograms/milliliter and two capsules giving a level of 0.614 +/- 0.160 micrograms/milliliter.[2,16]

Other studies use a variety of agents to improve Q10 absorption, including polyethylene, phosphorylate, tocopherols, poloxamer, polyvinyl, and hydrolyzed protein.[2]

Archie just showed up at my office one day. Archie was a rough-and-tumble logger and backwoodsman from the mountains above Christina Lake. He was a middle-aged man with a long beard, a paunch, and a plaid jacket. He had just come from the cardiologist's office. He said he had a heart attack several years prior and was on cholesterol, blood pressure, and blood thinning medications. He was very fatigued, short of breath, and had trouble walking a block or more. He took no vitamins and ate a typical meat and potatoes diet. His vital signs and lab tests all appeared within normal limits. I gave him a vitamin B12 shot, recommended a multi-vitamin, and told him to take coenzyme Q10. He left and I didn't see him for a year and a half.

A clean-shaven man in a plaid jacket showed up at my office one day. He asked if I remembered him. I said I didn't. He told me that he came from the cardiologist's office and his heart function improved by 40%. He was on the same medicine as before and the doctors didn't know why. They told him to keep on doing whatever he is doing. And more importantly, Archie said he felt much better and could now walk much further without fatigue or shortness of breath. He liked Q10 and said he thought it really helped him.

Sharon was a long-time cancer patient who had an inquisitive mind and a keen interest in alternative medicine. One day she said she had a present for me. She said that one of her best friends was the manager of a vitamin company. She took out what looked like a sack of dark, black capsules. She said here were the Q10 capsules that fell on the floor during the manufacturing process at the vitamin factory. They couldn't re-bottle them and just generally threw them away. She was allowed to collect some and was giving some as a sample for me. Now in my possession was several hundred or more 200 milligrams of high-quality encapsulated coenzyme Q10 for me to try. And so I tried them. Being a somewhat aggressive type A personality with a curious mind, I decided to see if more was better. I took upwards to 2600 milligrams of Q10 per day for about a month. My energy improved and I felt really good. As I was lap swimming at the time, I felt stronger and faster than before. I did not experience any side effects and I still slept well. I liked Q10.

Now to circumambulate the question, which is better ubiquinone or ubiquinol? The oxidized form of coenzyme Q10 as ubiquinone is interconverted to the reduced form as ubiquinol easily and rapidly in the body at many levels and then reconverted back again to its original form. Despite what some overzealous manufacturers suggest ubiquinol is not better or more active. The cumulative absorption data suggests that ubiquinol is probably better absorbed than ubiquinone. However, newer emulsions of ubiquinone have shown improved absorption profiles. If the extra cost of ubiquinol justifies taking a lesser dose to reach a therapeutic plasma Q10 level, then so be it. The current evidence suggests that both are fairly equally good.

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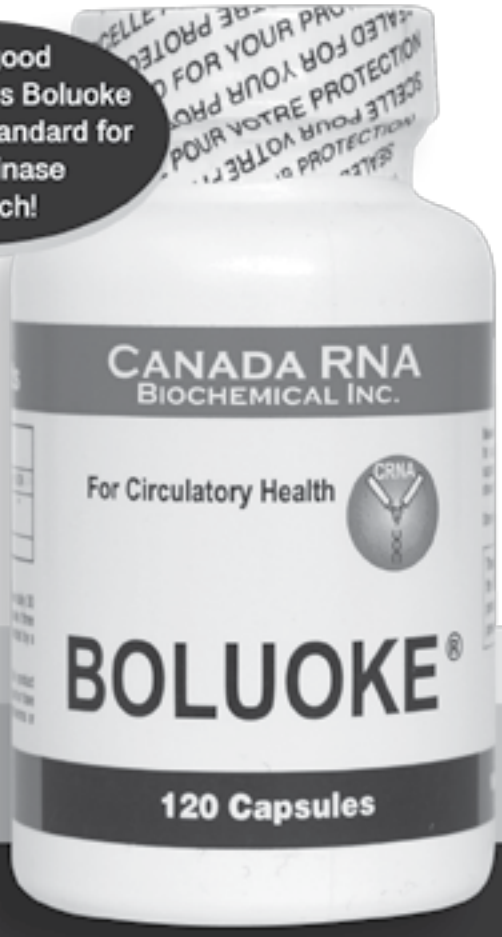

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A Grand Experiment: Air Pollution and Heart Disease Deaths

by Jacob Schor, ND

Two recently published studies have caught our attention and have been on my mind these last few weeks as we have stayed at home in COVID-lockdown mode. Both studies look at the association between changing levels of air pollution and mortality. This is relevant because our social distancing response to the pandemic has had a striking side effect: air pollution levels have fallen dramatically as most countries have instituted similar lockdown measures to slow the spread of the virus.[1]

Unwittingly we have all become participants in a global experiment testing whether lowered air pollution will be associated with improved health, decreased morbidity, and a reduction in mortality, in particular from cardiovascular diseases (CVD).

The first of these two studies was published in *Environmental Health* (February 17, 2020) and written by Bingyu Wang and others at Northeastern University in Boston. Wang used data from fifty-three million US Medicare beneficiaries (aged ≥65) with approximately 4 billion person-months of follow-up. They combined each individual's address and zip code to obtain data from the Environmental Protection Agency (EPA). Using meteorological and geo-temporal models they calculated individual exposure to PM2.5 over an eight-year period (2000-2008). They compared this calculated PM2.5 exposure against disease specific and all-cause mortality using Cox proportional models.

They found that PM2.5 was significantly associated with mortality from CVD, respiratory disease, and cancer. A 10 μg /m^3 increase in average PM2.5 in the 12 months prior to death was associated with a 5% increase in all-cause mortality, as well as an 8.8% increase in all cardiovascular disease (CVD), a 5.6% increase in all respiratory, and 2.5% increase in all cancer deaths, respectively, in age, gender, race, ZIP code, and socio-economic status (SES)-adjusted models. PM2.5 exposures, however, were not associated with lung cancer mortality. The results were the same across gender, race, age, economic status. There was no evidence of an exposure threshold beneath which PM2.5 was not associated with harm.[2]

The other study that got our attention was by Raymond Pranata et al and was published on March 13, 2020 in the *Journal of Evidence-Based Medicine.* It was a comprehensive review and meta-analysis of past studies on air pollution and CVD mortality. Data from 84 cohorts, comprising a total of 28,215,394 subjects, were combined. Increases in fine particulate air pollutants were associated with increases in all measures of CVD, acute coronary events, stroke, and high blood pressure. Mortality rates from CVD increased by 10% for the PM2.5 increases and 17% when the larger PM10 particles were tracked. Increases in NO were associated with a 17% increase in CVD mortality and a 23% increase in all-cause mortality.[3]

While these two most recent studies should perhaps carry the most weight there are other studies worth mentioning. Hayes et al reported in papers published in July 2019 and in February 2020 (n=565,477) that each 10 μg/m3 increase in PM2.5 was associated with a 16% increase in mortality from ischemic heart disease [hazard ratio (HR) 1.16; 95% CI 1.09-1.22] and a 14% increase in mortality from stroke (HR 1.14; CI 1.02-1.27).[4,5]

Wang's finding that lung cancer mortality was not associated with air pollution was not unexpected. Prior studies have also reported a similar null effect[6] though others have seen a positive association.[7] It may be that the harmful impact of smoking far exceeds that of background air pollution with lung cancer.

As I write this in early April 2020, the curve representing viral infections is still climbing.

We were first introduced to this concern about air pollution in 2015, by our friend Walter Crinnion, ND. At that time, the World Health Organization estimated that air pollution accounted for 1.3 million deaths worldwide every year. Dr. Crinnion concluded a review article he had written on the topic: "It is quite possible that one of the most effective preventive medicine modalities would be the installation of a high-quality air purifier in the home"[8]

Initially I thought he had exaggerated the benefits, but I've lost that skepticism and find that I now agree. In the half decade since, we've seen the publication of studies suggesting an association of air pollutants with a range of health conditions. The focus is now on the ultra-small particulates known as

PM2.5 that are fine inhalable particles with diameters that are generally 2.5 micrometers or smaller. As a follow up to Crinnion's initial review on air pollution, the *Natural Medicine Journal* (*NMJ*) has reviewed studies that report an association between PM2.5 exposure to obesity,[9] diabetes,[10] anxiety,[11] suicide,[12] psychosis,[13] low birth weight,[14] cognitive performance,[15] all-cause mortality,[16] lung infections,[17] and atherosclerosis.[18]

The strongest associations have been with cardiovascular disease. In 2017 Miller et al provided evidence for the mechanism underlying this. They demonstrated that inhaled nanoparticles translocate from the lung into the circulation and that the particles accumulate at sites of vascular inflammation. Particle translocation appears to be size-dependent, with greater translocation and accumulation of the smaller nanoparticles.

Earlier research had shown that acute exposure to diesel exhaust causes vascular dysfunction, thrombosis, and myocardial ischemia in healthy individuals and in patients with coronary heart disease.[19] Chronic exposure to particulate air pollution is associated with development and progression of atherosclerosis in both animals and humans.[20] Miller made it clear how this happens. Inhaled particles deposit deep in the lungs and trigger oxidative stress and inflammation.[21] The nanoparticles themselves penetrate the alveolar epithelium and translocate into the circulation and directly contribute to disease.[22] The nanoparticles probably trigger tissue inflammation, which increases the translocation of particles.[23]

The range of prognostic numbers we find in these papers by Wang, Pranata, Hayes and others might be used when looking at out current lockdown. These review predictions vary from a 5% increase in all-cause mortality (Wang), a 10% increase in CVD mortality (Pranata) to a 16% increase in mortality from ischemic heart disease (Hayes) for a shift of 10 $\mu g/m^3$ in average PM2.5. [I probably should slip in Pope et al in their 2015 study reported that, for a similar increase in fine particulate air pollution, there was a 12% increase in CVD deaths.[24]]

These findings provide a crude gauge with which to make estimates of what we might predict to see in future studies that look back on this time period in regard to CVD mortality.

In an article posted in early March on the academic website G-Feed, Marshall Burke, a professor at Stanford's Environmental Earth Systems Science Department, calculated that the decreased air pollution in China this past winter, may have saved twenty times more lives than were lost due to the COVID-19 infection in that country.[25] Burke relied on older Chinese research to make his calculation; neither Pranata nor Wang had been published when he was making his calculations.[26]

Inhaled nanoparticles translocate from the lung into the circulation.

Burke utilized the 2016 findings from Su et al who had analyzed data collected during the 2008 Summer Olympics and Paralympic Games. Recall how China went to great efforts to reduce ambient air pollution during the games by restricting traffic and shutting down pollution sources.[27] Burke estimated that the current shutdown in response to COVID-19, resulted in "…about a 10 ug/m3 reduction in PM across China in Jan-Feb of 2020 relative to the same months in the previous 2 years." He et al had reported, "…that a 10 percent decrease in concentrations reduces the monthly standardized all-cause mortality rate by 8 percent."[28]

Burke writes, "Putting these numbers together…yields some very large reductions in premature mortality.... I calculate that having 2 months of 10 ug/m3 reductions in PM2.5 likely has saved the lives of 4,000 kids under 5 and 73,000 adults over 70 in China."

Actually, on April 3, 2020, the European Union's Copernicus Atmosphere Monitoring Service announced that comparing the difference between the monthly average for February 2020 and the mean of monthly averages for February 2017, 2018 and 2019 indicates a reduction of about 20-30% in surface PM2.5 over large parts of China in February 2020 based on information from their satellite observations.[29]

The US started out with much cleaner air than China so perhaps these relationships will not apply the same way. Yet recall that Wang et al, reported, "…no evidence of a lower threshold for response or of lower Risk Ratios (RRs) at low PM2.5 levels." This suggests that lowering our own pollution levels may still result in significant improvements.

About 647,000 people die in the US each year from CVD.[30] If our staying at home were to lower this figure by 10% (to use Burke's conservative figure), that would prevent nearly 65,000 deaths from CVD alone, a change that should be noticeable. Pranata's 16% decrease could save over 103,000 lives a year.

In the coming months and years, we may see more accurate measures of the true impact air pollution has and perhaps be able to more accurately calculate its costs to communal health. Talk of any cost benefit analysis of our attempt to save lives by slowing viral spread are premature as we have yet to measure the actual impact of our actions. As I wrote, we're part of a large experiment; the data hasn't been collected or analyzed yet.

Unfortunately, our experiment may be confounded by other concurrent events. The EPA is rolling back certain pollution enforcement rules, and it may be difficult to account for the resultant harm this may cause when balanced against the health improvements from cleaner air. Job loss and the related shifts that unemployment have on heart health outcomes will also need to be taken into account.

Time will tell, but in the meantime, those who live in the city are enjoying cleaner air and bluer skies than we have seen in decades, even if we have to wear a face mask and do so from our front porch. ◆

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

Metabolic Flexibility – How to Reverse Metabolic Inflexibility to Heal Chronic Disease

by Bonnie Nedrow, ND

Metabolic Flexibility

Metabolic flexibility (MetF) is the ability to rapidly switch between oxidation of carbohydrates and fats based on nutrient availability.[1] MetF allows for the storage of fuel when food availability is high and utilization of that stored energy when food availability is poor. This metabolic elasticity is critical to human survival during periods of scarcity and allows for the enjoyment and celebration of food when in abundance.

Insulin is a key player in orchestrating metabolic substrate modulation. When a meal with carbohydrates is eaten, insulin increases, which stimulates oxidation of glucose and storage of both carbohydrates and fatty acids. In a eucaloric state, where food intake matches fuel expenditure, an individual will neither gain nor lose weight. When caloric intake exceeds fuel needs, excess calories are stored as fat to be accessed at a future date to fuel sub-caloric periods of time.

Historically, humans have repeatedly experienced periods of both feasting and famine – to some extent seasonally each year and with extended intervals of low caloric intake during lean years and excess consumption during plentiful years. This variation in caloric intake is also seen on a much smaller scale in the daily cycle of the fasted/fed states. On a daily basis, it is common for people to fast overnight for roughly 10-12 hours: a period longer than can be sustained by glucose metabolism alone. In lean healthy individuals, fatty acid oxidation increases during the overnight fasted state. Following a meal with carbohydrates, these individuals secrete insulin, thereby suppressing fatty acid oxidation and shifting metabolism to primarily glucose oxidation.[2] The daily fast/fed cycle in this example demonstrates metabolic flexibility.

When healthy lean people are exposed to prolonged fasting or prolonged exercise, fatty acids and ketones increase and energy is maintained despite an imbalance of fuel intake and expenditure. These are other examples of how MetF maintains optimal function despite environmental unpredictability.

Metabolic Inflexibility

Metabolic inflexibility (MetIF) is a modern malady linked to metabolic syndrome and to many chronic diseases. While it may seem obvious that overconsumption of calorie-dense food is the root cause, it turns out to be much more complicated. Other key contributory insults include poor sleep combined with high stress, environmental toxicants (chemicals that are detrimental to health), poor exercise habits, and a mismatch of activity to circadian rhythms. To reinstate metabolic flexibility in metabolically ill people, all these factors must be addressed.

Insulin, the conductor of metabolic substrate modulation, does not have the same impact on people who are obese and insulin resistant. Contrary to metabolically well people, this metabolic type shows reduced fatty acid oxidation in general, a lack of increase in fat burning during the fasted state, and minimal suppression of fat metabolites with an increase in insulin. These people end up with excess fuel in their blood stream and in storage but lack the ability to easily burn either glucose or fat. They are overweight, fatigued, and inflamed from this excess that does not fuel their body.

Someone who has become metabolically inflexible cannot easily mobilize fat from storage. Instead, they become dependent on frequent meal spacing to stay fueled with carbohydrates. This is driven by neuropenia, a shortage of glucose in the brain, usually due to transient hypoglycemia. It becomes increasingly difficult to stay on a eucaloric diet and nearly impossible to sustain a sub-caloric diet to achieve weight loss and re-establish metabolic flexibility. What was an advantageous metabolism for a world where food security was uncertain has become a curse in a society where abundant food is driving metabolic disease.[3]

Metabolic Syndrome

As stated earlier, MetIF is associated with metabolic syndrome (MetS): the clinical presentation of a human

system on the verge of chronic disease. Diseases associated with this condition include diabetes, obesity, cardiovascular disease, Alzheimer's, and non-alcoholic liver disease. MetS is defined as elevated blood pressure, truncal weight gain, high fasting glucose, high fasting triglycerides, and low HDL. More recently, elevated liver enzymes, in particular alanine aminotransferase (ALT) and gamma-glutamyl transference (GGT), have been added to the list of biomarkers associated with MetS. Looking beyond the clinical definition, metabolically ill people experience the all-too-common symptoms of weight gain, fatigue, and inflammation throughout their body. According to the National Health and Nutrition Examination Survey (NHANES), the incidence of MetS increased by 35% between 1998-2012 and is a common presentation in a large percentage of patients seeking medical care today.

Test	Optimal	Metabolic syndrome
HDL	>50	<50 women/<40 men
Triglycerides	50-90	>150
Fasting glucose	60-90	>99
ALT	teens	>23 women/>25 men
GGT	teens	>20
Hip/waist	0.8 or less	>0.85 women/>1.0 men
BP	60-75/120-125	>80/130 (either value)

Obesogens

In the past several years, the general knowledge and recognition of the health impacts of endocrine-disrupting chemicals has grown. However, the well documented phenomenon of obesogens, a sub-class of endocrine disruptive compounds, has been slower to be recognized. Given the world-wide epidemic of obesity and the comorbidities associated, there is a growing need for clinicians to incorporate diagnostic and therapeutic modalities aimed at a reduction of both exogenous and endogenous exposures to this class of compounds.

Obesogens are chemicals that interfere with healthy metabolic regulation through promotion of adipogenesis and induction of fat storage. One of the most studied mechanisms for these effects is the peroxisome proliferator-activated receptor PPAR-γ. PPAR-γ programs increased adipocyte number and size in the developmental years as well as promoting lipid accumulation and storage in adults. Additionally, there are many steroidal endocrine disruptive compounds that also induce obesity. Exposure to obesogens during development predisposes an individual to increased susceptibility to these same chemicals at a later date. In this fashion, long-term exposures to obesogens from conception onward drives the obesity epidemic.[4]

The list of endocrine disruptive chemicals (EDCs) stands at about 1000. Many EDCs have been identified as obesogens and that list is growing steadily as new compounds are added.[5] Table 1 offers some examples of classes of chemicals and common exposure routes.

Sleep

Sleep restriction and circadian rhythm disruption are both contributors to altered eating patterns and weight gain. Persistent short sleep patterns, measured as less than seven hours per night, predisposes adolescents and young adults to the development of obesity and increased waist circumference.[6] Assessment of the National Health and Nutrition Examination Survey (NHANES), with a sample size of nearly 14,000 adults over the age of 20, demonstrated a linear relationship of increased BMI and waist circumference in those who slept fewer hours. Not only were adults who slept the recommended 7-9 hours more fit, those who slept more than 9 hours had improved anthropomorphic measurements over those sleeping the recommended 7-9 hours per night.[7]

The suprachiasmatic nucleus (SCN) in the hypothalamus, referred to as the central clock, is the primary mechanism for synchronizing circadian rhythms. The SCN itself is controlled by zeitgebers, environmental and social cues including daylight, artificial light, mealtimes, and timing of exercise/activity. Light-dark cycles have the greatest impact on the SCN, which blocks melatonin production when light is present and stimulates the pineal gland to secrete melatonin when it is dark. Melatonin, in turn, induces sleep, has antioxidant capacity, modulates the SCN, and improves insulin sensitivity. Because all ➤

Table 1. Endocrine-Disruptive Chemicals

Chemical	Common Exposures
Organotin TBT	Seafood, polyvinyl chloride plastics, house dust
Nicotine	Fetal exposure from maternal smoking in pregnancy, children with passive smoke exposure
Perfluorinated chemicals	Seafood, house dust, contaminated water near industry
Phthalates	Cosmetics, body care products, plastic containers, dust, fatty foods
Bisphenol A, S and F	Food and drink packaging, receipts, breast milk and formula
Acrylamide	Produced when cooking carbohydrate-containing foods at high temperatures by frying, baking, or roasting
Food additives & preservatives: MSG, 3-BHA (common preservative), dietary emulsifiers carboxymethylcelluclose and P-80, the surfactants DOSS and Span-80	Processed foods
Glyphosate	Commercial foods
DDT	Fatty animal products, including meat and dairy
PCBs	Fatty animal products, including meat and dairy
Organophosphate pesticides	Commercial foods, contaminated water, dust
Arsenic	Water, cigarette smoke, CCA-preserved wood structures, arsenic containing pesticides, contaminated foods
Cadmium	Cigarette smoke, contaminated foods, plastics, paints, batteries

➤

the zeitgebers are controlled by lifestyle choices, this is a promising area of intervention for people with metabolic disease.[8]

There is an epidemiologic association of diabetes in people who work at night. This phenomenon is hypothesized to occur due to a misalignment between sleep/wake behavioral patterns and internal circadian rhythms, which are governed by daily light/dark sequence and the feeding/fasting cycle. Regardless of when a person sleeps, comparing normal night sleeping to daytime sleep of shift workers, there remains a consistent decrease by as much as 17% in glucose tolerance at 8 PM as compared to 8 AM. This is associated with insulin resistance that is commonly seen in those who work at night.[9]

Exercise

It has long been recognized that metabolism is modified by physical activity (PA). PA consists of structured exercise, sports, and activities of daily living, including occupation, leisure, and active transport. Metabolic impacts of PA include increased insulin sensitivity and insulin activity, with a reduction of insulin resistance, improved lipid profile, decrease in both fasting blood glucose and hemoglobin-A1C, and weight reduction, specifically visceral adipose tissue.[10]

While the light/dark cycle is the prime zeitgeber, exercise has been recognized as a secondary zeitgeber that can be used to entrain a health-promoting circadian rhythm. In shift workers and those who frequently change time-zones with travel, exercise has been effectively used to more rapidly re-establish healthy rhythms.[11]

There is currently significant interest in discovering the best time for exercise. While exercise performance as measured by strength, endurance, and power is more robust in the late afternoon and evening, this does not answer the question of what time of day offers the most optimal health promotion. Studies in mice, muscle cells, and humans confirm this diurnal pattern of enhanced evening performance and illustrate the greater dependance on carbohydrates to produce this exercise efficiency.[12] This phenomenon has been successfully utilized by athletes to optimize their performance and set personal athletic records. For metabolically inflexible people, evening exercise may be a successful strategy to lower blood glucose after the evening meal. Conversely, morning exercise may better enhance fat oxidation.

