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Vitamin C and Sepsis

Devaki Lindsey Berkson, DC

Addressing the Root Cause of Kidney Disease

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From the Publisher

VICTAS Trial Finds No Benefit of IV Ascorbic Acid for Sepsis

One of the sad things about hospital research of nutritional medicine, particularly vitamin C, is that rarely does the study demonstrate effectiveness. Years ago, when Pauling and Cameron wrote about ascorbic acid showing benefit in cancer patients, a Mayo Clinic surgeon, Charles Moertel, wrote that his trial with vitamin C did not show improved survival. In 2019 Dr. Alpha Fowler at the University of Virginia demonstrated that vitamin C shortened hospitalization and ICU time in patients with sepsis. Following a similar protocol established by Fowler, Dr. Jonathan Sevransky at Emory University carried out a multi-institutional placebo-blinded randomized study of vitamin C in treating sepsis.[1] His VICTAS trial used a low dose of ascorbic acid, thiamine, and hydrocortisone (HAT protocol). Not surprisingly, there was no benefit in the treatment group compared to the placebo group in survival, amount of time in the ICU, and amount of time hospitalized. The study published in *JAMA* in February 2021, demonstrating an absence of vitamin C effectiveness in sepsis was accorded CME status for doctors reading the article

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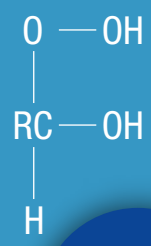
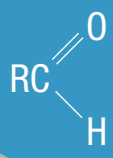
Peroxidic Compounds



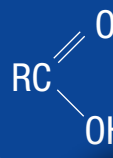
Hydrogen Peroxide

H_2O_2

Aldehydes



Acids



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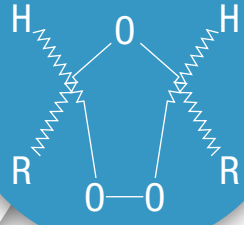

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Letter from the Publisher

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and passing a quiz; the take away was there is no need to consider vitamin C in septic patients and, presumably, patients with major infections.

As Michael Passwater critiques in this issue of the *Townsend Letter*, the study was "designed to fail." Among the major concerns noted by Passwater was the very low dose of ascorbic acid implemented in septic care. The study called for 1.5 grams of vitamin C to be administered intravenously every six hours for a period of four days. 1.5 grams! Really. This would be like administering 1 mg of Lasix to treat heart failure when typically, 40-80 mg is needed. Most integrative practitioners use 5-10 grams in a Meyer's cocktail IV slow push in treating chronic fatigue or fibromyalgia. How could there have been any expectation that 1.5 grams of vitamin C would accomplish anything? When old-timer Fred Klenner, MD, treated infected patients with intravenous ascorbic acid, he would always use 25-50 grams in an IV drip over one to two hours. Robert Cathcart, MD, not only did the same with sick patients, he would not infrequently use 75-100 grams. As Passwater points out in his critique, the protocol was not initiated in septic patients until 15 hours had passed. Why did the study design call for such a lengthy delay in treatment with such a low dose of ascorbic acid?

Unfortunately, MDs seeking their CME accreditation will only walk away thinking that vitamin C offers no benefit in their treatment armamentarium. So much for ascorbic acid becoming a mainstay in hospital treatment for sepsis and infection. This is truly disgraceful. Who will step up to repeat this trial using 25-50 grams of ascorbic acid every six hours and requiring treatment to be initiated immediately? No one, unfortunately. Intravenous vitamin C will remain, of all things, a "renegade" therapy that only a few patients will have access to.

Cover Story: Dr. Lindsey Berkson on Kidney Disease

Dr. Devaki Lindsey Berkson is a recognized nutritional consultant who specializes in complex hormone and gastrointestinal case management. Dr. Berkson has served as a research fellow at the University of Texas at Austin as well as Distinguished Estrogen Scholar at the Center for Bioenvironmental Research. She serves in teaching CME for professionals at A4M and PCCA. Berkson has authored numerous books and presented at dozens of conferences here and abroad. Berkson authored a three-part article in the *Townsend Letter* beginning in August/September 2020 entitled "Estrogen Vindication," citing the evidence about estrogen's effectiveness and safety in bio-identical hormone treatment (see www.townsendletter.com). Dr. Berkson invites the readership to consult with her to help manage complex cases (www.drlindseyberkson.com).

Berkson has a unique take on kidney disease; for sixteen years she suffered with chronic kidney disease following a nephrectomy for kidney cancer. Berkson attributes her kidney cancer and subsequent renal disease to the damage that diethylstilbestrol (DES) did to her in-utero. Despite impeccable nutrition, exercise, mindfulness, herbal supplementation, and nephrology care, her CKD did not improve. Her kidney specialists were unable to offer any answers as to why her kidney functioning was deteriorating.

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Letter from the Publisher

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Berkson's academic mindset pushed her to research the medical literature for answers. Her research shocked her that there were far more means to assess kidney functioning than measurement of creatinine, BUN, and estimated glomerular filtration rate. For starters, elevation in potassium is an important marker for kidney dysfunction. But a half-dozen other biochemical markers, having relevance in assessment of kidney functioning, are not routinely tested. A big one is trimethylamine-N-oxide (TMAO). An elevation in TMAO not only impairs kidney functioning but also damages endothelium and the heart. For those individuals with elevated TMAO, a vegan diet is indicated. As Berkson discusses in her cover article, other biochemical factors ignored by nephrologists play an unappreciated role in impairing kidney functioning. Nutritional management of these factors not only may manage kidney disease but may even reverse it. Berkson's chronic kidney disease is completely reversed.

Assessing Liver Function by Dr. Douglas Lobay

Readers of the *Townsend Letter* are familiar with Doug Lobay, ND's writing. Recent articles include "The Canary in the Coal Mine or How to Improve Kidney Function" and "Practical Nutritional Supplement De-Prescribing," both available on-line.[2,3] A graduate of Bastyr College (University of Health Sciences) Dr. Lobay has been practicing naturopathic medicine for many years in Kelowna, British Columbia. Lobay is the author of several books, including *Dr. Lobay's Natural Health and Healing* and *Dr. Lobay's Natural Medicine 101.*

For those of us who may be a little bit rusty on liver physiology, Doug's summary of liver functioning, particularly phase 1 and 2 biotransformation, is an easy-to-read review as well as a great synopsis to share with patients. One of the interesting aspects of liver testing has been the gradual increase in reference ranges for ALT and AST testing. Why should a normal ALT and AST be higher now than it was 30 years earlier? Could it be that a societal increase in obesity, occurring with an increase in metabolic syndrome and non-alcoholic fatty liver disease, has made a "normal" liver transaminase higher than the past? The point is that abnormal liver function is more prevalent, and we should be alert to assessing it in our patients. As Lobay writes in this issue's article on liver disease, quoting his mentor, the late John Bastyr, who himself quotes a wise sage: "If all else fails, treat the liver."

By all means take a gander at these Lobay articles online and others that he has written at www.townsendletter.com.

Jonathan Collin, MD

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Pathways to Healing

by Elaine Zablocki

Healing Trauma Through Nature-Based Mindfulness

Rochelle Calvert, PhD, CMT, SEP, has written a remarkable, exceptionally useful book called *Healing with Nature: Mindfulness and Somatic Practices to Heal from Trauma*. She offers a wealth of practices with nature for becoming more aware of bodily sensations, in an open, nonjudgmental way. She teaches ways to become somatically aware of the trauma(s) that are stored in our bodies, our minds, and our habits. We can explore new ways to heal old trauma, and we can draw strength from the natural environment to support the process of healing.

The book shares practices on developing mindfulness with nature, understanding somatic healing with nature, and living into aliveness with nature. It discusses ways to integrate our own personal healing into helping nature to heal.

Calvert has years of experience working with mindfulness-based methods. She was first exposed to mindfulness training as she pursued her PhD in clinical psychology. She moved on to serve as staff psychologist and director of clinical training for the University of California San Diego Center for Mindfulness. "At this point psychologists were looking at the Mindfulness-based Stress Reduction Program (MBSR) and starting to infuse it with additional forms of psychological knowledge such as cognitive therapy," she recalls. "The center was developing, researching, and teaching these new programs, and I was part of that."

In 2010 Calvert left the UCSD Center in order to do direct therapeutic work to help people who are struggling with anxiety, depression, trauma, and other problems. She founded the New Mindful Life Center in order to support people clinically in a variety of ways, tailored to client needs.

In recent years she found that practicing mindfulness in nature offers significant benefits. She started working with people outdoors, in beautiful settings. "When we're outside, the

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Pathways to Healing

Rochelle Calvert, PhD, CMT, SEP

body naturally wants to relax or soften. If I was working with someone I might say, now just let your eyes wonder around this natural environment and tell me what you see out here right now. It's a way of helping people be more present in their bodies and in the moment."

She finds that working with people in a natural environment supports them and helps them deal with embedded patterns of trauma. One core reason she wrote this book "is that I care deeply about people having a healthy relationship to their trauma," Calvert says. "Most people tend to pathologize trauma. I find we can look at it from a different lens and find healing modalities that can help so we aren't walking around with a reactive trauma as a permanent part of our experience." She adds that she is thinking of trauma very broadly, to include accidents and pain conditions, illness, assaults and combat, bullying, climate crisis and racism, and also experiences of loss and grief. "There are so many different ways people experience suffering in their lives. Depending on whether they were able to support themselves in a skillful way through that difficulty, that informs whether the trauma heals or causes long-term problems."

Moving Toward the Trauma

One chapter of the book is called "Moving Toward the Trauma," and that's not how we usually think about trauma. Usually we say, "This is a problem, it needs to go away. I need to fix it." But once we learn to be more present with all the sensations in our bodies, including those associated with our trauma, we can let go of our habitual interpretations and open to new ways of experiencing ourselves. "My goal is to give the reader skills to move safely towards that," Calvert says. "Do we feel our nervous system is supported? Are we getting enough sleep? Do we practice in an environment where we feel relaxed? Nature helps us use our senses to awaken to what's here right now. As we feel grounded and stably supported, that makes it possible for us to move towards traumatic and painful areas and start to work with them."

In a remarkable chapter called "Finding the Healing Currents," Calvert maps out specific ways to explore trauma in a healing way, without being overwhelmed. She describes a core healing practice called pendulation, in which we shift attention between two different objects of awareness. "You first establish awareness to an experience in your body that is grounded, steady, stable, and secure; or to something in the natural environment that feels this way" she writes. This creates "a sense of calm and ease to support you in working with the trauma."

Then, "slowly and gently you begin to move your awareness to the place in the body where you experience a sensation associated with your trauma, such as tightness, constriction, tension, or numbing.... It's important to bring a willingness to just be with any of these sensations as it is, not judging, not needing it to be different, not trying to change or fix it," Calvert writes.

You shift your attention between the sensation of groundedness and the sensations associated with trauma. Gradually you increase the time you stay present in each of them. "This practice cultivates your capacity to be trusting, patient and open. As you repeat it, space for healing will open.... You may experience a release or shift in the area associated with your trauma." Calvert emphasizes that it's important to start small and work slowly in this sort of practice, gradually increasing our ability to attend to trauma. "Treat your trauma with care, respect, and regard as you transform it into healing," she says.

Practice in a Variety of Settings

In order to provide nature-based therapy in a variety of settings, New Mindful Life has acquired a Sprinter Van, converted to support therapy and mindfulness practices. It now includes a small kitchen, couch, bathroom, and an awning that extends for outdoor shade. The van can support mindfulness-in-nature classes or retreats, providing water and tea, cushions and chairs. It can also offer an intimate, private space for personal counseling services, while still being close to nature so clients can directly experience the benefits of nature-based mindfulness therapy.

For the past 18 years Calvert has been based in San Diego, which has a reliable warm climate with limited rain, and supports her work with clients outdoors in nature. In the near future she plans to relocate to Taos, New Mexico. I asked her how these methods will be effective in a more challenging climate.

The van will go with her and will provide a relatively sheltered outdoor space. "I have been thinking about ways to manage the more extreme variations in the seasons," she says. "However, having taught nature-based work now for several years, I see there is a benefit when practicing in varying climates and conditions. More challenging experiences with nature can deepen and support your experience of these practices, what they teach and reflect to you, and how you can heal."

Many *Townsend Letter* readers are coping with major illnesses and long-term illnesses that Western medicine doesn't have effective ways to treat. Does nature-based healing offer something unique for these situations? "When we're in deep places of pain or difficulty, sometimes we may experience radical shifts, new ways to experience ourselves and connect to the world in a more intimate and integrative way," Calvert says. "There may be doorways we haven't thought about before, that traditional Western medicine doesn't really explore. I believe nature has an inherent healing wisdom for us. When we deepen our relationship with nature, that can be of profound benefit and help us face deeply challenging times."

Resources

Healing with Nature: Mindfulness and Somatic Practices to Heal from Trauma will be published on June 8, 2021. Website: https://newmindfullife.com/

This website includes links to courses and events, a newsletter, and a schedule for the van. Look especially for the Six-Week Introductory Training in Mindfulness, an online course. Also look for the newmindfullife YouTube channel. You will find wonderful training sessions such as:

20 Minute Body Scan – https://www.youtube.com/watch?v=pl4h2CZGB9w

Seated Mindfulness Meditation – https://www.youtube.com/watch?v=wMIttpNnpQw

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Elaine Zablocki is the former editor of CHRF News Files.

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Shorts

briefed by Jule Klotter
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Chronic Low Back Pain and Gluten

A retrospective case report of 110 patients, from a rheumatology clinic in Spain, indicates that a gluten-free diet is beneficial for some patients who have chronic, unmanageable low back pain (mean duration=15 years; SD 9.2 years). The rheumatology clinic, which is part of a university hospital, includes a unit that focuses on gluten sensitivity. The patients had clinical signs of spondyloarthritis (inflammation of spine and/or joints) but no clear cause for their severe pain (eg, fracture, tumor, infection). Authors Carlos Isasi and colleagues state that spondyloarthritis is associated with inflammatory bowel disease and non-specific gut inflammation.

For this report, patient records were selected from the unit's database. Patients with severe, chronic low back pain who followed a gluten-free diet (GFD) for at least four months were included in the study. Some patients also had a diagnosis of fibromyalgia, depression, or disc pathology. The strict diet followed guidelines from the Association of Celiac and Gluten-Sensitivity of Madrid. Patients also received vitamin and mineral supplements (unspecified) and were encouraged to restrict or eliminate dairy food. All patients were negative for celiac disease, according to testing (anti-transglutaminase, anti-deamidated gliadin peptide) performed before starting the diet. In addition to collecting data from patient records, the researchers contacted each patient by phone and used a structured questionnaire to assess the patient's clinical status and to fill gaps in the medical record.

Out of the 110 patients, 69 (62%) showed "demanding improvement": they reported significant relief in the low back pain plus at least one of the following: ability to return to normal life and/or work, discontinuation of opioids, >50% reduction of analgesic drugs, or pain remission (totally asymptomatic or only occasional non-severe pain). Fifty-six of this group reported eating gluten at some point; all but two of them said that their symptoms worsened with gluten.

Eighteen patients (16%) reported partial improvement on GFD; both pain and digestive symptoms had improved – but not to the point that it changed medication or their ability to function. Twenty-three patients (21%) showed no improvement after following the GFD for at least four months.

Patients with fibromyalgia were less likely to experience a benefit: "78% of 27 without fibromyalgia diagnosis reached demanding improvement versus 57% of 83 patients who had been diagnosed with fibromyalgia." Those who reported demanding improvement followed the GFD longest (median duration time 60 months). Median duration time for those reporting partial improvement was 24 months, and for those with no improvement median duration was 18 months. (Was the diet more effective with longer adherence, or did patients adhere to the diet for a longer time because it was effective? The article doesn't say.)

Because the diet's effects can take months to become apparent, the researchers looked at several variables in the hope of identifying which patients were most likely to respond to GFD. Variables included presence of genetic susceptibility for celiac disease, signs of autoimmunity, nutritional deficiency, and previous GI disorders. When looking at data from patients with demanding improvement, the researchers found statistically significant associations to oral aphthosis (mouth ulcers or canker sores; OR 12.06: 95%CI 3.97-36.58) and to having a relative with celiac disease (OR 7.90: 95%CI 1.01-62.02). Patients with the greatest response to GFD were also more likely to show evidence of malabsorption of ferritin, copper, and zinc (OR 5.93: 95%CI 1.28-27.51). Neither genetic typing nor duodenal biopsy results had a statistically significant association with demanding improvement to GFD. However, the authors point out, "The statistical analysis of potentially predictive variables is limited by the sample size and small number of patients who did not experience improvement."

Controlled, prospective studies are needed to test whether non-celiac gluten sensitivity is associated with chronic low back pain related to spondyloarthritis, say the authors: "This study is not intended to convey that 62% of patients having a GFD recommended are going to experience a significant

improvement, but it describes a clinically significant improvement in a selected group of patients….” This report does, however, support the observation that specific foods can cause joint pain – as Hal S. Blatman, MD, described in his *Townsend Letter* article “The Truth About Pain” (November 2018 and online).

Isasi C, et al. Non-celiac gluten sensitivity and chronic refractory low back pain with spondyloarthritis features. *Medical Hypotheses*. 2020;140:109646.

Vitamin C and Hemodialysis

Several studies have looked at benefits and risks of vitamin C (ascorbic acid) supplementation for patients with end-stage kidney disease who receive hemodialysis (HD). As Patrick Chaghouri and colleagues explain in their 2021 review article, vitamin C deficiency is common in HD patients. The HD process removes nutrients, including ascorbic acid (AA), along with uremic, water-soluble toxins from the bloodstream. In addition, kidney patients need to restrict their consumption of high-potassium fruits and vegetables, foods that may also contain ascorbic acid. One study found that “hemodialysis patients compared with healthy subjects have a fourfold smaller mean of AA concentration in serum collected before the dialysis procedure, which was 12 µmol/L.” Another study reported a mean concentration of 9 µmol/L in HD patients; AA deficiency is defined as <15 µmol/L.

The potential negative effects of AA deficiency are heightened by an increased need for antioxidants; chronic kidney disease and the process of HD itself produce increased oxidative stress and inflammation. Uremia, characteristic of kidney disease, causes metabolic changes, including mitochondrial dysfunction and overproduction of reactive oxygen species (ROS). Hemodialysis stimulates inflammation and immune response as leukocytes, thrombocytes, and plasma repeatedly contact the hemodialysis membrane, which is foreign to the body; “the higher the dose of dialysis, the stronger inflammation and oxidative stress can occur.” HD patients usually have higher serum concentrations of the inflammatory marker C-reactive protein (CRP). In addition, intravenous iron, used to treat anemia, also increases ROS production. Increased oxidative stress is a major contributing factor to cardiovascular disease, the leading cause of death among kidney patients: “…patients with AA concentration in plasma lower than 32 µmol/L were at almost a fourfold higher risk for major cardiovascular events and cardiovascular mortality compared to patients with AA concentration in plasma exceeding 60 µmol/L” [Deicher et al. *J Am Soc Nephrol.* 2005;16:1811-1818].

Several studies have investigated supplementation to increase AA levels in HD patients. Oral doses of 750 mg per week increased AA plasma concentration to normal range, without safety concerns. C-reactive protein levels decreased (16.8±27.9 to 10.8±25.4 mg/L) in patients receiving AA (250 mg three times/week), while CRP increased in patients who received a placebo or no intervention. Intravenous doses of 500-900 mg/week also raise AA levels, but IV supplementation has been linked to oxalate formation in HD patients. “The fact of exceeding saturation level brings a risk of oxalate deposition in tissues, mainly vessels, and bones,” the authors write. “Paradoxically, such a result of vitamin C overdosage would possibly precipitate the occurrence of cardiovascular diseases instead of preventing them.” Oral supplementation is less likely to have this effect. In addition to oxalate formation, intravenous AA has a *pro*-oxidant effect when given with intravenous iron. When infused together F2-isoprostane (a marker of oxidative stress related to inflammation and lipid peroxidation) increased along with an increase in the inflammatory markers interleukins 1 and 10 and tumor necrosis factor-α. The increase in these biomarkers did not occur when iron was administered on its own.

Chaghouri et al acknowledge that vitamin C supplementation for HD patients is still debatable. They conclude: “A physician…should take into consideration: concentration of AA in plasma and its relation to the reference values, the concentration of ferritin in serum, which is better to be lower than 500 µg/L, avoidance of simultaneous iron infusion, route of AA administration with the preference of enteral one, and avoidance of repeated large doses.”

Chaghouri P, et al. Two Faces of Vitamin C in Hemodialysis Patients: Relation to Oxidative Stress and Inflammation. *Nutrients.* 2021.

Microbiota Transplantation for Liver Diseases

Researchers are investigating fecal microbiota transplantation (FMT) as a possible adjunctive treatment for chronic liver disease. FMT, which FDA considers a drug and a biologic, is a standard-of-care treatment for recurrent *Clostridium difficile* infection, but its use in other conditions is experimental. Because worsening dysbiosis and changes in the microbiome are associated with liver disease severity, researchers hope to use FMT to modify the gut-liver-brain axis to slow or prevent progression to cirrhosis (end-stage liver disease) and the cognitive impairment of hepatic encephalopathy. Jasmohan S. Bajaj and Alexander Khoruts explain that “changes in liver disease-associated intestinal

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ON THE COVER: Devaki Lindsey Berkson, DC – Addressing the Root Cause of Kidney Disease (pg. 23); Glandulars and Autoimmune Disorders (pg. 40); Assessing Liver Health (pg. 33); Uric Acid and the Kidneys (pg. 30); Vitamin C and Sepsis (pgs. 2, 56)

Erratum: NIH and Ivermectin

National Institutes of Health removed its disapproval of ivermectin's use to prevent and treat COVID-19 on January 14, 2021 – not 2020, as stated in April's editor comment (page 70).

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Shorts

➤ *continued from page 11*

microbiota are driven by a multitude of host factors, including decreased bile acid production, altered mucosal biology, changed xenobiotic metabolism, different diet [and alcohol use], and various therapeutics that include antibiotics." Several therapies for liver disease target the GI microbiome: probiotics and prebiotics, bile acid/FGF analogs, antibiotics, laxatives, as well as FMT.

Bajaj and Khoruts prefer to use the term "intestinal microbiota transplantation" as the procedure now involves standardized, cryopreserved preparations. Delivery technologies to contend with variable GI transit times and medication use are still being developed. People with liver disease are often taking medications that impact the microbiota, including multiple courses of antibiotics that make them vulnerable to recurrent *C. difficile* (rCDI) infections. Dosing requirements for liver disease are also unknown. Patients with cirrhosis who received FMT to treat rCDI were more likely, than non-cirrhotic patients, to need multiple FMT treatments.

Many FMT liver studies focus on hepatic encephalopathy (HE). A 2019 study, led by Jasmohan S. Bajaj, looked at long-term effects of FMT in 10 recurrent HE patients who took part in a 2017 safety trial. In the 2017 randomized, controlled trial, the treatment group underwent five days of pre-FMT antibiotics (to promote microbial engraftment), followed by 90 ml (27 grams) of donor material administered via enema. The control group received standard of care (SOC). All participants were on lactulose, rifaximin, and proton pump inhibitors. For the 2019 study, seven patients were followed for at least 12 and up to 15 months. (Two in the standard of care group were excluded; one died and one had a liver transplant. And one in the FMT group died.)

During the 12-to-15-month follow up, the SOC group had a higher number of hospitalizations (n=10) than the FMT group (n=1) and more HE events (8 in SOC vs. 0 in FMT). Cognitive function, "which had improved in the FMT arm at Day 20 post-FMT, remained significantly better in the FMT arm compared to SOC…." The small size of this study, of course, is a limitation; and larger controlled trials are needed.

Bajaj JS, Khoruts A. Microbiota changes and intestinal microbiota transplantation in liver diseases and cirrhosis. *J Hepatology.* 2020;72:1003-1027.

Bajaj JS, et al. Long-term Outcomes After Fecal Microbiota Transplant in Cirrhosis. *Gastroenterology.* May 2019;156(6):1921-1923.

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Disclosure: The *Townsend Letter* publishes information about alternative medicine written by researchers, health practitioners, and patients. As a forum for the entire alternative medicine community, we present information discussing a wide variety of alternative and integrative medicine practices. In addition to publishing original research and literature abstracts and reviews, we encourage case studies and anecdotal reports. Detailed anecdotal reports are not viewed as proof but as possibilities that need further investigation. All authors are requested to submit their reports to other professionals for review.

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.