Exercise at 7 AM compared to both 1 PM and 7 PM in 20 prehypertensive men demonstrated improved blood pressure readings. Additionally, deep sleep and overall quality of sleep as measured by the number and duration of nocturnal wakening was significantly better in the early exercisers.[13]

Timing of exercise in relationship to a meal also has great impact. Pre-meal exercise significantly reduces appetite and food consumption. Research points to exercise-induced suppression of ghrelin, the hormone responsible for increasing appetite and adiposity. Of note, these effects are transient and demonstrate best efficacy when a meal is eaten within 30 minutes of exercise. Pre-meal exercise was also more effective than post-meal exercise at optimizing triglycerides and HDL cholesterol. This effect was longer lasting with effectiveness seen for many hours post exercise. Both pre- and post-meal exercise was effective for prevention of post-prandial hyperglycemia.[14]

Timing of Meals

While it is evident that energy expenditure must match caloric intake to avoid weight gain, less is said about the effects of the timing of a meal on metabolism. Triglycerides (TG) are higher and remain in the blood stream longer when a high-fat meal is consumed at night as compared to a meal eaten during the day. Comparing lunch to breakfast demonstrates that a mid-day meal produces the lowest blood TG levels whether or not a meal has been eaten at breakfast. This difference is hypothesized to reflect a greater uptake of TG into skeletal muscles cells mid-day. Glucose tolerance on the other hand is best in the morning, and carbohydrates are least tolerated in the evening. Amino acid absorption also shows a diurnal pattern with enhanced morning uptake as compared to the evening. Finally, the mismatch of the sleep/wake and feeding/fasting where calorie consumption is stacked in the evening, leads to metabolic disease and weight gain despite a eucaloric diet eaten that day.[15]

Not only does a mismatch of circadian rhythms and feeding patterns cause weight gain, but this mismatch is also an obstacle for weight loss and metabolism repair. In a large post-bariatric surgery study, eating the main meal on average 22 minutes later in the day was associated with a greater number of poor responders to this weight-loss therapy despite similar food composition, number of calories, and level of activity.[16] In a small study (n=32) of young women on a weight loss program, those who ate lunch at 4:30 PM, as compared to eating at 1:30 PM, showed decreased glucose tolerance and carbohydrate oxidation with a lower resting energy expenditure.[17]

Fasting

Intermittent fasting (IF) is rapidly becoming a popular and effective tool to address metabolic disorders from obesity to diabetes to cardiovascular disease. Models of IF include a reduced daily feeding window, exemplified in time-restricted feeding (TRF), and alternate day fasting (ADF) with a fasting day followed by *ad libitum* feeding day. ADF has also been modified to allow one meal on the day of fasting and is referred to as an alternate day modified fast (ADMF). Also popular is the 5:2 diet with 5 days of ad libitum feeding and 2 days of fasting, which can be back-to-back or separated by feeding days. When compared to daily caloric restriction (CR), these diets perform equally well for weight loss, diet adherence, and for optimizing most

cardiometabolic markers. However, fasting models consistently outperform CR for reducing insulin resistance.[18] For this reason, IF offers more promise for reversing metabolic inflexibility while weight loss goals are being met.

The effectiveness of intermittent fasting for weight loss is frequently attributed to an overall reduction in calories similar to CR diets. In a study comparing ADF with ad libitum 8-hour TRF, ADF demonstrated 4-6% weight loss in 12 weeks vs. roughly 3% in 12 weeks for TRF. This effect was hypothesized to be due to the overall greater caloric restriction of ADF.[19]

To date, IF and CR studies show inconsistent and conflicting results in terms of cardiometabolic improvements beyond the effects of IF on insulin. This may be due to additional factors such as exercise, sleep, stress, cultural norms and behaviors, macronutrient balance, and time of eating related to circadian rhythms.[20] Furthermore, food quality, optimal nutrient support, toxicant exposure, and genetic differences are likely to impact metabolic pathways driving metabolic disease. Finally, digestive health imbalances and microbiota dysbiosis are associated with and have been shown to drive metabolic illness. This topic alone requires an in-depth understanding beyond the scope of this article.

Where Modern Life "Messed It Up" and How to Get Back on Track

In industrial countries where MetS is prevalent, most people are exposed to calorie-dense nutrient-poor food on a daily basis, while rarely facing food shortage. This shifts metabolism toward fuel storage that is not needed at a future date. This one-way path leads to macronutrient excess in the blood stream as well as ever increasing fat stores. Metabolically, this is driven by inappropriate insulin activity and response.

It has long been recognized that the lifestyle modification of diet, exercise, and circadian rhythms is key to reversing metabolically driven chronic disease. While blood sugar dysregulation, excess weight, and obesity are common features of metabolic illness, caloric restriction and weight loss alone often do not heal the underlying disorder. This has been demonstrated repeatedly both clinically and scientifically. Cardiometabolic profiles do improve with weight loss achieved through caloric restriction; however the metabolically dysregulated profile returns as soon as a eucaloric diet is resumed. To achieve lasting health benefits, metabolism must return to the flexible state.

There is considerable disagreement regarding the best time for eating, sleeping, and exercise to achieve positive and permanent results. Likewise, there are conflicting arguments pitting a low-fat diet against a low-carb diet. Clinically there is always a balance between what science demonstrates and what the patient in front of the clinician exhibits.

This is where the art of medicine dictates intelligent experimentation and individualization. To heal metabolism, it is important to address an individual's cultural norms, personal preferences, and work requirements. The next step is to introduce a nutrient-dense minimally processed and low-pesticide diet. This is followed by sleep optimization and a manageable physical activity schedule. Once these measures are instated, assess and minimize toxicant exposure of obesogens and consider reducing endogenous stores of these compounds. The plan created for this individual is then assessed and adapted on a regular schedule over a period of months to years. Once metabolic flexibility is reinstated, a supported plan to maintain MetF is often essential to create lasting health.

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Diagnose and Treat Hypothyroidism in 2021, Part 1: New Endocrinology

by Alan B. McDaniel, MD

Introduction

This article reviews the functions of thyroid hormone and how to diagnose and treat its deficiency. Because the physiology of thyroid hormones is complex, featuring the processing of a pre-hormone to the active form – or its conversion to inactive and even inhibitory forms – good treatment of hypothyroidism is not as simple as many practitioners have been led to believe.

Important evidence is offered to help those who treat hypothyroidism achieve better success for their patients. Readers who in this article may recognize their own needs can show it to receptive providers. Four points are of paramount importance:

1. Thyroid hormone doses must be divided at least every 12 hours – *even levothyroxine*.
2. Therapeutic blood levels should be tested according to peak/trough fluctuations and *mid-way between doses works best*.
3. The **ratio** of *total*T3 (tT3) to reverseT3 (RT3) is the best indicator of actual thyroid hormone function in the body.
4. Many patients will need to take T3 along with T4 for their best clinical results.

What Is Hypothyroidism?

Hypothyroidism is best defined as "the clinical consequences of inadequate thyroid hormone in the body."[1] The lack of thyroid hormone is the world's most common endocrine disorder (unless you count menopause). It is estimated that about 5% of people in the US are hypothyroid[2,3] which may be conservative.[4] The disorder is four-times-more common among women than men and its prevalence significantly increases with age.[5]

Thyroid hormone metaphorically sets the thermostat for the metabolism – the process by which we make and use energy.[6] The *receptor* for this most-important effect of thyroid hormone is located within the cell nucleus. When active thyroid hormone (T3) binds to this receptor, the resulting protein-complex is a transcription factor – it activates the "reading" of the cell's genetic code.

Sections of DNA that encode thyroid hormone-sensitive programs are marked by "thyroid response elements," to which the thyroid transcription factor joins. Here, the transcription factor "unzips" the DNA to make messenger RNA.[7] This activates all genetic programs that up-regulate the activity of cells and their metabolism. Conversely, the DNA programs that reduce cellular activity are inhibited.[8] Low thyroid is truly a serious condition.

The symptoms of thyroid insufficiency come from low metabolism and depressed cellular activity. The British National Health Service lists many of them (*but not all*): Tiredness; being sensitive to cold; weight gain; depression; slow thoughts and movement; memory problems; constipation; muscle aches, cramps, and weakness; dry and scaly skin; brittle hair and nails; loss of libido; irregular or heavy periods, and carpal tunnel syndrome (pain, numbness and tingling in the hand and fingers).[9] Late symptoms can include low-pitched, hoarse voice; puffy face; loss of eyebrows; slow pulse; hearing loss, and anemia. Other useful and longer lists are available.[10]

Physiology 101: The Production of Thyroid Hormones

It is easier to fix something when you know how it works. So, before getting into the causes of thyroid insufficiency, let's review some basic facts – I promise that they are *all* relevant.

The production of thyroid hormones, their storage (a 100-day's supply[11]) within, and release from the thyroid gland into the bloodstream are regulated by the brain (hypothalamus) and the pituitary gland. Responding to the hypothalamus, the pituitary makes the appropriately named thyroid stimulating hormone (TSH or thyrotropin).[12] TSH released from the pituitary travels in the blood to the thyroid gland. There, it connects to receptors on cell membrane surfaces to stimulate all thyroid cell functions, including their proliferation, growth, and maintenance (trophic function). Without TSH, the thyroid gland cannot make hormone, and it shrinks (atrophy = "no trophic").

Thyroid hormones are made from the amino acid L-tyrosine and iodine. These are assembled by enzymes, which require also selenium and iron (at least).[13] Glutathione quenches their damaging oxidative by-products.[14] Thyroid hormones don't dissolve well in water, so after their release from the thyroid gland, >99% are bound to and carried in the bloodstream by various proteins.[15]

Thyroid hormones exert some "non-genomic" effects at receptors on cell surfaces, ion pumps and more[16]; but the *main event* involves the entry of free (unbound) hormones into cells *via* transport proteins. After running a gauntlet of transformative enzymes,[17] *activated* thyroid hormone enters the cell nucleus to unite with its nuclear receptor and exert its "genomic effect" on the DNA.

In the hypothalamus, circulating thyroid hormone regulates its own production by negative feedback. It blocks

the DNA sequence coding thyrotropin-releasing hormone (TRH) – the little protein that stimulates the pituitary to make TSH. With less TSH, less thyroid hormone is made. Conversely, low thyroid hormone allows TRH to rise, so that more TSH and thyroid hormone may be made.[18] Many clinicians consider a TSH value the most reliable indicator of low or high thyroid function – *though it is not*.

Pathology 101: Thyroid Gland Insufficiency

In the Victorian age, the function of the thyroid gland was not appreciated until Kocher had honed his surgical skills sufficiently to remove huge goiters …and discovered that this made patients even worse, causing "acquired Cretinism."[19] For the next hundred years, clinicians remained focused on the gland itself as the cause of hypothyroidism. In the 21st century, we also examine the processing and intrinsic effects of the four variations of thyroid hormone: T4, T3, RT3 and T2.[20]

Hypothyroidism is a common problem. Every practitioner who is so inclined will have opportunities to treat it. Evidence for this is seen in the lists of most-prescribed drugs in the US: Thyroid hormone has been among the top four for decades, recently along with opioids, statin drugs, and ACE-inhibitors.[21-23]

Causes of Hypothyroidism

The most common cause of hypothyroidism in the "West" is autoimmune (formerly "lymphocytic") thyroiditis (AIT).[24] The body's immune system attacks and destroys its own thyroid gland as though it were rejecting a mismatched transplanted organ. Indeed, this is the most common autoimmune disorder in the US: NHANES III found 13% of people have circulating anti-thyroid antibodies.[25] At the end of life, autopsy reveals lymphocytic thyroiditis is found in up to 50% of women and 20% of men.[26]

Surgical and radio-iodine[131] post-ablative hypothyroidism are the next most frequent in the US, from treatment for Graves', cancer, or goiter.[27] Congenital hypothyroidism is a newborn-nursery diagnosis, found once in about 3,500 live births.[28]

Iodine deficiency – when severe – is the world's leading cause of preventable hypothyroidism.[29] Deficiency of selenium and the presence of adverse chemicals (perchlorates, thiocyanates) worsen the problem. Milder iodine deficiency causes an enlarged thyroid gland (goiter) without frank hypothyroidism (as Kocher discovered).[30] In fact, in mild iodine deficiency, plasma T3 can be increased.[31]

Clinicians can expect to see other causes. High iodine causes *pseudo*-hypothyroidism.[32] The gland becomes TSH-resistant to protect itself from high iodine-exposure.[33] Lithium at doses used to treat type-I bipolar disorder cause toxic hypothyroidism in up to 20% of users by its effects on iodine-uptake into the gland and its "organification." However, lithium in these amounts more often produces a marked multinodular goiter.[34,35] (Lithium supplementation up to 10 mg daily seems safe.[36])

The TSH assay gives incomplete information and is prone to unreliable values.

Diagnosis of Hypothyroidism

Before starting to treat hypothyroidism, one must make a correct diagnosis. Mindful that the problem is common, we identify patients who are at-risk by their symptoms and physical examination.

Symptoms

Endocrine symptoms are notoriously non-specific – so that authoritative guidelines actually discourage the use of questionnaires.[37] However, we have been told that "patients who report multiple thyroid symptoms warrant thyroid testing."[2] Therefore I use a questionnaire, the severity of each symptom being graded from 0 to 4 by the patient (free on request).[38] It also provides a "baseline" inventory, against which the patients' progress (or lack thereof) later can be compared.

Be cautious about interpreting symptoms: Many symptoms of *hypo*thyroid function are *also* symptoms of *high* thyroid function. We will later examine some of the physiological reasons for this. Patients with either high or low thyroid hormone levels can complain of the following:

- Fatigue
- Heart palpitations
- "Brain fog"
- Irritable bowel
- Hair loss
- Muscle weakness
- Urticaria
- "Joint stiffness"
- Insomnia
- Anxiety, irritability
- Menstrual irregularities… and more.

It should also be remembered that some patients can be symptom-free…or wholly unaware of them. A patient with a palpably "bad" thyroid gland whose labs repeatedly showed TSH over 50 with low freeT4 denied any symptom. She finally agreed to try my treatment. On her return six weeks later, she was embarrassed to admit her co-workers were commenting on how bright and alert she had become and had been asking her what she was doing differently.

Before closing this section, remember that failing spontaneous remission, the end-stage of Graves' disease (*high* thyroid) is *low*-thyroid function. Ask your people about a remote history of Graves' symptoms, including a huge appetite without weight gain; being underweight; having felt hot or tremulous etc.[39] This history may influence treatment outcome.

Physical Examination

The physical exam is important; yet, after I've palpated their thyroid gland, many patients ask me what I had done, saying that nobody had *ever* examined them there. I am also dismayed by the prevalence of internet images showing practitioners supposedly examining the thyroid gland but nowhere near it – even on sites dedicated to the thyroid gland! Look at a diagram of thyroid anatomy: One of the best (unexpectedly) is on Pinterest.[40]

Operating many times on and around the thyroid gland has made me confident of finding it in the neck. I and others[41] examine patients face-to-face with the neck in a neutral position, not hyper-extended – this relaxes the strap muscles covering the gland. Place one thumb on the patient's "Adam's apple" (*for purists*: the laryngeal prominence of the thyroid cartilage). Place the other thumb on the cricoid cartilage (about 2 cm lower) … these landmarks are easily found; no worries.

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Noting the distance between your thumbs, drop the upper thumb from the Adam's apple to an equal distance below your cricoid thumb and nestle it in. It now rests on the trachea, below the thyroid isthmus – that's the spot! Now, put your cricoid thumb next to it, one on either side of the trachea and glide them up together. Before you get to the cricoid, you'll feel a "blip" as the thyroid gland slides under your questing thumbs. When you have identified the isthmus, circle about with your thumbs and palpate the lobes of the thyroid "bow tie."

What should we do when the larynx is ptotic and the gland is hidden behind the medial heads of the clavicles…or when it is buried deeply within an unusually stout neck? Keep your thumbs just below the cricoid and ask the patient to swallow. The thyroid gland is fixed to the laryngo-tracheal apparatus. With a swallow, the gland rises out of the depths and is palpable in its passage.

It is fine with me if your fingertips are more discerning than your thumbs: Alton Ochsner taught Tulane medical students to examine the thyroid gland from behind the patient. The excellent University of Washington web site is correct – this is a valid method, *if* you are examining the right spot.[41]

What should we expect to find? A healthy thyroid gland should be nearly as velvety as a lipoma. On examination, the inner voice says: "There it was, I think." A pediatric endocrinologist in my highest esteem has said we cannot feel a child's normal thyroid gland at all. Adult or child, when the gland is distinctly palpable, it is – to some extent – abnormal. If you can say "The thyroid is right here," it is probably unhealthy – and a biopsy usually shows fibrosis.[42]

As a rookie surgeon, I once thought hypothyroid people would have goiters. That's wrong; do NOT expect a big goiter – glands with lymphocytic thyroiditis are often smaller than normal.[43] The worst glands can feel like a piece of over-cooked liver – *firm* but usually not enlarged. Following palpation, the skin over the thyroid can flush redly for many minutes afterwards, a sign I associate with autoimmune thyroiditis.

Sometimes we can feel nodules, single or multiple, which take us beyond the scope of today's subject. Please know how to work them up. An authoritative guideline is free to download.[44]

Occasionally, a diseased gland feels perfectly normal on exam. This makes other, "secondary" signs of hypothyroidism more valuable. Is your patient overly-dressed for the ambient temperature? A wool sweater in July is a clue! Check for cold hands and fingers; flaky, raggedy fingernails; a slow pulse or a sluggish biceps brachii reflex. Thinning hair is a common complaint, which is usually "relative" but often noticed by their hairdresser. Less commonly, the lateral one-third of eyebrows can be disappearing; or there may be puffy eyes and signs of "myxedema" (the 19th century name for hypothyroidism before the thyroid gland was understood).

Most Graves' patients (many of whom are subclinical and not diagnosed)[45,46] end up *hypo*thyroid. Is your patient oddly slender? Observe their eyes but remember: Inferior scleral show can be "normal" and the diagnosis of proptosis is made properly with an exophthalmometer.[47,48]

Laboratory Examination

Our history and physical examination having identified patients who may have thyroid trouble, we trust the laboratory for confirmation. Quoth the Expert: "In the majority of patients, thyroid disease symptoms are subtle… so only biochemical testing or cytopathologic evaluation can detect the disorder."[49]

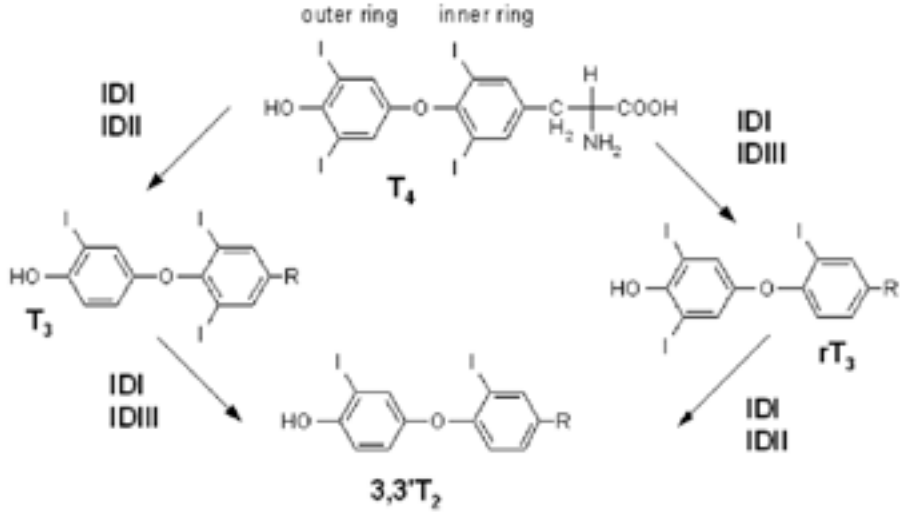
We are very fortunate to have an excellent variety of tests from which to select – more options than most providers understand how to use! The information they offer affords us a medical version of "measure twice and cut once" and helps to avoid therapeutic surprises. I prefer to order thorough testing, not a "bare-bones" work-up, although minimalism is officially encouraged.[50]

Physicians are concerned about the cost of laboratory tests. Lab bills to insurance look expensive but insurance pays a small fraction. Uninsured patients can get tests affordably from direct-to-consumer labs online. These results give accurate diagnosis (*priceless*) and prepare us to anticipate complications as we initiate treatment, and prevent disappointments – ultimately a great savings.