Literature Review & Commentary

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

delta-Tocotrienol for Nonalcoholic Fatty Liver Disease

Seventy-one adults (mean age, 44.4 years; mean body mass index, 31.2 kg/m^2) with nonalcoholic fatty liver disease were studied. All patients had ultrasound-proven hepatic steatosis and mild-to-moderate elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (not more than 4 times the upper limit of normal). The patients were randomly assigned to receive, in double-blind fashion, 300 mg of delta-tocotrienol twice a day or placebo for 24 weeks. The proportion of patients who showed a decrease in the severity of hepatic steatosis was significantly greater in the delta-tocotrienol group than in the placebo group (31.4% vs. 12.5%; $p < 0.05$). Compared with placebo, delta-tocotrienol significantly decreased mean values for ALT and AST, significantly decreased insulin resistance, and significantly decreased the mean concentration of C-reactive protein. The mean decrease in body mass index was significantly greater in the delta-tocotrienol group than in the placebo group (-2.38 vs. -0.73 kg/m^2; $p < 0.001$). No adverse events were reported.

Comment: "Vitamin E" is a collective term for eight naturally occurring compounds: four tocopherols (alpha-, beta-, gamma-, and delta-) and four tocotrienols (alpha-, beta-, gamma-, and delta-). Tocotrienols are found in relatively high concentrations in grains (e.g., oats, barley, and rye) and in certain vegetable oils (e.g., palm oil and rice bran oil). Studies in rats and mice found that tocotrienols, especially delta-tocotrienol, have antioxidant and anti-inflammatory effects, improve insulin resistance, and decrease hepatic steatosis. In the present study, administration of delta-tocotrienol improved biochemical markers of hepatocellular injury and steatosis, and decreased insulin resistance and inflammation, in patients with nonalcoholic fatty liver disease. delta-Tocotrienol is commercially available as an individual supplement (90% delta- and 10% gamma-tocotrienol).

Pervez MA, et al. Delta-tocotrienol supplementation improves biochemical markers of hepatocellular injury and steatosis in patients with nonalcoholic fatty liver disease: A randomized, placebo-controlled trial. *Complement Ther Med*. 2020;52:102494.

Vitamin E for Nonalcoholic Steatohepatitis in HIV-Infected Patients

Twenty-seven HIV-infected patients with nonalcoholic steatohepatitis received 800 IU per day of vitamin E (alpha-tocopherol) for 24 weeks. Compared with baseline, a significant decrease was seen in the median alanine aminotransferase level (from 50 IU/L to 23 IU/L) and in the median degree of hepatic steatosis. There was no significant change in body mass index.

Comment: Nonalcoholic fatty liver disease can manifest either as fatty liver alone (hepatic steatosis) or as a combination of fatty liver and hepatic injury (hepatitis). In the latter case it is referred to as nonalcoholic steatohepatitis. Several studies have demonstrated that alpha-tocopherol is beneficial for patients with nonalcoholic fatty liver disease who are not infected with HIV. The present study found that alpha-tocopherol is also useful for patients with HIV. Based on this research and the study on tocotrienols described above, it is possible that combining tocopherols and tocotrienols would be more effective than either treatment alone for patients with nonalcoholic fatty liver disease.

Sebastiani G, et al. Vitamin E is an effective treatment for nonalcoholic steatohepatitis in HIV mono-infected patients. *AIDS*. 2020;34:237-244.

Tocotrienols for Diabetic Kidney Disease

Fifty-nine Malaysian patients (median age, 67 years) with diabetic kidney disease (mostly stage 3A) were randomly assigned to receive, in double-blind fashion, 200 mg of tocotrienol-rich vitamin E (Tocovid SupraBio; Hovid Berhad, Ipoh, Malaysia) twice a day or a placebo for 12 months. The mean serum creatinine concentration at baseline was 1.38 mg/dl in the tocotrienols group and 1.33 mg/dl in the placebo group. Serum creatinine was measured every two months for 12 months. In the tocotrienols group, the mean creatinine level was lower than the baseline value at all time points, whereas in the placebo group the mean level was higher than the baseline

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value at all time points. The difference in the change between groups was significant after 4, 6, and 8 months, but not after 10 or 12 months. For estimated glomerular filtration rate (eGFR), in the tocotrienols group the mean value was higher than at baseline at all time points, whereas in the placebo group the mean value was lower than baseline at all time points. The difference in the change between groups was significant after 4, 6, 8, 10, and 12 months. Among patients with stage 3 chronic kidney disease (eGFR of 30-60 ml/min/1.73 m^2), at 12 months the difference in the change in eGFR between groups was 6.28 ml/min/1.73 m^2 (p = 0.022).

Comment: This study demonstrated that supplementation with tocotrienol-rich vitamin E prevented the decline in kidney function in patients with diabetic nephropathy. The mechanism of action is not clear.

Koay YY, et al. A phase IIb randomized controlled trial investigating the effects of tocotrienol-rich vitamin E on diabetic kidney disease. *Nutrients*. 2121;13:258.

Selenium, Coenzyme Q10, and Renal Function

Four hundred forty-three community-dwelling elderly Swedish individuals (aged 70-88 years) were randomly assigned to receive, in double-blind fashion, coenzyme Q10 (CoQ10; 100 mg twice a day) and selenium (200 µg per day from selenium yeast) or placebo for four years. The present study was a subgroup of analysis of the 215 individuals who agreed to provide blood samples during the entire intervention period and who also survived for the entire intervention period. At baseline, the mean serum selenium level was 67 µg/dl, which was below the "adequate" concentration of 100 µg/L. In the selenium/CoQ10 group, the mean serum creatinine concentration decreased from 1.04 mg/dl at baseline to 0.87 mg/dl after four years. The mean creatinine level did not change in the placebo group; and at the end of the treatment period, the level was significantly lower in the selenium/CoQ10 group than in the placebo group (0.87 vs. 1.03 mg/dl; p = 0.0002).

Comment: In this study, long-term supplementation with a combination of selenium and CoQ10 appeared to improve or slow the decline in renal function in elderly Swedish individuals. Low selenium intake is common in European countries, and serum selenium measurements at baseline suggested that mild selenium deficiency was common in this population. It is not clear whether the findings from this study would apply to regions where selenium status is adequate. It is also not known whether the beneficial effect on kidney function was due mainly to selenium, CoQ10, or their combination. Age-related decline in renal function is very common, so the possibility that this decline can be prevented warrants further study.

Alehagen U, et al. Selenium and coenzyme Q10 supplementation improves renal function in elderly deficient in selenium: observational results and results from a subgroup analysis of a prospective randomised double-blind placebo-controlled trial. *Nutrients*. 2020;12:E3780.

Vitamin D Toxicity Persists for a Long Time

A 25-year-old male presented with hypercalcemia and acute kidney injury due to vitamin D toxicity. He had consumed 50,000 IU per day of vitamin D for around seven months, with the last dose taken two weeks prior to presentation. His serum 25-hydroxyvitamin D (25[OH]D) level was reported as greater than 126 ng/ml (more precise quantification was done). Twenty-nine days after his last vitamin D dose the 25(OH)D level was 492 ng/ml, and 81 days after the last dose the level was 274 ng/ml.

Comment: This case report demonstrates that serum 25(OH)D levels can remain markedly elevated for months after high-dose vitamin D is discontinued. Because it is fat-soluble, vitamin D can accumulate in adipose tissue, and this accumulation may not necessarily be accompanied by a substantial increase in the serum 25(OH)D level. In one study, 29 subjects were randomly assigned to receive 20,000 IU of vitamin D3 or placebo once a week for three to five years. At the end of the treatment period, the mean concentration of vitamin D in adipose tissue had increased by 550%, whereas the serum 25(OH)D level had increased by only about 60%.[1] Therefore, in people taking large doses of vitamin D, a normal 25(OH)D level may not rule out the possibility of impending and persistent vitamin D toxicity.

Houghton CC, Lew SQ. Long-term hypervitaminosis D-induced hypercalcaemia treated with glucocorticoids and bisphosphonates. *BMJ Case Rep*. 2020;13:e233853.

Ivermectin for COVID-19

A chart review was conducted on 280 patients hospitalized with COVID-19 between March 15 and May 11, 2020, at four hospitals in Florida. Sixty-two percent of the patients received ivermectin at the discretion of the attending physician. Most patients, regardless of whether they were given ivermectin, received hydroxychloroquine, azithromycin, or both. The mortality rate was 15.0% in patients who received ivermectin and 25.2% in those who did not receive the drug (p = 0.03). Among patients with severe pulmonary involvement, mortality was markedly lower in those who received ivermectin than in those who did not (38.8% vs. 80.7%; p = 0.001). After adjustment for potential confounding variables and mortality risk, treatment with ivermectin was associated with a 73% reduction in mortality (p = 0.03).

Comment: Ivermectin, which was developed in the 1970s, is considered a safe and effective treatment for certain parasitic infections. Over the past 30 years, about 3.7 billion doses have been administered worldwide. Ivermectin has also demonstrated activity *in vitro* against a broad range of viruses, including HIV, influenza, and Zika virus. Recently, it was found to be a potent *in vitro* inhibitor of the COVID-19 virus, producing a 99.8% reduction in viral RNA after 48 hours. Some doctors are using ivermectin to treat COVID-19 patients,

continued on page 18 ➤

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but no randomized controlled trials have been completed at the time of this writing. The results of this observational study raise the possibility that ivermectin can substantially decrease mortality in patients with COVID-19.

Rajter JC, et al. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: The Ivermectin in COVID Nineteen Study. *Chest.* 2021;159:85-92.

Aloe vera for Atrophic Vaginitis, or More Iranian Research Fraud?

Sixty-six postmenopausal Iranian women with symptoms of atrophic vaginitis were randomly assigned to receive, in double-blind fashion, an intravaginal cream containing conjugated estrogens or *Aloe vera*. The treatment was administered nightly for two weeks, followed by three nights a week for another four weeks. Significant improvements in histologic findings and symptoms were seen in both groups, and there was no significant difference efficacy between groups.

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

1. Unusually rapid recruitment: During a 21-day period, 220 women were assessed for eligibility, and 66 were enrolled in the study. There was no mention of how many clinics were involved in recruiting patients. Based on the affiliations listed for the authors, it appears that there was a maximum of two clinics involved. Even with two clinics, it would be unusual for so many patients with atrophic vaginitis to have been evaluated and enrolled in such a short period of time.

2. Discrepancy regarding sample size: The paper stated that the sample size was 66 patients, whereas the registration document in the Iranian Registry of Clinical Trials (IRCT) stated that the target sample size was 50. Since the IRCT document was registered after the study was completed, it is difficult to reconcile this discrepancy.

3. Discrepancy regarding the treatment regimen: The paper stated that the two treatments were administered every night for two weeks, then three times a week for four weeks. The IRCT document stated that the treatments were administered every night for 10 days, then three times a week until six weeks. The paper also stated that each dose of each vaginal cream was 5 mg. This clearly appears to be a misprint, since 5 mg is a miniscule dose of cream, which would be very difficult to measure and administer. The fact that this apparent misprint was not caught by the reviewers speaks to the laxity of the peer review process.

4. Contradictory outcome measure: Satisfaction with the treatment was measured on a 5-point scale (very satisfied, satisfied, uncertain, dissatisfied, and very dissatisfied). It was not stated whether the higher numbers referred to better or worse outcomes. The paper stated that all patients in both groups were satisfied or very satisfied with their treatment. However, the mean score was 3.0 in one treatment group and 3.4 in the other treatment group (it was not clear which group had which score). A score of 3.0 corresponds to "uncertain" on the 5-point scale. It is therefore impossible for all patients in both groups to have been satisfied or very satisfied.

5. Funding issue: Double-blind studies are expensive, so it is difficult to believe that the funding source would have provided money for a randomized controlled trial when there had been no prior evidence from case reports or uncontrolled trials that *Aloe vera* vaginal cream is effective for atrophic vaginitis.

6. Implausible results: Call me overly skeptical if you wish, but I find it hard to believe that a cream containing 2% *Aloe vera* could be as effective as estrogen cream for improving symptoms and reversing histologic abnormalities.

Poordast T, et al. Aloe vera; a new treatment for atrophic vaginitis, a randomized double-blinded controlled trial. J Ethnopharmacol. 2021;24:113760.

Can N-Acetylcysteine Prevent Acetaminophen Hepatotoxicity?

Twenty-four healthy volunteers (mean age, 27.4 years) were given 1 g of acetaminophen four times a day for four days. During that time, they were randomly assigned to receive, in double-blind fashion, 300 mg of N-acetylcysteine (NAC) twice a day or placebo. On the fourth day, each person underwent a thermal pain test and then received 2 g of acetaminophen plus 600 mg of NAC or placebo (depending on their treatment assignment). The thermal pain test was then repeated after 1, 2, 3, and 4 hours. Two weeks later, the procedures were repeated, but each subject received the alternate treatment (NAC or placebo). The primary outcome measure was the pain-relieving effect of acetaminophen, as determined by the area under the curve (0-240 minutes) of pain intensity after thermal pain stimulation. Treatment with NAC did not decrease the pain-relieving effect of acetaminophen. After four days of treatment with 4 g per day of acetaminophen, the mean whole-blood concentration of glutathione was similar to its baseline value in the NAC group, but fell significantly in the placebo group ($p < 0.03$ for the difference in the change between groups).

Comment: Acetaminophen toxicity is the leading cause of hospital admission for acute liver failure in the United States, accounting for 56,000 emergency room visits per year. Acetaminophen depletes hepatic glutathione, and this depletion plays a role in the pathogenesis of the liver damage. NAC stimulates the production of glutathione, and intravenous NAC is the treatment of choice for acetaminophen toxicity. In the present study, oral administration of NAC decreased the acetaminophen-induced decline in whole-blood glutathione levels without compromising the pain-relieving effect of the drug. This finding raises the possibility that co-administration of NAC can decrease the risk of developing liver damage from acetaminophen.

Pickering G, et al. N-acetylcysteine prevents glutathione decrease and does not interfere with paracetamol antinociceptive effect at therapeutic dosage: a randomized double-blind controlled trial in healthy subjects. *Fundam Clin Pharmacol.* 2019;33:303-311.

References

1. Didriksen A, et al. Vitamin D3 increases in abdominal subcutaneous fat tissue after supplementation with vitamin D3. *Eur J Endocrinol.* 2015;172:235-241.

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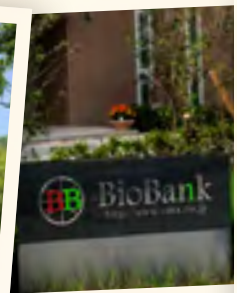

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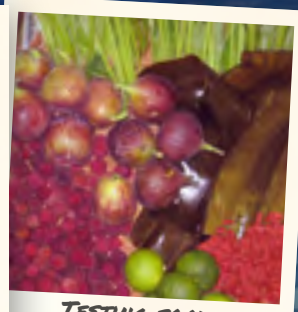

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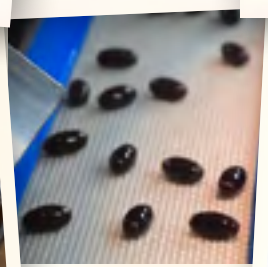

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In Memoriam
Richard A. Kunin, MD

Richard Kunin together with Linus Pauling and Matilda Kunin (Richard's wife) on the occasion of Pauling's 80th birthday party in 1981.

Richard A. Kunin, MD (1932-2021) earned his medical degree at University of Minnesota in 1955. His thesis, completed in 1953, *Losing Weight on a High Fat Diet*, was more than 50 years ahead of its time. Richard interned at Kings County Hospital in Brooklyn, New York, and completed three years of specialty training in psychiatry at New York Hospital. He served as a captain in the US Army for two years of active duty in Korea, followed by two years as staff psychiatrist at Valley Forge Hospital in Pennsylvania. After an additional year on staff at Minneapolis Veterans Hospital, he was board-certified in both psychiatry and neurology. From 1962 to 1963, Richard completed an NIH post-doctoral fellowship in neurology at Stanford University. There his published research, *EEG Studies in Animal Hypnosis*, was the first to report on hippocampal theta effects. Subsequently, he taught PhD-level practicum seminars at the Stanford Department of Psychiatry.

The next ten years in psychiatry focused on behavioral therapy and patient hypnosis, conditioning an *Inner Smile* that enables patients to face life and health challenges. This time also led to new insight, that situational cues elicit genetically programmed instincts and moods. Thus evolved his theory of *Operational Mind*, a natural strategy of intelligent adaptation, which proved exciting and clinically useful.

Major scientific breakthroughs of the 1960s inspired Richard to participate in now historic controversies on the role of diet and nutrients in medicine. He cofounded the California Orthomolecular Medical Society, served as the inaugural president of the International Society of Orthomolecular Medicine, and was a member of the editorial board of the *Journal of Orthomolecular Medicine*. He authored two bestsellers for McGraw-Hill, *MegaNutrition* in 1980 and *MegaNutrition for Women* in 1983. In 1994 he founded the Society for Orthomolecular Health Medicine and served as its president. His last appointment was as honorary board member to The Future of Medicine Foundation. Richard was research director and formulator for *Ola Loa Health Products* from 1997 to 2020.

A brilliant career in medicine, in his own words:

> Orthomolecular advances were initially perceived as fads in orthodox thinking, but over the past 50 years have emerged as correct and valuable. My practice involved documenting each patient's molecular needs with laboratory testing, providing a nutritional prescription and a partnership for informed self care. Investigations have included:
>
> - Mineral analysis and hair biopsy in the '60s
> - Megadose niacinamide in schizophrenia, 1968
> - Hypoglycemia and antioxidants in the early '70s
> - Amino acids in the '70s
> - Identifying heavy metal poisoning using hair analysis, 1972
> - Manganese in the treatment of tardive dyskinesia, 1974
> - Aspirin for niacin flush response, 1975
> - Prostaglandin theory of schizophrenia, 1975
> - Orthocarbohydrate diet, 1976
> - Omega-3 essential fatty acids in the '80s
> - Iron overload, 1985
> - Inflammation and oxidant stress, 1990
> - Tryptophan and the IDO switch, 1992
> - The autism epidemic, 1994
> - Methylation and DNA testing from 1998 onward
> - The role of homocysteine and methylation in autism and other health disorders with detailed review of cobalamin, folate, and betaine (TMG), 1999
>
> Orthomolecular Health Medicine is still in its infancy. We need to press on, learn more, and inspire others. What an exciting and fulfilling time to be a part of medical history – and to enjoy advances undreamed of at the outset of my medical career 65 years ago!

Downloadable copies of journal articles and professional papers by Dr. Kunin are available at www.olaloa.com/resources.

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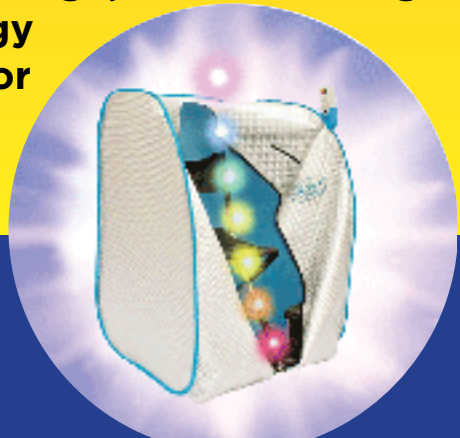

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On the cover

Kidney Disease – How to Protect Your Kidneys As You Age and a Call for Functional Renal Medicine

by Devaki Lindsey Berkson, DC

One out of three Americans are at risk of kidney disease.[1] This equals tens of millions of people.

Often kidney disease is silent. Many who have it don't know they have it. You might think an article on kidney disease doesn't pertain to you because you don't have symptoms and you are basically healthy. Or if you're a practitioner, not a kidney doctor (a nephrologist)…why care? Typically, patients with kidney problems go to kidney doctors.

However, kidney health, as you will soon learn, "drives" heart health. Chronic kidney disease (CKD) is a heart attack (myocardial infarct) equivalent. Heart disease is the number one killer in both men and women.

Also, when patients with kidney disease see a renal specialist, they mainly get their progress tracked, or their decline monitored. They rarely get better or reverse the stage of their kidney disease. There are five stages of renal decline, from mild kidney damage in stage one, to kidney failure in stage five. Kidney failure is loss of 85% of normal kidney function. Dialysis can improve renal function only a bit above this 15% functionality number. It is not a superb fix, even though it is lifesaving and life-prolonging.

Doctors typically measure how well kidneys filter waste from the blood by the "estimated glomerular filtration rate" or eGFR. *Estimated* means it's an equation based on a set of numbers. The eGFR is a number based on your blood test for creatinine, a waste product in your blood.

- Stage 1 CKD: eGFR 90 or Greater
- Stage 2 CKD: eGFR Between 60 and 89
- Stage 3 CKD: eGFR Between 30 and 59
- Stage 4 CKD: eGFR Between 15 and 29
- Stage 5 CKD: eGFR Less than 15.

We want both healthy kidneys and heathy hearts. I think we should also strive to reverse renal disease, if possible, if we have it. Thus, this article.

Diabetes is one of the leading causes of kidney disease. Half of the people with chronic kidney disease[2] (CKD) also have diabetes. But not all. I had kidney disease for 16 years and am thin, athletic, and without blood sugar or diabetic issues.

People with kidney disease in the early stages (stages one through three) have very few "symptoms." Kidney disease is one of the *silent diseases* (like cancer).

People with kidney disease are prone to excess levels of potassium in their blood.[3] When potassium builds up in the blood, it becomes dangerously toxic to many tissues. For example, too much potassium in the blood can cause heart block in the electrical conduction system of the heart and/or cardiac arrest, which is an abrupt loss of normal heart function.

As we age, renal filtering (or kidney function) starts to decline by 1% per year after the age of 40. If we have high blood pressure, this can also be harmful to the kidneys and can amplify this percentage of decline.

As kidney function falls – demonstrated by declining blood levels of eGFR (estimated glomerular filtration rate) and/or rising creatinine – potassium levels start to rise.

- Normal working kidneys easily clear potassium from the blood stream.
- Worsening kidneys do not.
- Higher levels of potassium become extremely toxic when the eGFR is below 30.

Increasing blood levels of potassium is a sign of worsening kidney disease. However, regulating blood potassium levels is complicated. Many foods we should eat plentifully, like fruits and veggies, are very high in potassium. Some important medications worsen potassium levels. This means that the treatment of kidney patients becomes a balancing act between diet, nutrients, and medications.

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Everything in the body is all about Goldilocks. The body likes "just right." Levels of potassium that are either too low or too high are not healthy for anyone, especially for those with renal disease.[4] Ideally, potassium levels should be near mid-4 millimoles per liter (mmol/L) and not creep up to 5 mmol/L or higher, especially in someone with kidney disease.[5]

There are nuances of testing potassium levels in the blood. Many don't realize that potassium goes up and down throughout the day. Potassium levels are higher after eating and lower with fasting. Therefore, in learning how your body and kidneys process potassium, it is best to use a fasting blood test.

The colon facilitates some excretion of potassium. In people with healthy kidney function, the colon helps rinse 10% of potassium out of the body that came in from food. In people with renal decline (chronic kidney disease or eGFR – estimated glomerular filtration rate – below 60), the colon can pick up some of the kidney slack and can excrete 30 to 35% of the potassium from what we eat. Thus, gut health intermingles with kidney health. If the colon isn't up to this "back-up" renal task, more potassium can build up in the blood.

Why diabetics have more vulnerability to excess potassium levels is complicated. There are several possible reasons. Diabetic patients are at risk of elevated blood potassium after taking certain medications for long periods of time, such as RAS blockers – renin-angiotensin system medications like angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor *blockers* (ARBs), or aldosterone receptor blockers – especially if not on diuretics at the same time. But long-term diuretics can contribute to the complexity mix, too. Excess protein going through the kidneys can damage renal tubules. Also, people with diabetic kidney disease may have several types of kidney disease at the same time such as renal tubular acidosis (4 RTA).

Nature is great, but she isn't simple.

*What else can elevate potassium levels in someone with lowering renal function***?** Potassium levels can rise due to too much fruit, other medications, NSAIDs, more veggies than a person's body can handle, and high blood pressure. Sometimes it is elevated by a laboratory artifact (lab tests can sometimes be wrong), a blood sample can sit around too long, or if the blood comes out very forcefully – red cells can lyse, (break apart) liberating the higher gradient of potassium inside the cell into the plasma, thereby artificially elevating potassium. This can also lower glucose artificially due to longer time in contact with metabolizing cells. Sometimes we just need to repeat the test to see if it's real.

Veggies and fruits are high in potassium. This is fine for someone with healthy kidney function, but potassium levels need to be monitored in someone with declining renal function. But as you will soon learn later in this article, I think this is not "root cause" but a manifestation of an ill kidney. It may be that nasty molecules are "banging" kidney tissue into worsening function, so that the potassium in healthy foods becomes elevated in the blood. It would be better to figure out why the kidneys can't process the potassium rather than avoiding all these healing foods. But for now…

Prunes, for example, are often used by seniors to treat constipation. They are very high in potassium. Potatoes are sky high in potassium. Fruits and veggies are healthy for many people but may not be good for you if you have kidney disease and excess potassium in your bloodstream – until you take other stress off your kidney, which we will go into soon.

Blood Pressure and Blood Sugar Medications

Blood pressure and blood sugar medications can complicate blood potassium levels. Some blood pressure medications are called "renal sparing" in that they slow down the progression of kidney disease. But they have to be taken in sufficient dosages to produce these protective actions. However, studies have repeatedly shown that only one in five patients with established kidney disease are receiving ACE and ARBs in the correct dose that is renal protective.

But these meds also have a potential shadow side. Long-term use of ACE and ARB medications can increase potassium. So treatment of these patients is a balancing act. Remember *It's Complicated*! the movie with Meryl Streep and Alec Baldwin?

To summarize, drugs that prevent progression of kidney disease may be being underutilized. But these same drugs may also worsen the issue by creating a need for other meds that lower potassium. In addition, diuretics, (especially hydrochlorothiazide and chlorthalidone), which may be helpful to kidney disease, may also rinse out critical nutrients that are protective co-factors for enzymes in the cardiovascular system or even elevate damaging molecules that worsen kidney (and heart disease) like TMAO (tri-methylamine-N-oxide).

Blood sugar issues can add complexities. Inadequacies of glucose control and degrees of insulin resistance (HA1C in the 7-9 levels) all contribute to elevated potassium in the blood. In fact, people with insulin and blood sugar issues are at the highest risk of kidney and heart disease.

Keeping potassium, blood sugar, and blood pressure balanced, and all responding to meds without making things worse, is complicated. Allopathic medicine prescribes meds to protect the kidneys, but other meds may be needed to protect against the side effect of the first meds. In addition, even more meds may be necessary to keep blood levels of protein, sugar, and minerals like potassium in ideal ranges.

Treating kidney problems can become a whirling dervish. Give a med to track a specific problem. Give another med to fix the problem the first med worsened. But all this while, "root cause" of *why* the kidneys are slipping down a rabbit hole is not being looked for nor addressed.

Hormones

Hormones[6-8] have a role in kidney health**.** Estrogen is exquisitely renal protective.[9-14] Normal levels of testosterone are also renal protective especially as we age,[15,16] although extreme levels of excess testosterone can be renal stressful.[17]

Body builders consuming high levels of protein (especially combined with testosterone supplementation) may be vulnerable to kidney damage.[18]

Kidney filtering begins to decline in our 40's due to hormonal waning. Our sex steroid hormones have started to slowly decrease since our mid-twenties, but this decline becomes steeper in our fourth decade.

Hormone replacement in individualized optimal amounts may be helpful in both men and women to protect kidneys. However, sex steroid hormonal support is not enough once kidney disease is established.

Molecules of Mass Destruction

What I have come to realize is that there are specific molecules that "drive" kidney disease. When these molecules are elevated, they damage kidney tissue. They "bang" against kidney cells and are the real cause of why potassium levels elevate, protein leaks, and kidney function gets worse.

High potassium is not a cause of kidney disease; it is a result. But at the molecular level, what is causing the kidney disease besides age or bad luck?

Identifying and addressing "cause" gets better patient results. Once these dangerous molecules are isolated, they can be *normalized* or *optimized* through dietary and nutrient intervention – without meds and while avoiding the pharmaceutical dance of complexity caused by meds.

Often the stages of kidney disease reverse. No matter the age of the patient.

I refer to these molecules that in excess "drive" kidney disease (and heart disease) as "the molecules of mass destruction."[19] Testing and optimizing these molecules, I believe, holds tremendous clinical promise for other portals to improve renal health, regardless of the age of the patient or the stage of their decline.

My Story

I had a nephrectomy because of a renal tumor, secondary to a drug my mother was given when pregnant with me. I had perfect kidney function before the surgery. I was at stage two and then stage three renal disease for 16 years following the surgery. My mother, along with millions of women from 1938 to 1971, were given this drug, diethylstilbestrol (DES), as a "prenatal vitamin" to make a normal pregnancy more normal or to stop bleeding and protect a "threatened" miscarriage. Many, not all, DES sons and daughters, including myself, had tumors and cancer because of this in-utero drug exposure.

I was the perfect patient: ate mindfully, exercised, on individualized hormone replacement, saw my trusty (I thought) nephrologist for all that time. However, no matter how often I saw my kidney doctor or how healthily I lived, my kidney function kept declining.

I would continually plead with my doctor, "How can this be happening? I am your exemplary patient!" He would shake his head; he had no idea. "But come back next year. I really like talking to you so if you want to come in every six months, do." But he had no answers to my continual questions as to why this was happening and how to reverse it.

Then…three things happened.

First, I ended up starting a drug company with one of my original kidney doctors. (We had to stop being doctor/patient once we started working together, of course). This involved a drug for dialysis and diabetic patients. It was an amazing experience to have the opportunity to work alongside Dr. Jack Moncrief in his clinic and dialysis center. He's a kidney rock star.

Excessive levels of TMAO, galactin-3, and other molecules drive kidney disease.

Dr. Moncrief co-invented the home unit of dialysis (CAPD), came up with the original idea of telemedicine, and successfully lobbied and personally got President Bush to sign the bill to legalize it. Dr. Moncrief had a catheter named after him, brought organ transplantation to Austin, Texas, and opened the first dialysis center in Austin. Dr. Jack was honored at Stony Brook University, New York, at a huge renal industry gala, as being one of seven kidney doctors that made nephrology "what it is today."

I worked side by side with this visionary man for many years. Dr. Moncrief would always point out: "Kidney health drives heart health."[20] Many heart docs don't know this – or don't practice as if they do.

Second, it just so happened that I met another iconic physician: Dr. Mark Houston. Dr. Houston is also a visionary doctor. He is a cardiologist with a specialty in hypertension and looking for "root causes" of cardiovascular disease.

Dr. Houston created the concept and genre of "functional cardiology." He developed and teaches the entire 24-hour module at A4M (Anti-Aging Certification Course and Residency for MDs, NPs and pharmacists). I also teach at A4M, in the gastroenterology module. After teaching all day, we were having dinner one night. Dr. Houston discussed with me how he tests and teaches that specific molecules "drive" heart disease.

There are hundreds if not thousands of peer-reviewed research articles on these molecules, demonstrating how they initiate and propel, on the molecular level, plaque, stroke, and heart attacks.

Remembering what Dr. Moncrief said, I started to take a look at these same molecules with renal disease. I thought, maybe these are the molecules that "tie" kidney and heart disease together.

In exploring PubMed I found that there are thousands of articles that implicate these molecules, when in excess, as the "main driving force" behind why kidney disease starts in the first place, and why it isn't responding to meds alone in the second place. This science explained why these molecules influence rising potassium levels, increases in uric acid, declining filtering function, and ultimately why all of this seems so impossible to turn around.

The third thing that happened was my testing these molecules on myself. This demonstrated that most of them,

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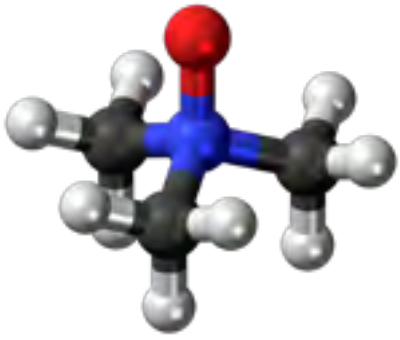
in my blood, were many-fold elevated. Taking nutrient and dietary actions to normalize their levels (back to Goldilocks "just right" middle ranges) helped me conquer my 16-year-long battle of stage two and three kidney disease, to achieve completely normal kidney functioning. In 10 months!



Trimethylamine-N-oxide (TMAO)

Meet "The Molecules of Mass Destruction"

Trimethylamine-N-oxide[21-30] (TMAO) is known to drive heart disease, but it also drives kidney disease. When it is elevated, it predicts increased renal complications. High TMAO blood levels often demonstrate a dysbiotic gut biome (more *bad* than *good* gut microbes) but can also be caused by an elevation of the liver enzyme that makes it (FMO3). This enzyme can be elevated by endocrine disruptors,[31,32] especially in fetal exposure in the womb. This can have life-long effects on offspring.

TMAO note: There is the phenomenon of the "TMAO Paradox" (coined by Berkson). Some studies found an elevated TMAO is linked to adverse cardiac and renal issues, and others have not. Also, TMAO blood levels can be elevated by what we have regarded historically as healthy foods, such as fish and fiber. If TMAO is so "bad" then why does eating good foods like fish, raise blood levels? An Australian group of researchers[33] tackled this controversial sticky wicket over TMAO. They found that TMAO levels, in a rodent model, were in fact not linked to atherosclerosis itself. But in fact, it was linked to a deeper tissue dive. High TMAO was linked with atherosclerotic plaque instability. Thus, it's linked to an increased risk of heart disease but at more nuanced levels. It may also be that TMAO is responsive to overall gut milieu and diversity. Researchers[34] found, in a cross-over feeding trial, that those with less biome diversity and more Firmicutes than Bacteroidetes genus, had much more elevated TMAO after consuming fish. And fascinatingly enough, fish oil[35] has been found to be one of the elements that helps reduce blood TMAO levels.

It may also be that TMAO is a "bad actor" for some, while a benign actor for others. Sort of like IOP, intraocular pressure of the optic nerve. In healthy persons, elevated IOP is not big deal. Their healthy optic fibers can take ups-and-downs of pressure swings and even highs. But in unhealthy optic nerves, elevated IOP drives fiber destruction and threatens visual acuity. So, it may be that elevated TMAO is a risk factor for those genetically or lifestyle-wise "set up" for sensitivities to it. Time will tell as the TMAO/health link is being looked at more and more. I hope to write an in-depth article on TMAO, real or red herring, to do a deeper look-see into this. But in clinical practice, people feel better when TMAO levels decline, when these people are ill with renal disease. I even had one patient with intractable anxiety that had it all go away, including intractable insomnia, when her TMAO levels normalized.

Galectin-3[36] is a cytokine that when elevated predicts kidney disease.[37] Galectin-3 has been observed in elevated levels in many DES offspring. It's been linked to causing or driving kidney tumors in Syrian hamsters exposed to DES in-utero.[38,39] I am a DES daughter, exposed to this DES drug in the womb, and one of the tumors I had was renal.

Transforming Growth Factor Beta1 (TGFB1) is elevated in diabetic kidney disease[40] and drives fibrosis in renal disease.[41] I discussed this molecule with many of the original DES researchers, since I worked at an environmental estrogen think tank (*Center for Bioenvironmental Research*) with many of these scientists. Dr. William Toscano (who left Tulane to become academic dean of the University of Minnesota School of Public Health) told me that they realized early on that many, if not all, DES offspring had elevated TGFB1, but they weren't sure what to make of it. Science now clearly shows that excessive levels of TGFB1, as many functional/environmental doctors now also know, is quite immunosuppressive. It also "drives" all fibrosis and this is part of the worsening tissue changes in both kidney and heart disease.

Asymmetric dimethylarginine (ADMA)[42] inhibits nitric oxide synthases and, when elevated, extremely enhances oxidative stress on the kidneys and cardiovascular system. Increased plasma ADMA levels are strong and independent risk factors for chronic kidney disease as well as various cardiovascular diseases such as hypertension, coronary artery disease, atherosclerosis, diabetes, and heart failure. After kidney failure there are dramatic increases of systemic ADMA and L-NMMA. These are kidney-nasty molecules.

N-monomethyl l-arginine (L-NMMA) works similarly to ADMA and elevates while the kidneys are declining and then increases enormously after kidney failure.

Symmetric dimethylarginine (SDMA)[43] – both asymmetric and symmetric dimethylarginine – are very toxic, non-proteinogenic aminos, which are uremic toxins that inhibit nitric oxide (NO) production and play multifunctional roles in many human diseases, especially kidney and heart.

Potassium and uric acid, of course, need to be tracked meticulously, and there are many nutritional interventions to correct these without having to severely limit certain foods, like vegetables.

Cystatin-C[44,45] monitors renal inflammation more sensitively than eGFR and is a great way to see if the intervention we are using is working.

When I ran these kidney damaging molecules on myself, I was shocked to see "all" of them in dangerous elevated ranges. All the while, my nephrologist kept saying I was stable and there was nothing left to be done. Yet…

- My TMAO, which should be below 6, was over 66.
- My galectin-3, which should be under 17, was 55.
- My cystatin C was high.
- Everything was high.
- But my kidney doctor said I was stable and fine and no worries.
- My labs looked like I might go into renal failure within a few years, if one reads all the data behind these molecules.
- But I was instructed to keep doing what I am doing and just keep coming back to the office once a year to get basic blood tests and say hi.

My mentors at Tulane, where the environmental estrogen think tank was, confirmed that many DES offspring are high in many of these molecules. It wasn't a toxic gut that was elevating my TMAO; it was the DES in the womb that up-regulates the enzyme that makes it in the liver.

So Now What?

Even if the seed of my kidney issues in adulthood were sown inside the womb, what could I do to save my lonely solo kidney and protect my life?

I sleuthed the literature for how to lower or optimize each of these molecules. It took dietary changes and nutrient interventions. I had to be careful of how many nutrients I used and which ones, as many of these are processed through the kidney. I had to be very careful how much magnesium and minerals to take in, how to keep the kidney alkaline throughout the day, as kidneys love alkaline, and how to turn the flow of the clinical river without making things worse.

I made a lot of changes, even though by all standards I already ate really well. I gave up animal products and ate almost no protein except veggies and beans for three months to give my lone kidney some *breathing space*.

In addition, I took specific nutrients that the peer review research suggested could normalize levels. For example, I used modified citrus pectin to bring down the galectin-3. My uric acid was extremely high, so I went on herbs, quercetin, and tart black cherry juice, as well as vitamin C, and gave up all animal products. For a while. I monitored my potassium and let this guide my veggie intake. And re-ran my labs. And, within 10 months…all were normal!

I hadn't felt ill. But now that these "molecules of mass destruction" were back in Goldilocks ranges, I felt fantastic. You don't know when you are feeling less and less until you feel better more and more.

Who discovered these molecules, and why don't more doctors test and treat them?

The Cleveland Clinic discovered many of these molecules and how they drive the beat of kidney and heart disease. There are over 4,000 peer review articles on galectin-3 and

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1700 articles on TMAO. But still they have not reached most clinical trenches.

The peer review articles on these molecules establish their influence and toxicity when in excess and illustrate how to normalize them through various interventions – dietary and nutrient intervention.

My kidney doctor had never heard of any of these molecules except, of course, uric acid and potassium. I worked in Tulsa, Oklahoma, in 2011 when cystatin C was first recommended by the American Nephrology Association over eGFR, and we ran this kidney test there for $15 a pop. When I tried to order this test in Austin, it costs almost $600. My kidney doctor wouldn't run it as he said my insurance wouldn't cover it due to the high cost. I asked if any kidney doctors in Austin run it. He responded without hesitation, "I doubt it."

I wanted to hear why my kidney doctor didn't know about any of these exotic molecules of mass destruction. I've been going to the same good guy for most of these 16 years and asked how it could be that he didn't know about these. Dr. Rodriguez shook his head, "My association doesn't mention them, thus, I am not guided to use them."

I let out a huge sigh of frustration, "You know, I have been coming to you for 16 years, giving my kidney health into your hands. It's very upsetting that I have been asking all those years why I can't turn this around. Have you ever gone home and sleuthed the science to see how this might be happening to me? You know I eat so well, work out daily, do everything right but just keep getting worse. Be honest now, have you ever gone home with me in mind and hit the books?"

"No," he sighed, "we just don't know why."

Well, I am a DES daughter. As it turns out, DES exposure in a developing fetus causes lifelong elevations of many of these molecules, the very molecules that drive kidney disease. But that never came up in our office visits (nor with any other doctor, honestly).

Let's take galectin-3, for example. When experimental animals are exposed to DES in the womb, they develop excessive levels of galectin-3, which promote the development of kidney tumors.[46]

My kidney doctor shook his head. "Look, why don't you do what you are planning on doing and retest your function in so many months. If you drop to stage two from stage three, I'll change the way I practice, and I will teach functional nephrology."

That's what he said.

I huffed, "You can't teach functional medicine. You'd have to study it first! But if you see that I improve, why don't you and I together form a functional nephrology module and train others?"

To Dr. Rodriguez's credit, he agreed. And he only required I improve by only one stage. But when I ran my labs 10 months later, I had recovered to "completely normal function," even with one kidney, for the first time in 16 years.

I have to go back and see what he says. Will he add testing these molecules to his practice? Will he and I team up to spread the "functional nephrology" word?

He's a smart younger man. He and his wife have gone vegan. They are cleaning up their diet. Why didn't he know, as a kidney specialist, how excessive levels of TMAO can damage the kidney and how vegetarian-type diets can dramatically and quickly lower this molecule of mass destruction? Yikes!

I have a young 11-year-old type-1 very brittle (hard to control) diabetic, with worsening renal issues and chronic blood and protein in his urine. He has been seen by his nephrologist, a urologist, and his family doctor. None of them understand why this is happening. They continue testing and find nothing to give a drug for. The boy keeps urinating blood and having pain. And, of course, his mother is going out of her mind with worry.

So, I encouraged his mother to ask his nephrologist to run these molecules of mass destruction. Stunningly, the nephrologist refused. He said he didn't know what these were or how to interpret them. The mother said I could work with him to show him what I have been finding out.

He simply refused to be a team player or to work with my office on this. Although his office had no answers, he was not willing to take a look at other possible causes and answers, despite the fact that there are thousands of peer review articles linking these molecules to kidney disease. *That's how so much of this stands today.*

I got so angry; I could grind my teeth to powder. What is a renal patient to do besides watching their kidney function worsen?

Functional medicine tries to identify "root cause" issues that drive disease, such as these molecules driving kidney disease. But presently there are no functional medicine renal modules anywhere in the world.

I have been offering to start teaching modules and CME courses in this. So far, the main certification courses for functional medical practitioners have not agreed to my proposals. Many doctors are not interested in renal care, as it seems to be the "rabbit hole" of medicine where patients just get worse and that's expected. And accepted.

Well-intentioned kidney doctors can't do much other than give you meds, tell you to drink more water, and track your progress as you most likely continue to decline.

I am presently working part-time at the Naples's Center for Functional Medicine. (I am not able to fully pull myself away from my "Keep Austin Weird Lifestyle" in Texas, yet.) I look forward to working with patients with renal decline, to help get them back to normal kidney health. No matter their age.

This article is a start.

Got declining kidney disease? Come see me in Florida.

Be well.

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

HYPERCOAGULATION

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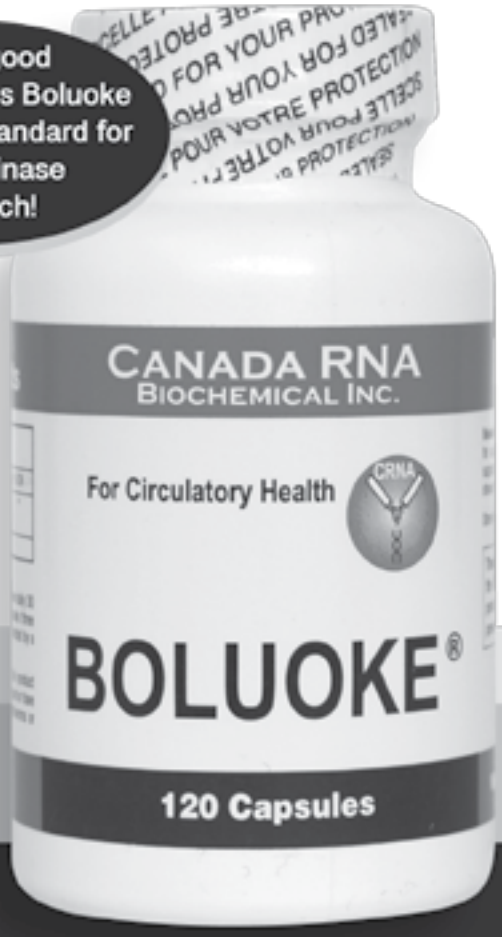

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Uric Acid and Inflammation

by Jenna Henderson, ND

A high level of uric acid is an often-unrecognized contributor to many disease states. While the uremic wastes creatinine and BUN are measured on a basic metabolic panel, a blood test for serum uric acid (urate) is usually not run unless the patient complains of gout symptoms. Gout is the most well-known consequence of high uric acid, but only one of many conditions impacted by uric acid.

There may be a classical presentation of gout in the big toe or tophi with uric acid crystals forming nodules in various places. Gout may occur in the context of kidney weakness but is also seen in patients with normal creatinine and BUN. If other renal indicators are normal, diet and lifestyle factors are to blame.

Conversely low uric acid can also be problematic. Depending on the conditions, uric acid can be both pro-inflammatory and anti-inflammatory. Too much or too little uric acid can be detrimental depending on the patient's health status.

Processing of Uric Acid

Uric acid is produced in the liver cells by the major catabolic pathway of purine degradation. Uric acid is not metabolized in the liver but is excreted by the kidneys and intestinal tract. The enzyme directly responsible for the formation of uric acid is xanthine oxidase (XO), and many medications for uric acid target this enzyme. Other published approaches to lowering production of uric acid include the inhibition of purine nucleoside phosphorylase (PNP), just upstream from XO.[1]

Hyperuricemia induces the expression of hepatic inflammatory molecules by activating the pro-inflammatory NF-κB signaling cascade. It is also associated with higher levels of hsCRP, fibrinogen, complement C3, ferritin, and ESR. However, uric acid can also act as an antioxidant and free radical scavenger depending on the microenvironment.[1]

The pro-oxidant effects of uric acid mostly relate to its copper reducing, as Cu(+) can initiate lipid peroxidation. Uric acid also increases alpha-tocopherol consumption. The presence of nitric oxide, however, completely inhibited the pro-oxidant activity of uric acid.[2]

Demographics

A variety of factors can make one more susceptible to hyperuricemia.

- Alcohol consumption
- Obesity
- Binge eating
- Genetics[3]
- Chronic kidney disease
- Heavy meat diet
- Dehydration
- Advanced age[4]
- African Americans[5]
- Hyperparathyroidism (even in the absence of renal disease)[6]
- Tumor lysis syndrome seen in cancer and chemotherapy, as there is a rapid release of the cell's contents.[7]

Lab Tests

Serum uric acid is the most direct way to check the patient's status. In human blood plasma, the reference range of uric acid is from 3.6 to 8.3 mg/dL. There may be a more acidic urinary pH as the kidneys are passing uric acid or a higher urinary pH if the uric acid is crystalizing into stones.[7]

Uric Acid and Kidney Health

It is often hard to separate cause and effect. High uric acid can result from kidney weakness, but uric acid itself can contribute to kidney damage.

Hypertension: Uric acid increases salt sensitivity and xanthine oxidase-related oxidative stress causes endothelial dysfunction and renal vasoconstriction.[8]

Nephrotic syndrome: Increased xanthine oxidase activity and uric acid are associated with an increase in the pro-inflammatory compounds toll like receptor 4 (TLR4) and fibronectin. Expression of these compounds is part of a maladaptive immune response associated with proteinuria. Use of allopurinol was seen to reduce proteinuria.[9]

Loss of filtration: High uric acid can be a causative factor in the progression of chronic kidney disease, altering tubular epithelial cells, endothelial cells, and vascular smooth muscle cells, leading to a pro-inflammatory, profibrotic state.[10]

Uric acid kidney stones: After oxalate stones, uric acid stones are the second most prevalent type. Some kidney stones are mixed in composition. As oxalates are only found in plants and uric acid is associated with a heavy meat intake, knowing the patient's eating habits is helpful in determining a course of action.