Before You Test

Even the best laboratory tests are vulnerable. "Pre-analytical errors" are largely avoidable.[51] Ask patients to stop biotin supplements 48 hours before the tests: Doses of 5 mg/ day can interfere with most immunoassays and may produce wholly misleading results.[52] We should enquire about other potentially interfering agents: Steroids, OCP and HRT; amiodarone; "hormone-free glandulars" (which legally can contain T3); large lithium doses and iodine supplements greater than 1.1mg/ day.[53] Remember

Figure 1. Deiodinase enzymes convert T4 to T3 or ReverseT3 – and then deactivate both to T2.



From: Wikipedia. https://en.wikipedia.org/wiki/Reverse_triiodothyronine

that patients may be unaware of taking even large doses of iodine – or may, for their own reasons, withhold information about taking thyroid hormone.

"Analytical errors" occur, producing misleading assays. Immunoassays are vulnerable not only to biotin but to "heterophile" antibodies – immunoglobulins produced by the patient's immune system that cross-react with the assay components.[54,55] When needed, liquid chromatography/tandem mass spectroscopy is a better method.[56] Blood spot assays are for screening newborns…I don't trust them for this work.

Perhaps the most important issue is post-analytical error, which could be paraphrased: *The ordering Doc doesn't know what the results mean*.[57] Even the most basic test, TSH should not be taken simply at face-value.

Thyroid Stimulating Hormone

An accurate TSH assay shows how much of that hormone was recently released from the pituitary gland (its half-life is six hours). When the thyroid gland is diseased, TSH becomes abnormal before freeT4 does; therefore, it is considered the "gold-standard" diagnostic test of hypothyroidism.[49] However, a thyroid-stimulating hormone assay doesn't prove normal or abnormal thyroid hormone function.

Researchers state TSH is "neither normatively fixed nor a precise marker of euthyroidism."[58] At best, it reflects the freeT4 concentration that acts on the hypothalamus and influences the pituitary.[49]

There are other issues with the TSH test. Clinical laboratories do not use a truly scientific "normal range" of TSH values.[59] Analysis by the statistical method shows the median TSH value is 1.5 µIU/L and the reference interval (-2SD to +2SD) *should* be 0.40 to 2.90.[49] However, the upper limit of "normal" has been extended to bring the reference-interval into line with expectations based on treatment results. In the last twenty years, the upper limit has been reduced from "10" to "4.5" in most national labs…but *statistically*, TSH = 3.0 is a high value.

TSH results can be misleading in other ways: Major issues include heterophile antibody interference and importantly, the abnormal amplitude of pulsatile TSH-secretion when the gland is damaged ("spikiness"). This was demonstrated in the laboratory[60,61] and can be observed in mildly hypothyroid patients.[62] Other complex issues have been raised that are beyond our present scope.[63,64]

The error of depending on TSH alone was demonstrated in a medical malpractice case: A woman was declared hyperthyroid because her TSH was low and her gland was ablated with radioiodine-131. She did badly on replacement therapy, so she was referred to an "Ivory Tower" endocrinologist. He also relied on TSH to regulate her T4 dose with similarly poor results. A few years – and a few doctors – later, an Emergency Department CT scan identified the adenoma crushing her pituitary and impairing her ability to make TSH.

Physiology 102: Thyroid Hormones

Most authorities state tests for thyroid hormones are unnecessary, unless the TSH value lies between 5 and 10 (when low fT4 distinguishes "true" from subclinical hypothyroidism) …but I disagree. The TSH assay gives incomplete information and is prone to unreliable values. For these and other reasons, I also test thyroid hormones: freeT4, freeT3, totalT3 and reverse T3 (RT3). Reviewing more physiology will help readers to understand why. Let's get to know the players.

The "fully-loaded" thyroid hormone carries four iodine atoms. It is called 3,5,3',5'-tetraiodothyronine (T4) and it is the most abundant (90%) of the three main hormone-products released by the thyroid gland.[65-67] The other two have three iodine atoms, lacking one on the outer (T3) or inner rings (reverseT3). Like the teeth on a key, the positions of the iodine atoms determine the functions of these variants.

We've seen that after release from the thyroid gland, the great majority of thyroid hormones are carried on proteins.[68] This permits their passage in the aqueous (watery) bloodstream,[69] and protects them from spilling out through the urine and from being broken down in the liver. Importantly, it also maintains a large, inactive but ready-reserve of hormone.

Modern assays are so sensitive they can accurately report the tiny amounts of *free* T4 and T3 (down to 2 pg/mL – that's 10^{-12} of a gram!). Most practitioners, knowing that only free hormones can enter cells,[70] order "free" hormone tests, not "total." Besides, "total" measures are significantly distorted by anything altering the liver's production of these binding proteins, including oral contraceptives, pregnancy or women's hormone replacement therapy; liver or kidney disease; insulin resistance, and severe illness.

T4 is a pre-hormone and T3 is active.

Most importantly, as you provide and monitor patient care, *remember*: **T4 is a *pre*-hormone** with little genomic effect. The 19th-and-20th-century focus on the thyroid gland only – its ability to produce T4 – is no longer adequate. We must know how the pre-hormone is being "processed."

To activate T4, cytoplasmic *deiodinase* enzymes within the cells of *many* tissues[71] remove one iodine atom from the outer, "prime" ring, making T3[17] (See Figure 1). Why does the gland release a pre-hormone instead of making all active T3? For the same reason Campbell's puts soup in cans instead of steaming hot bowls: It is safer to transport; it has a long shelf-life; and you should be able to open it anytime you want.

As stated, T3 "sets the thermostat of the metabolism." Its genomic effect stimulates every DNA program that increases cell metabolism and activity – and impedes the DNA programs that slow them.

Conversely, removing one iodine atom from the inner ring of T4 makes reverseT3 (RT3), which everyone agrees has absolutely no *stimulatory* effect and *cannot* be retro-converted to T3 (Figure 1). Increased RT3 has long been noted to indicate an adaptive down-regulation of thyroid hormone effect during stress (injury, illness, starvation, or psychological distress).[72-74]

Remember this paragraph Thus, the deiodination of T4 to either T3 or RT3 determines thyroid hormone function at the cellular level.[71] This "processing" of T4 is tightly controlled[75,76] and it is the primary means of regulating the biological activity of thyroid hormone.[20] The best indicator of this is the ratio of T3 to RT3, both in clinical use and in research.[77,78] Blood tests of these hormones are reliable too, accurately reflecting their values in tissue samples.[79]

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Calculate the Ratio of T3 to RT3

Even using the best assay (LC/MS-MS), there is too little *free* reverseT3 in the blood to be measured; thus, "*total*RT3" is reported. Because the amounts of binding proteins are so variable, the critical T3:RT3 ratio must be calculated comparing RT3 to *total*T3 – apples-to-apples, *total*-to-*total*. Efforts to compare freeT3 to RT3 are ultimately doomed to fail – as I learned years ago, when a congenitally athyreotic patient became pregnant.

The relative amounts of T4 and T3 within their "normal" ranges *and* the totalT3/totalRT3 ratio show how the body is processing its hormones. The value of analyzing these multiple parameters has been supported.[80] Patient 2 will show their clinical significance (Table 1): If T4 is a "can of Campbell's soup," does the body have a can-opener?

Table 1

TSH Ref Int.	0.663 0.45--4.50	0.711 Same
free T4 Ref Int.	1.66 0.82--1.77	0.80 "L" Same
free T3 Ref Int.	2.9 2.0--4.4	4.1 Same
total T3 Ref Int.	87 71--180	151 Same
Rev. T3 Ref Int.	36.1 H 9.2--24.1	13.3 Same
tT3/tRT3 ratio	2.4 "L" (10--14)	11.4 Same
Blood Drawn	6/ 12	6 / 14:08 12
Taking:	T4 112 1/2 q12h	T4 25+25 T3 10+7.5

Examine the values for all five tests I've recommended in the same critical way a basketball coach watches his five players on the court: Is each one where he should be and doing his job? Are all five coordinated and running the same play – or is someone out of synch and hurting the team?

Pathology 102: Define the Cause of Hypothyroidism to Treat It Skillfully

It is important to diagnose the cause of your patient's thyroid problem – and as my Med-Mal anecdote suggests, skipping this step can be harmful. We should test for autoantibodies; here's why:

We know that autoimmune thyroiditis (AIT) is the most common cause of hypothyroidism in the US. There are two main forms of AIT: Hashimoto's disease, which we all understand to cause hypothyroidism and Graves' disease – the most common cause of *hyper*thyroidism. Both can cause hypothyroidism, but they can respond very differently to our treatment efforts.

Hashimoto's is a T-cell mediated, destructive process.[81] Its hallmark autoantibodies react with the thyroid peroxidase enzyme that constructs thyroid hormone (TPO-Ab) and with thyroglobulin, the protein in which thyroid hormone is manufactured and stored (Tg-Ab).[13] These antibodies are probably cytotoxic, though that has been debated.[82]

Graves' disease involves both stimulating and destructive events: B-lymphocytes release antibodies that bind to thyroid cells' TSH-receptors (TSH-R) and, by molecular mimicry, make the cells respond exactly as they do to TSH.[4] Most Graves' patients *also* make the destructive autoantibodies typical of Hashimoto's disease.[83]

Always remember that any hypothyroid patient could have end-stage, "burned-out" Graves' disease.[24] This can affect your therapy: As long as a Graves' patient has a shred of functioning thyroid tissue, the TSH-receptor-stimulating antibodies (TRs-Ab or TSI, *formerly* LATS) can drive that residual thyroid to produce hormones unpredictably. We'll discuss this and other types of "autonomous function" presently.

Test Thyroid Autoantibodies

When a patient's thyroid gland is palpably abnormal, I test for both TPO-Ab and Tg-Ab. Yes, the medical literature now supports the value of testing Tg-Ab.[84] Various other anti-thyroid antibodies exist for which no commercial tests are available.[85]

If the history and examination raise a question of prior Graves' or give a hint of autonomous function, order either TSI (a biological assay) or the faster, less-expensive immunoassay for TR-Ab (which does *not* differentiate between stimulating and blocking antibody).[86] This complements your comparison of TSH and thyroid hormone levels and helps to predict autonomous function or unreliable TSH values. Identifying or anticipating such problems can improve treatment outcomes.

Disappointingly, not every case of AIT can be proven by these antibody tests. Probably because Hashimoto's is primarily a T-cell mediated disease, autopsy series have found up to 10% of glands with histological AIT are antibody-negative.[87] Ultrasound can help,[88] and I've learned to trust palpation.

Tests for Less-Common Causes of Hypothyroidism

Most post-ablative hypothyroid patients report their status; sometimes a surgical scar is the tip-off. Nutritional issues can be more challenging. As above, low iodine can cause goiters but less often hypothyroidism. In the US, we are more likely to see pseudo-hypothyroidism due to iodine toxicity,[32,89] often from people following ill-considered internet suggestions.

For iodine, test overnight-fasting blood or get a first-voided morning urine specimen – it is routinely used by the WHO, which considers 100 mcg of iodine/L "replete."[90] Others prefer a 24-hour-urine collection. I will not use the "iodine-loading test,"[91] which I believe is bogus – and *not* wholly safe.[92]

Pharmacological doses of lithium can cause hypothyroidism in up to 20% of chronic users.[34,35] More often, lithium in the amounts used to treat type-I bipolar disorder will produce a marked multinodular goiter. If you test, know that "therapeutic" blood values are actually thyroid-toxic, with cumulative effects.[93]

Basal Temperatures

It is tempting to measure basal axillary temperatures on waking in the morning. I believe low axillary temperatures imply low metabolic rate and may support laboratory testing,[94,95] but they do not prove low thyroid function. I have tried and will testify: Basal temperatures cannot be used to safely guide doses of thyroid hormone replacement.

Therapeutics 101: Treat Hypothyroidism…Successfully.

It is unlikely that any practitioner in the US will need to treat iodine-deficient hypothyroidism. To the many clinicians who give supplementary iodine, a caution: The iodine-depleted thyroid

gland enlarges and up-regulates all of its mechanisms for taking up iodine and incorporating it into thyroid hormone. Therefore, *hyper*thyroidism can occur if iodine is rapidly or excessively replaced; it is not uncommon and is sometimes severe.[96,97]

The amount of iodine supplementation should be moderate.[98] NHANES-III found elevated urinary iodine (>401 mcg/L) is associated with higher risk of all-cause mortality, whereas low iodine was not.[99] Some patients arrive for consultation with first-voided urine iodine values in the thousands of micrograms per liter.

Thyroid Hormone Replacement

It is important to ask if your patient has a preference for any particular form of thyroid treatment. For the sake of an orderly presentation, let's begin with a patient who prefers "orthodox" replacement with levothyroxine (T4).[100] Levothyroxine is synthetic but biologically identical. Proponents have touted the fact that T4 is a pre-hormone as evidence of its safety: They state that only the required amount of T3 will be made.[101] Critics ask if it *can* be…but that's for later.

Current guidelines encourage us to treat patients whose TSH value is >10 µIU.[100] Those patients with TSH between 5 and 10 may have "subclinical hypothyroidism,"[102] so treatment is recommended only if TSH is *consistently* elevated *and* freeT4 is low, regardless of their symptoms. Semantically, perhaps sub-*laboratory* is a more correct term. We'll re-visit this, at which time the truth of this statement will be validated: "(Our) needs include the development of superior biomarkers of euthyroidism to supplement thyrotropin (TSH) measurements."[100]

Pre-Treatment Considerations

Before starting treatment with levothyroxine (T4), always assess the patient's overall health, the nature of the thyroid disease, and the adequacy of other endocrine systems. For example, patients with no gland whatsoever – whether congenitally absent or ablated by operation or iodine 131* – are often said to be the *most* difficult: They have no endogenous production to "back them-up"[100] when they miss a dose *or* if our treatment efforts go off-target.

The adrenal glands are essential to our metabolism; if thyroid sets the thermostat of the metabolism, the adrenal is the furnace. The entire spectrum of adrenal dysfunction, from Addison's to the lightly regarded "adrenal fatigue" should be addressed.[103] Decreased adrenal mass is associated with long-term hypothyroidism, following experimental abnormalities of all three components of the hypothalamic-pituitary-adrenal axis.[104] Correcting the thyroid deficiency can create increased demands for adrenal steroids.[105] Thus, adrenal issues should be addressed before or concurrently with thyroid hormone replacement – *not* deferred to afterwards.

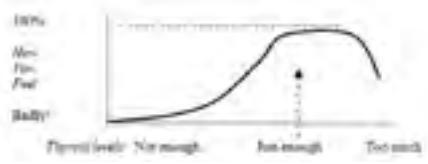
Steroid sex hormones also can be important: Postmenopausal women have complained that thyroid treatment provokes symptoms of estrogen deficiency. These included vasomotor flashes, mood swings and insomnia – none of which correlated to peak-and-trough fluctuations of thyroid hormone. This may be mediated by crosstalk at receptors in the nuclei[106-108] or perhaps simply by increasing the hepatic metabolism of estradiol.

Give Informed-Consent Talk Before Starting Treatment

The goal of treatment is to restore normal thyroid hormone effect at the cellular level, resolving the symptoms and signs of hypothyroidism. The coincidental restoration of desirable blood levels is both a goal and our guide, for we use the laboratory to monitor therapy.[100] In certain cases, slightly more thyroid hormone replacement is given to suppress TSH, as after thyroid cancer treatment[109] or to shrink a goiter.[110]

Risks should be discussed. Treatment can harm patients if we give too much hormone, or too little – or if a patient disregards our instructions and self-medicates according to whim. In IC-talk, emphasize that provider and patient are jointly responsible and both must cooperate. As above, age and other health issues influence risk. Otherwise, harm is possible only if the patient is allergic to some "inert" component of the tablet or if he chokes on a pill. Fertility can be increased, menstrual cycles may resume, and rarely, allergies might get stronger as this unwanted portion of the immune system is strengthened.

Explain the therapeutic dose-response curve: Too little treatment does nothing; just the right amount achieves all that T4 can – and too much makes things worse. Make sure the patient hears these words: "If you feel worse with treatment, we may have increased the dose too quickly, *or* the dose is incorrect, either in the amount or its timing[111,112] *or* there is an unsuspected problem."



Trusting our history, physical and lab findings, we expect treatment to do good things. Importantly though, every new thyroid prescription begins a treatment-trial. If it does not help, the reason must be determined. ◆

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

Alan McDaniel, MD, is a 1977 Tulane medical graduate. He trained in general surgery and emergency medicine before becoming Board-certified in otolaryngology with sub-specialties in neurotology and allergy. He has practiced privately since a two-year faculty appointment at the University of Louisville.

He has presented at various national meetings in the US (AAO-HNS, AAOA, ANS, AAEM, IFM, PAAS) and Mexico. Topics of his lectures and publications have included general surgery and otolaryngology; otology and neurotology; allergy; chronic fatigue and endocrinology. He has been a faculty member for the American Academy of Otolaryngic Allergy Basic and Advanced Courses and for the American Academy of Environmental Medicine. His two-day course "New Endocrinology" has been presented at the AAEM and elsewhere since 2005, to physicians from five continents. Work with dizziness and allergy in the 1980s led him to seek solutions for chronic fatigue syndrome. In turn, these investigations extended to the endocrine aspects of this and related conditions.

Since basic surgical training emphasizes the need to know several alternative approaches to an operation, he saw the logic of studying integrative and controversial medical methods. He has endeavored to understand these in the light of new facts from research, mindful that medical history shows innovation begins as a minority opinion.

Vaccination Support

by Debby Hamilton, MD, MPH

Introduction

The issue of how to vaccinate people safely and effectively is at the forefront of thought as we try to tame a pandemic of SARS-CoV2. If we accomplish this, we should be able to achieve herd immunity and return to a familiar way of living more quickly. Both the safety and the efficacy of vaccines are critical. The vaccines need to protect against infection and disease in order to dampen the pandemic. They also need to be safe so that enough people will not become ill from the vaccine itself. While there will always be side effects from vaccines, there are ways to naturally support the body to lessen these side effects without decreasing the efficacy of the vaccines. This nutritional support can be easy for patients to implement surrounding the time of vaccination and are applicable for all vaccines.

Types of Vaccines

The definition of a vaccine is a biological product that is used to induce a protective immune response to an infection that causes a disease when exposed subsequently to the infection.[1] Not all vaccines are the same in terms of development or efficacy. Vaccines have traditionally been defined as live or non-live (inactivated). Live vaccines such as the MMR are attenuated replicating strains of the pathogen. Traditional live vaccines produce a strong immune response. The concern is in immunosuppressed hosts that a live pathogen vaccine can spread the organism to the host or close immunosuppressed contact.[1]

Non-live vaccines contain a component that has antigenic properties to stimulate an immune response. These range from killed whole organisms (for example, inactivated polio), purified pathogen proteins (ex, acellular pertussis), recombinant proteins (ex, Hepatitis B vaccine) or polysaccharides (ex, pneumococcal vaccine).[1] Toxoid vaccines such as the tetanus vaccine use formaldehyde-inactivated proteins. The non-live vaccines do not produce as strong an immune response as the live vaccines. In order to increase the immunogenicity of the non-live vaccines, adjuvants are added. Adjuvants are substances that drive innate immune system pattern recognition receptor (PRR) activation.[2] Because the most common adjuvant is aluminum salt there have been health concerns because of the potential toxicity of excess aluminum. New adjuvants are being developed such as liposome based or oil in water emulsions.[1] Additionally, vaccines contain preservatives such as polysorbate 80 and stabilizers such as gelatin and sorbitol. From development of the vaccines, some contain small amounts of antibiotics, egg proteins, yeast proteins, and formaldehyde.

The first two COVID vaccines use a new mRNA technology. They use mRNA which is messenger RNA that instructs our cells to make a spike protein found on the outside of the SARS-CoV2 virus. The cells make the protein from the mRNA directions, but the mRNA never enters the nucleus of the cells where the DNA resides. This newly made spike protein is displayed on the outside of the cell which triggers an immune response to the SARS-CoV2 virus.[3] After two doses, both vaccines appear to have a strong immunogenic response. Additional ingredients in these vaccines include polyethylene glycol (PEG) to help the mRNA enter the cell. The concern with this ingredient is a potential allergic reaction from PEG antibodies from previous exposure to the chemical.

Protective Immune Response

Much like a natural infection, vaccines trigger an innate immune response that activates an adaptive immune response. The adaptive immune response contains both a cell mediated immune response by activated T lymphocytes and humoral immunity from B cells producing targeted antibodies.[4] This creates long-term immunological memory and protection from infection from antibodies and memory cells.[4]

Risks for Decreased Immune Response to Vaccination

The immune response to vaccination can vary greatly between individuals. Increased age is one of the primary factors associated with a decreased response to vaccines. Aging is associated with a shift toward anti-inflammatory interleukin-10, which is associated with a decline in CD8 T cell response.[5] The immune response to vaccines as people age is overall associated with decreased antibody and cellular immune responses.[5] Neonates can also have lower antibody responses, lower cellular immunity responses, and poorer response to polysaccharide antigens.[6]

Variation in immune response in individuals can include multiple other factors in addition to age. The microbiome plays a role in the immune

system. Changes of specific microbiota strains in the intestine and the lungs have been associated with decreased immune responses.[7-9] Current viral infections and the use of antibiotics may lessen immune response also.[5] Knowing this information may help with the timing of vaccines away from other illness. Behavioral factors that influence general immunity such as sleep, stress, alcohol, and smoking can also play a role in altered vaccine immunity.