High Uric Acid Conditions

Uric acid does not just damage the kidneys. High uric acid can be an exacerbating factor in a variety of non-renal conditions:

Myocarditis: Hyperuricemia is associated with increased coronary artery disease, heart failure, and sudden death.[11]

Atherosclerosis: Uric acid increases erythrocyte aggregation and blood viscosity, increasing risk of atherosclerosis.[12]

Hypertriglyceridemia: Serum uric acid strongly associated with high triglycerides independent of age, gender, smoking, alcohol consumption, obesity, and insulin resistance.[13]

Cancer: High uric acid levels are positively associated with colorectal, hepatobiliary, kidney, non-melanoma skin, other cancers in men, and head and neck and other cancers in women.[14]

Obesity: Uric acid stimulates fat accumulation independent of caloric intake.[15]

Metabolic syndrome: Uric acid-induced insulin resistance can independently predict risk of diabetes.[16]

Diabetic neuropathy: High uric acid can contribute to various peripheral neuropathies, including sensory functions in diabetics.[17]

Non-alcoholic fatty liver: Hyperuricemia predicts steatosis with NAFLD.[18]

Crohn's disease: Patients with inflammatory bowel disease have higher rates of nephrolithiasis. A high uric acid to creatinine ratio correlates with disease activity in Crohn's disease, but not ulcerative colitis.[19]

Colorectal polyps: High uric acid is associated with increased prevalence of colorectal polyps.[20]

COPD: High uric acid is significantly associated with reduced functional expiratory volume and cardiovascular comorbidities in COPD patients.[21]

Hypothyroid: Thyroid hormones may affect uric acid metabolism. Low thyroid is associated with higher serum creatinine, and uric acid is often elevated when creatinine is higher.[22]

Psoriasis: Higher uric acid is found with psoriasis patients in Western Europe, but this trend was not seen in other ethnic groups.[23]

Rosacea: Serum uric acid along with CRP was found to be significantly higher in rosacea patients than in the control group.[24]

Cataracts: Patients with posterior subcapsular cataracts show increased uric acid in the aqueous humor and urate deposits.[25]

Bipolar disorder: High uric acid has been associated with both manic and depressive episodes of bipolar disorder.[26]

Preeclampsia: High uric acid levels with preeclampsia have been considered part of renal dysfunction in pregnancy. Further study is looking into possible mechanisms of action and the effect of uric acid on the mother and baby.[27]

High uric acid levels damage kidneys and can be a factor in non-renal conditions, too.

Surprising Benefits of Uric Acid

Uric acid actually has a stimulating effect on the cerebral cortex and may enhance cognitive function.[28] While many other animals have the enzyme uricase to break down uric acid, humans lost the ability to make uricase due to a mutation in primates traced back to the Miocene epoch. It has been hypothesized that a higher uric acid level was a factor that allowed for the development of increased brain mass and intellectual performance. It may have even given a survival advantage by helping to maintain blood pressure in a low-salt environment.[29]

Although uric acid can wreak havoc, surprisingly, it also has a neuroprotective function. Optimal levels of uric acid seem to follow a U-shape. Some disease states are actually associated with low uric acid levels.[30]

Stroke: Low uric acid is associated with stroke mortality.[30]

Alzheimer's: Reduced uric acid concentration is linked to Alzheimer's disease.[31]

Multiple sclerosis: Low serum uric acid is linked to multiple sclerosis.[31]

Parkinson's disease: Patients with Parkinson's disease appear to have a lower homeostatic set point for uric acid, which contributes to less protection from oxidative damage.[32]

Amyotrophic lateral sclerosis: There was a 39% reduction in risk of death for each 1 mg/dL increase in uric acid.[33]

Optic neuritis: Although some peripheral neuropathies are more common with high uric acid. Low uric acid is associated with optic neuritis.[31]

Glaucoma: Low uric acid was found in patients with primary open angle glaucoma and correlated with worsening parameters.[34]

Prion diseases: The antioxidant properties of uric acid inhibit neurotoxicity with bovine spongiform encephalopathy (BSE) and variant Creutzfeldt-Jakob disease (vCID).[35]

Cancer: Some cancers show an inverse relationship with uric acid including pulmonary and central nervous system cancers in men, and breast, lymphatic, hematological and CNS malignancies in women.[14]

Osteoporosis: In post-menopausal women, osteoporosis was less prevalent among those with high uric acid than those with normal uric acid levels.[36]

COVID-19: Kidney injury may be part of the complications of COVID-19. Increased mortality risk is associated with higher creatinine and BUN, but surprisingly low levels of uric acid were also associated with higher mortality.[37]

Mixed Results in the Elderly: High uric acid levels do predict higher mortality in the elderly.[38] However, higher uric acid levels in the elderly are associated with better muscle strength and reduced sarcopenia.[39] There is also better functional recovery with cardiac rehabilitation with higher uric acid.[40]

For many of these conditions, increasing certain animal products and even light alcohol, is congruent with existing recommendations. Fish consumption lowers stroke risk,[41] and light to moderate alcohol consumption lowers the risk of hemorrhagic stroke.[42] Adequate B-12 is important for managing multiple sclerosis.[43] Having higher cholesterol may slow the progression of Parkinson's disease.[44] High homocysteine may also play a role in many neurological conditions, including Parkinson's and amyotrophic lateral sclerosis.[45] There was even found to be high homocysteine in tears of glaucoma patients.[46]

Medications That Raise Uric Acid

Although diet is most often the driving factor in elevated uric acid, many medications can also elevate serum uric acid levels.

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Uric Acid

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Aspirin	Diuretics
Caffeine	Calcineurin inhibitors
Cisplatin	Diazoxide
Epinephrine	Ethambutol
Levodopa	Methyldopa
Metoprolol	Nicotinic acid (vitamin B3)

Saccharomyces cerevisiae

Medications That Decrease Uric Acid Levels

Allopurinol	Azathioprine
Cinacalcet	Clofibrate
Corticosteroids	Estrogen
Febuxostat	Glucose
Guaifenesin	Mannitol
Probenecid	Sevelamer
Warfarin	

Although colchicine is used for symptomatic relief with gout, its effect is due to decreasing inflammation of urate crystals, rather than lowering serum uric acid.[47] Colchicine, however, can be difficult to use as there is a narrow therapeutic index and a lack of clarity between a non-toxic, toxic, and lethal dose.[48]

Dietary Interventions

Reducing intake of purine-containing foods is a good first step. This change can be difficult if the patient has found a ketogenic diet helpful. Often these foods do not need to be eliminated entirely but simply consumed in smaller portions. These foods include eggs, red meat, white meat, and seafood, but also soft drinks, fruit juices, and alcohol.[49]

Dairy products do not contain purines. In fact, milk consumption is helpful to lower uric acid.[50] Unless patients have a clear intolerance to dairy, many patients do well with raw milk and raw milk kefir.

Legumes do contain purines but generally do not appear to contribute to increased serum uric acid.[51]

Whole soybeans, soy milk, and soy protein powder were all observed to increase uric acid.[52]

Added high fructose corn syrup can raise uric acid. However, fresh fruit contains vitamin C, flavonoids, and fiber, which appear to offset the effects of fructose.[53]

Some forms of alcohol have a greater effect on uric acid levels than others. Beer is the most associated with gout attacks. Spirits also had a correlation with gout. Moderate intake of wine, however, did not appear to be an aggravating factor.[54]

Coffee consumption lowers uric acid. Results were found in both men and women, although women required more coffee for the uric acid lowering effect.[55] A similar effect was found with decaffeinated coffee, suggesting that a component other than caffeine is responsible for the effect.[56]

Celery (*Apium graveolens*) is a functional food, decreasing uric acid, by inhibiting hepatic xanthine dehydrogenase and xanthine oxidase.[57]

Although fruit juice is not encouraged for those with high uric acid, an exception to this rule is tart cherry juice which lowers uric acid and improves gout symptoms.[58] A similar effect was also found with Bing sweet cherries.[59]

Supplementation

Probiotics: The specific strain of *Lactobacillus plantarum* GKM3 was found to lower uric acid levels,[60] while Bifidobacterium longum 51A reduced the inflammation of gout.[61]

Vitamin C: Many kidney patients hesitate to use vitamin C over perceptions that it increases nephrolithiasis. However, vitamin C intake in men was found to have an inverse correlation to serum uric acid levels.[62]

Curcumin: Curcumin and its metabolites inhibit xanthine oxidase.[63]

Cinnamon: Cassia oil extracted from cinnamon markedly lowered hepatic xanthine dehydrogenase and xanthine oxidase.[64]

Noni (*Morinda citrifolia*), a traditional gout remedy, lowers xanthine oxidase.[65]

Grapeseed procyanidins were found to reduce serum uric acid in a murine model.[66]

Glycine combined with tryptophan was found to reduce triglycerides as well as uric acid. Results were attributed to increased solubility of uric acid.[67]

Humulus lupulus: Although beer drives up uric acid, an extract of flavonoids from the hops plant was found to lower uric acid.[68]

Olive leaf inhibits xanthine oxidase.[69]

Rumex crispus: This lesser-known anti-diabetic herb reduces xanthine oxidase comparable to allopurinol.[70]

Green tea reduces formation of uric acid but also increases renal excretion of uric acid.[71]

Vitamin D: High uric acid levels suppress 1-αhydroxylase, leading to low levels of 1,25(OH)2D and higher PTH.[72]

Sauna Therapy? Not So Fast

One approach to high levels of uremic toxins is to sweat them out. Sauna can be a useful way to excrete creatinine, urea nitrogen and ammonia, but not uric acid. No uric acid is detected in human sweat.[73] In fact, sauna can increase serum uric acid. This increase appears to be due to three factors – increased purine degradation, reduced renal excretion, and dehydration – making uric acid more concentrated. The additive effect of sauna bathing while drinking alcoholic beverages is particularly concerning.[74] While infrared sauna is a helpful adjunct therapy for many with marginal kidney function, if the patient complains of achiness immediately after a sauna and/or has a very high serum uric acid, it's good to proceed with caution.

In conclusion high uric acid levels are very common among diabetics, the obese, and those with cardiovascular disease. Other conditions, especially conditions of the nervous system, are associated with low serum uric acid. Serum uric acid levels are easily tested. A variety of supplements and dietary changes can assist in the management of uric acid. ◆

Dr. Jenna Henderson's practice, Holistic Kidney, is dedicated to the unique needs of renal patients. A kidney patient herself since 1993, she has experienced all stages of kidney disease firsthand. She is a graduate of the University of Bridgeport. Dr. Henderson has had several articles on kidney health published in *Natural Medicine Journal*, *NDNR* and the *Townsend Letter*. She has lectured extensively across the US to naturopathic doctors, kidney patients, and kidney professionals.

Dr. Henderson seeks to bridge the gap between mainstream nephrology and natural medicine. In her practice she helps patients sort through often conflicting information to understand what is appropriate for their individual needs and stage of kidney function. She is often able to help patients delay the need for dialysis. For those already in kidney failure, she helps patients find optimal wellness with dialysis or a transplant.

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

Assessing Liver Function?

by Dr. Douglas Lobay, BSc, ND

"Is life worth living? It all depends on the liver," the quick-witted 19th century raconteur Williams James once said. William James was an American philosopher and psychologist who was thought to be one of the foremost philosophers of his time and is often regarded as the father of American psychology. His statement reminds us of the virtues of a healthy life affecting not only the liver, but also the body and mind.[1]

I preceptored with a naturopathic doctor in North Vancouver while I was a student at Bastyr College of Naturopathic Medicine in 1991. His primary diagnostic methods involved applied kinesiology and muscle testing. While I had trouble wrapping my brain around his methods of testing, I still learned something. I observed that many patients he treated were diagnosed with liver problems. He prescribed dietary and lifestyle changes and seemingly innocuous liver supplements. Most patients seemed to get better. I was reminded of an unwritten and oft used tenet of naturopathic medicine "that if all else fails, treat the liver."

The Greeks used to believe that the liver was the seat of the soul. According to Greek mythology, the ancient titan Prometheus was banished and chained to a rock by Zeus. Every day an eagle would peck at his body and eat part of his liver. By night the liver would re-grow and regenerate back. The philosopher Plato said that the liver is the seat of the darkest emotions, especially jealousy, wrath, and greed. The Talmud wrote that the liver was the seat of anger. In traditional Chinese medicine the liver is equated with anger, resentment, frustration, irritability, and bitterness. In Ayurvedic medicine the liver is associated with anger and hatred.[2]

I asked myself the question, "what is the best way to diagnose liver function?" As I look back at close to 30 years of practice in the natural medical field, I like to think I am firmly grounded in the scientific method of inquiry and can make a reasonably cogent diagnostic assessment of liver dysfunction. I still like to use a blend of unproven naturopathic methods of observation mixed in with more rigorous conventional scientific assays. In the name of brevity and trying to avoid a diatribe of pseudo-science, I am not going to discuss non-conventional tests that may be used by some alternative practitioners to assess liver function. I will instead try to limit myself to a discussion and a more rigorous naturopathic interpretation of conventional tests.

I began to reacquaint myself with basic physiology and pathology of the liver. It had been a long time since I referred to Guyton's *Textbook of Medical Physiology* and Robbin's *Pathologic Basis of Disease*. Now it appears that Google and Wikipedia are much faster and easier to refer to for basic medical information. I relearned that the liver is the large organ in the upper right quadrant of the abdomen. It weighs an average of 1.5 kilograms or 3.3 pounds, slightly lighter for females and slightly heavier for males. The liver has been estimated to have over 500 different and vital functions. Among its most important functions are detoxification, synthesis of proteins, and production of biochemicals necessary for digestion and gut health. It also is involved in glucose metabolism, glycogen storage, decomposition of red blood cells, production of cholesterol and hormones, storage of fat-soluble vitamins, and production of bile involved in fat metabolism. It receives blood from the hepatic artery and the portal vein connected to the intestines. The functional unit of the liver is called the hepatic lobule and is made up of millions of functional liver cells called hepatocytes, supporting cells, Kupffer cells and endothelial cells. Sinusoid spaces are surrounded by hepatocytes and are connected to bile ducts, central veins, hepatic veins, and other vasculature. Connective tissue cells, including stellate cells, help to support the hepatocytes. Seventy to 80 percent of the liver volume is parenchymal hepatic tissue. Non-parenchymal tissue accounts for the rest of the volume. The liver can use up to 20% of the body's resting oxygen supply under normal circumstances and can store up to 10% of the body's blood supply. The liver has an incredible capacity for regeneration with as little as 25% required for full recovery.[2]

The next part of my research focused on assessing liver function related to biotransformation, drug metabolism, and phase 1 cytochrome P450 reactions and phase 2 conjugation reactions.

Biotransformation is generally the process of altering an amino acid, nutrient, toxin, or drug in the body from something more active and toxic to something that is less active and less toxic. Water-insoluble compounds are altered to become water soluble and then can be excreted by the kidneys and liver. In phase 1 reactions in the liver, oxidative, reductive, and hydrophilic processes occur. A polar group is added

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to a non-polar molecule to make it hydrophilic. In phase 2 reactions, small hydrophilic molecules are added to compounds to improve water solubility and to inactivate chemical reactivity. Glucuronic acid and sulfate are the two main examples of molecules that are conjugated to compounds to make them inactive and water soluble.[3]

Drug metabolism involves the breakdown of a chemical in the body. Phase 1 reactions involve cytochrome P450 oxidase enzymes that remove a hydrogen atom or add an unpaired oxygen atom to a compound. This creates a short-lived, potentially reactive and oxidative chemical that then becomes more polar and water soluble. It is then passed to phase 2 reactions where transferase enzymes such as glutathione add a polar molecule, in this case a sulfhydryl group, to the original compound. Again, this increases polarity and improves water solubility. In phase 3 reactions further conjugation occurs by efflux transferase enzymes, then the altered compound is pumped out of the cell for elimination. Phase 3 reactions involve further conjugation involving glutathione, acetylcysteine, or mercapturic acids.[4]

Cytochrome P450 is a group of monoxygenase related enzymes with heme as a cofactor. They oxidize steroids, fatty acids, drugs, and other xenobiotics. They are mitochondrial and microsomal cytochrome P450 membrane bound enzymes inside cells. Mitochondrial cytochrome enzymes generally involve terminal oxidase enzymes in the electron transport, like nicotine adenine dinucleotide phosphate (NADP). Microsomal cytochrome enzymes also involve NAD molecules. The name P450 is derived from spectrophometric profile of this group of enzymes at the 450 nanometer wavelength or blue light spectrum. These cytochrome enzymes deliver an unpaired electron, oxygen anion, protein ion, and reduced iron.

The nomenclature of cytochrome enzymes first gives a number that codes for the gene family involved, followed by a capital letter for gene sub-family and then a number for the specific gene. In humans, 57 genes and 59 pseudo-genes coding for individual cytochrome enzymes have been identified. Some cytochrome enzymes have a very narrow window of activity and specificity while others are very wide and broad.

Cytochrome activity is responsible for breakdown of about 75% of all drugs. Many drugs can increase or decrease cytochrome enzyme activity. The interaction of other drugs or other compounds, including vitamins and herbs, may affect cytochrome activity either by increasing or decreasing function. For instance, St. John's wort can increase CYP3A4 activity and decrease CYP1A1 and CYP1B1 activity. Goldenseal and berberine can interfere with CYP2C9, CYP2D6 and CYP3A4 activity. Additionally, foods like grapefruit can also interfere with specific cytochrome function, including CYP3A4, CYP1A2, CYP2C9 and CYP2D6.[5]

Phase 2 pathways involve unique major pathways of conjugation, including glutathione, sulfation, glycine, taurine, glucuronidation, acetylation, and methylation. Glutathione conjugation and sulfation involves the addition of sulhydryl groups to compounds. Drugs, including acetaminophen, toxic metals, petroleum distillates, alcohol and bilirubin, are examples of compounds that are conjugated via glutathione and sulfation pathways. Glycine conjugation involves the addition of the amino acid glycine to compounds. Salicylates, organic acids, bile acids, and narcotics are examples of compounds that are conjugated via the glycine pathway. Taurine conjugation involves the addition of the amino acid taurine to compounds. Organic fatty acids and bile acids are examples of compounds that are conjugated via the taurine pathway. Glucuronidation conjugation involves the addition of glucuronic acid to compounds. Many drugs, including salicylates, acetaminophen, digoxin, steroids, phenols, and hormones, are examples of compounds that are conjugate via the glucuronidation pathway. Acetylation conjugation involves the addition of acetyl groups to compounds. Drugs like isoniazid and hormones are examples of compounds that conjugated via the acetylation pathway. Methylation conjugation involves the addition of methyl groups to compounds. Morphine and other drugs, xenobiotic toxins, and hormones, including adrenaline and dopamine, are examples of compounds that are conjugated via the methylation pathway.[4,10]

A careful patient and history examination is useful in diagnosing liver disease, including subclinical naturopathic liver disorders. The patient's age, weight, body mass index and vital signs are important. Risk factors, including diet, lifestyle, sexual habits, and intravenous drug use, provide useful information. Questions about alcohol consumption, drug use, and potential toxin exposure should be explored. The occurrence of comorbid conditions such as congestive heart failure, kidney disease, hemochromatosis, Wilson's disease, thyroid disorders, and muscle diseases should be considered. Questions about family genetic diseases and autoimmune diseases should also be considered. Questions about digestion should be entertained, including symptoms of maldigestion, heartburn, ulcers, hemoptysis, gas, bloating, nausea following eating, gallstones, celiac disease, gastro-intestinal bleeding and diarrhea. A good physical examination is necessary paying close attention to signs and symptoms that include abdominal distention and ascites, peripheral edema and swelling, occurrence of hepato-splenomegaly, jugular-venous distention, the color of the sclera, Kayser-Fleischer rings on the iris, the soft palate appearance, skin tone and color, pallor, jaundice, rhinophyma, erythema, skin capillary telangiectasias, varicose veins and hair distribution patterns.[6,7]

To assess liver function, we were taught in school to perform basic serum tests that were part of a blood chemistry panel. Tests involving liver function on basic laboratory tests include the liver enzymes AST, ALT, GGT, alkaline phosphatase, conjugated and unconjugated bilirubin, LDH or lactate dehydrogenase, albumin, urea, glucose, cholesterol and triglycerides. Less common tests that also give insight into liver function include 5'-nucleotidase, ceruloplasmin, AFP or alpha feto protein, PT or prothrombin time, and other blood coagulation factors.

The liver enzymes include aspartate aminotransferase (AST), also formerly known as serum glutamic-oxaloacetic transaminase (SGOT), alanine amino-transferase (ALT), also formerly known as serum glutamate-pyruvate transaminase, and gamma glutamyl transferase (GGT), also formerly known as gamma glutamyl transpeptidase (GGTP). These enzymes are found inside liver cells in the cytoplasm and basically catalyze chemical reactions by transferring one chemical group to another. AST is a vitamin B6-dependent transaminase enzyme that catalyzes the reversible transfer of an amino group between the amino acids aspartate and glutamate. The average current lab values for AST on most chemistry panels are between 5-40 units/ml. ALT is a transaminase enzyme that catalyzes the transfer of an amino group from alanine to alpha ketoglutarate. The average current lab values for ALT on most chemistry panels are between 5-43 units/ml. GGT is a transferase enzyme that catalyzes the transfer of a glutamyl functional group from compounds such as glutathione to an acceptor that may be an amino acid or short peptide molecule forming glutamate. The average current lab values of GGT on most chemistry panels are between 5 to 60 units/ml.

Alkaline phosphatase is an enzyme that is produced in the liver, primarily in the bile ducts. It is also produced by other tissues, including intestines, kidney, placenta, and bones. The average current lab values for alkaline phosphatase are between 35-115 units/ml.

Bilirubin includes both unconjugated and conjugated forms. The average lab value of unconjugated bilirubin ranges from 2 to 21 units/ml and conjugated bilirubin ranges from 0 to 8 units/mL. Up to 5% of the general population have a genetic defect in bilirubin conjugation and have high unconjugated bilirubin levels due a deficiency of UDP-glucuronyl transferase enzyme activity in the liver.

Liver enzyme tests, like AST, ALT, and GGT, show liver cell damage and inflammation.

Liver enzymes such as ALT, AST and GGT are not unique to the liver and can be found in other tissue, including heart, muscle and kidneys. As such, the interpretation of liver specificity demands investigation of the overall clinical picture. It is also important to realize that liver enzymes such as AST, ALT and GGT really do not reflect liver function as much as they show liver cell damage and inflammation. Suffice it to say that ranges and upper limits of these basic liver enzyme tests vary from lab to lab. I find it an interesting phenomenon to discover that upper limits have been increasing over time. More than forty years ago, as an example, the upper limit of ALT was determined to be 30 units/ml for males and 20 units/ml for females by some labs. Then the upper limit increased to 30 units/ml and now more recently I have seen the upper limit as high 65 units/ml by one lab. I believe that lab values are pre-determined by the bell-curve distribution of a large sample size of the general population. Could this mean that over time the overall general health of our liver is getting worse? I surmise that this may be so.[6-9]

In my naturopathic general family practice, I generally order basic lab tests on most new patients including CBC or complete blood count, chemistry, and thyroid tests. Liver enzymes and bilirubin are a part of the basic liver check up. To assess liver inflammation, I scrutinize the returned values of these tests for each patient. I generally consider a reading of half the value of the upper limit of each test to indicate fairly good liver quality. Commonly, one or more enzymes or bilirubin will be elevated. In clinical practice, I see patients with elevated liver enzymes caused by viral infection, alcohol consumption, toxic exposure, biliary congestion, heart disease, and more insidious disease such as cancer. Other causes of elevated liver enzyme include vigorous physical exercise, muscle damage, autoimmune disease, congestive heart failure, ischemic hepatitis, Budd-Chiari syndrome, alpha-one antitrypsin deficiency, celiac disease, endocrine disease (including hypo and hyperthyroidism), hemochromatosis, Wilson's disease, and glycogen storage disease. Up to 8.9% of the adult general American population will have one or more liver markers elevated on a standard chemistry panel. Asymptomatic liver enzyme elevation without clinical symptoms appears to be fairly common.

However, I believe the most common cause of slightly elevated liver enzyme(s) is non-alcoholic fatty liver ➤

disease (NAFLD) or hepatic steatosis. In fact, up to thirty percent of adult American population may be affected by fatty liver. I am interested in monitoring therapy and gauging improvement in liver health in this fairly common subset of the adult general population. Henceforth, I have been retesting these basic liver markers after treatment with diet and administration of supplements, particularly the herb milk thistle. I usually consider a decrease of liver enzyme of 5 units/ml to be a moderate improvement but more often like to see a drop of 10 units/ml or more to be significant and meaningful. Also a corresponding drop in bilirubin levels is also targeted. Occasionally, I see very high levels of liver enzymes or other markers. If this is the case, then I will order other tests, including an imaging test such as an ultrasound, or refer to a specialist if required.[7,8,9]

One of my naturopathic eureka moments is the discovery of meaningful liver function tests in the form of detoxification profiles that assess phase 1 and phase 2 reactions. It was at a 1999 naturopathic conference in Vancouver that I picked up Great Smokies Diagnostic Laboratories Reference Manual that included a wonderfully illustrated explanation of liver detoxification. It succinctly explained phase 1 and phase 2 pathways and offered useful interpretations and recommendations. Although I must confess, I only occasionally order phase 1 and phase 2 detoxification testing, I often refer to my understanding of the detoxification pathways to enhance a patient's capacity to eliminate toxins and improve liver function with the use of dietary changes, foods, nutraceuticals, and natural supplements.[10]

The caffeine clearance assay can be used to evaluate phase 1 detoxification pathways. As an example, 200 milligrams of caffeine is administered in the morning. Two salivary samples are collected at two and at eight hours following caffeine ingestion. Caffeine clearance can then be determined to be low, normal, or high depending on the amount of caffeine recovered in the samples. A low caffeine clearance would have potentially high values of caffeine in the salivary samples. A high caffeine clearance would have potentially low values of caffeine in the salivary samples. This can indicate the general functional capacity of specific phase 1 cytochrome P450 enzymes. This would partially explain why some individuals are very sensitive to caffeine due to a slow caffeine clearance, while others barely notice its effects and have a rapid clearance.[10]

Acetyl salicylic acid (ASA) and acetaminophen are two drugs that are used to evaluate specific phase 2 detoxification pathways. As an example, 650 milligrams of both ASA and acetaminophen are administered in the evening before bedtime. Total urine is collected for 10 hours, and sample is analyzed for levels of lipid peroxides. Plasma samples are also taken to analyze both acetyl salicylic acid and acetaminophen and their conjugated metabolites, including glutathione, glutathione peroxidase, super oxide dismutase, plasma cysteine, and plasma sulfite levels. Acetyl salicylic acid is primarily metabolized through the glycine and glucuronidation pathways. Acetaminophen is primarily metabolized through the glutathione and sulfation pathways. High levels of either metabolites indicate a high level of phase 2 activity pertaining to that particular pathway(s). Low levels of either metabolites indicate a low level of phase 2 activity pertaining to that particular pathway(s).[10]

I remember talking to a now deceased naturopathic colleague about natural treatments for hard-to-treat cases. He informed me that he had preceptored with the late Dr. John Bastyr, the eminent and renowned early naturopathic pioneering doctor for whom my esteemed alma mater was named. He said that the astute and wise sage told him in no uncertain terms that "if all else fails, treat the liver." As I get older and seasoned as a naturopathic practitioner, I have come full circle and now adhere to this advice more often. I still believe that good assessment of liver function begins with a keen observation, astute diagnostic acumen, and a shrewd accurate assessment of basic laboratory data.

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Dr. Douglas Lobay is a practicing naturopathic physician in Kelowna, British Columbia. Dr. Lobay graduated with a Bachelor of Science degree from the University of British Columbia in 1987. He attended Bastyr College (now University) of Health Sciences in Seattle, Washington and graduated with a Doctor of Naturopathic Medicine (ND) in 1991. While attending Bastyr, he began to research the scientific information on the natural supplements and therapies. His published books include *Dr. Lobay's Natural Health and Healing*, *Dr. Lobay's Natural Medicine 101*, *21st Century Natural Medicine*, *Creating Vibrant Health, Unlimited Health and Amazing Natural Medicines,* and *Uncle Mickey the Barber*. Dr. Lobay enjoys research, writing, and teaching others about the virtues of natural health and good nutrition. When he isn't practicing, researching, or writing, he enjoys spending time with his family, hiking, bicycling, playing tennis, skiing, and hockey.

The Powerful Role of Nitrates and Nitric Oxide in Intestinal Health

by Elizabeth Shirley, RPh CCN

The gastrointestinal (GI) tract encompasses a complex balance of microbes, hormones, neurotransmitters, and enzymes. The health of our gastrointestinal system is dependent upon this balance and is extremely important for longevity and well-being. The GI system not only controls physical wellness, it also is integral to mental health. This is due to the gut-brain connection, the communication between the intestinal tract and the brain, which plays a critical role in our mental as well as physical well-being. Severe gut dysfunction could exacerbate the symptoms of brain disorders, significantly affecting quality of life.

The intestinal microbiome also influences metabolic and immune pathways, as well as genetic and epigenetic factors that shape all aspects of physiology. Disruption of the intestinal microbial ecosystem, known as dysbiosis, has major impacts in health. Dysbiosis has been associated not only with gastrointestinal, but also neurological, cardiovascular, respiratory, metabolic, and oncological diseases. Therefore, a rich, diverse intestinal microbiome is essential to our mental, intestinal, and overall health. Yet, according to the Centers for Disease Control (CDC), five out of six individuals in the US receive one antibiotic prescription each year. This leads to alteration of the microbiome and increases dysbiosis.

A nitrate-rich diet, which supports the nitrate to nitrite to nitric oxide pathway, may help prevent dysbiosis and promote gastrointestinal health as well as support the gut-brain axis and maintain homeostasis. The highest nitrate-containing food sources include arugula (aka rocket), spinach, butter lettuce, bok choy, celery, and beets. Dietary nitrates and their metabolites are correlated with healthy oral, gut, and intestinal microbiota. Furthermore, nitrates may modulate inflammatory, immune, and oncological pathways. Nitrates also provide protection against toxicity induced by LPS (lipopolysaccharides), an endotoxin that increases proinflammatory cytokines and which is associated with a more permeable gut lining, leading to leaky gut. This paper will review the strong association of dietary nitrates and balancing nitric oxide levels with a healthy gastrointestinal tract. It will present the science showing that supporting healthy nitric oxide levels is an underutilized means of maintaining GI health.

Nitric Oxide Protects the Gastric Mucosa

Having a healthy mucus layer is our first line of defense against pathogenic bacteria in our gut. It is a critical protective layer that balances good and harmful bacteria.[1] Mucosa of the GI tract is continuously exposed to potentially damaging substances that can affect the gastric mucosal integrity.

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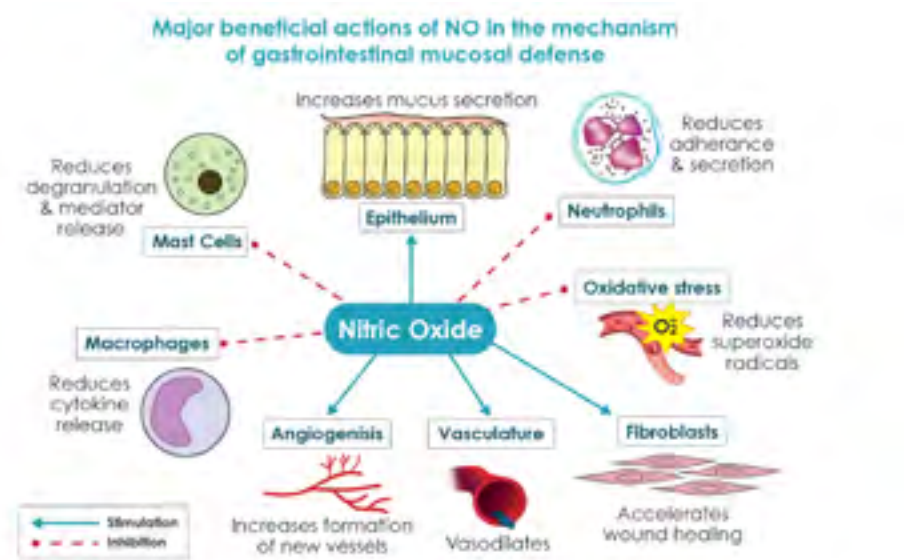

Diagram: Magierowski, M.; Magierowska, K.; Kwiecien, S.; Brzozowski, T. Gaseous Mediators Nitric Oxide and Hydrogen Sulfide in the Mechanism of Gastrointestinal Integrity, Protection and Ulcer Healing. Molecules 2015, 20, 9099-9123.

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Ethanol, nicotine, drugs (e.g. NSAIDs), *Helicobacter pylori*, hyperosmolar solutions, bile salts, ischemia/reperfusion of gastric tissue, and chronic stress all can be causal factors in mucosal damage and gastric ulcers.[2]

Nitric oxide (NO) appears to be one of the most important signals for mucus secretion as it is the mediator responsible for cholinergic-stimulated mucus release.[3] NO increases mucosal blood flow, which acts to dilute toxic substances, neutralize them, and remove them before they accumulate to damaging concentrations.[3] Supporting the nitrate to nitrite to NO pathway increases mucosal blood flow and vasodilation, increases mucus production and thickness, modulates mucosal immune response, prevents acute peptic ulceration, and can even repair NSAID damage to the intestinal tract.[3]

Nitric Oxide and Intestinal Barrier Integrity

Tight junction proteins play a vital role in epithelial transport and are responsible for barrier integrity of the intestinal tract. Loss of tight junction proteins results in the breakdown of the intestinal barrier called leaky gut. There is decreased gastric expression of the tight junction proteins occludin and claudin 5 during dysbiosis. However, following nitrate consumption, both protein levels rebound.[4]

Brain-derived neurotrophic factor (BDNF) may play a vital role in homeostatic regulation of intestinal barrier integrity by affecting the expression of tight junction proteins.[5] For example, decreased BDNF increases irritable bowel syndrome.[5] BDNF also plays a role in depression, anxiety, learning and memory. It is important to note that NO is an essential mediator of BDNF activity.[6]

Antibiotics and Nitric Oxide

Broad spectrum antibiotics decrease microbial richness and diversity. The use of antibiotics has long been linked to intestinal disorders, leaky gut, and even mental health symptoms, including anxiety, depression, brain fog, and severe fatigue. Dietary nitrates have a supportive role to play during antibiotic treatment. Dietary nitrates taken during antibiotic therapy down-regulate gastric mucosal inflammatory pathways and prevent overt inflammation, and the resulting increased intestinal epithelial permeability.[4] Nitrates may increase microbial biomass and act as a substrate for the existing microbial communities allowing them to thrive and prevent dysbiosis.

A nitrate-rich diet may help prevent dysbiosis, reduce inflammation, and promote a healthy gut-brain axis.

The oral microbiome may modulate the activities of the gut microbiome. Studies have shown that alterations in oral flora can cause an imbalance in the gut flora, which can increase the pathogenesis of gut disorders. It is known that 45% of the bacteria in the oral cavity and large intestine overlap, and we are constantly seeding the intestinal tract every time we swallow or eat. Nitrates increase nitrate-reducing bacteria on the tongue and decrease levels of bacteria that are associated with poor oral health.[7] Nitrate supplementation is able to prevent or reduce bacterial dysbiosis and stimulate eubiosis by increasing the beneficial, healthy bacteria and decreasing levels of disease-associated bacteria.[8]

Several recent studies have suggested that nitrite can be used as an alternative to standard antibiotic therapies owing to its ability to disrupt the protective biofilm formed by pathogenic bacteria.[9] Furthermore, supporting the nitrate to nitrite to NO pathway ameliorates inflammatory cell infiltration, regulates microbial dysbiosis, and restores beneficial bacteria.[10] Nitrates protect the gut microbiome under inflammatory conditions and restore local immune and inflammatory responses.

Nitrate, Nitrite, NO, Inflammation, and Immune Cells

A T cell is a type of lymphocyte and a helper T cell (TH) directs the immune response. Nitrates rebalance the ratio of TH cells in the peripheral blood. Nitrates also decrease proinflammatory TH1 and TH17, which are closely associated with inflammatory bowel disease (IBD).[9] Nitrates decrease IL17 in the colon, thus decreasing inflammation. IBD is a major risk factor for colorectal cancer, and nitrates may help prevent colitis and colorectal cancer.[9] Additionally, nitrates increase Treg cells to maintain homeostasis and self-tolerance.

During inflammatory events, there is increased expression of myeloperoxidase, which is involved in the antimicrobial response by increasing reactive oxygen species (ROS). Another way in which nitrates and NO support a healthy inflammatory response in the GI tract is by decreasing myeloperoxidase activity in gastric mucosa.[4]

Furthermore, nitrite and NO can regulate the activity of mast cells.[11] Mast cells are white blood cells that are part of the immune system and function as a bridge between the immune and nervous system. Mast cells modulate the inflammatory processes in depression, anxiety, brain fog, and insomnia.[12] Mast cells become activated in the absence of NO production, and increased superoxide production contributes to mast cell activation.[11] Conversely, nitrites and NO are an effective inhibitor of mast cell dependent inflammatory events. Nitrites and NO suppress antigen-induced degranulation and mediator release, including histamine and cytokine expression.[11] In addition, nitrites and NO inhibit leukocyte endothelial cell attachment and inhibit generation of ROS by mast cells.[11]

Reducing the Effects of Stress on the GI Tract

Mast cells are important effectors of the gut-brain axis by translating stress signals into release of neurotransmitters and proinflammatory cytokines. Chronic stress causes inflammation and damage to all cells in the body, including in the GI tract. Stress can cause the following:[13]

- Alter GI motility,
- Change GI secretion,
- Increase intestinal permeability,
- Decrease regenerative capacity of GI mucosa and mucosal blood flow,
- Have negative effects on intestinal microbiota, and
- Inhibit production of NO through the arginine/NOS enzyme.

Supporting the GI tract with nitrates addresses these multiple adverse effects of stress. Furthermore, nitrate and replenishing NO levels can enhance mental health, leading to improved sleep, less anxiety, and less symptoms of depression, thereby affecting factors that can indirectly lead to impaired GI health.[14]

Can Nitric Oxide Really Damage the GI Tract?

It is controversial whether the increased NO from iNOS, or any other source, causes GI injury, and there are questions about the role of peroxynitrite in the production of tissue injury.[3] The use of L-NAME (nitro-l-arginine methyl ester), an iNOS inhibitor, which leads to some decrease of tissue injury and inflammation, may not be due to inhibition of the production of cytotoxic concentrations of NO.[3] There are other actions of L-NAME that may be at play here.[15] Administration of large amounts of NO does not cause detectible damage to the mucosa or vasculature of the intestine, and the majority of available data point to NO serving a critical role in protecting the GI mucosa from injury induced by ROS and other cytotoxic substances.[3,16]

Conclusion

Dietary nitrates clearly play an important role in protecting GI health. Nitrate inhibits the inflammatory process and down-regulates and scavenges oxidative stress. Furthermore, nitrate is a powerful modulator of the microbiome, and microbiome diversity is the foundation for health and longevity.

A nitrate-rich diet, which supports the nitrate to nitrite to nitric oxide pathway, may help prevent dysbiosis, promote a healthy gut-brain axis and therefore support both gastrointestinal and mental health, and maintain homeostasis.

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Over the last 12 years, Beth has spent time working with some of the leading thought leaders in the world of nitric oxide research and through this has developed an in-depth knowledge on the topic and its potential applications in patient care. She currently is the executive director of the Berkeley Life Scientific Advisory Board.

Glandulars for Immunity and Autoimmune Disease

by Linda L. Isaacs, MD

Most of my patients have a past or present diagnosis of cancer, and it is important in such patients to support the immune system. Glandular products are a key part of my protocols, which also involve extensive diet and lifestyle changes, along with detoxification. Although autoimmune disease hasn't been a research or publication focus for me, neither now nor historically in my work with Dr. Nicholas Gonzalez, because of its prevalence and the undiscerning impact of cancer, I do see patients with autoimmune issues. I will review three particularly interesting cases of lupus in which glandulars were a key part of the treatments applied, and the success that was seen with them.

What Are Glandulars?

Glandular substances are specially treated preparations of different animal-sourced organs, such as the pancreas, thyroid, or adrenal gland. There are a variety of glandular products available, some more processed and purified, some less. Dr. Gonzalez and I found that the most effective products were made by a special freeze-drying technique known as lyophilization. This method removes the water but leaves everything else in the gland still present in the final product.

When glandular substances are prepared in this fashion, they contain a variety of substances, including nutrients, proteins, growth factors, and other cofactors found in the gland. These include enzymes and their precursors that are normally found in pancreatic tissue, vitamins and minerals that are found at high levels in the liver, and – with a glandular such as adrenal or thyroid gland – extremely small amounts of naturally occurring hormone-type substances, so little that their beneficial effect cannot be explained pharmaceutically.

Any autoimmune issues, such as with the adrenal or thyroid gland, may be modified by glandular supplementation.

We believe the glandular products can provide the raw materials such that the gland can actually fix itself. But another possible mechanism of action is via oral tolerance, where a swallowed substance can downregulate the body's inappropriate immune response. Therefore, any autoimmune issues, such as with the adrenal or thyroid gland, may be modified by glandular supplementation.

Immune Support for High-Risk Patients

Many of my patients fall into a high-risk category for infections, being older or having co-existing conditions. They describe global fatigue and a tendency to catch frequent colds.

With patients such as this, I use three glandulars – the thymus, adrenal, and pancreas gland – and I find that they work together synergistically. Adrenal and pancreas glandulars can have an effect on immune function, in addition to their other roles in my program. Patients with fatigue frequently need the adrenal glandular; patients with poor digestion and gastrointestinal complaints, the pancreas glandular. The enzymes and their precursors found in pancreas glandular may be helpful for breaking up cytokines and various protein mediators of infection.

The thymus, of course, is the home of the T cells that are more directly involved with viruses and the like, while the spleen is the home of the B cells that make antibodies. Although I have found that the thymus glandular works well for a wide variety of patients, there are some people with frequent infections for whom the spleen glandular can be very helpful.

Most of my patients take thymus glandular; and for years and years now, I have told them to take a higher dose at the first sign of symptoms if they feel like they are getting a cold or the flu. Many of the patients have said that if they start taking it in this manner the moment they start to feel sick, it can help to prevent or mitigate the illness.

Typically, I advise patients to take three capsules of thymus glandular three times a day if they are starting to come down with something. However,

recently many of my patients are more concerned about getting sick and/or have a higher risk of infection exposure. I advise them to take one capsule of the thymus glandular three times a day or a regular basis. Overall, people have been doing quite well with this, and it seems to be helpful in keeping a high-risk population healthy. Of course, there hasn't been a full study to test out either of these protocols, but I feel I have enough anecdotal evidence to suggest this to my patients.

Case Studies in Autoimmunity

Each of these three patients were diagnosed with lupus, an autoimmune disorder that can be very, very deadly, or it can be relatively mild. Two were patients of Dr. Gonzalez, one of mine, but all were treated with the methods Dr. Gonzalez and I utilized during our 25-year association.

We never decided to publish these cases because it wasn't our, or now my, primary focus. But it also is difficult to demonstrate real value in the field of autoimmunity because the natural history of the disease can be so variable. In other words, some people seem to do fine over the long haul, and some people rapidly deteriorate and die not so long after being diagnosed. It's hard to know from the get-go which patient is which. Some orthodox autoimmune disease regimens are based on expert opinion as opposed to clinical trials because it is hard to recruit patients and generate meaningful data.

Research and even expert opinions in autoimmune disease can also be cloudy because a lot of physicians using orthodox treatments for autoimmune disease don't ask the patients what they are doing in addition to the medications they are taking. So, it is quite possible that a lot of the people who had a "spontaneous remission" in fact modified their diet or were taking supplements and that's why they got better – but if you don't ask them, you'll never find that out.

The first patient I will discuss came to see Dr. Gonzalez in 1992. She was in her mid-thirties at the time she was diagnosed with lupus, as were all of these patients. She was on the verge of needing dialysis due to kidney involvement; she was extremely sick, and completely exhausted. She went on the protocol and continued to be treated by him right up until the time he passed away in 2015. All her symptoms and signs of lupus actually resolved. She started out on quite a few medications, all of which were tapered, and she did great.

Lupus nephritis is generally a very bad sign. In his notes of his last visit with her, which was 22 years after beginning treatments, she credits the program with saving her life.

Another case was a woman diagnosed with lupus whose mother had died of the disease. When she first saw Dr. Gonzalez in 1992, she was ➤

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completely exhausted to the point that she could barely get up and walk around. She also did extremely well; her symptoms completely resolved, and she was doing very well in 2014, which was the last time she came to see him.

I heard from her in early 2020, and she told me that she went to see a rheumatologist who questioned whether she ever had lupus in the first place. Her father was a physician, and she had been diagnosed by reputable physicians with a clear-cut case of lupus, so neither Dr. Gonzalez nor I had any doubt that she had the disease. But she was doing so well that the rheumatologist simply did not believe her story.

Finally, the third case is a patient of mine who developed lupus in her mid-thirties. She began treatment with me in 1999, while continuing hydroxychloroquine. She discontinued hydroxychloroquine in 2004, and continued to do well. When I last communicated with her in 2014, she had had no further symptoms of lupus and was off all lupus-related medications.

With all of these patients, one of the common threads in their treatment was high doses of the thymus glandular – from three to nine capsules a day, taken with meals, for years and years. Another supplement taken by these patients was a pancreas glandular product, taken away from the meals. Pancreas is obviously high in the various enzymes the pancreas makes and their precursors, and I believe that it may be helpful with autoimmune disorders because proteolytic enzymes can help break up some of the autoimmune complexes that are at the heart of the disease.

Glandulars alone are not sufficient: diet and detoxification are extremely important as well. Our patients are told to eat a high-quality diet, and they all perform detoxification routines such as coffee enemas. While most approach the coffee enemas with some trepidation, almost all report it becomes their favorite part of the protocol.

So, these are three representative patients with a difficult-to-treat autoimmune disorder who have done extraordinarily well using glandular products, with the usual caveats about lupus and its unpredictable course. I have seen a fair number of patients with autoimmune disorders over the years who have done particularly well like this. Symptomatically, with these supportive protocols, including glandulars as well as dietary modifications and detoxification, patients with autoimmune disorders or fatigue-type syndromes typically start to feel somewhat better in around three to six months.

Contraindications and Medication Interactions

In my experience, the glandulars are really quite safe. Rarely have I seen a patient have a problem with the pancreas, thymus, or spleen glandular. With the adrenal glandular, every now and then a patient may start off being very sensitive to it, or they may become sensitive to it. When the adrenal gland is working better, such a product is no longer needed, and the body may display sensitivity symptoms.

As an example, I had a patient once who came to see me because of breast cancer, but she also had been exhausted for years and years before she got the cancer. I put her on a protocol that included the adrenal glandular and she improved rather dramatically. Initially she took adrenal glandular three times a day, but she got to a point after five or six years on the protocol that she would get fatigue if she didn't take the adrenal at all, but if she took more than one capsule every five or six days, she got headaches. So, she herself, with some guidance from me, figured out how often she needed to take it, and with that approach, her energy levels were excellent.

Patients or other doctors sometimes worry about adrenal suppression with adrenal glandular supplementation, but the amount of active hormone in glandulars from a reliable source is extremely small. I believe that the glandulars can actually help patients recover from adrenal suppression that corticosteroids have caused, by giving a source of raw materials for repair. With many of our patients, there comes a time that the supplement is no longer needed, which would suggest that repair can occur.

In terms of interaction with other medications, I haven't found any problems, though from a theoretical point of view, pancreas glandular should probably be taken away from any medication that is in a time-release preparation.

Conclusion

I hope in this article to have given you some food for thought about how the use of glandular extracts may be helpful to your patients with autoimmune disorders, as well as patients with other conditions. Thymus, adrenal, and pancreas glandulars are all pillars of the work that I do; and I believe that they can be useful in almost any clinical practice. ◆

Linda L. Isaacs, MD, received her Bachelor of Science from the University of Kentucky, graduating with High Distinction. She attended Vanderbilt University School of Medicine, then completed her internal medicine training at the Department of Veterans Affairs Medical Center at New York University School of Medicine. She is certified by the American Board of Internal Medicine and is enrolled in their continuing Maintenance of Certification program.

She and her long-time colleague Nicholas J. Gonzalez, MD, published multiple articles in scientific journals together, as well as a book, *The Trophoblast and the Origins of Cancer*. Since Dr. Gonzalez's untimely death in July 2015, Dr. Isaacs has dedicated herself to continuing the work they both shared. Her website is www.drlindai.com.

Diagnose and Treat Hypothyroidism in 2021, Part 2: New Endocrinology

by Alan B. McDaniel, MD

Part 1 of this three-part article (published May 2021) presented the complex physiology of thyroid function and discussed symptoms and diagnosis of hypothyroidism.

Start T4 Treatment: Dose and Timing

Despite optimistic declarations in the medical literature that starting with a "full dose" of T4 is safe in all but the elderly or infirm,[100] I *never* do that. Whether treating with T4, "natural" thyroid or T3, *all* my patients receive gradually increasing doses. This is a good idea with T4 and *imperative* when treating with T3. I prescribe levothyroxine 25 mcg tablets, which can be divided to give the smallest accurate increment.

Typical T4-doses vary from 50-200 mcg/d daily.[113] What daily dose will a particular patient probably need? It is wise to anticipate a safe maximum before writing the prescription. Lean body mass is proven to be the best initial indicator of the ultimate levothyroxine dosage.[114] Age and gender differences mainly reflect different proportions of lean mass vs. total body weight.

Guidelines state the usual maximum daily-T4 is **0.73 mcg per pound** of body weight (1.6 mcg/kg) when TSH is markedly elevated.[100] With experience and attention to situational clues and lab values, you will learn to modify the dose for frail or overweight people (hunters call such adjustments "Kentucky windage"). For safety, always bring patients back for follow-up *before* increasing their dose to reach the estimated "maximum."