Nutrition plays a large role in the maintenance of a strong immune response. Poor nutrition or a decrease in essential nutrients that are integral for a strong immune system can lessen the response to a vaccine. Vitamin D is one of the most researched nutrients for immune response to vaccination. In terms of the immune system, vitamin D plays a role in innate, humoral, and cellular immune responses.[10] Vitamin D supplementation before vaccination leads to higher immune markers of a positive immune response for both tetanus and influenza vaccines.[11,12] Vitamin A also plays a role in both innate and adaptive immune responses.[13] Several studies have shown the supplementation of vitamin A and D in infants lead to stronger immune responses.[13,14] Vitamin C is well known for its role in immune support. It impacts multiple immune functions, including function of both innate and adaptive immune cells, phagocytosis, and antibody function.[15,16]

Micronutrients and minerals also play a role in supporting immune function. Micronutrient deficiencies lessen immune function and decrease resistance to infections.[15] The mineral zinc is important for both innate and adaptive immune function. Zinc deficiency is one of the more common mineral deficiencies. If zinc is low it can negatively impact the function of lymphocytes, intercellular cytokine communications, and decrease first line innate immunity.[16-18] Overall malnourishment can contribute to decreased vaccine responses also. Research on malnourished children has shown decreased immune responses to multiple vaccines.[5]

Immune Support and Nutritional Support

In order to maximize the immune reaction to a vaccine, the immune system needs to be healthy and strong. General nutritional supplementation with a targeted multi-vitamin can have a large impact. I usually recommend one week before to two weeks after a vaccine, a general immune and nutritional support program along with detoxification support described below.

I begin with the basics of a multi-vitamin with minerals such as the Physician's Daily (Researched Nutritionals) or individual supplementation of vitamin A 2500 IU's daily, vitamin D 2,000 IU's daily (or more if levels are low), zinc 25 mg, and vitamin C 1,000 mg plus. With COVID there is evidence that elevated intake of vitamin C of several grams a day helps decrease morbidity and mortality.[19,20] Because of this, I add extra vitamin C; and since liposomal C is better absorbed with lower GI side effects,[21] I often recommend liposomal C-RLA (Researched Nutritionals) at 3,000 mg a day.

Detoxification Support

While vaccines provide us with immune protection from infection, they are also pharmaceuticals and contain adjuvants such as aluminum and other ingredients that the body needs to process. As we are introducing foreign substances into the body, it makes sense to support the detoxification pathways in the body to process these substances safely. The liver is one of our major detoxifying organs, and it relies on the master antioxidant, glutathione, to perform its role. In addition, intracellular glutathione levels impact lymphocyte function.[22] Depletion of intracellular glutathione inhibits activation of lymphocytes by an antigen, which is what we need for activation of an immune response to a vaccine antigen.[23] Intake of glutathione has been shown to increase the function of natural killer cells.[24] For glutathione, I recommend Tri-Fortify® Liposomal Glutathione at 450 mg daily one week before vaccine to two weeks after, depending on whether doing a one or a two dose vaccine series. The liposomal form of glutathione has been shown to improve absorption.[24]

In order to maximize the immune reaction to a vaccine, the immune system needs to be healthy and strong.

Detoxification is also aided by binders in the intestines and tissues that help the body eliminate toxins more efficiently. Binders can range from humic and fulvic acid, charcoal, to chlorella (an algae). Liver support and kidney support, which are two primary organs involved in elimination of toxins, can be supported by glutathione, dandelion, quercetin, and taurine to support bile acid function. ToxinPul™ (Researched Nutritionals) combines binders with detoxification support of the liver and kidneys in order to support the body properly processing the ingredients in the vaccines. Since some vaccines contain aluminum as an adjuvant, silica was included in the product to aid the body in aluminum removal.

Autoimmunity and Inflammatory Syndrome Post-Vaccination

Evidence from both clinical and experimental research models have shown post-vaccine autoimmunity.[25]

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In 2011, the term autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was developed to encompass vaccine-induced and adjuvant-induced autoimmunity and autoinflammatory diseases.[26] One of the primary adjuvants is aluminum, and it has been associated with adverse immune events, including autoimmunity.[26] In addition to the vaccine and adjuvants, other things contribute to the development of autoimmunity in a complex interplay of genetics and environment such as other infections, dysbiosis, and potentially underlying immune imbalance.[2,27] The combination of vaccines and/or adjuvants can also contribute to an innate inflammatory response termed an autoinflammatory response.[2]

Post Vaccine: Immune Modulation

It takes approximately two weeks after vaccination for an immune response to develop for some vaccines such as the COVID-19 vaccines.[28] For vaccine efficacy this is important to let the body develop these antibodies and cellular immune response. The concern is the long-term development of autoimmune and inflammatory issues in those people who are susceptible based on environmental and genetic factors. People with underlying autoimmune disease or chronic infections such as Borrelia are more likely to develop autoimmune reactions. Women are also at increased risk of the ASIA post-vaccine syndrome. Dysbiosis increases the risk of autoimmune disease because it is a pro-inflammatory state that drives up the Th17 cells and decreases the T-regulatory cells.

With this information, after immunity has developed, it is important to be able to balance and support the immune system. This includes decreasing inflammation to decrease Th17 and increase Treg cells to decrease autoimmune disease development. It also includes increasing Th1 to fight infections and decrease Th2 to decrease development of allergic reactions.

I recommend after two weeks, adding immune modulation with Transfer Factor Multi-Immune™ (TFMI) and CytoQuel®. TFMI contains transfer factors released by T-helper cells to support a strong cellular immune response. TFMI has research showing an increase in cells supporting both an innate and adaptive Th1 immune response.[29] It also contains a mix of medicinal mushrooms, astragalus, zinc, selenium, and antioxidant herbs that help modulate and support the immune system. Unpublished research shows an increase in IL-10, which supports T-regulatory cell function to decrease the development of autoimmune disease.[29]

CytoQuel® contains CurcuWin (highly absorbable curcumin), resveratrol, EGCG, tocotrienols, and NAC. Published research shows a decrease in pain and activating cytokines.[30] Adding CytoQuel® two weeks post vaccine can help modulate the potential ASIA response.

Conclusion

For vaccination to be successful, it has to lead to a strong effective immune reaction while also having a high safety profile. Since various factors from age to nutritional deficiency can weaken immune responses, it is important to support a person's immune system as well as possible before vaccination. Being able to detoxify and safely process the vaccine can also be supported by natural supplementation. Long-term risks of vaccines can involve autoimmune and autoinflammatory conditions, so I recommend targeted nutraceutical support for the patient.

Recommendations Summary

1. Begin one week before, through at least two weeks after vaccination
   a. Physician's Multi™
   b. C-RLA™
   c. ToxinPul™
   d. Tr-Fortify® Liposomal Glutathione
2. Begin two weeks after vaccination
   a. Transfer Factor Multi-Immune™
   b. CytoQuel®

For ongoing immune and detoxification support, the physician may recommend continuing nutraceutical support.

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Debby Hamilton, MD, MPH, is a pediatrician with experience in primary care, integrative medicine, research, speaking, and writing. Her education includes an undergraduate degree from Wesleyan University followed by a medical degree from Chicago Medical School, where she graduated with honors. She is board-certified in pediatrics, physician nutrition, and integrated/holistic medicine (AIHM), and has a master of science degree in public health (MPH).

Dr. Hamilton founded Holistic Pediatric Consulting in Colorado in 2005. Her practice focused on treating children with chronic diseases such as autism and ADHD, and preconception counseling based on her book, *Preventing Autism and ADHD: Controlling Risk Factors Before, During & After Pregnancy*. Her book led to her collaboration in the writing of *The Healthy Child Guide* through the Neurological Health Foundation. She has also contributed chapters for *Child Decoded: Unraveling Learning and Behavioral Disorders*.

In 2017, Dr. Hamilton joined Researched Nutritionals. She now splits her time between clinical work and expanding Researched Nutritional's clinical research on the efficacy of nutritional supplements, working on product development, and promoting the education of healthcare professionals.

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Laboratory Diagnostics in Chelation Therapy

by E. Blaurock-Busch, MSc, PhD

Chelation therapy is gaining recognition. During such treatment, metals are removed from the system by converting them to a chemically inert form that can be excreted. The chemical agents used to accomplish this are administered orally or intravenously; and to practice safely, specific laboratory diagnostics must be considered.

Parenteral Chelation: Which Renal Function Test?

The parenteral administration of chelating agents requires a healthy renal system. While experienced physicians have noted that a slightly compromised renal function does not necessarily need to exclude chelation therapy as an option, it is advised not to use IV chelation when renal function is impaired. Before the first treatment involving any type of parenteral chelation, it is essential to evaluate renal function. When renal function is impaired, parenteral chelation with chemical chelating agents such as EDTA or DMPS may not be the treatment of choice, especially by an inexperienced therapist. The following are some of the basic renal function tests.

Purpose of the Tests

- To evaluate kidney function and aid in the diagnosis of kidney disease.
- To monitor the progression of renal insufficiency.
- The BUN-to-creatinine ratio may aid in the evaluation of a person's state of hydration.

Special Concerns

- A diet rich in meats can cause transient elevations of serum creatinine and creatinine clearance.
- A high-protein diet or dehydration elevates BUN levels.
- Exercise may increase creatinine clearance.
- Some medications may affect BUN levels, serum creatinine, and creatinine clearance.

If a renal function test, such as Serum Creatinine is borderline high or high, a more in-depth evaluation is needed.

Below is a list of renal function tests aiming to create an understanding of function and necessity. Bevor laboratory diagnostics are implemented, evaluate the patient's medication and renal history.

Creatinine, General Information: Creatinine is a waste product of muscle metabolism and of creatine phosphate, the chemical that is produced by the body to supply energy, mainly to muscles. Age, ethnicity, gender, height and weight are used to calculate the creatinine level.

Creatinine is excreted exclusively by the kidneys, and its level in the blood is proportional to the glomerular filtration rate (GFR). When kidney function is impaired, less creatinine is excreted, thus its concentration increases in blood. Variations from normal creatinine levels could indicate kidney dysfunction and muscle problems (like rhabdomyolysis).

Serum Creatinine: The serum creatinine concentration is dependent on muscle mass, the patient's sex and age, race, and the amount of dietary protein consumed. In general, a serum creatinine test can give a good estimate of the actual glomerular filtration rate (GFR). It is the screening test most recommended for evaluating renal function. If results are doubtful, Cystatin C should be used to ascertain renal function.

Cystatin C: This is a low-molecular weight protein produced by all cells of the body with a nucleus. Unlike creatinine, cystatin C is not significantly affected by muscle mass, race, or diet.

When released into the blood, cystatin C is freely filtered in the kidneys. After glomerular filtration, cystatin C is reabsorbed and broken down at a constant rate. When kidney function is impaired, less cystatin C is excreted, and its concentration increases in the blood.

Cystatin C (in serum) could replace Serum Creatinine. It is recommended when renal function is not clearly established.

Urine Creatinine: This test reflects on fluid intake and renal function. A urine creatinine level of 0.8 to 1.2 g/L is considered normal for an unchallenged urine sample. A level below 0.8 indicates that the sample is diluted. The higher the fluid intake (through infusion fluid or drinking), the lower the urine creatinine level.

This test is commonly part of a urine metal analysis evaluation. It is used to calculate milligram or microgram per liter measurements to milligram or microgram per gram creatinine. This conversion reduces the potentially great margin of error that otherwise can result from a faulty sample collection and an incorrect sample volume.

A urine creatinine value of < 0.3 g/L is internationally used as the low borderline level for the conversion of test values to mg/g and mcg/g creatinine. When lower creatinine

levels are measured (usually due to a high fluid intake during urine collection time), the borderline value of 0.3 g/l is used for the conversion.

If a challenged urine sample shows creatinine levels higher than those seen in the unchallenged baseline urine, dehydration and/or kidney stress is indicated.

Creatinine Clearance: Usually a 24-hour urine collection is collected for this test. Note: The twenty-four-hour creatinine clearance overestimates GFR in patients with poor renal function.

Glomerular Filtration Rate (GFR): The GFR measures how much creatinine is in the blood and how much of it reappears in the urine. It is an overall indicator of kidney function. Age, ethnicity, gender, height and weight are used to calculate the GFR.

- Blood sample: Blood collection should be done simultaneous with urine collection and can be drawn at the beginning or end of the urine sample collection. A blood sample that has been collected in previous days is not suitable for the creatinine clearance test.
- Calculate creatinine clearance (glomerular filtration rate – GFR) from a timed urine collection (time, volume, and creatinine concentration), and plasma creatinine. In pediatrics, it is generally corrected to a body surface area of 1.73 m^2 (standard body surface area of an adult). Most laboratories provide the calculated rate.
- The National Kidney Foundation website allows you to simply calculate the GFR https://www.kidney.org/professionals/KDOQI/gfr_calculator
- Also see https://www.calculatorpro.com/calculator/gfr-glomerular-filtration-rate-calculator/

The exact value of GFR is difficult to determine. eGFR is estimated using equations based on serum creatinine or cystatin C levels.

Blood urea nitrogen (BUN): This test provides a rough measurement of the glomerular filtration rate, the rate at which blood is filtered in the kidneys. Urea is formed in the liver as an end-product of protein metabolism. Urea is carried to the kidneys for excretion and nearly all kidney diseases show an inadequate urea excretion, resulting in elevated BUN levels in the blood. Other causes of high BUN levels include gastrointestinal bleeding and steroid treatment.

Before the first treatment involving any type of parenteral chelation, it is essential to evaluate renal function.

What Tests Prior to Oral Chelation Treatment?

Oral chelators such as DMPS, DMSA and d-Penicillamine have a history of use. These chelating agents are swallowed, generally on an empty stomach. Oral chelators first pass through the gastrointestinal (GI) tract, the first binding site. Metals found in the GI tract are bound, forming metal-chelates, which are easily excreted via feces and also via urine.

It thus makes sense to start any type of oral chelation treatment with a GI cleanse, including liver and colon support. It should be noted that metal-chelate bonds are strongest in a slightly alkaline environment. *Lactobacillus acidophilus* and other probiotics are microorganisms that are able to improve pH and/or restore the gut flora. Probiotics are considered generally safe to consume but may cause bacteria-host interactions and unwanted side effects in rare cases.

Constipation or diarrhea must be treated prior to oral chelation, or else the patient may experience side effects such as intestinal cramping.

Liver function test might be recommended prior to chelation.

Sensitive patients should be started with a dose lower than the recommended one. For example, for DMSA the recommended oral dose is 10 mg/kg BW. A sensitive patient may have to be started with a starting dose of 50 or 100 mg. If no negative reaction is noted, the dosage can be increased according to body weight, age, condition, medical and pharmaceutical recommendation.

The absorption rate and binding ability of oral chelators is lower than that of those applied parenterally. For example: the binding ability of 250 mg DMPS applied orally is approximately 50% of the equal dose administered parenterally.

A body suffering from chronic metal exposure problems developes symptoms over time and often adjusts to its toxic environment. To slowly reduce a system's toxic burden will take time, but the body appreciates a gentle reversal of its chronic condition to health.

The efficiency of the metal detoxifying process can be determined through urine and fecal testing.

Fecal Metal Test: Testing maybe performed before and/or after oral chelation treatment. A comparison of pre- and post-results will indicate how effectively metals are bound in the GI tract. Patients suffering from digestive disorders (liver, colon etc.) must be carefully evaluated before oral chelator are given.

Pre-Sampling Suggestions

- Take probiotics, one to three times daily for one to two weeks prior to oral chelation.
- Four days prior to chelation, stop consuming fish and algae products such as chlorella.
- Two days prior to chelation, stop taking nutritional supplements or metal-containing medications (such as antacids), unless medically needed.
- Make sure the patient had a good bowel movement prior to chelation.
- On the day of chelation, give the oral chelator with one glass of water (200 ml room temperature) on an empty stomach unless otherwise indicated.
- For most oral chelators, DMSA included, the main metal binding will occur during the first three to six hours. after intake. Provide one more glass of water during that time. No tea or coffee should be consumed.

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- Two hours after the intake of the chelator, bread, fruit, or a boiled egg may be eaten.
- After sample taking is completed, the patient should drink enough water. He may eat normally.

Pre-Chelation Sample:

1. Before the fecal sample is taken, write patient name on the test tube provided by the laboratory.
2. Place clean toilet paper or a paper towel in the toilet to collect some feces.
3. Use spatula to fill one or two scoops of fecal matter into the test tube provided by the laboratory. Leave spatula with fecal sample in test tube. Do not fill up test tube.
4. Make sure the test tube containing the stool sample is tightly closed. Place it in the protective cover and send with patient information to the laboratory. Overnight shipping is not needed.

Chelation Sample: After the oral chelator intake, collect some of the first stool sample. This should not be sooner than three to four hours after the oral chelator intake. Follow Step 1 to 4 as outlined under *Pre-Chelation Sample*.

After sample taking is completed, the patient can resume his normal food and fluid intake. Please note that a sufficient water consumption helps to flush the renal system.

A comparison of test values will demonstrate how the oral chelator affected metal binding in the GI tract. For instance, if the arsenic concentration is higher before chelation, this indicates that some form of arsenic was ingested before chelation. If the arsenic concentration is higher in the post-chelation test, we can assume that the arsenic-excretion increased due to oral chelation process.

Urine Tests to Evaluate Metal Chelation

Urine is a liquid waste product. This fluid produced by the kidneys consists of excess water and the toxic waste products from food and drink. It normally is a clear, transparent fluid of amber color. The urine of an inadequately hydrated person is more concentrated and darker in color, while the urine of a well hydrated person is light. The more hydrated a person is, the more watery the urine. When taking riboflavin-containing B-vitamins, urine turns dark-yellowish. After the consumption of red beets, urine turns purplish red, because the beet color is not metabolized by the body, and thus excreted as is.

The average amount of urine excreted in 24 hours is from 40 to 60 ounces (about 1200 cubic centimeters or 1.2 liters). Chemically, the urine is mainly an aqueous (watery) solution of salts (sodium chloride and other metals), urea and uric acid. Normally, urine contains about 960 parts of water to 40 parts of solid matter. Abnormally, it may contain sugar (in diabetes), albumen (as in some forms of kidney disease), bile pigments, or abnormal quantities of one or another of its normal components.

Urine contains minerals, trace elements, including toxic ones and is, in most cases, an easy-to-obtain material. When we compare a nonchallenged versus a challenged urine sample, we assess the chelating agent's effectiveness and the detoxification process.

Following is an excerpt from Margret E. Sears' "Chelation: Harnessing and Enhancing Heavy Metal Deotxification – A Review," published online at *Scientific World Journal* (April 18, 2013). This review clearly states the importance of comparing levels of metals in urine before and after the administration of chelating agents.

> One of the most effective methods to evaluate net retention, or at least the biologically readily available metal load, is to compare the levels of metals in urine before and after the administration of a pharmaceutical chelating agent such as $CaNa_2EDTA$, DMSA, or DMPS (Hoet 2006) Variously known as "mobilization," "chelation challenge," or a "provocation" test, this procedure is not universally accepted as standard of care. Criticisms have included risks of the chelating drugs, and inappropriate comparisons of the provocation results with population norms rather than with patient baseline concentrations [85]. Indeed, some go so far as to say that any testing for metals when the exposure has not been identified; that is, when there is no reason for suspicion based upon known environmental history that toxins may be elevated, is inappropriate because of the possibility that false positives may lead to inappropriate, ineffective therapies and their attendant risks (Hoffman 2007). The use of chelation for diagnostic purposes, following dental amalgam removal or in asymptomatic patients with baseline urine or blood levels approximating population norms was deemed inappropriate in 2005 by staff of the Agency for Toxic Substances and Disease Registry (Risher 2005). Another criticism of use of a provocation test to judge net retention is the lack of a standard protocol, and laboratory reference ranges or guidance for interpretation of results (Brodkin 2007). Nevertheless, these shortcomings do not fundamentally invalidate the concept; work in this regard has started. Hansen et al. established such norms for protocol involving an oral DMPS test with four-hour urine collection, among 2223 citizens in Luxembourg (Hansen et al).
>
> Pre- and post-challenge testing may allow the clinician to identify which chelating agent is the most effective for the patient, and if oral agents are employed, possible absorption or tolerance problems may be identified. An open research question has to do with changes in metals excreted over an extended course of chelation treatments; whether in a person with high levels of multiple metals, one will be preferentially chelated initially, with a second then third being excreted over time with repeated treatments. This research would aid interpretation of chelation challenge tests, as well as enhance knowledge of chelation therapy itself.
>
> Comparison of baseline and provoked urine levels is entering standard practice and was used to determine inclusion in a trial of chelation therapy for children with autism. In this trial, however, a few children experienced worsening symptoms. Such worsening is ascribed to

redistribution of toxic metals, with insufficient excretory mechanisms in place, leading some practitioners to prefer unprovoked analyses up front, in sensitive, fragile patients. Therapy may be guided by parental, caregiver, and patient observations.

Baseline Urine Collection Protocol

Before the chelator is administered, patient must void bladder. Of that a small sample of 5-7 ml is collected and serves as the baseline urine.

If a 24-hour collection is needed, follow this procedure unless told otherwise.