My patients start taking 25 mcg T4-daily. Although remaining vigilant, I expect no problem, particularly as all have begun taking nutritional support for their adrenals and *other* steroid-forming tissues. I give written directions for the patient to increase the dose by 25 mcg weekly – as *tolerated* – and put it in writing on a fill-in MS Word form (free upon request).[38] Figure 3 shows typical instructions for a person who may need as much as 125 mcg T4 daily:

In their place, data for other drugs can represent the likely levothyroxine kinetics. Graphic representations of blood levels for topirimate[118] and methadone[119] in once- and twice-daily doses are available online. They clearly show that divided doses maintain therapeutic blood levels and avoid the supra- and sub-therapeutic values seen with once-daily doses.

Figure 3: Levothyroxine dose instructions to achieve 100mcg/day

Rx: Levothyroxine 25mcg (GF: Synthroid®); biologically-identical T4

Week	Dose	AM	PM	Tablets	Special Instructions
#1	T4	12.5 mcg +	12.5 mcg	(½ + ½)	Cut your caffeine dose in half
#2	T4	25 mcg +	25 mcg	(1 + 1)	Cut the caffeine in half again
#3	T4	37.5 mcg +	37.5 mcg	(1½ + 1½)	– and again
#4	T4	50 mcg +	50 mcg	(2 + 2)	Here, please be stimulant-free

Let me challenge you: If our goal is to restore normal hormone levels, why do we give thyroid treatment once daily? This is *so not* physiological! The healthy gland releases steady amounts of hormones throughout the day. Thus, circulating thyroid hormones remain quite stable all day.[115] Yes, TSH varies a bit, rising from about 1.5 in the day to 2.2 at night – that's +/- 0.35 …no big deal.[116] Healthy bodies do best with blood levels close to the "normal physiology."

Once-daily levothyroxine doses were suggested as a marketing strategy in the 1950s. Using tests that weren't available back then, we find this creates abnormal blood levels: A big peak of T4 occurs around three hours after the pill is swallowed,[117] then the level drops steadily until the next dose. Because levothyroxine was approved long before good assays were available, no proper pharmacokinetic studies were, or ever have been published.

If a patient asks, "What is the best way to take thyroid?" I may tell him the ideal would be to take a tiny tablet every minute; that impossible schedule would best-mimic normal physiology. Yes, most people can tolerate once daily-doses – but dividing it every 12 hours often works better. Osler, acclaimed as the greatest physician of the last century, prescribed desiccated "natural" thyroid every *eight* hours.[120]

Similarly, when someone asks me, "What is the best time to take thyroid?" I usually answer, "three hours before you wake up." People get out of bed a lot more easily with peak blood levels of thyroid than at trough. Although some practitioners endorse once-daily T4 doses at bedtime,[121] taking divided thyroid doses, on waking and about 12 hours later, seems better for most patients. *Caution*: Avoid taking take the PM dose less than four hours before bedtime, as peak levels make it harder to fall asleep.

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I am an agnostic regarding the stickers that pharmacies place on prescription bottles, advising that T4 should not be taken with food (especially soy) or supplements (particularly calcium and iron).[122] The studies proved malabsorption is *statistically* significant,[123] but experience shows it is *rarely* clinically significant in adults – except in this way: Patients' efforts to follow this instruction commonly disrupt their doses.

So, my patients take thyroid every 12 hours, regardless of meals – though I ask them to avoid a bolus of soy.[124,125] The patient should always have a few doses with them. My wife has a little pillbox in her purse; men can put a small pill-cylinder on their keychain. Also, reminders are helpful: Set an alarm on the cell phone to ring when the PM dose is due (that's the one most likely to be missed).

Dose Escalation: The Initial Phase of Treatment

While lean body mass predicts the maximum dose, the patient's symptomatic response to treatment helps to define the "optimal." From any dose adjustment, there are only three possible outcomes: The patient feels better, the same or worse. It takes up to a week before this can be determined with any certainty; each step results in many changes and protein-bound hormones are slow to reach their new equilibrium.

At the end of each week, the patient assesses her response to the current dose and decides upon the next step. Caution her that if any dose increase feels worse, she should reduce it: Drop back just one step and contact me (*I'm emphatic about this!*). If it seems unlikely that her dose would be too high, take a careful history for the use of stimulants and seek clues to any other, unexpected problem. If none can be found, ask her to continue the new, lower dose and after two weeks, check blood levels.

When Your Patient Unexpectedly Feels Worse

The most common reason people feel "worse" during the dose-escalation phase is simply over-stimulation from caffeine. I know this from my personal experience. People with hypothyroidism need something to give them energy and caffeine is the most available legal solution – I had a two pot-daily coffee habit.

As thyroid hormone levels rise towards normal, the high caffeine intake begins to produce the jitters and naturally, the thyroid replacement is blamed. Be pro-active: Their former "best-friend" caffeine must be tapered-off during build-up and temporarily discontinued (Figure 3) – even decaf products, which still have too much. The prohibition can be relaxed after the safe, effective thyroid dose is established.

Thyroid replacement can also reveal symptoms of low blood sugar and estrogen deficiency. However, it is unusual to get any such call using levothyroxine. People rarely feel worse during T4-escalation.

Schedule your first follow-up visit at the end of the planned build-up time – four weeks in the illustration given in Figure 3. By design, she will be taking *less* than the estimated "maximum." Her clinical response will then guide the next steps.

The First Follow-Up Visit

Inventory symptoms: If your patient feels 100% well, maintain the current dose and check blood levels to ensure safety and efficiency. This can be done after two weeks on a stable dose. Some writers prefer to wait four weeks or more.[126]

When symptoms persist – with no evidence of over-replacement – I recommend cautious increments of just 12.5 mcg T4/week until reaching the estimated maximum dose. Laboratory tests are then needed. When symptoms are resolved, the lab should validate the dose. If symptoms persist, your blood tests should show you the problem.

Daniel Boone was once asked if he had ever gotten lost. He replied no, but he had once been bewildered for three days. If you are ever "bewildered" about how to proceed, it is always appropriate to check blood levels on an equilibrated dose – the way a modern Boone checks her location by GPS.

Pathology 201: The First Laboratory Follow-Up

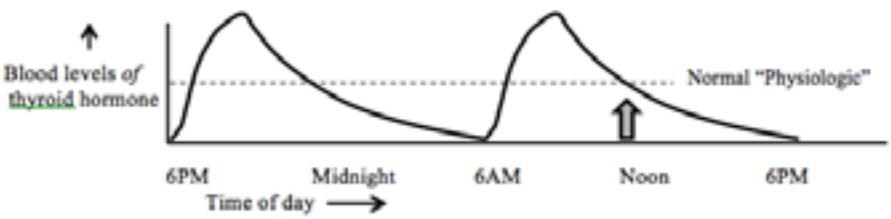
Let's re-visit "pre-analytical error": When a patient regularly takes levothyroxine, at what time should her blood be drawn? Graphs of peak and trough therapeutic values indicate random tests are imprecise. Accuracy requires specimens to be drawn in relation to doses…but when? It was written that *free* hormone values can vary by 30% following a dose (*in an article I can't find, alas!*). The best pharmacokinetic data I can find state thyroid hormones peak "some 3 or 4 hours" after a dose.[127]

Internists usually test at trough, just before the AM dose. This most sensitively detects insufficient treatment. However, excessive dosing can be missed – for example, among 25,862 health fair-attendees, 40% of all people taking thyroid hormone had out-of-range TSH values – 90% of which were low, suggesting over-treatment.[2]

Followers of the Belgian endocrinologist Thierry Hertoghe[128] draw blood specimens three hours after the thyroid dose (at peak), which best reveals high levels. As the converse of the internists' method, it may be expected to miss *under*-treated patients – and it will (see Patients 4 and 5, following).

Given such uncertainty, I prefer to test my patients' blood levels exactly mid-way between evenly spaced doses, which are divided as evenly as possible. This tactic gives me an average: Half of the day, therapeutic levels are higher, and they're lower the other half (Figure 4). Admittedly, therapeutic values may be high when tested at peak or low if tested

Figure 4: Test thyroid hormones mid-way between evenly timed doses.



at trough – even with Q 12 hour divided doses.

Patient 1 provides a good example. Her endocrinologist tested her at "trough," 24 hours after her last AM dose of T4 125 mcg. Her values were TSH=**5.2** H; freeT4=0.8 and freeT3=2.9. The Doc increased the T4 dose by 25 mcg, but she felt no better and consulted me.

I suggested dividing her T4 to 75 mcg Q 12hrs., then testing in two weeks. But she was in a hurry: Late that afternoon, we checked her levels as close to mid-dose as possible – just before the lab closed. These values were typical of excessive levothyroxine treatment: TSH 0.488; freeT4=**1.96** H, freeT3=2.7 …and RT3= **39.6** H.

Testing at mid-dose is successful in my practice. I have no objection when other physicians adhere to a different strategy they like better, as long as they are consistent, minimize pre-analytical error before performing their tests, and are aware of relative drawbacks of their choice. However, I cannot endorse random testing.

However, you prefer to test, keep good records to both facilitate your therapeutic choices and validate them. On receiving a lab report, I send the following form to my patient by e-mail (Figure 5). I ask her to copy it and paste it into an e-mail to me; then fill-in the blanks and return it for her records. I review many files from other physicians, and it is disappointing how little value reports offer without the dose and timing information.

Confirm Treatment Results with "All 5" Thyroid Hormones

The "ideal" therapeutic TSH-level is a matter of opinion. The 2014 American Thyroid Association (ATA) guidelines simply recommend "a value within the reference range" for adults (0.4-4.0 µIU/L) and no higher than 2.0 for children, lest their development lack support.[100] Online, the ATA suggests 0.5 to 2.0 for all patients,[129] which I and practitioners around me prefer. A Norwegian writer has suggested 0.5-1.5.[130]

If your goals include suppressing TSH, *first* be sure that the patient feels *well* on her levothyroxine. If not, taking more T4 will probably make her feel worse. Only after all other aspects of her therapy are satisfactory will I increase the replacement dose to suppress TSH.

In addition to TSH, it is important to check freeT4, freeT3, totalT3 and RT3. This is especially true when a patient's symptoms have not responded to treatment – yours or that of other physicians for whose failures you were consulted. If you are not yet inspired by the metaphor of the basketball coach, keep reading….

Subsequently, it is wise to follow your patient with an office visit and mid-dose labs at around three months and again at some six months after proving the "optimal dose." Then, schedule annual check-ups. As reviewed just below, thyroid function can be unstable, and adherence may be undisciplined. In the first year, it is prudent to metaphorically keep a finger on the pulse.

Therapeutics 102: Problems with Levothyroxine Treatment

Levothyroxine treatment should be sufficient – so we've been taught for 60 years. However, there are a number of potential problems. Among them is our dependency on the patient's (diseased) gland to keep producing.

It is not unusual to find patients taking T4 have undesirable TSH values,[2,131,132] whether due to patient non-adherence, prescriber technique, or progressive disease. However, unless the T4 dose suppresses the patient's TSH, her gland will still contribute to the total amount of circulating thyroid hormone. With ongoing thyroiditis (e.g. Hashimoto's), the progressive failure of the patient's residual function is predictable – and she will need increasingly large replacement doses. For this reason, lab values must be followed at least annually and *any* time the patient seems to take a down-turn.

Pharmacies participate too: My patients have received incorrect prescriptions on occasion. Once dispensed, the pills can be damaged: A patient left her 90 days-supply of T4 on the dashboard in July, where the heat inactivated them and sparked great perplexity. Other, undiagnosed conditions also can prevent a good response.[133]

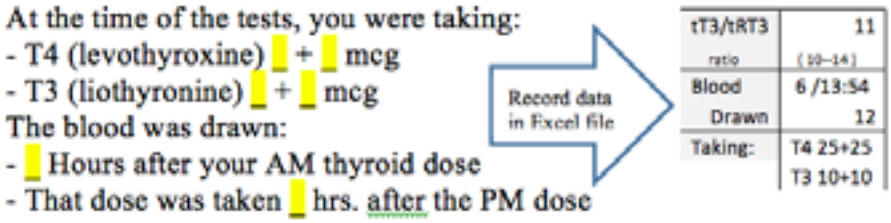
Autonomous function is unfortunately common, especially among "difficult" patients. You will hear from them during the escalation phase, earlier than you would expect. Because of this autonomy – whether undiagnosed Graves, "toxic" multinodular goiter, functioning adenoma, or even Hashitoxicosis – your calculated replacement dose will give them more than they can tolerate. Tests of "all-5" hormones should reveal this.

Spuriously elevated TSH can be deceiving. If you've correctly calculated the replacement dose, this patient won't be hyperthyroid at her first follow-up: As she increased the T4 dose, her (normal) hypothalamic-pituitary-thyroid (HP-T) axis will have reduced its production to maintain normal thyroid hormone levels. If she takes too much T4, though, she will feel worse and "5 tests" show the mismatch between the bogus TSH value and high thyroid hormone levels.

Up to 16% of patients report poor results using T4, despite normal test values for TSH and freeT4.[134-137] That is one of every six people! The voices of this unfortunate minority have become increasingly angry.[138,139]

Lately, they have been given proper academic attention: Multiple centers sent a survey to their hypothyroid patients asking them to grade their satisfaction with thyroid replacement treatment on a scale of 1-10. They received 2,146 responses: Satisfaction with levothyroxine treatment was "5." Combined T4 and T3 treatment (as given) was better ("6") and best of all was "natural" thyroid, scored "7."[134] ➤

Figure 5: Post-test dose and timing questionnaire and Excel record



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Correct the Failure of T4 Treatment

Patient 2 was a 31-year-old woman on her arrival for consultation. She had been hypothyroid for 14 years due to Hashimoto's disease. She was unhappy with her results on once-daily levothyroxine 112 mcg Q AM: In the previous two years, she had three confirmed 1st-trimester miscarriages (ICD-10: N96) and a fourth had been likely.

Despite normal TSH and freeT4 on treatment, she had many symptoms suggesting low thyroid, including fatigue, feeling cold, cold hands and feet, tired on waking, gas and bloating, constipation, reduced libido, and dry skin. Adrenal issues were suggested by symptoms such as orthostatic lightheadedness and craving salt. She had 28-day cycles; no PMS; menstrual flow lasted three days with clots and pain for one day. Her diet had long been gluten-free (Dad has celiac). Her BMI was 19.6.

She began taking neonatal bovine "adrenal glandular" and divided her T4 dose to 56 mcg q 12h. After two weeks, she had blood drawn six hours after her AM dose; it showed: TSH= 0.663; fT4= 1.66, fT3= 2.9; tT3= 87, RT3= **36.1** H. Ratio tT3/ RT3= **2.4** (L)

We agreed to replace some of her T4 with T3. I used the common semi-equivalency that 25 mcg T4 ≈ 5 mcg T3 (5 to 1), though a few studies have used 3:1.[140] Figure 6 shows her instructions[38] for the four weeks of transition.

After two weeks on T4 25+12.5 mcg and T3 10+10 mcg, she felt much better. Blood was drawn 6 hrs. after her AM dose: TSH= 0.463; fT4= **0.59** L, fT3= 4.2; tT3= 152, RT3= 10.3 and tT3/RT3 ratio = 14.8 (*a more complete discussion of the ratio will follow*).

We had to increase T4 – which was lower than anticipated because she was again pregnant! Binding proteins are greatly increased with pregnancy, and like most women, she now needed a larger dose: T4 37.5+37.5 and T3 10+10. She delivered a healthy boy at term and after six weeks, she required less T4.

A year later, during her second pregnancy, she once again needed the same greater thyroid dose. She delivered her second healthy baby and in the postpartum, again reduced her T4 dose. Years later, her latest test results at mid-dose, taking T4 25+25 mcg and T3 12.5+ 10 mcg (divided Q 12 hours) were: TSH= 0.711; fT4= **0.80** "L" (0.82-1.77), fT3=4.1; tT3=151, RT3=13.3 and tT3/RT3 ratio= 11.4 ("10-14").

Physiology 201: Why Does T4 "Fail" So Many People?

Patient 2 raises important issues. Although the pre-hormone levothyroxine restored TSH and freeT4 to their normal ranges, the initial set of "5-labs" proved that her body could not efficiently activate T4 to T3; she made RT3 instead. The *first* therapeutic move was to divide her dose. Let's examine the reasons for this:

Figure 6: Plan to transition from T4 monotherapy to combined T4 plus T3.

Rx: _Levothyroxine (T4) 25mcg tablets and liothyronine (T3) 5mcg tablets_

		Dose: AM		PM	Tablets:
Now on:	T4	56 mcg	+	56 mcg	(112: ½ + ½)
Week	Change to:				
#1	T4	50 mcg	+	50 mcg	(2 + 2)
	T3	2.5 mcg	+	2.5 mcg	(½ + ½)
#2	T4	37.5 mcg	+	37.5 mcg	(1 ½ + 1 ½)
	T3	5 mcg	+	5 mcg	(1 + 1)
#3	T4	25 mcg	+	25 mcg	(1 + 1)
	T3	7.5 mcg	+	7.5 mcg	(1 ½ + 1 ½)
#4	T4	25 mcg	+	12.5 mcg	(1 + ½)
	T3	10 mcg	+	10 mcg	(2 + 2)

The healthy hypothalamic-pituitary-thyroid (HP-T) axis continually "trickles" hormones into the bloodstream. In contrast, once-daily thyroid hormone floods the body with a bolus of T4 sufficient to last 24 hours. This rush of T4 signals "*hyperthyroidism!*" during the hepatic "first pass" and with supra-physiological free T4 blood levels peaking in three hours.[117]

Excessive T4 redirects deiodinase enzymes from producing T3 to instead make RT3[141] – and deactivate T3 to T2 (Figure 2). An elevated T4/TSH ratio exerts the same effect.[80] This has been reported in Graves' disease,[142,143] for which it is considered adaptive and protective. When T4 is taken for hypothyroidism, it is neither.

Some patients treated with levothyroxine have frankly low values of T3,[100] which can correlate with symptoms.[144] In such cases, increasing the T4 dose can ultimately produce T3 levels somewhere in the "normal" range (there was no mention of symptom improvement).[145] However, higher than normal RT3 levels consistently accompany once-daily oral levothyroxine, in both humans[146,147,148,149] and beasts.[150,151] I find no report to the contrary.

Like most patients whose activation of T4 is somehow dysfunctional, Patient 2 had hypothyroid symptoms and signs (miscarriages); normal TSH; normal T4 levels but a low ratio of tT3/ RT3. Unfortunately, even though taking divided T4 doses, Patient 2 continued to have both symptoms and excessive RT3 relative to T3.

Dysfunctional Deiodination and Low tT3/ RT3 Ratio

Prescribing T4 without testing the patient's ability to activate it might be compared to charitably sending cans of food to starving Third-World children without ensuring they have a can-opener. The thyroid "can-opener" is a 5'-deiodinase enzyme (there are two isoforms).

While 80% of the T3 we humans need daily is derived from T4,[152] not everyone is able to efficiently perform this conversion. For some, the enzyme responsible for making 50-70% of our T3 (type-2 deiodinase, 2-DI)[153] is faulty. A 2009 report showed that 16% of Britons carry loss-of-function mutations of the

gene (DIO2) encoding this enzyme.[136] The "mutated" patients responded significantly better to combined-therapy with T4 and T3 than to T4-alone. Patient 2 has Northwestern European ancestry.

Patient 2 also has hypothyroidism due to Hashimoto's disease (AIT). Research has strongly associated AIT with the excessive production of RT3 ($p<0.00002$).[147] Many other factors can direct deiodination of T4 away from T3 to RT3, including drugs (*particularly* epinephrine,[154] steroids,[155,156] beta-blockers,[157,158] and amiodarone[159]); iron-deficiency[160]; inflammatory cytokines[161,162]; bacterial endotoxin[163,164]; mold mycotoxins[165]; elements of metabolic syndrome[166]; and even some tumors.[167,168]

The effects of stress are also important: The acute stress response to severe illness reduces both TSH-release and peripheral T3 production. Thus, the metabolism slows to a low energy-consuming, conservative state.[72-74] This can be adaptive in cases of serious injury, illness and starvation.[169] However, it becomes maladaptive when inappropriately prolonged[170-172] and is called "euthyroid sick syndrome" (ESS) or "non-thyroidal illness" (NTI).[161,173,174]

Emotional stress can also initiate this response, to the detriment of the patient. ReverseT3 can rise rapidly as patients enter a surgical suite[175] or simply experience pre-operative anxiety.[176,177] This has also been reported among medical students taking examinations.[178]

But the Problem Is Not "Low" T3

The alert reader may now ask: How can I say Patient 2 had dysfunctional deiodination? Her freeT3 and totalT3 values were normal all along! This question perplexes scientists studying ESS/ NTI.[161,173] At first, it was called "low T3-syndrome" – until it became evident that indeed, *low* T3 was *not* the hallmark of the problem.

Harvard researchers wrote that altered deiodination may cause physiological hypothyroidism – "disruption of thyroid hormone signaling" – while T3 levels remain within the normal range.[171] If not low T3, what test result identifies this physiological aberration – and what causes the severe ill-effects of ESS/NTI?

Elevated RT3 is characteristic of ESS/NTI, and it predicts a bad clinical outcome.[172,179,180] However, a far more accurate diagnosis of this problem is established by a low **tT3/RT3 ratio**, which has a ten times-greater prognostic significance than elevated RT3 alone.[77] This ratio is our best indicator of thyroid hormone signaling; to some, it seems even a better marker of euthyroid status than TSH.[78]

Inhibitory Thyroid Hormones: The Actions of RT3

Many ideas are proposed to explain ESS/NTI. "Occam's razor" states the simplest of these is the most likely to be valid: ReverseT3 inhibits the effects of thyroid hormone. Lying buried in the medical literature is a surprising amount of evidence supporting this hypothesis.

The existence of an inhibitory thyroid hormone-metabolite was recently proven with the discovery that 3-iodothyronamine (3-T1AM) can ➤

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rapidly and reversibly cause tissue-hypothyroidism.[181,182] The validity of these observations is generally accepted. Reverse T3 is a parent molecule of 3-T1AM, but the accumulated evidence that RT3 also is thyroid-inhibitory has not been reviewed in a publication. Here's a brief summary.

Inhibitory effects of RT3 were reported in some of its earliest studies.[183-186] Its hypometabolic effect comes partly from antagonizing the actions of T3.[187] Perfused RT3 blocks the genomic effects of T3 at a number of hepatic thyroid-response (T3-stimulated) genes.[188] Studies show T3 cannot displace RT3 that is bound to the nuclear thyroid-receptor – and vice-versa.[189,190] Thus, RT3 and T3 have the same relationship with the thyroid-receptor as do antihistamine and histamine at the histamine-receptor.

Reverse T3 exerts various non-genomic effects independently of T3.[191-193] Acting at critical regulatory effectors, RT3 deactivates both 5'-deoidinase enzymes that convert T4 to T3: Type-2[194-198] and type-1.[199-201] An active role for RT3 was indicated in a well-designed study by the administration of RT3 to volume-depleted dogs, which resulted in significantly elevated death rates.[202]

Intriguing evidence for the inhibitory role of RT3 comes from AIDS patients, whose infections almost uniquely lead to pathologically *low* values of RT3.[203,204] Low-RT3 and *not* high T3 correlated with their hyper-metabolic state and weight loss – apparently because their metabolism is disinhibited by the lack of RT3.[205] Conversely, greater RT3 has been associated with increased whole-body fat mass and decreased lean mass in healthy men.[206]

Pathology 202: Laboratory Tests for Dysfunctional Deiodination

Well, this is news to *nearly* everyone. How can we use the laboratory to validate complaints of patients who are dissatisfied with their response to levothyroxine – who may have, in effect, ambulatory ESS/NTI?[207] If so, the problem may be corrected.

Measuring ReverseT3 alone is insufficient, either to diagnose ESS/ NTI[208] or to monitor therapeutic response[209]; it is just the *denominator*. We rely upon the tT3/ RT3 ratio: It quantitates hormone effect at the thyroid receptor, comparing the binary and competitively antagonistic products of T4 deiodination. The ratio also minimizes some common concerns about thyroid testing, including observed non-Gaussian distribution[206] and vagaries of binding proteins (as long as we compare the *total* values of both!).

As an indicator of thyroid function, the tT3/RT3 ratio is as significant to the body as the annual profit/loss statement is to your practice. Think of T4 as representing billing, a necessary potential; consider T3 your collections, essential cash – and RT3 represents your operating costs. You *live* off the surplus!