- You will be given 1 or more containers for collecting and storing your urine. A brown plastic container is typically used. You will need to transfer the urine from the collecting container to the storage container. You will need to keep it cold.
- The 24-hour collection may start at any time during the day after you urinate. But your healthcare provider may tell you when to start. It is common to start the collection the first thing in the morning. It is important to collect all urine in the following 24-hour period.
- Don't save the first urine. Flush this first specimen and make a note of the time. This is the start time of the 24-hour collection.
- All urine, after the first flushed specimen, must be saved, stored, and kept cold for the next 24 hours.
- After 24 hours (of the start time) try to urinate to finish the collection process. No problem if you can't urinate at this time.
- Once the urine collection has been completed, a small (5-7ml) sample of the urine needs to be taken into a test tube provided by the lab. To do this, gently shake/invert the container before you use the syringe to draw the needed 5-7 ml of urine into the tube. This is the sample needed for the metal test.

  Note: A 24-hour urine collection is a safe, easy test. People can collect urine on their own, but certain factors may affect the accuracy of a 24-hour urine collection. These include the following:
- Forgetting to collect some of your urine
- Going beyond the 24-hour collection period and collecting too much urine
- Losing urine from the specimen container through spilling
- Not keeping urine cold while collecting it
- Acute stress
- Vigorous exercise
- Certain foods, such as coffee, tea, cocoa, fish, algae and supplements may be high in minerals or trace elements.

The Urine Challenge (Provocation) Test

- Before the chelation agent is administered, the patient should empty his/her bladder.
- Thereafter, it is best not to urinate for the duration of the chelation treatment i.e. allow urine to collect in the bladder. If this is not possible, urine should be collected in a clean container.
- The Urine Collection time for most chelators is the chelator's half-life plus the time it takes to administer it. Specifics are listed under each chelator.
- For specifics about the consumption of food or drink during the chelation treatment, see information as provided for the individual chelating agent.
- After the infusion time is finished and if patient collected urine in the bladder, he/she can urinate directly into a small urine cup. Of that 5-7 ml is needed for the post urine metal test. Specifics are listed under each chelator.
- For the remainder of the day, the patient should drink plenty of water and eat normally.

A comparison of metal excretion values before and after chelation indicates the effectiveness of the chelation treatment

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The Microbiome-COVID-19 Connection

by Ross Pelton, RPh, PhD

The purpose of this article is to publicize and discuss recent studies that link the gut microbiome to the risk and severity of COVID-19. Scientific understanding of the SARS-CoV-2 virus and COVID-19 disease is growing and evolving at an unprecedented rate. There are over 65,000 listings indexed in PubMed with COVID-19 in the title, as of October 2020, and over 3,800 clinical trials targeting COVID-19 have been registered around the world.[1]

COVID-19 and the Gut Microbiome

There are many lifestyle and environmental factors that play significant roles in the infectivity and relative virulence of COVID-19. Similarly, the gut microbiome influences and is influenced by many of the same lifestyle and environmental factors. Research assessing the relationship between the gut microbiome and COVID-19 is accelerating rapidly. A PubMed search revealed that in the past 12 months alone, there have been hundreds of studies published on the relationship between the gut microbiome and COVID-19.

COVID-19 is primarily thought of as a respiratory disease because the SARS-CoV-2 virus attacks the lungs, causing severe respiratory infections (SARS stands for Severe Acute Respiratory Syndrome). However, results from recent studies indicate that the composition of the gut microbiome can influence an individual's infectibility after they have been exposed to the virus as well as how severe the resulting COVID-19 infection might become. This fact takes on greater significance with the realization that the microbiome is a modifiable risk factor that has a significant impact on an individual's response if they are exposed to the SARS-CoV-2 virus.

Link Between COVID-19 and Dysbiosis: An individual's intestinal bacteria may influence the severity of COVID-19. Studies have reported that the gut microbiome is significantly altered in patients with COVID-19 compared non-COVID-19 individuals. Follow-up also revealed that the microbiome in patients who have been infected with COVID-19 is likely to remain significantly altered for at least 30 days after recovery from COVID-19.[2] COVID-19 patients with a perturbed microbiome are found to have elevated concentrations of inflammatory cytokines and also elevated levels of several inflammatory blood markers such as C-reactive protein (CRP) and interleukin-6 (IL-6).[3]

Researchers utilizing 16S ribosomal RNA genetic sequencing technology reported that patients with COVID-19 had significantly reduced bacterial diversity, significantly higher levels of numerous strains of bacterial pathogens, and reduced abundance of beneficial strains of bacteria compared to the microbiome in healthy controls.[4]

COVID-19 – The Importance of a Healthy Microbiome

The gut microbiome is increasingly being recognized as an important modifiable risk factor to COVID-19 disease.[5] Thus, it is important to educate people about the actions they can take to improve and/or maintain a healthy microbiome, which can play an important role in reducing their susceptibility and severity of COVID-19 infection.[6]

Vitamin D-Microbiome-COVID. Numerous studies have reported that vitamin D deficiency increases the risk of becoming infected with COVID-19 and the seriousness of outcomes. This article is summarizing the science linking dysregulation of the gut microbiome/dysbiosis with COVID-19 risks. What is less well understood is how vitamin D deficiency also causes negative changes in the gut microbiome, which weakens immune function. And of course, weakened immunity increases risks of viral infections.

An Epidemic of Epidemics

Mankind is now experiencing an epidemic of epidemics. We have an epidemic of heart disease, diabetes and metabolic syndrome, cancers, arthritis and inflammatory diseases, insomnia and sleep disorders, autoimmune diseases, Alzheimer's disease and dementia, osteoporosis, autism, ADHD, acid reflux, constipation, gut problems/dysbiosis, etc.

Three hundred years ago, none of the above epidemics existed. I propose that mankind is experiencing a gradual decline in immune function due to the following two major changes that have occurred over the past 300 years: vitamin D deficiency and disruption of the gut microbiome.

Vitamin D is known to regulate over 1,000 genes, many of which regulate immune function.[7] It is also estimated that from 70-80% of the immune cells in the body are located in the intestinal tract.[8]

The industrial revolution, which began around 1760 in Britain and gradually spread throughout the world, resulted in much of humanity (adults and children) to move off the land and work indoors in factories. In the 20th century, the widespread use of indoor lighting and air conditioning increased the trend for

people to spend more time indoors. Thus, over the past 300 years most humans have experienced a significant decline in exposure to sunlight, which has resulted in the current global epidemic of vitamin D deficiency.[9]

Vitamin D Deficiency ⍰ Dysbiosis

Just within the last couple years, studies have been published reporting that lack of exposure to sunlight and the resulting vitamin D deficiency upset the gut microbiome.[10,11] Thus, vitamin D deficiency and gut microbiome dysbiosis are linked, and both significantly contribute to a decline in immune function. Additionally, there are many other factors that contribute to dysbiosis. Some of these additional factors are diets high in highly processed, fiber-deficient foods, agricultural insecticides and herbicides, antibiotics, and other microbiome-disrupting drugs, etc.

COVID-19-Microbiome Risk Factors

As scientific understanding and clinical experience of COVID-19 grows, it is becoming clear that many COVID-19 risk factors are directly related to the gut microbiome. The following points illustrate the Microbiome-COVID-19 connection:

- **Age:** The diversity of the gut microbiota in elderly individuals has been shown to be reduced compared with that of younger adults. These changes are associated with a weaker immune system and chronic inflammation, which are COVID-19 risk factors.[12]
- **Diabetes:** Studies reveal that the composition of the gut microbiome is altered in patients with diabetes.[13] Diabetes mellitus (DM) is a comorbidity that is a significant risk factor for mortality from COVID-19.[14] Patients with COVID-19 who also have diabetes have a two-fold increased risk of mortality compared with non-diabetic COVID-19 patients.[15]
- **Hypertension:** Hypertension is associated with increased gut wall permeability and alteration of the gut microbiome.[16] Also, patients with hypertension have been found to have lower levels of important short-chain fatty acid (SCFA) postbiotic metabolites in their gut microbiome. Elevated blood pressure is a common comorbidity associated with a more severe course and mortality amongst patients with COVID-19. Nearly 30% of patients hospitalized for COVID-19 had hypertension,[17] and the presence of hypertension was associated with a 2.5-fold increased risk of mortality due to COVID-19.[18]

A healthy microbiome can play an important role in reducing susceptibility and severity of COVID-19.

Microbiome CD8+ Cells: Gut microbiota are regulators of key immune cells named CD8+ T cells. The CD8+ T cells (also called cytotoxic T lymphocytes) are referred to as *guided missiles of the immune system.* CD8+ immune cells in the GI tract are very important for immune defense against intracellular pathogens, including viruses and bacteria.[19] It has been shown that intestinal CD8+ T cells are dramatically reduced in patients with COVID-19.[20]

- **Short-Chain Fatty Acids (SCFAs)** are a class of postbiotic metabolites produced by numerous strains of probiotic bacteria. The SCFA butyrate is the preferred energy source for colonic epithelial cells, it helps maintain gut barrier functions, and it provides immunomodulatory and anti-inflammatory properties.[21] Butyrate and, to a lesser extent, propionate directly modulate numerous genes that are involved in the regulation of the immune response against COVID-19 infection.[22]
- **Microbiome-Disrupting Drugs:** Many people take one or multiple drugs that are known to disrupt the microbiome. As an increasing number of studies implicate an association between COVID-19 and the microbiome, it seems likely that microbiome-disrupting drugs are another risk factor that can influence susceptibility and poor outcome in COVID-19 patients.[23] Classes of drugs known to disrupt the gut microbiome include antibiotics, antacids and acid-suppressing drugs, non-steroidal anti-inflammatory drugs (NDAIDs), statins, oral contraceptives, opioids, atypical antipsychotics, metformin and most types of chemotherapy.[24]
- **Obesity:** Individuals with obesity are more likely to have intestinal permeability, LPS endotoxemia, and inflammation, which explains why COVID-19 severity is greater in obese individuals who frequently have a dysregulated microbiome.[25]
- **Bacteriocins** are a class of postbiotic metabolites that have well-documented activity against a range of pathogens in the gut microbiome. An increasing number of studies have been reporting that various bacteriocins have anti-viral activity against a number of different viruses. This suggests that bacteriocins produced by probiotic bacteria in the gut microbiome play a role in helping to protect humans against viral infections.[26] Individuals with dysbiosis or a compromised gut microbiome are less likely to produce a sufficient quantity or quality of critical bacteriocins.
- **Gastrointestinal symptoms** are increasingly being recognized in COVID-19 patients, which include nausea, vomiting, diarrhea, abdominal pain and loss of appetite. The Center for Disease Control (CDC) states that these GI symptoms can coexist with respiratory symptoms OR they can be the only symptoms present.
- **SARS-CoV-2 virus enters the GI tract:** The SARS-CoV-2 virus can enter the body orally or nasally and be carried by saliva into the GI tract. The virus is usually inactivated in the strong acid environment in the stomach which is a pH of 2-3.[27] However, people with elevated gastric pH (more alkaline) due to hypochlorhydria and/or people who take acid-suppressing drugs (PPIs, H2 Blockers, antacids) have been found to have worse COVID-19 clinical outcomes, including death.[28,29] Creating a more alkaline gastric pH may allow the SARS-CoV-2 virus to survive passage through the stomach.
- **Microbiome, ACE2 Receptors, and COVID-19:** It is well documented that the SARS-CoV-2 virus enters cells by attaching to the ACE2 receptor on the surface of cells. It has been reported that the prevalence of ACE2

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receptors is 100-times higher in the gastrointestinal tract (especially the colon) than in the respiratory system.[30] Thus, if the gastric pH is more alkaline, the SARS-CoV-2 virus can gain access to the lower GI tract, where it can enter cells, replicate, and spread throughout the body.

Many people think about taking probiotics when they want to improve their gut microbiome and decrease the symptoms of dysbiosis. However, probiotics have some limitations which prevent most people getting maximum benefit from the probiotics they consume.

Shortcomings of Probiotics

1. **Probiotics** are known to play a role in promoting health. However, there are thousands of strains of probiotic bacteria, and various strains of bacteria may function differently in different individuals. This makes it difficult to make therapeutic recommendations because when it comes to probiotics, the adage "one size fits all" does not apply.[31] Also, probiotic bacteria must be provided with a wide range of dietary fibers in order to be effective.
2. **Dietary fiber** is the primary 'food' for probiotic bacteria. Probiotic bacteria ferment undigestible dietary fibers in the colon, which results in the creation of compounds called postbiotic metabolites. A growing body of science is learning that probiotic bacteria themselves do not provide health benefits in and of themselves. It is rather, the postbiotic metabolites, which are created when bacteria ferment dietary fibers that provide a wide range of health-regulating benefits to the host. A lack of dietary fiber is rampant in the United States. Results of a 2012 survey revealed that 90% of American children and adults DO NOT consume the recommended amount of dietary fiber.[32] Without fiber, probiotic bacteria are largely ineffective because they cannot create postbiotic metabolites. Postbiotic metabolites are so important, they are being referred to as "The New Frontier in Microbiome Science."[33]
3. **Probiotic benefits are strain specific**. For example, when a specific strain of *Lactobacillus* is found to provide a health benefit due to a specific postbiotic metabolite, it cannot be assumed that other strains of *Lactobacillus* bacteria will produce the same postbiotic metabolite or the same quantity of the specific postbiotic metabolite.
4. **Postbiotic Metabolites: A Revolution in Microbiome Science.** A revolutionary concept in microbiome science is based on the understanding that the primary function of probiotic bacteria is to ferment dietary fibers and convert them into compounds referred to as postbiotic metabolites, which play critical roles in regulating health.[34] This process takes place in the human intestinal tract, and it is also responsible for the health benefits of fermented foods such as sauerkraut, kimchi, tempeh, and miso. However, a lack of dietary fiber severely reduces the production of postbiotic metabolites.

Postbiotic Metabolites

In nature, bacteria create a wide range of postbiotic metabolites by fermenting dead plant material in the soil. The postbiotic metabolites created in soils create the optimal ecosystem in a plant's root ball. This attracts beneficial probiotic bacteria into the plant's root system, which in turn, regulate the production of the plant's required nutrients and delivery of nutrients into the growing plant. Thus, postbiotic metabolites in soil are absolutely essential for plant life.

A similar process takes place in the human digestive tract. Probiotic bacteria ferment ingested dietary plant fibers. This results in the production of postbiotic metabolites that regulate digestion, absorption of nutrients, and which are increasingly being found to be key regulators of many aspects of human health. However, as reported earlier in this article, approximately 90% of American children and adults do not consume adequate daily dietary fiber. Hence, the microbiome in the vast majority of Americans do not produce adequate postbiotic metabolites. This is one of the most important reasons why Americans are experiencing an epidemic of health problems. We actually have an epidemic of epidemics: cancers; metabolic syndrome and diabetes; heart disease with high blood pressure, heart attacks, and strokes; autoimmune diseases; autism; ADHD; and on and on.

There are two additional ways humans can receive the benefits from postbiotic metabolites.

1. **Fermented foods:** Humans have consumed fermented foods for millennia. Initially, fermentation was a means of preserving foods, which is due to bacterial production of slightly acidic postbiotic metabolites such as short-chain fatty acids (SCFAs), nucleic acids, organic acids and fulvic acids. These postbiotic metabolites create a slightly acidic environment in the food, which suppresses the growth of harmful bacteria. The same process happens in the human digestive tract. Slightly acidic postbiotic metabolites suppress the growth of pathogens and maintain a healthy ecosystem in the gastrointestinal track as well as regulating many other aspects of human health.

   Although some cultures regularly consume fermented foods, most Americans do not. A study conducted by the *American Gut Project* revealed that the vast majority of Americans rarely or never consume fermented foods.[35]
2. **Fermented Food Probiotics**. Some companies are utilizing a fermentation process to create fermented food probiotics. In one instance bacteria are allowed to ferment a wide variety of fiber-rich foods in large 80-gallon fermentation vats for up to five years. The resulting product contains probiotics, prebiotics, and over 500 postbiotic metabolites in each capsule.[36] The ingestion of fermented food probiotics is a fast, efficient way to directly deliver postbiotic metabolites directly to the intestinal tract. When they arrive, the postbiotic metabolites immediately begin to reduce inflammation, kill pathogens, and provide multiple other health benefits.

Postbiotic Metabolites vs Probiotic Bacteria. Directly ingesting postbiotic metabolites provides benefits to the microbiome much faster than simply ingesting commercial products that contain probiotic bacteria. When

probiotics are ingested, they must survive transit through the harsh acid in the stomach. Then, when they transit the GI tract and arrive in the colon, they must locate dietary fibers and begin the process of fermenting the fibers to create postbiotic metabolites. *This all takes time*. Some companies utilize a multi-year fermentation production process, which results in a final product that contains hundreds of postbiotic metabolites.

Directly Ingesting Postbiotic Metabolites. When postbiotic metabolites are directly ingested, they pass through the stomach unharmed. Upon arriving in the intestines, they immediately begin to impart benefits such as reducing inflammation, suppressing the growth of pathogens, accelerating the growth of healthy new epithelial cells, and much more. For those wishing to take a deeper dive into the fascinating and rapidly emerging science on postbiotic metabolites, read an article titled "Postbiotic Metabolites: The New Frontier in Microbiome Science," which was published in the July 2019 issue of the *Townsend Letter*. To access this article, type the following words into your search engine: Pelton Postbiotic Townsend.

Metabolomics and Metagenomics

Postbiotic metabolites are so important, they are responsible for the creation and rapid development of two new scientific disciplines, metabolomics and metagenomics. These new branches of science are barely twenty years old. They were created to facilitate the discovery of small molecules that are produced in biological reactions. One of the primary classes of compounds being researched are nano-sized compounds referred to as postbiotic metabolites. Rapid advances in metabolomics have resulted in the discovery of thousands of new postbiotic metabolites.[37] Metagenomics is defined as the *genomic analysis of microorganisms.* This new branch of science enables scientists to discover the genes that enable various bacteria to produce specific postbiotic metabolites.[38]

Conclusion

It is becoming increasingly obvious that the gut microbiome is a modifiable risk factor associated with the infectibility and severity of COVID-19. Thus, people are encouraged to take proactive steps to maintain a healthy microbiome. Two of the most important recommendations to achieve the goal of a healthy microbiome follow:

1. **Consume more dietary fiber,** with attention to increasing both the quantity and diversity of ingested fiber-rich foods. Within the last 100 years, which is a metaphorical nanosecond in the evolution of mankind, humans have transitioned from a primarily plant-based high-fiber diet to a diet that contains a huge amount of highly processed, fiber-deficient foods. The lack of dietary fiber has altered the gut microbiome and is a major contributing factor related to our current era of chronic degenerative diseases.
2. **Take a fermented food probiotic.** Probiotics that are created using a multi-year fermentation production process contain hundreds of postbiotic metabolites which, when ingested, immediately begin to improve conditions in the microbiome system.

Be kind to your 100 trillion bacteria and feed them well. If you do not feed them well with a diversity of different types of dietary fibers, they will not thrive and survive. If you feed them well, they will work hard to produce postbiotic metabolites that help you stay healthy and safe during COVID-19 times, and always.

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Applied Kinesiology Assessment and Management of Female Hormone Imbalances: A Chiropractic-Endocrinology Case Report

by Scott C. Cuthbert, DC

Introduction

Early in the development of applied kinesiology, Goodheart (1965) observed a fairly consistent relationship between weak muscles associated with specific organ or gland dysfunction. Goodheart noticed that when an organ or gland was in a state of dysfunction, there was usually a specific muscle or group of muscles that would be inhibited when assessed by manual muscle testing.

The first therapeutic approach that recognized this association – other than simply correlating a pectoralis major (sternal division) weakness with liver problems – was Chapman's lymphatic reflexes. Chapman, an osteopath, used these reflexes to enhance lymphatic drainage of organs and glands. The Chapman reflex, which influenced the sternal division of the pectoralis major muscle, was the liver reflex. In applied kinesiology, Chapman's reflexes are referred to as neurolymphatic reflexes. These were correlated with muscular weakness by Goodheart for muscle-organ/gland associations throughout the body.[1]

Applied kinesiology (AK) evaluates muscle function using the manual muscle test (MMT), a diagnostic test that has shown good reliability and validity for patients with muscle strength impairments.[2-3] The use of MMT procedures is for three purposes in AK: (1) to aid in the diagnoses of structural, chemical, and/or mental aspects of health dysfunctions, (2) to offer the potential for shortening the course of treatments through "challenge" procedures**,** and (3) to determine the effectiveness of treatments. In so doing, AK's testing methods used for the discovery of structural, chemical, or biopsychosocial disorders that produce these muscle strength impairments guide the treatment given to the patient.[2-5,10-11]

In AK, muscular dysfunction is thought to reflect neural function. First the Kendalls in the 1950s,[2,12] then Goodheart and Janda in the 1960-1990s,[13] followed by many others have expanded the construct validity and the clinical usefulness of the MMT[2-21] because of the recognition that muscular imbalance is a key characteristic of spinal, neuromuscular, and articular dysfunction. AK suggests that muscle function is a transcript of the central integrative state of the anterior horn motoneurons, summing all excitatory and inhibitory inputs.[11] In other words, the locus of muscular dysfunction ultimately rests with the nervous system.

AK is a diagnostic and therapeutic technique that has gained peer-reviewed published support within the chiropractic, medical, osteopathic, dental, biofeedback, acupuncture, veterinary, and other health care literature.[15-20] The research underlying the AK manual muscle testing procedures as this relates to the treatment of female and male endocrinopathies has some substantiation as well.[2,18-21,24]

Clinical Features

A twenty-two-year-old female presented to our Makati, Manila Philippines, office for help with severe premenstrual abdominal pain and irregularity since the start of her menstrual periods. Her gynecologist treated her problem medically in 2018 with the insertion of a hormonal IUD (intrauterine device). This procedure exacerbated her chronic menstrual problems. Because the IUD would not be removed during the course of her treatment, the clinical thought process involved assessing the patient for excess progesterone and estrogen, which are the hormonal components of the IUD.