Neither totalT3 nor RT3 is part of "standard thyroid panels"; they must be ordered separately. The tT3/ RT3 ratio is calculated with the values expressed in the same units. On request, LabCorp USA reports both tests (in ng/dL) and provides the ratio with a single order code: 002193. Your Rep can activate it for use in your online portal. The ICD-10 code for dysfunctional deiodination is E07.81. If you prefer to use Quest or any other lab, just contact them and *ask*.

"Normal" tT3/ tRT3 Ratio

What value is desirable? First, thyroid hormones are released from the thyroid gland in a 10:1 ratio: 90% T4, 9% T3 and 0.9% RT3.[65-67] Thus, the "baseline" ratio of T3/RT3 is 10. A lower value implies deactivation. But what is "good?"

Three studies measured and reported tT3/ RT3 in their healthy control groups: The average values ranged from 11.03 to 12.5 with narrow variation (+/- 0.5).[210-212] In contrast, groups of unhealthy people with metabolic syndrome *and* their age, BMI and TSH matched-controls had tT3/ RT3 of 8.8 and 7.3, respectively.[213] Following treatment results, I find my patients feel well in the 10 to 14 range and I believe it can or should be a bit higher in adolescents. In comparison, Patient 2 had a ratio of only 2.4 while taking only T4 – that is *unusually* poor.

Therapeutics 201: Options for Patients Who Fail to Benefit from T4

For years, my efforts to remove or remediate the above-listed causes of dysfunctional deiodination without using T3 were unsuccessful. Importantly, a 2012 review reported that *most* comparison trials indicate replacement with both T4 and T3 is superior to T4-only.[214] Now, responsible voices of endocrine experts have stated that combined T4 and T3 therapy can improve results for at least some hypothyroid patients.[215-217] The long-term safety of combined treatment has been demonstrated.[218]

The simplest and most generally acceptable method of adding T3 is demonstrated by Patient 2. Let's examine a few issues before moving to our next treatment option.

Replace Some T4 with T3: What Happens?

First, please understand that when TSH has been restored to "normal," adding T3 while maintaining the same T4 – even divided Q 12H – will fail. T4 must be reduced as T3 is added. This is why:

Continuing the same T4 that had "normalized" TSH as you add T3 will predictably suppress TSH. Abundant T4 and suppressed TSH can be expected to maintain so much RT3 production that even *robust* T3 cannot restore a good tT3/ RT3 ratio…that's "no joy."

Adding T3 to the treatment increases blood T3 values. Reducing the T4 dose decreases RT3 levels, because **95% of circulating RT3 comes from T4**-deiodination.[65] After replacing *some* T4 with T3, your patient has more T3 and less RT3, which improves and ultimately, can restore normal tT3/ RT3.[219]

How Much T4 Should We Replace?

Physiology informs us: People need *some* T4. It is the precursor of T3 and of RT3. In addition, T4 (like RT3) has many non-genomic functions.[220] Results of an ill-planned trial disregarding this fact validate the statement: People taking T3 with immeasurably low T4 do badly.[221]

The variable determining the amount of T4 we need to prescribe is the patient's *own* thyroid hormone production, which is 90% T4. If her gland is surgically absent or otherwise ablated, T4 replacement is essential – in my experience, at least 75 mcg daily. When hypothyroidism is mild, a person might need little added T4; she'll make some of her own if your T3 dose doesn't suppress TSH.

Patient 2 is a typical case: She arrived with normal TSH and robustly normal freeT4. It was safe to use the 5

mcg T4=1mcg T3 replacement. It was wise to make small steps as tolerated. **I recommend reducing the T4 dose to no less than 70% of the total thyroid replacement** until blood test results prove that ratio should be altered.

The "70% T4/ T3 30%" suggestion may surprise some readers. The healthy human thyroid produces only 10% T3. The *PDR* informs us that "natural" thyroid (desiccated thyroid extract, porcine USP – currently in medical literature "DTE") is only 20% T3. In fact, some endocrinologists advise giving no more than 5% T3 in combined T4 and T3 treatment.[222] Compared to healthy human thyroid or DTE thyroid, why give patients so much T3?

These people have dysfunctional deiodination; they need more T3 than "normal." Also, they are taking hormones orally and about 20% will *not* be absorbed.[223] Furthermore, some of the oral T3 is destroyed in the hepatic "first pass," for all of which we accommodate by following clinical indicators and blood values (discussed below). Reviewers have recommended individualized treatment for each patient,[214] and I certainly agree. Patient 2 is quite well now, currently taking 70% T4 and 30% T3.

Repeat for emphasis: For optimal T3 treatment results, WE MUST DIVIDE T3 DOSES. T3 has a short half-life.[224] In healthy people, a single T3 dose peaks at 2½ hours and reaches its nadir at 12 hours.[225,226] Our more-sensitive patients often prefer taking doses every 8 hours, as advocated by Osler in 1901.[120] Interestingly, I find that after switching from Q 12 hours to Q 8 hours, patients may require slightly less T3 daily.

Problems During T3 Escalation Are More Noticeable

The instructions given to Patient 2 (Figure 6) demonstrate a cautious T3 dose escalation, as though the patient were being given her initial thyroid replacement. Predictably, the problems associated with restoring thyroid function are more frequently and emphatically reported by patients taking *active* hormone. Some of these were discussed above, including issues of adrenal support, estrogen replacement, and interacting caffeine and stimulants.

Unlike Patient 2, some patients who fail T4 treatment would rather *not* become pregnant. Therefore, warning of increased fertility is an important part of informed consent-talk before adding T3. Everything seems to work better with good thyroid replacement, including every aspect of reproduction. Women can discover they were not menopausal, just amenorrheic due to poor thyroid function.

With correctly prescribed T3 treatment, two issues in particular can be remarkable. First, the potency and short half-life of T3 makes missed doses more consequential; people can feel the *lack* of it!

Patients also complain more often of anxiety, jitters, and tremulousness. Against expectation, it rarely occurs from too much T3 – their thyroid blood tests are usually fine. Before ordering labs, ask when the symptoms occur: If neither at peak nor trough – and the adrenals are supported – then reactive hypoglycemia is the probable cause, via the adrenergic counter-regulatory response. When excessive RT3 slows the metabolism, the glycemic and insulinemic responses are blunted. T3 "frees" the glucose to swing up and down, so it gets blamed; but the *real* problem is a sugary/starchy diet. I recommend a Mediterranean, Paleo, or ketogenic diet for most of my patients.

Other problems will be encountered: Even the best verbal and written instructions may be forgotten or ignored. Patients may not consider the dose-response curve when building T3. If too much makes one feel tired again, he can choose to take more – and upon feeling worse, *still* more!

People may build their T3 dose to greater than optimal – or ignore your directions and take more than you had recommended. Mildly high T3 may feel stimulating for a few people but it is risky; don't consent to it.

When patients get "too busy" to come back for follow-up, it implies they feel well but it bodes ill. The lack of follow-up is never desirable – especially when taking T3.

For these reasons, schedule a timely follow-up appointment for your patients, preferably before they leave your office with the Rx for T3. Hold them to keeping it! It is wise to prescribe no more tablets than will be sufficient to allow for a couple of goofs and one reschedule; limit their refills to ensure safety. A test to validate the dose is needed before authorizing multiple Rx refills is sensible.

A final caution: Low tT3/RT3 ratio is adaptive in some circumstances.[227] A rare patient "needs" low tT3/RT3 and if so, T3-treatment can "dis-inhibit" protective adaptation. Two patients have been intolerant of even tiny doses of T3: One had received multiple courses of cancer chemotherapy; the other took four mitochondria-toxic psychoactive medications. I believe their elevated RT3 was adaptive, and my efforts were misdirected.

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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.

Natural Approaches for COVID-19 and Its Many Mutations

by Sue Visser

The COVID-19 pathogen is elusive and to call it just a virus does not tell the whole story. Exclusively targeting cures and vaccines for an ever-mutating virus is frustrating enough. It offers no support for the patient in any other way, especially if they have a weakened immune system and have pre-existing co-morbidities. The reason that ivermectin is having a universally victorious run is because it addresses parasites as well as COVID-19 and has anti-inflammatory effects. Similar properties are common to a number of other naturally occurring substances. The world has faith in ivermectin as a result of the extensive patient trials to demonstrate its in vitro and in vivo effects to prevent as well as treat COVID-19.

Some people are more susceptible to the COVID-19 virus and its entourage of pathogens due to nutrient deficiencies or lifestyle-related and other co-morbidity factors and already take a lot of medications. According to herbalists and naturopaths I talk to, ivermectin offers a more viable option to vaccines. One doctor said that "more people may die as a result of taking the vaccine than being infected." He combines medical treatments with supplements and herbs like artemisia, olive leaf, *Nigella sativa* among others and has also found them to be very helpful during the pandemic. We call him Doctor Gadget because he relies on biofeedback devices for diagnostics and a Rife resonator for most of his treatments. He, like many of my doctor friends, shares my passion for integrative medicine. Ironically, many of our modern drugs are derived from natural sources. Where would we be without the willow tree that provides salicylic acid for aspirins that are still used as blood thinners! And now ivermectin, derived from avermectins that are naturally occurring compounds derived from soil-based organisms.

Herbs that have been used for thousands of years to treat a broad spectrum of microbes, pathogens, and parasites have always been there for us. Some are shown to be effective against COVID-19, plus they can help to reduce inflammation, support cardiovascular health, lower blood sugar, and facilitate weight loss as well as relieve hypoxia and other breathing issues. Others can improve thyroid function, fight cancer, and so on. Introducing more of these natural anti-viral multitaskers to the world of science is an exciting prospect. Obviously, all the material needs to be reviewed extensively, as is the case with ivermectin. A growing number of scientific studies have already shown that the leaves of *Artemisia annua*, which can be ingested in capsules, extracts, or teas, have significant activity against COVID-19 and parasites, especially tapeworms – as well as against inflammation, fevers, breast cancer, and prostate cancer without any serious side effects.

A year of raising false hopes with highly acclaimed big hitters such as hydroxychloroquine or remdesivir has done little to boost the credibility of modern medicine. Trying to create vaccines against an ever-mutating virus makes no sense, especially when doctors say they are not even 25% effective against the newly mutated strains. Side effects include the possibility of being disabled and even killed by them. We know this has been the case, with growing statistics. Our hopes for better treatments have been raised by research teams who continuously examine both new and existing drugs for potential treatments against our common enemy, COVID-19. The Front Line COVID-19 Critical Care Alliance (FLCCC), for instance, was created in March 2020. It is led by Professor Paul E. Marik to examine incoming research to develop a treatment protocol for COVID-19. The FLCCC now recommends ivermectin, a repurposed anti-parasitic drug for both the prophylaxis and treatment of COVID-19. They maintain it should be systematically and globally adopted due to its impressive performance. Remedies such as ivermectin that not only eliminate viruses and parasites but also reduce inflammation can also assist us with respiratory, metabolic, and cardiovascular issues and could pave the way to an even more successful outcome in the future.

What Is ACE2 and Why Is It Associated with Staving Off Cytokine Storms?

Firstly, what is a molecular bonding potential? Thousands of drugs, herbs and chemicals are screened to determine their molecular bonding potential. This is their ability to latch onto angiotensin 2 enzyme (ACE2) receptor sites that are present on protein spikes of the COVID-19 virus that it uses to bind to target cells. The

greater the presence of hydrogen links, the higher the bonding rate, or score. It is the highest common factor used in laboratory testing around the world to determine the anti-covid potential of a substance. The remedies we hear about – remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, Artemisia and so on – are thus selected and then tested in vitro to demonstrate their knockout potential against the COVID-19 virus.

ACE2 (anti-inflammatory) is expressed in tissues that include alveolar epithelial cells within the lungs, pancreatic beta cells, and enterocytes of the small intestine to ward off the ravages of inflammation. The nose and mouth are known to have high levels of ACE2 receptors. Prolonged angiotensin 2 (pro-inflammatory) expression remains a troublemaker of note. It plays a key role in the renin-angiotensin-aldosterone system (RAAS), a pro-inflammatory trigger that drives insulin resistance and cardiovascular problems. It is degraded by the ACE2 enzyme into angiotensin 1–7 (ACE 1-7) that is anti-inflammatory, to reduce insulin resistance by decreasing cellular oxidative stress, enhancing insulin signalling and insulin-stimulated glucose transport activity. It thus reduces inflammation as well as vasoconstriction and blood clotting by reducing RAAS activation.

Does a High Molecular Bonding Score Exclusively Justify the Widespread Use of a Remedy Against COVID-19?

Early achievers with good bonding scores were the anti-malarial drugs - chloroquine and hydroxychloroquine.[1] They fell out of favor after months of heated debates as to their safety and efficacy. When used in vivo (on live patients), their success rates varied, depending on the accompanying zinc and vitamin D supplements and antibiotics such as Zithromax.[2] Some patients recovered, others didn't. As a much-acclaimed preventative measure against the COVID-19 pandemic, hydroxychloroquine slunk out of the limelight. It was only a matter of time before serious shortcomings and adverse effects (SAE) began to emerge. Other results from therapeutic trials done on medicines thought effective for COVID-19 found a lack of impact on mortality with the use of remdesivir, lopinavir/ritonavir, interferon, convalescent plasma, tocilizumab, and monoclonal antibody therapy. Stipulating a lengthy testing period to demonstrate the safety and efficacy of such remedies is an inhibiting factor and their premature release seems to be unjustified.

Doctors became wary of prescribing hydroxychloroquine because of the way it caused electrolyte imbalances that affected the cardiovascular health of susceptible patients. Often the traditional dosage needs to be stepped up and this poses further risks to patients. Arteminisin fell out of favor due to insufficient in vivo trials, and novel drugs never seem to move out of their test tubes and into the marketplace. (Arteminisin is an extract of *Artemisia annua*). As an isolated chemical it is not effective against COVID-19. However, the entire herb works synergistically and has convincing anti-viral as well as anti-parasitic properties.)

Treatments That Can Assist COVID-19 Patients

Ivermectin, olive leaf, artemisia, and *Nigella sativa* (kalonjie or black cumin seed) are remedies that have bonding scores similar to and even higher than hydroxychloroquine. But they excel because they are not exclusively anti-viral drugs. Their effects encompass the control and elimination of associated parasites – the hiding places, the transport, and accommodation that larger parasites such as tapeworms provide for viruses!

By encompassing the lowest common denominators, we can potentiate treatments for the COVID-19 virus, its complications, its mutations and the entourage of accommodating parasites that sabotage our health in general. The work of the late naturopath Hulda Regher Clarke outlines the relationship that viruses have with their not-so-charming parasite hosts in great detail.[3] Who would have known that adenoviruses, for instance, have a close relationship with tapeworm eggs and cysts? They evade the immune system within these snug little vehicles that create misleading surface antigens to outwit the immune system.[4] (I assume that the same applies to the COVID-19 strain and its mutations.) I know of doctors who have averted the common cold for decades by paying attention to the regular elimination of parasites – especially flukes, worms, and other hosts of adeno- and coronaviruses that cause colds and flu.

Parasites harbor and transport viruses, including adeno- and coronaviruses.

Hulda Regehr Clarke maintained that it is the exposure of mold, especially aspergillus, that sets off our resident adeno- and coronaviruses hordes to produce colds and flu. She said that vitamin C kills mold and that is why we take it in mega doses to forestall an oncoming cold. Although we still cannot find an effective vaccine against these viruses – let alone a cure for the common cold – getting rid of sources of mold in our diet and environment can help to shush the viruses. Exposure to mold may have contributed to large outbreaks of COVID-19, so up the vitamin C when you suspect there is mold in the area. And clean it off tiles, drains, toilets, and showers with bleach or spirit vinegar.

Now we know! Getting rid of parasites helps us to reduce our microbial load and, hence, our vulnerability to these viruses. Parasites deplete us of vital nutrients such as minerals and antioxidants that support our immunity against viruses, especially zinc. This is why remedies that have high bonding scores for COVID-19 (anti-viral ability) that also eliminate parasites – especially tapeworms, are so helpful – especially if they have anti-inflammatory effects. Ivermectin was originally developed to rid animals of ➤

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parasites and thus provides additional benefits apart from its antiviral and anti-inflammatory ability. Pork-eating communities are riddled with tapeworm, so it is no surprise that ivermectin is gaining the upper hand in South American countries.

The herb artemisia (wormwood/ *Artemisia annua* and *afra*) packs a punch against viruses and parasites.[5] In April, the California biotech company Mateon Therapeutics announced in a press release that tests showed artemisinin inhibited the replication of SARS-CoV-2, the novel coronavirus that causes COVID-19.[6] A powerful body of scientific evidence, built over the last 40 years, has revealed that the components in the leaves of *Artemisia annua* are highly active against a broad range of human diseases, including viruses, parasites, and cancers. This natural herb contains a range of active compounds that make it a naturally occurring, side-effect free, combination therapy for malaria, fevers, hot flushes, and COVID-19 symptoms. It has been used as a herbal medicine for over 2000 years and has an excellent safety record. Pregnant or breastfeeding women and infants should not take artemisia/wormwood. Artemisia is called wormwood and the early trials in China last year, although anecdotal also showed its efficacy as an anti-viral agent as well as worm and parasite eliminator.

Olive leaf has a number of therapeutic effects, including lowering blood pressure, improving insulin functionality, warding off colds and flu, and eradicating viruses – including COVID-19, microbes, and parasites.[7] It does not wipe out beneficial gut flora and is deemed safe for pregnancy and breastfeeding. Unlike many of the popular anti-malarial drugs, no drug resistance has been reported with olive leaves. The most studied active components of olive leave are oleacein and oleuropein; but in nature, the synergy from the entire leaf or plant component is always more effective than its mere extracts.

Nigella sativa. In vitro studies have shown that it can decrease the replication of severe acute respiratory syndrome coronavirus (SARS-CoV). Some of its components have a high affinity to many SARS-CoV-2 proteins and enzymes. The main active constituent found in kalonjie (*Nigella sativa*) is thymoquinone – a volatile oil that comes from these tiny black seeds. In a 2016 study kalonjie oil was found to have anti-influenza viral activity. For the COVID-19 protocols, 1 teaspoon twice a day was used to good effect. Black cumin has immune-suppressing (in states of inflammation) or immune-boosting (in states of infection) abilities that play a key role in protecting us from pathogens as well as cytokine storms. Benefits include immunomodulation, anti-inflammatory and antioxidant, anticancer, hypoglycemic, antihypertensive, and anti-asthmatic effects. It has a broad antimicrobial spectrum, including malaria, Gram-negative, Gram-positive bacteria, viruses, parasites, Schistosoma (bilharzia), and fungi. Apart from helping to control pain, epilepsy, Parkinsonism, and anxiety, black cumin (kalonjie) improves learning, memory, and alertness and is mood elevating.

Biofilms also harbor viruses and bacteria that are protected from the immune system within the coating of mucus they provide.[8] Eighty percent of chronic infectious diseases are mediated by biofilms that result in persistent inflammation and tissue damage. Interrupting quorum-sensing pathways, used by bacteria and other germs to communicate, will inhibit biofilms from forming in your mouth, lungs, and intestines in the first place. Iodine and anti-parasitic/anti-microbial herbs such as olive leaf and artemisia, also penetrate biofilms and effectively help to control many potentially infectious diseases such as malaria that are beyond the scope of regular meds and antibiotics.[9,10]

Every 17 minutes, blood that circulates around our iodine reserves in breast and thyroid tissue is treated to a blast of iodine in order to kill off microbes on a continuous basis, providing we do not have an iodine deficiency. We can also use iodine topically and in mouthwashes and nasal sprays as it is a broad-spectrum germ and virus killer of note. Studies from the Connecticut School of Medicine suggest that even a weak concentration of 0.5% of iodine could completely inactivate the COVID-19 virus.

Some foods, herbs, and essential oils have been shown to inhibit quorum sensing and are referred to as QS inhibitors. Essential oils, especially clove oil contain solvents called phenols which may enable them to cut through biofilms throughout the body. Essential oils also kill off viruses, bacteria, parasites and fungi. Tea tree and eucalyptus essential oils are effective against *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *E. coli*, *Pseudomonas aeruginosa*, and *Candida albicans* biofilms. Eucalyptus, peppermint, clove bud, tea tree, and lemongrass essential oils have been used safely and effectively both topically and internally, for instance, in Lyme disease patients diagnosed with biofilm colonies.

Basic Deficiencies of Glutathione, Zinc, Vitamins C and D

There seems to be a link between insulin resistance and the severity of COVID-19 to patients who suffer from cardiovascular problems, elevated blood sugar, metabolic disorders, and other debilitating conditions that require chronic medications. These patients are unable to control glucose levels in their bloodstream and are very vulnerable to hyper inflammation, vasoconstriction and blood clots even prior to the ravages of COVID-19. Last year, one of the few convincing, life-saving treatments for COVID-19 was the use of corticosteroids as outlined by Dr Horby.[11] Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus infections, strongyloidiasis, pneumonia or tuberculosis). Cortisone is helpful, a lifesaver from raging inflammation, and has been very helpful against cytokine storms. However, we need certain micronutrients to maintain our immune system; and it is as a result of these deficiencies that patients get into trouble in the first place.

Dr Horowitz, renowned for his Lyme disease research, suggests that we address a glutathione deficiency as a causative factor for a respiratory crisis.[12,13] He found that after an hour of glutathione administration to his patients who were unable to breathe, they experienced dramatic, almost immediate relief. "Although anecdotal," he said, "I have heard from patients who were on n-acetylcysteine (NAC) and glutathione after exposure to COVID-19, that they did not get sick or test positive for the virus, when others around them did." Glutathione is one of the body's master antioxidants and plays an important role in our defenses to regulate cytokine responses and immunity. It is a small protein molecule composed of three amino acids: cysteine, glutamate, and glycine, called GSH precursors or building blocks.

Humans do not make their own vitamin C because glutathione is our primary antioxidant. Vitamin C supplements support glutathione and are being used extensively to help COVID-19 patients. While physicians and researchers are studying the effects of high-dose intravenous (IV) vitamin C, some doctors are adamant that no supplement, including vitamin C, can prevent or treat COVID-19. Oral glutathione supplements that include bioavailable precursors such as vitamin C and N-acetylcysteine can effectively increase glutathione production and hence improve the outcome of patients. For the emergency treatment of coronavirus-infected patients, some forms of glutathione can be inhaled into the lungs or used trans-dermally or intravenously. A dose of N-acetylcysteine immediately loosens up a tight mucous-bound chest.

Zinc plays a central role in the immune system and is one of the most effective ways to reduce inflammation and deactivate the replication of the coronavirus's RNA. Zinc also reduces the risk of bacterial co-infection, especially against *Streptococcus pneumoniae* infection (considered the most common cause of pneumonia), tuberculosis, HIV AIDS, measles and malaria. Zinc supports the respiratory epithelium and assists the clearance of mucus. A severe zinc deficiency has been observed in 80% of patients who were admitted to hospital with severe COVID-19 related complications. Supplementation with 10 mg zinc gluconate in Zn-deficient children resulted in a nearly twofold reduction of the number of episodes of acute lower respiratory infections and hastened their recovery.[14] As an ionophore or zinc facilitator, quercetin assists zinc as an alternative to hydroxychloroquine and is a safer option. A loss of taste and smell indicates a zinc deficiency, as does small white flecks on the fingernails. Daily recommended doses range from 15 – 20 mg for adults.

A loss of taste and smell indicates a zinc deficiency.

Vitamin D deficiencies are linked to weakened immunity, especially during phases of lockdown when people are denied a daily dose of sunshine. Countries with high COVID-19 mortality rates seem to have higher levels of vitamin D deficiency compared to countries that were not as severely affected by COVID-19.[15] Patients with low vitamin D levels who are infected are more vulnerable to hyper-inflammation, cytokine storms, and respiratory complications. Research suggests that vitamin D could play a role in the prevention and treatment of co-morbidities such as type 1 and type 2 diabetes, hypertension, and multiple sclerosis. The recommended dietary allowance (RDA) for vitamin D is 600 IU, but some supplements suggest 5,000 or 10,000 IU per day.

Quercetin is a natural antihistamine and anti-inflammatory plant pigment that boosts the immune system. It helps zinc to exert its antiviral effect on COVID-19 and is a better alternative to hydroxychloroquine as an ionophore.[16] This helps to kill viruses as well as inhibiting replication of already infected cells. It helps to fight obesity, high blood pressure, and insulin resistance. It also prevents blood clotting - a critical factor for COVID-19 patients.

In January 2021, the FLCCC update recommends the following supplements for use in conjunction with ivermectin[17] (0.2 mg/kg per dose. One dose daily for a minimum of 2 days and a maximum 5 days):

- Vitamin D3 (4000 IU) and zinc (100 mg per day) and aspirin (325 mg), unless contraindicated.
- Vitamin C (2,000 mg) plus quercetin (250 mg twice a day).
- Melatonin (10 mg before bedtime as it causes drowsiness).