Energetic testing of separate vials of estrone, B-estradiol, as well as progesterone, weakened the patient's previously strong indicator muscles. However, with simultaneous (or "two-point") therapy localization (TL)[26] to the alarm point for the liver, this muscle

inhibition was negated, indicating that the liver was failing in its role of detoxifier for the body and that she had abnormal amounts of estrone, B-estradiol, and progesterone hormones in her system.

Additionally, positive therapy localization to the large intestine's viscerosomatic reflexes was positive, and simultaneous (or "two-point") TL to the liver cleared this problem as well, the patient was advised to go on a broad-spectrum antimicrobial, (anti-fungal, anti-bacterial, anti-viral, anti-parasites), anti-inflammatory, and immune stimulant herb to reduce the burdens on the liver. *Morinda citrifolia* (also known as *noni*) has been used for hundreds of years throughout Polynesia for a variety of conditions.[25] Morinda has been shown to increase dopamine and serotonin, which could help alleviate depression. It has been used as a folk remedy for depression for hundreds of years, and this is a potential explanation behind why it has traditionally helped. This patient has been so pleased with the use of Morinda that she now says, despite her restoration to an asymptomatic state, that "I am afraid to go without it."

The first treatment consisted of the detection of numerous viscerosomatic reflexes related to her endocrine system, primarily the liver, bowels and adrenal glands. The viscerosomatic reflex arises from afferent stimuli coming from visceral disturbances. These modify somatic tissues, particularly the skeletal muscles and skin overlying the dorsal horn of the spinal cord near the segmental level that supplies the organ involved.[2] Palpable tenderness and decreased and increased skeletal muscle tone have been shown to result from nociceptive viscerosomatic stimuli.

The pectoralis major (sternal division) muscle is associated with the liver.[2] It has been clinically realized that liver dysfunction permits excessive hormones to produce symptoms in the patient, as the job of the liver is to both filter the hormones and the bowel. Bowel dysfunctions were also related in the patient's history; and therapy localization to the alarm point of the bowel and the acupuncture point LI-4 (large intestine 4, the so-called "Source point" for the large intestine meridian in Traditional Chinese Medicine) were present.

The clinical deduction was made that relieving the liver of the distress it was undergoing from the patient's bowel dysfunction, would improve the liver's capacity to better filter the excess hormones coming from her IUD, producing her menstrual problems.

From a biochemical point of view, just before menstruation the liver must conjugate (prepare for elimination) increased amounts of progesterone and rising amounts of estrogen. By leveraging a woman's web of endocrine wellness to do this, the body's excretion of these hormones on a monthly basis occurs smoothly with very little, if any, symptomatology. The primary job of the liver is "to clean the bowel." Whenever a patient has a hormone imbalance, a bowel disruption, or a liver problem, the other interacting aspects of their glandular and digestive function must be addressed for complete restoration of health. With this therapeutic approach, PMS can become a thing of the past.

On her first visit, inhibition of the sternocleidomastoid muscle was also corrected with treatment of the cranial system, involving inspiration and expiration assist cranial dysfunction corrections. This scenario has been reported dozens of times in the Collected Papers of the International College of Applied Kinesiology by physicians practicing AK around the world.[1-2,21] In fact, up-regulation of the signal from the neuro-endocrine axis to the ovaries (from the reduction of the cranial system dysfunctions) can create the onset of a menstrual period within minutes. It is our observation that cranial stress resolution through chiropractic manipulations to the skull and TMJ upregulates both the pineal and pituitary glands, allowing them to fully function as the master neuroendocrine transducers amplifying the innate intelligence of the neuroendocrine system and improving the HPA-axis.

Gastrointestinal irritation and/or inflammation may be caused by dietary imbalances, allergy, stress factors, local bowel flora changes due

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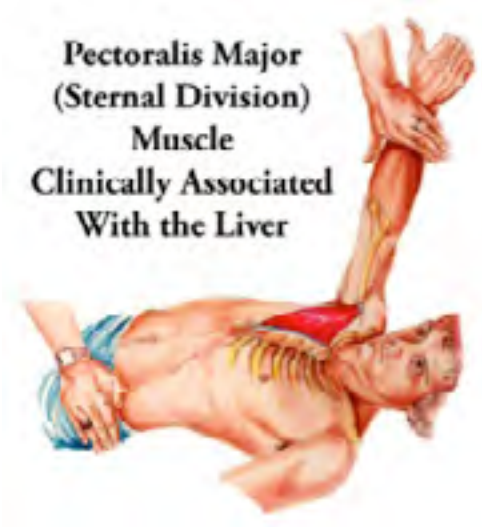

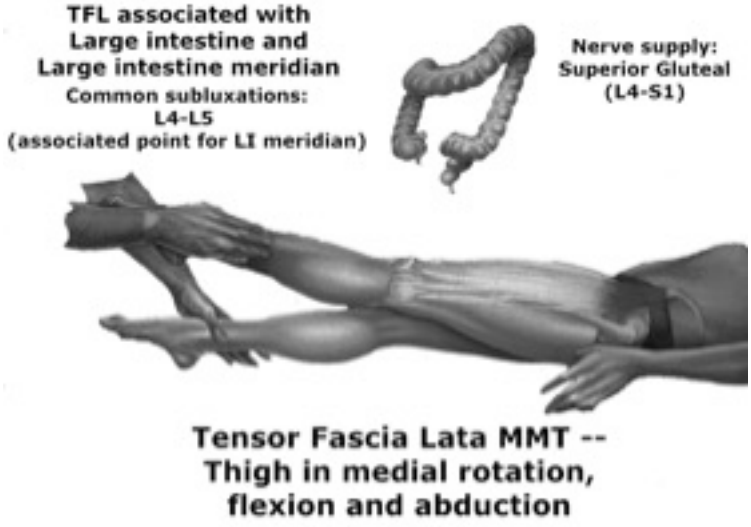

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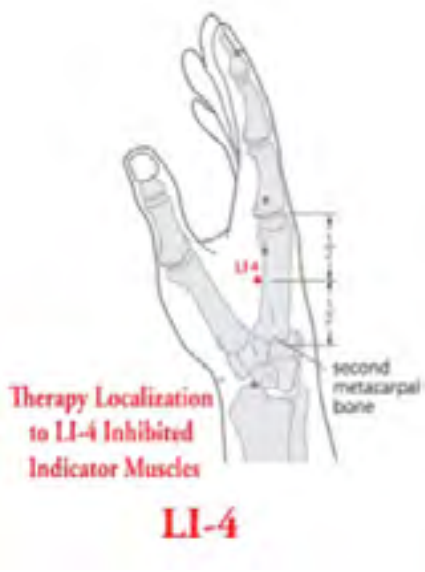
to use of medication (e.g., antibiotics), environmental pollution or other factors, resulting in altered gut ecology. This process involves depleted beneficial bacterial function, reduced protective secretory IgA levels and increased gut permeability.

This sequence of adaptations to previous or ongoing events results in larger than desirable molecules being absorbed from the gut, potentially triggering allergic reactions, as well as overloading liver function, with the possibility of autoimmune and hormonal consequences. The patient's excessive pain syndromes and hormonal imbalances were likely related to this pattern of inflammation from the gut mucosa.

Results

The correction of cranial and spinal dysfunction, in addition to the use of Morinda for the bowel, as well as milk thistle for the liver, and ashwagandha for the adrenal glands brought about a rapid improvement in this patient's clinical picture. The clinical findings of the first four visits are reviewed in Table 1.

One week later the patient was seen for her second visit. She was moving her bowels twice a day and no longer had any low back pain. We found and corrected a category one right, pelvic-spinal subluxation, TMJ muscle



imbalances, and bilateral talus bone joint dysfunctions in the feet.

The patient was seen a week later, and she noted that her period had passed with very little pain, right on time, and of the correct length, for the first time in over two years. She continued to feel better and was happy with the outcome. Her anxiety levels were markedly reduced after the initial correction of a hyperventilation syndrome or breathing pattern disorder, found with muscle testing to be a failure of all indicator muscles on full expiration challenge. Her sleep was also improved with the reduction in her anxiety.[22] We found and corrected a category 1 pelvic-spinal subluxation, with C4 PR. The patient reports that she has also lost weight and inches around her waist and has found this pleasing and noteworthy.

Discussion

Applied kinesiology is employed in the treatment of patients with a wide range of diseases and conditions, unrelated to obvious biomechanical problems. This situation emphasizes a basic requirement of AK practice – the necessity to consider the individual features of each patient and condition, and the background of chronic stressors (biomechanical, biochemical, and psychosocial) that a patient brings to the examination. It is also important to recognize that viscerosomatic reflex activity occurring in a patient's musculoskeletal system may be determined before any symptoms of visceral change are evident and that this

Table 1

AK examination finding	Corrective Treatment/Outcome
• Sternocleidomastoid (SCM) on the left and anterior scalene muscles inhibited bilaterally	• Right inspiration, left expiration assist cranial fault corrections to the temporal bones bilaterally (strengthened SCM on left and anterior scalene bilaterally)
• Positive therapy localization (TL) and challenge (producing inhibition to previously strong indicator muscles) to the left TMJ on sagittal opening of the jaw	• Strain-counterstrain and percussion used on the medial and lateral pterygoid muscles (this muscle surrounds the eustachian tube) and abolished challenge and TL to the left jaw on sagittal opening
• Positive challenge (producing inhibition to previously strong indicator muscles) for a category I pelvis with a right posterior ilium	• SMT (spinal manipulative therapy) to the pelvis (DeJarnette wedges) abolished challenge to the pelvis and strengthened the left hamstring muscle
• Positive TL to acupuncture point Large Intestine 4 (LI-4) and the alarm point for the Large Intestine (ST-25) (TL to LI-4 and ST-25 produced inhibition in previous strong indicator muscles).	• Simultaneous TL to the alarm point for the liver corrected challenges to the bowel viscerosomatic reflexes
• Positive TL to neurolymphatic reflex (NL) for the adrenal glands and emotional neurovascular reflexes (produced inhibition in previous strong indicator muscles)	• Use of Ashwagandha corrected both findings
• Bilaterally inhibited gluteus maximus muscles	• SMT for upper cervical fixations strengthened gluteus maximus muscles bilaterally

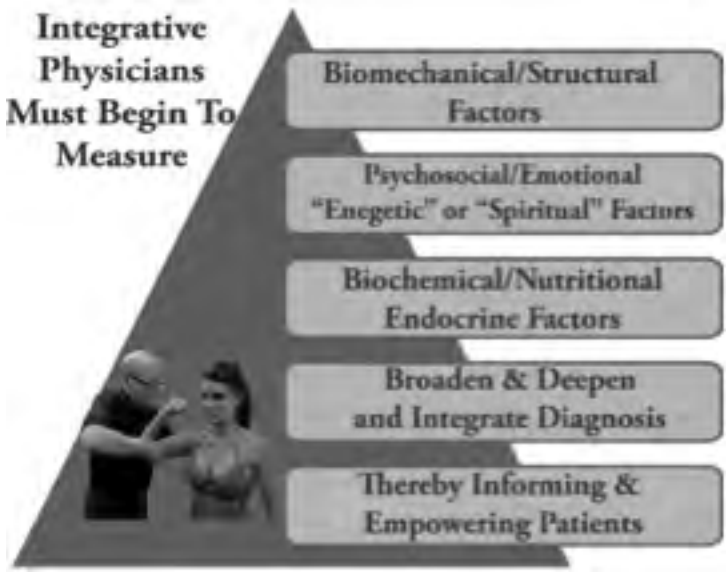
phenomenon (the muscle inhibitions resulting from viscerosomatic reflexes) has potential prognostic and diagnostic value.

The methods used in AK for the investigation of digestive dysfunctions and the viscerosomatic or viscero-muscular reflexes involved in these cases have been described by the author previously.[2] Applied kinesiology suggests that subluxations might result from three areas of concern, which comprise chemical and mental elements in addition to structural. AK recognizes how nutritional, hormonal, and emotional elements influence neural function as reflected by muscle tone that is evaluated by an established muscle testing protocol whose reliability and validity have been shown.

Applied kinesiology essentially sees the locus of muscle dysfunction ultimately within the nervous system, which brings us back to the founder of chiropractic, D.D. Palmer, and his concept of "tone." Thus, AK advocates a multi-model program with treatment inclusive of spinal manipulative therapy (SMT) for subluxations, cranial manipulative therapy, specific muscle testing and correction, biochemical evaluation and treatment, and psychosocial evaluation and treatment in order to improve muscle dysfunction (reflective of neural dysfunction) throughout the body in a holistic way.

It was apparent in this case report that altered biochemistry affected this patient's mood; her altered mood changed her blood chemistry; her altered structure (improved posture from her increased muscle strength and speed) modified her total body function and therefore impacted on her chemistry (e.g., liver function) and potentially on her mood.

An imbalanced estrogen-progesterone ratio is associated with premenstrual syndromes (PMS) and is characterized by mood disorders. The PMS group of symptoms shows water and salt retention, abdominal bloating, mastalgia and weight gain that is associated with high aldosterone levels. This patient suffered most of these signs and symptoms. These kinds of patients are also characterized by blood sugar handling stress (premenstrual craving for sweets – especially chocolate) increased appetite, palpitation, fatigue, headache, and even syncope. Her craving for carbohydrates has improved and is the most likely reason for her weight loss.



PMS is usually associated with persistence of high estrogen after the normal mid-cycle ovulatory spike. This is usually due to insufficient clearance of circulating estrogen by the Phase II detoxification pathway in the liver. An increasing body of scientific data supports the hypothesis that conjugation (sulfation) and deconjugation (desulfation) of estrogens by the liver is important in the regulation of biologically active steroid hormones in target tissues as well.

Cranial treatment for this patient is suggested to have improved the rapidity of her recovery. Clinical observation has shown that the normal function of the motion of the cranial vault up-regulates the function of the neuroendocrine axis, or where the brain folds in upon itself and becomes the endocrine system. This takes place in the middle of the brain and includes the pineal, pituitary, and hypothalamic endocrine glands. These glands are known as the master endocrine control center. These glands control the sleep-wakefulness cycles (or circadian rhythms), reproductive cycles, stress-handling capabilities, and structural integrity.

In this case, functional restoration of the neuroendocrine axis most likely facilitated the return of balance and this patient's ability to sleep in a normal manner. When it gets dark outside, the pineal gland secretes melatonin, which eventually causes a person to fall asleep. Inadequate stimulation of this gland by lack of cranial motion, may reduce its production of this key hormone, and thus create downstream problems. This treatment should be the very first line of therapy for sleep disorders, as it is simple, cost effective, and non-invasive.

Conclusion

This holistic approach to wellness is the practice of the future as more people focus on preventative, wellness care rather than crisis care. There are today a number of notable institutions and clinic systems growing throughout Asia that have already begun treating and teaching their patients and students using these approaches. The author serves at Intercare Chiropractic Clinics

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in Makati Manila, the Philippines, where a combination of chiropractic, general medical consultations, rehabilitation and sports medicine, physiotherapy, medical massage and acupuncture are part of the integrative clinical encounter for each patient.[23]

Countries in the developing world must find ways of building up national resources for prevention, health promotion, and mind/body medicine so that the complexities and causes of functional, chronic illness can be addressed. Throughout the world, resources are constrained and so the ever-growing use of expensive, invasive treatments for functional illnesses is not the best choice for either the first nor the developing world.

From the beginnings of applied kinesiology, practitioners have observed an association between muscle-joint function and visceral-autonomic dysfunction. It is exciting to see accumulating research and developing models from a wide range of academicians and clinicians converging toward concurrence with the field of applied kinesiology.[2] This development will, ideally, lead to more coordination with physicians from other fields and backgrounds to work synergistically with clinicians utilizing applied kinesiology methods in the treatment of patients with functional illnesses.

Successful management guided by AK MMT chiropractic methods (involving biomechanical, biochemical, and meridian system factors in the treatment) for a 22-year-old female with a life-long history of hormonal and menstrual irregularities is presented. Four treatments that consisted in the analysis of muscular impairments (inhibition on MMT) and their relationship to organic, articular, soft tissue, hormonal and nutritional disorders, which were treated with chiropractic adjustments, resulted in elimination of the muscle weaknesses found and elimination of years of previous musculovisceral suffering.

Many of these muscular and viscerosomatic impairments have been shown to be reversible: improvements in muscle and hormonal function after chiropractic treatment has been documented in the literature.[24] Applied to the general population with endocrine, liver, and digestive dysfunctions, strategies designed to optimize muscle strength and associated autonomic and visceral functional components may have the potential to reduce a vast burden of disability, dependence, and cost.

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26. Therapy localization is a diagnostic procedure unique to AK that consists of placing the patient's hand over areas of suspected involvement and observing for a change in the MMT. This method assists the doctor in rapidly finding areas that are involved with the muscle dysfunction found on MMT and has been used clinically for nearly 40 years. Cuthbert et al, Rosner et al, and Pollard et al in recent literature reviews outlined the research supporting the AK concept of therapy localization. Collectively these data suggest that stimulating or stabilizing the muscles, joints, ligaments, and skin – and their associated cutaneomotor reflexes – can produce changes in muscle function.

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Dr. Scott Cuthbert practices AK at Intercare Chiropractic Clinics in Makati Manila. Dr. Cuthbert is the author of *Applied Kinesiology Essentials: The Missing Link in Health Care* (2014), and *Applied Kinesiology: Clinical Techniques for Lower Body Dysfunctions* (2013), and *Whiplash Dynamics and Manual Muscle Testing* (2019), all of which are available at Amazon Kindle. He has published 15 Index Medicus clinical outcome studies and literature reviews, and over 50 peer-reviewed articles on AK.

Vitamin D Overdose – A Case Study

by Ronald Hoffman, MD

A 39-year-old male was referred to my practice by his mother who was concerned over his overzealous consumption of vitamin D.

The patient reported that, during the early months of the pandemic he began taking high doses of vitamin D because he had read that "Dr. Fauci recommended it."

He claims to have taken four capsules of vitamin D twice daily for four days per week (he did not take vitamins on weekends). When I asked him the potency of the vitamin D supplements, he showed me a picture on his iPhone which indicated each capsule delivered 5000 International Units (125 mcg) of vitamin D3.

He had been doing this consistently since April or May and, at the time of our visit, at the end of December, had only stopped taking it for two or three days.

I calculated that this meant he had been taking in excess of 22,000 IUs of vitamin D per day, on average, for eight or nine months.

The patient had no complaints and stated he was in excellent health. He was a runner and completed three-to-six-mile runs three times weekly on average, sidelined only by occasional hip flexor soreness.

He denied fatigue, generalized muscle aches, headaches, flank pain, or changes in appetite or thirst. His physical exam was unremarkable.

He was instructed to stop taking vitamin D for the time being and to hydrate well. Blood and urine tests were performed

Discussion: Hypervitaminosis D is occasionally described in patients taking as little as 10,000 IU per day over sustained periods. One case report of a 73-year-old male with congestive heart failure taking that dose for many years revealed incipient renal failure with a creatinine of 7.43 and a serum calcium of 12.3 (normal = less than 10.6).[1] The patient's creatinine and calcium normalized within 28 days after aggressive hydration and cessation of vitamin D.

Of course, compromised renal, or hepatic function are predisposing factors for hypervitaminosis D. So, too, are certain conditions: hyperparathyroidism, tuberculosis, sarcoidosis, and histoplasmosis, all of which affect calcium metabolism.

Symptoms of vitamin D excess resemble those of hypercalcemia[2]:

- Fatigue
- Loss of appetite
- Weight loss
- Excessive thirst
- Excessive urination
- Dehydration
- Constipation
- Irritability, nervousness
- Ringing in the ear (tinnitus)
- Muscle weakness
- Nausea, vomiting
- Dizziness
- Confusion, disorientation
- High blood pressure
- Heart arrhythmias

Long-term consequences of prolonged hypervitaminosis D may include the following:

- Kidney stones
- Kidney damage
- Kidney failure
- Osteoporosis
- Calcification (hardening) or arteries and soft tissues

The tolerable upper limit, or the maximum daily intake of vitamin D that is unlikely to result in any health risks, has been set at 4,000 IUs per day, but in my experience some patients require more to achieve optimal levels of vitamin D, and do so safely. I have never encountered a genuine case of vitamin D toxicity, although I've advised some patients to cut back when their blood levels surpassed the normal threshold.

Nevertheless, the specter of vitamin D excess looms, especially for patients taking multiple supplements simultaneously, each of which contain vitamin D, as when someone takes a multi, a bone support formula, and an immune supplement, along with additional D.

Results: The blood and urine tests for this patient were all within normal range. His renal function was unaffected. He showed no evidence of hypercalcemia, with neither serum nor ionized calcium elevations. His parathyroid hormone, as might be expected, was in the low normal range. There was no evidence of excess urine calcium or the presence of crystals that would signal risk for kidney stones.

Unsurprisingly, his 25OH vitamin D clocked in at 97 ng/ml, which is close to the lab's upper limit of 100 ng/ml; the 1,25OH vitamin D was 72 pg/ml, which was near the top threshold of 75 pg/ml (reference values vary from lab to lab). But these values did not reach the toxic range.

Take-home: While the risk of vitamin D toxicity is real, especially when vitamin D's benefits are so widely touted, this case suggests that, especially for young healthy individuals, there's a significant margin for error. High-dose vitamin D supplementation is not without risks, especially in patients with comorbidities, so it is advisable to frequently monitor renal function, calcium and D levels, and to suspect overzealous supplementation if a patient presents with symptoms suggestive of hypervitaminosis D.

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Dr. Ronald Hoffman is recognized as one of America's foremost complementary medicine practitioners. He was founder and medical director of the Hoffman Center in New York City, and now maintains a private practice there. He is also author of numerous books and articles for the public and for health professionals, and is host of the popular nationally-syndicated radio program and podcast, Intelligent Medicine: https://drhoffman.com/listen/weekly-radio-show-podcast/

Letters to the Editor

Re: COVID-19 Treatments

I love *Townsend Letter* and the articles you publish. I recently read your Letter from the Publisher, "The Fragile State of COVID-19 Science," and felt a need to email you with a few of my thoughts. Both HCQ (hydroxychloroquine) and ivermectin, when added to other treatments, are very effective in early outpatient treatments.

1. Re your statement that "HCQ has not proven to be an effective drug": The literature published by Peter McCullough, et al. says the opposite. [See "Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)." *Rev Cardiovascular Med.* 2020;21(4): 517-530]
2. Ivermectin is amazing in treating COVID. See "Review of the Emerging Evidence Supporting the Use of Ivermectin in the Prophylaxis and Treatment of COVID-19" by Pierre Kory, G. Umberto Meduri, Jose Iglesias, et al, at https://covid19criticalcare.com/.
3. Association of American Physicians and Surgeons' "A Guide to Home-Based COVID Treatment," for patients to print and give to their doctor, is available at https://aapsonline.org/CovidPatientTreatmentGuide.pdf.
4. AAPS also has a list of doctors offering these early treatment protocols: https://aaps.wufoo.com/reports/z1tdq8q714w7gyj/.
5. You also state, "China's no-nonsense, absolute isolation, and quarantine policies achieved far better results compared to Sweden and the US. Science appears unable to explain these geographic differences." According to a nurse we know, who is from China and still very much in touch with what is going on there, said China set up checkpoints to go from one section of the city of Wuhan to the next, early on in the pandemic. In order to pass the checkpoint, a person needed to drink a cup of freshly brewed herbs that the guards kept cooking all the time. She thinks the formula consisted of astragalus, forsythia, honeysuckle, and maybe some version of lotus. The forsythia and honeysuckle are the main herbs in the Chinese herbal formula *Yin Chiao*, which is one of the parts of the Source Naturals Herbal Resistance Liquid. Astragalus is thought by Chinese medicine to be the best herb for strengthening the initial outer defenses of the immune system. And the lotus was apparently added simply because it grows around Wuhan and might inspire some local pride, even though it seemed to neither add nor detract any effects to or from the situation.
6. Also, in a webinar, John Chen, OMD, DPh, stated that when the hospital MD's in China were not getting desired results with Western medicine pharmaceuticals in late January 2020, the Chinese government called in the (medically-trained) Chinese herbalists. These herbalists put together herbal formulas that greatly improved outcomes.

I've tried to keep this letter relatively brief and to the point. If you wish, I can send you more information on this topic with links to various articles and videos, including links to Senate hearings in November and December 2020, where a number of physicians were essentially begging that these treatments be implemented as early outpatient treatments. You can also look on the AAPS website: aapsonline.org.

Linda C. Wright, MD

Re: Compounded Bioidentical Hormones and Saliva Tests

I am writing in response to the recent National Academies for Science, Engineering, and Mathematics (NASEM) report on compounded bioidentical hormones, as well as David Zava's recent report "Topical Therapy with Estradiol, Progesterone and Testosterone and Their Distribution in Saliva, Capillary Blood Serum, and Urine" (*Townsend Letter*, January 2021). While both had impressive graphs and charts, justifying scholarly work, I disagree with the conclusions of each.

Just because something is published, be it a NASEM report or an article in *Townsend*, does not mean it is true but may be grounds for further inquiry with valid observers. Both articles attempt to justify the authors' narrow interpretation in order to convince readers of the outcome, with little willingness to include a broader discourse. With Zava's work, perhaps the salivary information may be useful for general use in women without the significant mood issues we work with, but we have found it often inaccurate in our work.

Early in our studies we found women, desperately in need of primary estrogen (E2=estradiol), were told from saliva tests that they were estrogen dominant, which was often not the full story. A woman could be very low in estrogen and still be called 'estrogen dominant' if she had even less progesterone available to mitigate. We used blood tests and saw repeated evidence of low serum estradiol in the demographic of depressed women.

These women were helped enormously in terms of depression when they got *enough* transdermal estrogen. We repeated measurements of estradiol and found increased levels over time as women improved.

We also measured blood levels of progesterone and found that once we had a progesterone baseline, we rarely need to retest as progesterone increases slowly and symptoms of anxiety and irritability tell the story. We believe that if a laboratory test does not mirror symptoms, then it is not a useful tool.

The only point in the entire NASEM report that made sense to me was that symptoms were acknowledged as being useful in treating menopausal women, backed up by blood tests when necessary.

Transdermal hormones are the safest way to use hormones, as there are receptors everywhere. Most women absorb these hormones readily through the skin. While Zava's goal may be to support use of bioidentical hormones, he makes the same type of error, failing to identify that women with mood issues improve when using compounded creams, and how easy these are to work with and adjust.

The NASEM report states that estradiol patches are better than compounded cream because the E2 cream had lower levels of E1, yet a lower level of E1 is actually a good thing, given that E1 is the most toxic estrogen! This kind of error is pervasive throughout the entire report.

I agree with the rebuttal that Rachael Pontikes, a partner in the Life Sciences Health Industry Group at the international law firm Reed Smith LLP, sent to the FDA on behalf of a coalition of traditional compounding pharmacies and outsourcing facilities, in which she states:

> We…request that FDA reject the conclusions and recommendations published by The National Academies of Sciences, Engineering, and Medicine ("NASEM") in its report titled *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use* (the "Report"). FDA cannot adopt the Report or rely on it in any way, because the Report patently fails to represent an independent perspective and is rooted in striking biases.

Phyllis J. Bronson, PhD

Re: COVID-19 Vaccines and Guillain-Barre Syndrome

In the November 2000 issue of *Townsend Letter*, page 104, is my letter regarding the Sabin oral polio vaccine I received in 1987, and the subsequent chronic fatigue syndrome because of it. Later, specialists revised the diagnosis to Guillain-Barre syndrome, as I had lost my knee reflexes and I had profound muscle weakness, which has continued to the present time.

On December 14, 2020, Dr. Fauci made an announcement that those who have or had Guillain-Barre syndrome *should not* receive the COVID-19 vaccine.

It has taken over 20 years for the government to acknowledge Guillain-Barre syndrome and the danger vaccines can cause.

My letter was signed as Kolodie Brave-Woman, which is my given name.

Barbara Kolodie

Neglected Balance of Estradiol and Progesterone

Dr. Jerilynn C. Prior is a tireless researcher of women's hormonal functions and related health problems. She has identified and published information striking at the social myths that prevent good therapy. Ignorance, lack of good science, and poor translation to clinical use abound.

Recently, she shared "Women's reproductive system as balanced estradiol and progesterone actions – A revolutionary, paradigm-shifting concept in women's health" (https://www.sciencedirect.com/science/article/pii/S174067572030013X).

She decries the notion of estradiol being the "women's hormone" and the subsequent practice of focusing treatment on estradiol only for women and relegating progesterone's utility only for the uterus.

Progesterone is a far more prevalent hormone and behaves in a yin-yang dance with estradiol. The two hormones enhance the function of receptors for each other. They produce opposite effects. Estrogen is a stimulant. It promotes growth of tissue. Progesterone helps cells mature and decreases proliferation. In bone remodeling, estradiol slows the rate of bone loss; but it is progesterone that stimulates new bone growth. Without this constant break down and rebuilding, good quality bone cannot happen.

At perimenopause, women can experience aberrations in heart rate because estradiol levels can be at their highest during the lifespan. Progesterone restores the heart's electrical activity to normal. In the brain, estradiol increases excitation, progesterone is calmative. Dr. Prior writes a thorough review of various body systems to enlarge the importance of balance.

One of the myths, she has identified is that if women bleed regularly each month, they produce adequate progesterone and that they have ovulated. She found that missed ovulations can be a regular event and the generous production of progesterone that should follow doesn't happen. She calls for easy, inexpensive, home testing for ovulation to guide us.

You can benefit by taking the time to review Dr. Prior's comprehensive webpage at www.cemcor.ubc.ca.

Carol Petersen, RPh, CNP

Send your Letters to the Editor to editorial@townsendletter.com

Examining the COVID-19 Pandemic

The following excerpts are from Dr. Joseph Mercola and Ronnie Cummins' new book *The Truth About COVID-19: Exposing the Great Reset, Lockdowns, Vaccine Passports, and the New Normal* (Chelsea Green Publishing, April 2021) and is reprinted with permission from the publisher. This book investigates the origins of the virus, how the elite are using it to slowly erode our personal liberties and freedoms, and how we can take back control of our health using successful protocols that have been suppressed. Dr. Mercola and Cummins team up to expose the truth – and end the madness – about COVID-19.

Remdesivir – A COVID Treatment Scam

Drug companies are often portrayed as benevolent entities that pour billions of dollars into research so they can create new drugs and vaccinations for the greater good. However, they spend far more on marketing than they do research. According to a *New York Times* column on the antiviral drug remdesivir, biotech giant Gilead Sciences started distributing remdesivir on a compassionate-use basis in January 2020.

That drug companies offer medications to patients in crisis is again deemed noble and altruistic. The *Times* column even noted, "Given the stakes involved, it seems perverse not to root for Gilead's success … there should be no Big-Pharma haters in pandemics." The reality, however, is that the pharmaceutical industry develops drugs using our taxpayer money, and then turns around and sells them back to us at enormously inflated prices.

The actual "donation" to treat patients on a compassionate basis is virtually insignificant since the drug costs them very little. The positive press by publications like the *New York Times* provides them with a halo that allows them to convince clinicians to prescribe this expensive drug, which has never shown any established clinical benefits and has not been proven to reduce the potential for death in those with severe disease. As such, it's a perfect example of Big Pharma's emphasis of profit over people.

The long-awaited price for remdesivir was announced June 29, 2020, by Gilead Sciences. While the drug has demonstrated only questionable benefits, Daniel O'Day, chairman and CEO of Gilead Sciences, believes Gilead balanced corporate profits and public health when they settled on $520 per vial, which equates to $3,120 for the recommended five-day course of treatment (on the first day, a double dose is given).

Meanwhile, the Institute for Clinical and Economic Review (ICER) released the calculated total cost of production, packaging, and a small profit margin on May 1, 2020. The cost was rounded to $10 per vial. While the exorbitant price of remdesivir is partially based on the assumption that it will reduce the length of hospital stays by four days, some physicians, including Dr. George Ralls with Orlando Health, report that the drug actually *increases* the length of hospital stays. He told ABC News: "Once they start on this medication … they need it for five days, so they are in the hospital longer than they would have normally been. So that could be a reason why our inpatient numbers have ticked up a little."

Remdesivir Studies Lack Positive Results

Although Gilead Sciences continues to move forward in its distribution of remdesivir, other scientific evidence has not supported its use. In one study, published in the *New England Journal of Medicine*, the scientists changed the end point measurements for the study, moving all to secondary outcome measures except the number of days to recovery, which was the single primary outcome measure at the conclusion of the study.

Although there were significant problems with the research design, and consequently the data, the release of the study generated enthusiasm and triggered immediate action across many countries, including the US, to the point that the US Food and Drug Administration issued an emergency-use authorization for remdesivir on May 1, 2020. This opened the door for compassionate use of the drug.

However, a randomized, double-blind, placebo-controlled investigation into remdesivir proved it doesn't work. Two hundred thirty-seven patients in 10 hospitals were enrolled and randomly assigned to either a treatment group or a placebo group. The results showed remdesivir was not associated with statistically significant clinical benefits, and had to be stopped early because it was believed to have caused adverse events.

In another paper, published in the *International Journal of Infectious Diseases*, scientists reported the outcomes for five of the first patients treated with remdesivir in France. All of the patients had been admitted with severe pneumonia related to SARS-CoV-2 infection. Of the five, four experienced serious adverse events.

A randomized controlled study published in the May 16–22, 2020, issue of *The Lancet* also failed to find a clinical of benefit for remdesivir treatment. Importantly, more than twice as many patients in the remdesivir group discontinued their treatment due to adverse effects than the control group (12 percent compared with 5 percent of those given a placebo).

And yet, at the time of this writing, even after over one year of treatments with no better data to back up its effectiveness, remdesivir is the only approved treatment by the FDA.

The Treatment of Acute COVID-19

As you may have guessed, I don't believe remdesivir is the answer for COVID-19. Fortunately, there are now several

treatment options that have demonstrated high levels of effectiveness and success. I review these in my new book *The Truth About COVID-19,* starting with the one I believe to be the most valuable.

Nebulized Hydrogen Peroxide – The Most Effective Therapy for Acute COVID-19

Nebulized hydrogen peroxide, originally pioneered in the early 1990s by Dr. Charles Farr, is probably the single most effective intervention for those who have acute COVID-19. It's my favorite intervention for acute viral illnesses in general, and I strongly believe it would prevent the majority of people from dying from COVID-19 if used.

If you use the search engine on mercola.com to search for "nebulized hydrogen peroxide," you will find a very detailed explanation of why this therapy works and how to do it. Alternatively, an instructional video can be found on Bitchute.com, as YouTube has censored it.

In terms of mechanics, it's highly likely that the peroxide forms a very powerful signaling function that stimulates the immune system to defeat whatever viral threat it's exposed to. Your immune cells actually produce hydrogen peroxide. This is, in part, how they kill cells that have been infected with a virus. It appears that nebulized hydrogen peroxide merely enables your immune cells to perform their natural function more effectively.

In addition to being highly effective, it's inexpensive and has no side effects when used at the very low doses recommended (0.1 percent, which is 30 times less concentrated than regular drugstore 3 percent peroxide).

The key is to have your nebulizer already purchased and ready to go so that you can use it at the sign of first symptoms. You can also use it concomitant with vitamin C, as they likely have a powerful synergy and use different complementary mechanisms.

There are basically two types of nebulizers: small handheld devices that use AA batteries and devices that you plug into the wall. The ones you plug into the wall are far more effective, so be sure to use one of those. The PARI Trek S is my favorite and used to be available on Amazon but now requires a business account. So you can order it at justnebulizers.com and say Dr. Mercola recommended it, as the device requires a physician order. I don't receive any commissions for orders.

As for the hydrogen peroxide, since you are diluting it by 30 to 50 times, stabilizers are not likely to present a problem, but to be safe, your best bet is to use *food-grade* peroxide. Also, do not dilute it with plain water, as the lack of electrolytes in the water can damage your lungs if you nebulize it. Instead, use saline, or add a small amount of salt to the water to eliminate this risk.

You need about one teaspoon of salt in a pint of water or a half a teaspoon in an eight-ounce cup. This will create a physiological solution that will not harm your lungs when you inhale it. You could use regular table salt but ideally, use a healthy salt, such as Himalayan, Celtic, or Redmond salt.

The Way Forward

As we explore in our book *The Truth About COVID-19*, we don't yet know whether the recklessly engineered SARS-CoV-2 virus was *deliberately released* or whether it *accidentally escaped* from a negligently managed, accident-prone dual-use biodefense/bioweapons lab in Wuhan, China. We do know, however, that a powerful network of global elites, including… the World Economic Forum, Big Tech, the Rockefeller Foundation, and the Pentagon clearly anticipated what was coming, and then consciously took advantage of the crisis by seeding and nurturing panic to advance their economic, technocratic, totalitarian, anti-democratic agenda.

We also know that it is an existential imperative that we continue to expose the international gene engineers and scientists whose criminal negligence brought on this disaster and put an end to the genetic engineering and weaponization of viruses and bacteria once and for all, so that nothing like this pandemic ever happens again.

As we continue to gather more evidence that SARS-CoV-2 was lab-engineered and that all of the global elite's misleading science, medical malpractice, and pandemic-mongering are being weaponized in a coordinated and diabolical plan called the Great Reset, we must begin to unite a critical mass of the educated, angry, and dispossessed.

As Arjun Walia of *Collective Evolution* points out, our most powerful rallying cry is simply this: "Is this the world we truly want to create? Is this what we are limited to creating, and if not, what holds us back?"

Will we regretfully look back on 2020 as a dress rehearsal for the Great Reset? Do we want to live in fear and/or guilt and wear a basically useless, fear-inducing, socially isolating mask for the rest of our lives?

Of course not.

Natural health and meditation advocate Dawson Church puts it well: "We're in the middle of this mass contagion of fear, and it is depressing our immune systems, rendering us less resilient, affecting us psychospiritually, making us less able to cope. That's when we need a bigger dose of positivity, joy and gratitude. We need to do that deliberately. That means meditation, it means consuming positive media. It means not exposing yourself to needless negative emotions."

But if we want to stop the Great Reset that is being furthered by power-intoxicated globalists, and instead build a world from the grassroots up that is based upon peace and justice, tolerance, freedom, individual choice, privacy, freedom of speech, religion, constitutional rights, and regenerative health, food, farming, and land use, we must do more than just complain in private or tweet about it to our followers.

Now is the time to get organized.

We need a new family-farm-based agricultural system that can provide "food as medicine," organic and healthy food for all, while regenerating the environment and biodiversity.

We need a new economic system that provides meaningful, socially and environmentally responsible work and a decent standard of living for all who are willing to work.

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We need to object to and refuse any and all efforts to mandate COVID-19 vaccines. This includes rejecting the fake "choice" of voluntary vaccination in the face of draconian restrictions for those who refuse to get it.

The Threat of Central Bank Digital Currencies

We also need sound money, be it in the form of physical cash or decentralized, block-chain-type digital currencies that protect our privacy and independence. The Great Reset brings with it a brand-new all-digital system that is not based on currency in the way we currently know it.

It's really a social control system, because by removing paper currency and replacing it with a central bank digital currency (CBDC), your ability to engage in transactions can be weaponized to destroy your privacy, surveil you, and prevent you from making purchases or even make a living.

Everything you buy and sell will be monitored, and punishment can be meted out if a transaction, your behavior, or even your thoughts are deemed undesirable by whatever "standards" that happen to be in vogue that week.

The transhumanist agenda is also part of this. Through the use of injections or some other means of getting biosensors into you, your actual physical body will be connected, literally, to the financial system. Transhumanism and technocracy fit hand in glove and can best be described as a digital slavery system where you are monitored and controlled 24/7.

Decentralized-Everything Is the Way Forward

Perhaps most important of all, we need a decentralized government and internet where the threat of censorship is eliminated and free speech is assured. As just one example of many, anyone who questions pharmaceutical products on any of the social media platforms now faces the risk of being deplatformed. Many also find themselves booted from digital finance platforms such as PayPal at the same time, which proves the point I was trying to make in the previous section.

You, the individual, should have the most rights, because laws are best applied as specifically and locally as possible. The concentration of global and federal powers comes at the expense of your individual rights.

Mercola.com and a number of similar websites have even been labeled a multinational security threat by British and American intelligence agencies, which are collaborating to eliminate "anti-vaccine propaganda" from public discussion using sophisticated cyberwarfare tools.

Ask yourself, does concern for public health really justify censoring and eliminating financial transaction capabilities of those who raise questions about vaccine safety and mandatory vaccination policies? The fact that they're trying to shut down all conversations about vaccines – using warfare tactics and economic blackmail, no less – suggests that the planned mass vaccination campaign has little if anything to do with keeping the public healthy and safe. It's about controlling the public and ensuring compliance.

The question is: *Why?*

The medical industry, and the vaccine industry in particular, have severe trust and credibility challenges that they themselves created and continue to grow with the help of Big Tech and national intelligence agencies, which are going to extreme lengths to prevent counternarratives from getting out.

Never before has the US government allowed this kind of blanket censorship of the public discourse. It would never be allowed if the government did it, but by delegating the censorship to private corporations it is allowed. It should be indisputable that censorship is anathema to a democratically run, free, and open society. While there may not be a benefit to allowing misinformation to be disseminated, the risks of censoring are simply too grave to be justifiable.

Censorship will never be applied just to the information you despise. It will be applied to any information that is threatening to the elite class that is attempting to further control us.

Big Tech censorship is actually even more insidious than government censorship, because it's far more opaque. At least if the government says it's going to censor certain kinds of expression, there's some level of transparency in how that's being done. Private tech companies, on the other hand, move the goalpost at will, and they're never entirely clear about who will be censored, for what, exactly, or how. What's more, there's no real process for appeal.

The problem we face now is that censorship fortifies power and is very difficult to end once it has taken hold. This in turn does not bode well for individual freedom or democracy as a whole. Censorship is a direct threat to both. With that in mind, the fact that US and U.K. intelligence agencies are getting involved in censoring tells us something important.

It tells us it's not really about protecting public health. It's about strengthening government control over the population. The fact that intelligence agencies view vaccine safety advocates as a national security threat also tells us that government is now in the business of *protecting private companies*, essentially blurring the line between the two.

If you criticize one, you criticize the other. In short, if you impede or endanger the profitability of private companies, you are now viewed as a national security threat, and this falls squarely within the parameters of technocracy, in which government is dissolved and replaced with the unelected leaders of private enterprise.

The right and freedom to critique the government is a hallmark of democracy, so this state-sponsored war against truthful information is clear evidence of a radical turn toward technocratic totalitarianism.

Standing at a Crossroads – Which Way Will We Go?

The hour is late, but there is still time to turn things around. We stand at the crossroads – will we choose dictatorship, offered to us by our transhumanistic, technocratic "overlords," or freedom and democracy? I invite you to join us in the fight for our lives and the lives of future generations. Join us as we educate and organize for a healthy, equitable, and regenerative future.

By thinking and acting locally – buying local foods and products, and engaging in local politics and local organizing – we start to cut off the lifeblood of individuals and companies that are pushing us in the wrong direction. As David Klooz warns in his book, *The COVID-19 Conundrum*: "If the COVID-19 hoax does not convince you to divest from the politicians and the corporations they serve, including divesting from big-business' goods and services, nothing will. Special interests just beta-tested turning entire nations into virtual prisons. If people allow it this time, their ability to do it again and to an even greater and more disruptive degree is all but guaranteed…."

Each one of our personal choices creates consumer-market-driven pressure that affects change from the bottom up. Forget top-down authoritative solutions. It always ends up biting us when we look to federal politicians to do something good for us, as lobbyists and lawyers – whose pockets are far deeper – are always working to make things better for the elites, not the general population.

Realize that federal and international agencies are captured by technocrats and oligarchs, so work within your community, and within yourself.

We likely can't stop the medical establishment from doing exactly what it wants to do – remain a slave to Big Pharma and treat symptoms rather than address fundamental root causes of disease. But you can opt out of these systems to keep yourself, your family, and your community healthy and resilient.

Dr. Joseph Mercola is the founder of Mercola.com, the world's most visited natural health website. A family physician and multiple *New York Times* best-selling author, his vision is to change the modern health paradigm by providing people with a valuable resource to help them take control of their health.

Ronnie Cummins is founder and director of the Organic Consumers Association (OCA), a nonprofit, US-based network of more than two million consumers dedicated to safeguarding organic standards and promoting a healthy, just, and regenerative system of food, farming, and commerce.

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Ask Dr. J

by Jim Cross, ND, LAc
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PPF Diet

I love mountain lions for many, varied reasons but mostly for this one: there are no mountain lion nutritionists. They intuitively understand that deer, especially Bambi, contain all the macro- and micronutrients needed to sustain an optimally healthy mountain lion. So, what happened to *Homo sapiens*? The answers to that question would occupy way more space than Dr. Collin would be willing to lease to me. For myself, the axiom "food is medicine" rings incredibly true. The specific foods that are consumed in each uniquely metabolomic individual is, for me, the most important of all medical prescriptions. What we eat influences every system of our body positively or negatively at each meal and snack, each and every day of our lives. Hopefully, we all can metamorphose into a proverbial mountain lion and decipher what specific foods we must consume in order to construct an internal milieu comparable in functionality to Michael Jordan at the height of his basketball prowess.

Let me, then, project here a very simple dietary prescription for humans to follow: the PPF/Paleocarb/Protein/Fat diet. Robert Crayhon, who helped develop Designs for Health,[1] which is a science-based nutrition and natural medicine company, coined two words: paleocarb and neocarb. Over time I have come up with my working definition of the two words. For me, a neocarb is any foodstuff that digests quickly and raises serum glucose and more importantly serum insulin to pathological levels: any monosaccharide like glucose, disaccharides like maltose, and/or any flour, whether whole or white. Paleocarbs are what our ancestors ate in their natural form: nuts, beans, seeds, legumes, tubers, veggies, fruits. Paleocarbs contain fiber, which mitigates the glucose/insulin effect in the serum and phytochemicals, which assist our bodies in detoxifying the myriad exogenous and endogenous chemicals we are exposed to.

My other two ingredients are high quality fat/protein. By high quality, I mean the sources of these two substances. Many people have written about high quality fat and protein, so I won't go into detail here. I'll give you two brief examples. From Figure 1 below, you can see that grass-fed beef has approximately one-fourth the saturated fat that grain-fed beef does. In Figure 2, you also observe that grass-fed cattle have approximately three times the anti-inflammatory omega-3 fat levels and half the pro-inflammatory omega-6 levels of grain-fed.

My focus for the remainder of this article is one simple word: **YOU**. Yes, you, not your significant other, not someone who lives in South Beach, and definitely not anyone who thinks that they understand your body better than you. Let me repeat this word one more time: **YOU**!

I am attempting to educate my patients to listen to their bodies. I remind them that their bodies are infinitely smarter than they are. Please give them the optimal fuel that they require, stay out of their way, and look out Michael Jordan. Of course, what do I recommend as the optimal fuel.

I will food allergy test them first to eliminate any foods that their bodies are not copasetic with. From there, I will go over the remaining foods that fit my P/P/F framework from above.

Next, I will attempt to refine their food intake one level deeper by giving them a diet diary to fill out for each meal they consume. After each meal they consume, I want them to keep track of two parameters: brain fog and fatigue. They need to assess those two factors immediately after each meal and hourly until the next meal. Those are the two most reliable indicators I have found that tell me if a particular food being consumed is problematic for that particular individual. Also, I tell them that if they ate an excessive

Figure 1. Total fat content (in grams) per 3 oz. serving[2]

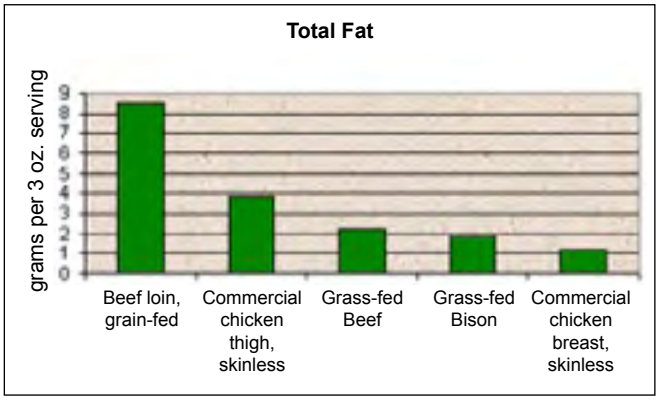
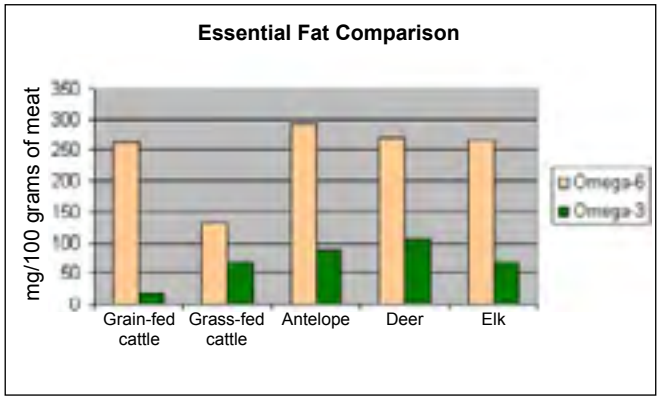


Figure 2. Essential fatty acid content[3]



amount of food to record the specific meal in which they did, and I won't pay particular attention to that meal.

Exactly, what am I looking for? I'll use myself as an example. If I have eaten optimally for my metabolome, I will have ample energy and a clear mind immediately after the meal and up to six hours later (I intermittently eat/fast, so it's easy for me to go up to several hours in between my two meals.). My wife knows immediately if I've eaten the wrong foods: I fall asleep on the couch, or I start to hesitate in phrasing my thoughts.

Essentially, I am attempting to educate my patients on how to consume a diet that makes their bodies hum like a 1968 Rambler. No fuss, no muss. I also relay the message that I am teaching them how to eat so I don't have to give them herbs, supplements, or pills to correct/prevent metabolic syndrome, cardiovascular disease, or any other common 21st century malady. This way of food consumption is also emphasizing the importance of what food they introduce into their bodies. As a result, I am striving to correct poor food choices they have made in the past rather than improving on their former choices.

Should a patient of mine from 10/20/30 years ago read this blurb, they might wonder at my sanity as my dietary guidelines back then were slightly different than my present ones. If I'm still cognitively aware 10 years from now, they may have slightly modified to a certain extent again. Alas, the insecurities associated with being a member of *Homo sapiens*. As a result, if I must return to this dimension again in my next life and I'm allowed a species choice, I am most definitively choosing mountain lion. Way fewer nutritional and psychological bills!

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CALENDAR

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: HEALING SKIES CONFERENCE: Cultivating the Inner Naturopath online. 20 CEs. CONTACT: https://ndnews.lpages.co/sanp/

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.

AUGUST 26-29: 12th ANNUAL INTEGRATIVE MEDICINE FOR MENTAL HEALTH CONFERENCE in Atlanta, Georgia, and live online. CONTACT: https://www.immh2021.com/

SEPTEMBER 24-26: ADVANCED INTEGRATIVE ONCOLOGY in Scottsdale, Arizona, and Live Online. CMEs available. CONTACT: Sharon Phillips, phone 954-540-1896; Email: sharon@aampconferences.com; https://aampconferences.com/

OCTOBER 14-17: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE FALL CONFERENCE – Immunity, Inflammation, and Autoimmunity in San Diego, California. CONTACT: http://aaemconference.com/

OCTOBER 14-17: 16th ANNUAL CARDIOMETABOLIC HEALTH CONGRESS in National Harbor, Maryland. CONTACT: https://www.cardiometabolichealth.org/2021/cmhc-16th-annual.html

Please visit www.TownsendLetter.com for the complete calendar.

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Transcendental Meditation™ for Cardiac Patients

Several recent studies on Transcendental Meditation™ (TM) have caught my attention; these studies suggest we should expand our treatment protocols for patients with coronary heart disease to include TM.

Let's start with a study by Bokhari et al published in the *Journal of Nuclear Cardiology* in September 2019. These researchers asked whether adding TM to standard therapy or standard therapies along with a cardiac rehab exercise program might do these patients any good. They recruited fifty-six African American patients with coronary heart disease, including those with recent heart attack, coronary artery bypass, or angina. The patients were divided into four groups and assigned to cardiac rehabilitation (CR), Transcendental Meditation (TM), Transcendental Meditation plus cardiac rehabilitation (CR+TM), or just usual care.

Testing was done at baseline and after 12 weeks. Patient response was assessed using a state-of the-art technique, myocardial flow reserve (MFR), that was assessed by 13N-ammonia positron emission tomography (PET). This technique is fast becoming the gold-standard of heart function assessment. This method of measuring cardiac flow reserve is increasingly being used "… to assess coronary artery disease, to guide revascularization decisions with more accuracy, and it allows robust quantitative analysis of both regional myocardial blood flow (MBF) and myocardial flow reserve (MFR)."[1]

Participants in the TM groups were taught Transcendental Meditation and instructed to practice twice a day for twenty minutes.

Of the 56 initial study participants, 37 completed the post-testing. Myocardial blood flow increased by 20.7% in the group that did both Transcendental Meditation and cardiac rehabilitation. Blood flow in the group that practiced Transcendental Meditation alone increased 12.8%. Those in the cardiac rehabilitation only group improved by only 5.8%. The patients who received only "usual treatment" declined; their myocardial blood flow decreased by -10.3%.[2]

Granted this was a small study, but these results suggest that getting patients to practice TM at home yielded twice the benefit as having them attend cardiac rehab classes. Add the numbers up, compared to the 'usual', getting these patients to also do cardiac rehab to exercise their hearts and TM to rest their minds increased cardiac blood flow by 31%. That's enough of a difference we should pay attention.

Transcendental Meditation was brought to the West more than half a century ago by the Indian Maharishi Mahesh Yogi. His technique became very popular in the 1960s, and 1970s. Promoters of the practice adopted the idea that this technique could and should be evaluated scientifically and encouraged researchers to study the effect it had on practitioners. Wallace, Benson and Wilson were the first to describe the wakeful hypometabolic state induced by the practice in the literature in 1971.[3] The earliest clinical trial listed in PubMed is Dilbeck's 1977 report that TWO weeks of practicing TM (n=33) produced a significant decrease in measured anxiety compared to sitting with the eyes closed.[4]

Practitioners and researchers described a distinct state of consciousness induced by the practice that differed from sleeping, dreaming or normal wakefulness, a state of restful alertness, what they labeled a "fourth state of consciousness."[5] "The purpose of meditation is the elimination or reduction of thought processes, the deceleration of the inner dialog of the mind. This reduction of the thought process aims to increase this state of higher consciousness and, thus, could lead to a great sense of physical and mental tranquility."[6]

Research on TM has been aided by the comprehensive training program instructors undergo and the standardization of instruction. The resultant reproducibility and availability of subjects along with active encouragement by the organization teaching the technique has over the intervening years led to the publication of a substantial body of scientific data describing the effects of the practice.

The hypothesis that practicing TM might reduce risk of CVD was presented early on; remember that now discarded premise that highly stressed Type A personalities were more prone to heart attacks? Randomized controlled trials of the effects of TM on hypertension were first published in the mid-1990s.[7,8]

In a 2004 review on TM and heart disease, Walton et al suggested that, at that time, there was already a substantial body of research that comprised over 600 papers. That is the most recent published tally that I've come across, but it is clearly out of date. There have been at least THREE dozen papers on TM and heart disease published in the past two decades since then. This new Bokhari paper just mentioned is one of a half a dozen recent papers to suggest TM has potential benefit for patients with heart disease.

A number of theories have been put forth to explain why TM might offer protection: "Evidence for its ability to reduce traditional and novel risk factors for CVD includes: 1) decreases in blood pressure, 2) reduced use of tobacco and alcohol, 3) lowering of high cholesterol and lipid oxidation, and 4) decreased psychosocial stress. Changes expected to result from reducing these risk factors, namely, reversal of atherosclerosis, reduction of myocardial ischemia and left ventricular hypertrophy, reduced health insurance claims for CVD, and reduced mortality, also have been found with TM practice. Research on mechanisms suggests that some of the CVD-related benefits as a result of this technique could arise from normalization of neuroendocrine systems whose function has been distorted by chronic stress."[9]

Although those connected with the TM movement have long argued that the practice is distinct from other meditation techniques, the scientific literature often groups all meditative techniques under similar search headings and, as a result, it is hard to distinguish between studies which meditation exactly the practitioners were doing. Thus, it is not always easy to discern whether a study is describing participants following "do it yourself" instructions (for example, those published in *The Relaxation Response* by Herbert Benson in 1976 on how to imitate TM meditation, or those following online instructions for mindfulness meditation, or some technique they learned at a yoga studio). Followers of Maharishi always insist that the TM technique they practice is unique and that these other practices do not have the same effects.

Neurohormonal effects of TM have been documented in numerous studies and were summed up by Newberg & Iversen in 2003. They reported that practicing TM increased GABA, glutamate, and dopamine in the brain while decreasing cortisol and noradrenaline.[10]

The results reported in this current Bokhari study are in line with earlier publications. Data published in 2012 in *Circulation* also suggested a significant benefit. In a randomized controlled trial (n=201) of African Americans with coronary heart disease (CHD), following endpoints of all-cause mortality, myocardial infarction (MI), or stroke during a 5.4 year follow up, there was a 48% reduction in the TM group.[11]

An October 2019 paper by Schneider et al, reported that in a randomized controlled trial TM prevented left ventricular hypertrophy. In this study, African American adults (n=85) were assigned to either a TM intervention or a health education control group. At baseline and six-month follow up, participants' left ventricular mass index (LVMI) were compared. The TM group's LVMI was significantly lower.[12] That's what we want to see.

TM researchers routinely select African Americans as study participants for their cardiovascular studies. The authors of these studies explain this recurring to recruitment as due to the fact that African Americans have a higher than average risk of heart disease and that this increase may be a result of psychosocial stress. Thus, a stress-reducing intervention might have a greater impact on their relative risk than it might on the general population. One would assume that their results should still translate to wider populations, but one must wonder if TM 'works better' in Blacks.

Of course, one of the weaknesses of all of these TM studies is the amount of personal contact that the TM practitioners receive from their instructors as they learn the technique. This attention might produce a not insignificant placebo effect.

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Even if this were the case, one might still argue that the ends justify the means in that anything that reduces cardiovascular mortality to the extent reported with so little risk is desirable.

The other reservation that some may have about these research papers is that they are consistently done by adherents or proponents of this technique and one might question their objectivity. Truthfully, similar questions about objectivity could be raised about a good percentage of other studies, especially when the research is sponsored by financial interests who desire specific outcomes.

The bottom line remains that practicing TM may help and it is unlikely to hurt. Currently this meditation technique is taught by a non-profit organization. Their sliding scale fee-schedule is posted on their website and is a model of transparency that many of us might emulate.

The American Heart Association came to a similar but more eloquently written conclusion in a 2017 position paper on meditation, writing in part:

> Studies of the effects of meditation on cardiovascular risk have included those investigating physiological response to stress, smoking cessation, blood pressure reduction, insulin resistance and metabolic syndrome, endothelial function, inducible myocardial ischemia, and primary and secondary prevention of cardiovascular disease. Overall, studies of meditation suggest a possible benefit on cardiovascular risk, although the overall quality and, in some cases, quantity of study data are modest. Given the low costs and low risks of this intervention, meditation may be considered as an adjunct to guideline-directed cardiovascular risk reduction by those interested in this lifestyle modification, with the understanding that the benefits of such intervention remain to be better established….[13]

Refer patients to the national organization's website for further information about learning the technique and finding a certified instructor: TM.org

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would lead to the erroneous conclusion that T3 therapy is not helpful for anyone. One would think that an open-minded doctor would allow compelling clinical and laboratory evidence to overrule the conflicting results from research.

Or maybe the doctors did not want to put in the extra time that would be required to become proficient in managing hypothyroid patients with a T3/T4 combination (Carlton Fredericks often remarked, "People tend to be down on what they are not up on."). A lack of proficiency would be a particularly weak excuse for the psychiatrist because there is a long history in psychiatry of using T3 to treat depression. Or maybe the doctors were skittish because liotrix is no longer commercially available, so it has to be compounded by a compounding pharmacy.

Whatever their reasons were for refusing to try T3, these doctors lost an opportunity to help a long-suffering patient who had fallen through the cracks of modern medicine. Practicing high-quality medicine requires taking your patients seriously, even if what they tell you falls "outside the box" of what you have been taught. From my personal experience as a practicing physician, I would venture to suggest that there is great joy to be found outside of that box.

Alan R. Gaby, MD

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Why Did These Doctors Not Listen to Their Patient?

I recently consulted with a man in his sixties who had a 35-year history of chronic fatigue and a 20-year history of depression and anxiety. He had been diagnosed with hypothyroidism about 30 years ago, for which he was prescribed Synthroid (levothyroxine). He was also taking three different psychotropic medications, which were prescribed by his psychiatrist. Several months previously, laboratory tests had revealed an elevated thyroid-stimulating hormone (TSH) level, with normal T4, and a T3 level below the reference range. Based on the high TSH level, his Synthroid dose was increased, which normalized the TSH level, while T4 remained normal and T3 remained below normal. Unfortunately, the increase in the Synthroid dose did not help his fatigue or depression, and it seemed to make his anxiety worse.

Based on the patient's laboratory tests, it seemed that he had an impaired capacity to convert T4 to its biologically active metabolite, T3. The conversion of T4 to T3 depends on the action of deiodinase, an enzyme that catalyzes the removal of one iodine atom from T4. Two such enzymes, deiodinases 1 and 2, occur in humans. Common variants of the genes for each of these enzymes have been identified,[1,2] and there is circumstantial evidence that some of these variant genes code for the production of a functionally defective enzyme. I suggested to the patient that he might do better with a thyroid preparation that contains both T3 and T4. I was not in a position to write the prescription myself because I am no longer in clinical practice. So, I suggested that he discuss this possibility with his doctors.

The patient was pleasantly surprised by my recommendation. He remarked that around 25 years ago he was not doing well on Synthroid, as it made his chronic fatigue much worse. He consulted a holistic doctor who switched him to liotrix (brand name, Thyrolar®), which contained both levothyroxine (T4) and triiodothyronine (T3) in a 4:1 ratio. While on liotrix, he had no fatigue and no side effects, and all of his laboratory tests for thyroid function stayed in the normal range. He continued on liotrix for a number of years and did "extremely well" (his words). However, the holistic doctor moved to a different state, and the patient was unable to find another doctor willing to continue the liotrix prescription. So, he was forced to go back on Synthroid and has felt bad ever since.

I told the patient that his compelling story, combined with his subnormal T3 level on the lab test, should be enough to persuade any reasonable physician to agree to a trial of switching to liotrix. Out of an abundance of caution, the switch could be done gradually; perhaps one-third of the dose every two to four weeks. Unfortunately, I was wrong; the psychiatrist and the patient's primary care physician were both unwilling to approve a trial of liotrix.

I found this hard to understand. Here the patient tells his doctors exactly what he needs, and he provides laboratory evidence to back it up. Did the doctors just not listen to him? Or maybe they did listen, but didn't believe him. Or maybe they believed him but were unwilling to risk the consequences of deviating from whatever "standard of care" they were locked into by whoever it is that dictates "standards of care." It is true that the research is conflicting on whether patients fare better with T3/T4 than they do with T4 alone. However, those studies likely included at least two different types of patients: those who did not need T3 and felt worse when they took it, and those who did need T3 and felt better when they took it.[3] Averaging the results from those different types of patients

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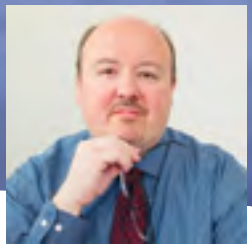

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