***Coleus forskholii* and Licorice**

Coleus forskholii is an herb that has been used for treating respiratory complications for over 3000 years, yet little attention has been paid to the way it could assist COVID-19 patients. It can assist patients with breathing difficulties, inflammation, and obesity. Today coleus is mainly used to assist weight loss by breaking down adipose tissue and preventing production of further fatty tissue. It contains forskolin, a chemical that activates cyclic AMP to help treat hypertension, mild congestive heart failure, asthma, psoriasis, digestive problems, glaucoma, and persistent urinary infections.[18] It has anti-inflammatory and antihistamine properties and is soothing to the nervous system. The anti-hypertensive properties of coleus forskolin were confirmed in a 2011 study by the *Journal of Research in Ayurveda*.[19] It was also found to be an efficient treatment for angina or chest pain. A 2009 study, published by Natural Product Communication, indicates that it also has activity against the HIV virus. We look forward to more studies to confirm these effects on COVID-19 patients.

Coleus forskholii can increase stroke volume, which is the amount of blood pumped with each heartbeat. It was shown to reduce the risk of blood clots, and it lowers high blood pressure by relaxing the arterial walls.[20] Being a bronchodilator with an antihistamine action, it could be useful for breathing difficulties to reduce airway resistance

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and increase air volume capacity of the lungs. For patients with obesity and insulin resistance, it stimulates the metabolism by increasing thyroid hormones and promotes the secretion of insulin, helping to lower glycated hemoglobin. A double-blind test found that people taking forskolin showed an increase in fat loss over those taking a placebo, as well as an increase in lean body mass and bone density. A boon for obese patients!

Licorice root extract has also shown potential as an antiviral to treat the new coronavirus, according to an initial study by researchers in Beijing.[21,22] It functions as an antioxidant and has antidepressant, neuroprotective, anti-inflammatory, and therapeutic effects on patients with heart disease. It regulates aldosterone to maintain a balance between sodium and potassium and this helps to prevent dehydration. Napoleon marched his troops across the desert and licorice prevented a dry mouth (a lack of saliva), a dry cough, dehydration, and fatigue. Anecdotal – but good to know!

Repurposing Well-Established Drugs for COVID-19

Researchers are currently repurposing drugs that are ongoing patent remedies for bipolar disorders, alcohol abuse, diabetes, scabies and cataracts, etc. as anti-COVID-19 cure-alls. The molecular bonding affinity of well-known patented drugs as potential remedies for treatment as well as preventative agents for the COVID-19 pandemic circumvents the need for dosage guidance and safety trials. Ivermectin was identified as having one of the highest or among the highest of binding affinities to spike protein S1 binding domains of SARS-CoV-2 among hundreds of molecules that were collectively examined. Ivermectin is a treatment for roundworm, hookworm, and tapeworm infections as well as scabies and rosacea. It kills parasites by super-relaxing them, so they lose their grip on the host. Originally intended as a veterinary drug, ivermectin has become a popular drug for humans as well, being invaluable for treating river blindness and a large variety of flukes and worm infestations.

When ivermectin was widely distributed among populations in 2020 with a high incidence of COVID-19 infections, the results of its efficacy as both a prophylactic and therapeutic remedy were carefully scrutinized by the FLCCC after extensive patient trials in South America, India and other regions; and the whole world took note.[23,24] The FLCCC concluded that ivermectin is a cheap, affordable remedy to prevent the transmission and development of COVID-19 disease in those exposed to infected patients. Ivermectin is classified as a GABA-agonist.[25] In other words it works as an activator of GABA, our chief inhibitory neurotransmitter. They reported that ivermectin also hastens the recovery of patients and prevents the deterioration of those with mild to moderate disease if treated early after symptoms appear. Mortality in critically ill patients with COVID-19 was reduced with lower case-fatality rates in regions with widespread use of ivermectin in the select regions.

The post-viral/chronic fatigue syndrome with disabling symptoms such as fatigue, shortness of breath, joint pains and chest pain, impaired memory and "brain fog" are often a problem. The FLCCC ivermectin trials indicated a recovery rate of 87.9% of the patients after two doses. They claim that "the safety of ivermectin is nearly unparalleled given its near nil drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered." Paul Marik, MD, FCCM, FCCP, founder of the alliance and a professor and chief of the division of pulmonary and critical care medicine at Eastern Virginia Medical School added that ivermectin "is a safe drug that is exceedingly cheap." He agreed that "what is truly remarkable – this was a gift to us – ivermectin has high activity against COVID-19."[26]

SAHPRA, the South African Health Products Regulatory Association, was unable to confirm the efficacy of ivermectin against the COVID-19 virus during its patient (in vivo) trials. Despite the public outcry demanding its use against COVID-19, the regulators insisted that it is not effective at the recommended dose. Days later they withdrew their objections and placed the responsibility in the hands of the doctors who would be prescribing this drug. The biggest problem here is that ivermectin for human use is hard to obtain and now farmers and unscrupulous dealers are selling veterinary versions of ivermectin at exorbitant prices and the dosage guidelines are for animals, not humans. In South Africa, I was offered a few syringes of it from an online dealer – but I am not a cow or a pig! The United States Food and Drug Administration warns members of the public not to self-medicate with ivermectin products intended for animals.

Ebselen is another useful repurposed drug to look at for COVID-19-related benefits. In the past, doctors have used Ebselen to help treat bipolar disorder, cataracts and hearing loss. Recent studies show that it inhibits the virus's main protease (Mpro).[27,28] As a consequence, scientists have already shown that Ebselen is safe. It also exerts a powerful antibacterial effect on drug-resistant strains like *Staphylococcus aureus* and significantly reduces elusive biofilms. It doubles up as an anti-inflammatory and can reduce cytokine levels. Ebselen is a selenium-based organic complex, which can mimic the activity of glutathione peroxidase. It is a strong antioxidant, which increases the efficiency of glutathione and has a strong neutralizing effect against free radicals, especially when it comes to inflamed airways.

Antabuse, a drug that is commonly used for treating alcohol abuse offers a number of benefits as a treatment for SARS-CoV-2.[29,30] The generic is called disulfiram and as previously demonstrated in vitro with SARS and MERS coronaviruses, it inhibits the main coronavirus protease (Mpro) and stops it from replicating. It also helps the body to compensate for a loss of glutathione. As we now know, a glutathione deficiency (antioxidant, anti-inflammatory, anti-

viral) is the leading cause of respiratory distress and cytokine storms. The drug is not expensive and has the advantage of doubling up as a treatment for alcoholics. For South Africa this has additional benefits, as many of the specially appointed coronavirus/ pandemic beds are occupied by the victims of alcohol abuse.

Caveats, Drug Interactions, and Contraindications

Ivermectin has a number of potentially serious drug-drug interactions. Please check for potential drug interaction at Drugs.com: "Ivermectin Drug Interactions." The most important drug interactions occur with cyclosporin, tacrolimus, anti-retroviral drugs, and certain anti-fungal drugs. With ivermectin, numerous studies report low rates of adverse events, with the majority mild, transient, and largely attributed to the body's inflammatory response to the death of the parasites and include itching, rash, swollen lymph nodes, joint paints, fever and headache. Serious events occurred in less than 1% and were largely associated with administration for Loa loa parasites, causing paralysis and possibly death.

Ivermectin has been used safely in pregnant women, children, and infants. We are reassured that ivermectin is safe because it does not cross the blood brain barrier. But if you have the MDR1 gene that allows ivermectin to enter the brain, it causes neurological damage that could result in coma and death. (I would presume that ivermectin is only guaranteed to be safe if you don't have this condition and your blood brain barrier is perfectly intact. Investigating this potential may be a good idea prior to taking it.) If ivermectin is given at high doses (in which case, brain levels peak 2–5 hr after administration), it may enter the brain. When given simultaneously with CYP3A4 inhibitors that include statins, HIV protease inhibitors, many calcium channel blockers, and glucocorticoids such as dexamethasone, lidocaine, and the benzodiazepines, then there is no guarantee that ivermectin will stay out of the brain.

The anticoagulant warfarin would require dose monitoring. Another special caution is that immuno-suppressed or organ transplant patients who are on calcineurin inhibitors such as tacrolimus or cyclosporine or the immunosuppressant sirolimus should have close monitoring of drug levels when on ivermectin given that interactions exist which can affect these levels.

Natural or herbal remedies and supplements usually carry no serious risks or side effects but may duplicate the effects of medications if taken concurrently. Olive leaf, black cumin, artemisia, and *Coleus forskholii* also lower blood pressure, reduce blood sugar, and prevent blood clots; so we are warned not to take these herbs with medications that do likewise. If you wish to use them instead, do not immediately stop taking your medication. First discuss your drug-weaning schedule with a practitioner, so the drugs can be stepped down in alternate phases while the dose of the herb is increased.

Olive leaf is safe to take in conjunction with a flu shot, histamine blockers, and traditional cold medications. Unlike over-the-counter remedies, which have been shown to be detrimental to the health of young children, olive leaf may be used by persons of all ages. Laboratory experiments performed on live tissue and animals and use by thousands of humans have shown the leaf components to be extremely safe and non-toxic. In addition, recorded medical use since the early 1800s makes no mention of adverse side-effects. While being one of the safest herbs to take, the effects of concentrated extracts on disease microbes, blood pressure, and blood sugar make it wise to follow a few guidelines when taking it, especially for the first time. A Herxheimer of die-off effect causes nausea, diarrhea, or vomiting while toxins and parasites are being purged. [31]

Artemisia is not suitable for pregnant or lactating women. Users report it as a safe drug to use. There are no severe adverse effects associated with the drug when used within the recommended dosage level.[32]

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

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The VICTAS Trial: Designed to Fail

by Michael Passwater

Orthomolecular Medicine News Service

A recent clinical research article concludes, "Among critically ill patients with sepsis, treatment with vitamin C, thiamine, and hydrocortisone, compared with placebo, did not significantly increase ventilator- and vasopressor-free days within 30 days. However, the trial was terminated early for administrative reasons and may have been underpowered to detect a clinically important difference."[1] For some medical professionals, that study is proof that "HAT Therapy" (Hydrocortisone, Ascorbic acid, Thiamine), and vitamin C is not helpful in the treatment of sepsis. But such a conclusion is a dangerous over-generalization of the study's findings.

Rather than focus on the early termination of the study, a more concerning aspect is its design. The treatment for the subjects included in the analysis was not required to begin quickly. The study treatments were given many hours (median 14.7) after subjects' sepsis symptoms worsened into cardiovascular or respiratory failure. The intravenous (IV) vitamin C dose was limited and fixed at 1.5 g every six hours (86 mg/kg/day; 6 g per day for a 70 kg subject), and the duration of treatment was limited to four days. The protocol did not require measurements of vitamin C, thiamine, or cortisol in study subjects before, during, or after treatment, and no measurements were reported in the article. Further, no measures of other co-nutrients were included. For instance, a low vitamin D level is an established biomarker of all-cause mortality in the ICU setting.[2] Low zinc, magnesium, and selenoprotein levels, as well as anemia, have also been associated with poor outcomes in critical care, including viral sepsis.[3-8] The article does not say whether the treatment and control groups were balanced at study entry with respect to vitamin C and other nutrient levels, nor whether adequate vitamin C was given to maintain plasma levels in the therapeutic range during the study. The "Limitations" section of the article acknowledges "...a higher dose or dosing based on plasma vitamin C concentrations might yield different results."

In both the test and control arms of the study, the per protocol mortality before ICU discharge was 16.6% and 17.0% respectively (p=0.91), and at 180 days was 39.5% and 36.8% respectively (p=0.57). Neither standard treatment nor the delayed addition of low dose IVC for a short duration improved the poor survival of sepsis in this study. The overall conclusion that one can draw from this VICTAS trial is that vitamin C is safe, but that too little, too late, for too short of a duration is inadequate.

Fifty years ago, Dr. Frederick R. Klenner published a summary of his experience and prior publications.[9] He encouraged a daily IV dose of 350 - 700 mg vitamin C per kg of patient body weight (25,000 - 50,000 mg for a 70 kg / 154 lb subject), increasing the dose and frequency as necessary until the patient recovered:

> It is a demonstrated principle that the production of histamine and other end products from deaminized cell proteins released by injury to cells are a cause of shock. The clinical value of ascorbic acid in combating shock is explained when we realize that the deaminizing enzymes from the damaged cells are inhibited by vitamin C. It has been shown by Chambers and Pollock[10] that mechanical damage to a cell results in pH changes which reverse the cell enzymes from constructive to destructive activity. The pH changes spread to other cells. This destructive activity releases histamine, a major shock producing substance. The presence of vitamin C inhibits this enzyme transition into the destructive phase. Clark and Rossiter[11] reported that conditions of shock and stress cause depletion of the ascorbic acid content of the plasma. As with the virus bodies, ascorbic acid also joins with the protein factor of these toxins effecting quick destruction. The answer to these emergencies is simple. Large amounts of ascorbic acid 350 mg to 700 mg per kg body weight given intravenously. In small patients, where veins are at a premium, ascorbic acid can easily be given intramuscularly in amounts up to two grams at one site. Several areas can be used with each dose given. Ice held to the gluteal muscles until red, almost eliminates the pain. We always reapply the ice for a few minutes after the injection. Ascorbic acid is also given, by mouth, as follow up treatment. Every emergency room should be stocked with vitamin C ampoules of sufficient strength so that time will never be counted-as a factor in saving a life. The 4 gram, 20 cc ampoule and 10 gram 50 cc ampoule must be made available to the physician.

The CITRIS-ALI study used 50 mg vitamin C per kg patient weight per treatment (200 mg/kg/day; 14g per day for a 70 kg subject) – more than double the dose used in the VICTAS Trial – yet less than one third of the upper range promoted

by Dr. Klenner. Moreover, the CITRIS-ALI study showed a clear survival benefit (mortality was a secondary endpoint in that trial).[12] This dose of 200 mg/kg/day was also used by the earlier Phase I safety trial of IVC in sepsis.[13]

Why, years later, did the VICTAS Trial choose to use less than half that dose? What would happen if a trial was done using efficacious doses – those shown for over 70 years to help real people recover from critical illness? Doctors who utilize this protocol don't go back to treating patients without it.

In the January 20, 2021 OMNS article "The Treatment of Infectious Disease Using Vitamin C and Other Nutrients," Margot DesBois nicely covers the early history of IVC use in serious illness.[14] In addition to Drs. Frederick Klenner, Claus Jungeblut, Robert Cathcart, and William McCormick, more recent clinical medicine pioneers, including Drs. Hugh Riordan, Ron Hunningshake, AA Fowler, Paul Marik, and Joseph Varon, can be added to the list.[15-21]

Of note, the most successful published protocol for COVID-19 hospital treatment in the USA includes 3 g IVC per dose along with a corticosteroid and thiamine every six hours, and the use of 25 g IVC doses if rescue therapy is needed. And the treatments are not stopped at 96 hours. The idea that giving vitamin C beyond 96 hours might be dangerous has no scientific or clinical basis. See the full COVID-19 treatment plan,[22] and the Riordan Clinic IVC protocol.[23]

As a reminder for those conducting and reviewing nutrient research, here are "rules" published by vitamin researcher Robert P. Heaney.[24]

The VICTAS Trial[1] satisfied none of these five rules for conducting nutrient research.

Box 1 Rules for individual clinical studies of nutrient effects.

1. Basal nutrient status must be measured, used as an inclusion criterion for entry into study, and recorded in the report of the trial.
2. The intervention (i.e., change in nutrient exposure or intake) must be large enough to change nutrient status and must be quantified by suitable analyses.
3. The change in nutrient status produced in those enrolled in the trials must be measured and recorded in the report of the trial.
4. The hypothesis to be tested must be that a change in nutrient status (not just a change in diet) produces the sought-for effect.
5. Co-nutrient status must be optimized in order to ensure that the test nutrient is the only nutrition-related, limiting factor in the response.

Box 2 Rules for study inclusion in systematic reviews and meta-analyses.

1. The individual studies selected for review or meta-analysis must have met the criteria listed in Box 1 for nutrient trials.
2. All included studies must have started from the same or similar basal nutrient status values.
3. All included studies must use the same or closely similar doses.
4. All included studies must have used the same chemical form of the nutrient and, if foods are used as the vehicle for the test nutrient, all studies must have employed the same food matrix.
5. All included studies must have the same co-nutrient status.
6. All included studies must have had approximately equal periods of exposure to the altered intake.

Recent research has shown the importance of vitamin C in sepsis and other acute life-threatening illnesses. Vitamin C has a multitude of essential for life effects within the human body, and due to its short half-life, is often the rate limiting factor in these biochemical processes. It is the primary extracellular antioxidant and is important for scavenging damaging electron radicals. At very high levels it is involved in redox regulation, is a pro-oxidant, and can cause DNA and/or protein damage. This is useful in the treatment of cancer. It is an essential co-factor in the synthesis of catecholamines, vasopressin, steroids, neuropeptides and some neurotransmitters. It is also essential in the synthesis of collagen and elastin – which are important

Why did the VICTAS Trial use less than half the dose used in the CITRIS-ALI Study?

molecules throughout the body, including in arteries and joints. Vitamin C is also important for epigenomic regulation of genes and is necessary for many cell types of the adaptive immune system. These biochemical functions are essential for improved immune cell function, endothelial cell function, hemodynamics (circulatory function), and wound healing.

Stress, including cold temperatures, toxins, infections, and trauma greatly increase the cellular demand for vitamin C and disrupt the body›s ability to recycle oxidized vitamin C (dehydroascorbic acid or DHAA) back into the reduced form of vitamin C (ascorbic acid). Vitamin C has a short half life in the body (minutes to hours). In 2008, the prestigious journal *Cell* published the discovery that the red blood cells of humans (and other mammals unable to produce vitamin C) express a large number of GLUT1 transporters – more GLUT1 than on any other human cell type.[25] These GLUT1 transporters are apparently misnamed, as they might more properly be called DHAA1 transporters. The human RBC GLUT1 transporter is co-expressed with the protein stomatin which switches it into a DHAA transporter rather than a glucose transporter.[25] The result is 20-30 trillion red blood cells in healthy humans circulating through miles of blood vessels "soaking up" DHAA and – if adequate levels of the selenoprotein glutathione peroxidase are present in the red blood cells – reducing the DHAA back to AA and sending it back into the blood. A similar recycling system is present in the brain between astrocytes and tanycytes.[26] This supports the concept that keeping the blood, vasculature, and brain bathed in adequate ascorbic acid is important.

Humans in acute distress from toxins, viruses, and bacteria have been successfully treated with high-dose vitamin C injections for over 70 years. Recent studies have shown a synergistic benefit to endothelial cells when vitamin C and cortisol are injected into blood vessels simultaneously. Decades of experience have underscored the importance of early intervention, and increasing the dose and duration as needed to neutralize the acidosis and/or toxins.[27-53]

Below is a graph courtesy of Dr. Paul E Marik of an ICU patient's C-reactive protein level (biomarker of inflammation) during 3 g IVC and a corticosteroid co-administration every six hours for 96 hours, stopping the treatment, and then resuming the treatment. Continued vitamin C treatment until full recovery, tapering from IV to oral administration as the patient

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VICTAS Trial

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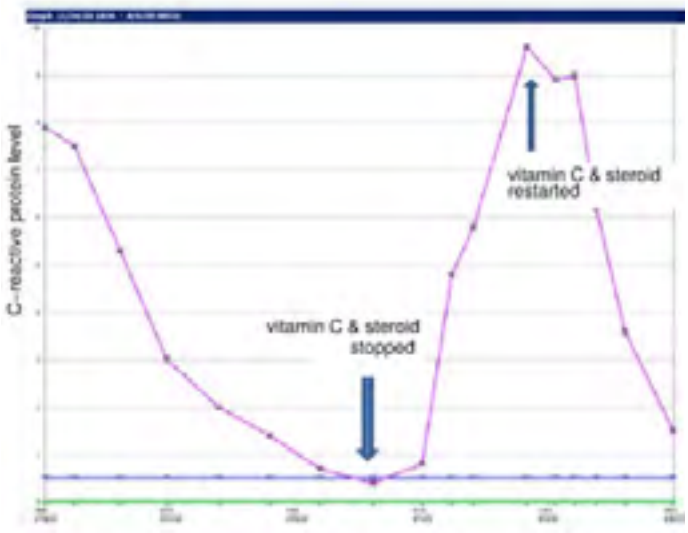
recovers, is important. It takes ongoing administration of vitamin C to achieve and maintain the tissue saturation levels needed to treat sepsis and septic shock.



Is 70 years of successful treatments to thousands of patients insufficient evidence? If more studies are needed, who will put the 350-700 mg/kg/day IVC dose to the test without the dangerous and artificial 96-hour limitation?

Acknowledgements

I would like to acknowledge Benjamin Rakotoambinina, MD, PhD, professor of physiology at the University of Antananarivo, Madagascar in collaboration with Laurent Hiffler, MD, of the Cellular Nutrition Research Group for their critical review and feedback; and Drs. Robert G. Smith and Andrew Saul for their critical review and editorial support. ◆

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Novel Aromatic-Oil Compound Effectively Inhibits Harmful Microbial Proliferation and Activity-Induced Abrasive Injuries

by Bill Misner, PhD

During physical activity, areas such as the feet, medial area thighs, groin, armpits, and chest nipples may result in blisters, capillary bleeding, bruising, and bacteria, yeast, and mold proliferation that require preventative treatment before and after any activity. Cohen wrote:

> Special chamois creams are available at bike shops. Despite proper hygiene…yeast and fungal infections can develop. Measuring the Q-angle checks for tibial torsion, genu valgum [knock-knee], and genu varum [bow-legged], and yeast vaginitis may be a recurring problem for women riders. Appropriate antimycotic creams and tablets, and thorough drying of the perineum after cleaning, usually achieve satisfactory results.[1]

Speaking February 4 at the 69th Annual Meeting of the American Academy of Dermatology (Academy), dermatologist Dr. Brian B. Adams, MD, MPH, FAAD, associate professor of dermatology at the University of Cincinnati School of Medicine, discussed skin conditions resulting from skin-to-skin contact among athletes and how to prevent outbreaks in sports teams. "Outbreaks of ringworm, herpes, and methicillin-resistant Staphylococcus aureus (MRSA) have occurred at the high school, collegiate, and professional level throughout the world," said Dr. Adams. "These skin conditions are highly contagious and can spread through sports teams quite quickly, especially if they are not immediately diagnosed and contained."[2] Active people need to be aware of these risks and how to spot the warning signs of both skin irritations and infections.

Increased chaffing irritations and microbial-proliferation in the skin occur in the armpits, medial thigh areas, the gluteal seat bones even when clothed with the best chamois-padded cycling shorts. Feet clothed in socks and the best shock-absorbing running shoes may blister, bruise, or become infected with aerobic bacteria, yeast, or mold-spore proliferation resulting in both injury and infection. The apparent solution is application pre-exercise and post-exercise with a cream to reduce friction and inhibit proliferation of aerobic bacteria, yeast, and mold in enclosed areas where friction, heat, and moisture occur during activities.

The axillae (armpits), when not exposed to evaporative cooling and light, generate moisture with chemical waste products (such as 2-methyl-2-hexenoic acid) produced by detrimental bacteria (which reside on the skin) that interact with secretions from various apocrine sweat glands, located in clothed, enclosed regions of the body. Human eccrine and apocrine sweat glands profusely sweat in order to reduce excessive internal body core heat temperatures. Eccrine sweat consists largely of water. However, apocrine sweat contains proteins, minerals, pheromones, and urea that tend to accumulate in clothed recessed areas of the body such as the armpit, groin, genitals, feet, and anus. A variety of microbial organisms living on all skin surfaces are particularly attracted

Table 1. Aerobic Bacteria Test Counts Taken per Square Inch Ischial Tuberosities, Clothed with Padded Professional Cyclist Shorts

Tests	Aerobic Bacteria	Yeast Mold
Pre-Exercise Test: Subject wore professional cycling shorts chamois for 24 hours with no lubricant applications prior to 90-minute aerobic exercise.	+1,000,000 Aerobic bacteria per square inch	+100 yeast-mold per square inch
Post-Exercise Test: Subject wore professional cycling shorts with chamois with Botanix Plus proprietary cream prior to 90-minutes exercise.	+1000 Aerobic bacteria per square inch	No Yeast-Mold per square inch
4-Hours Post-Exercise	+100,000 Aerobic bacteria per square inch	No Yeast-Mold per square inch
8-Hours Post-Exercise	+100,000 Aerobic bacteria per square inch	No Yeast-Mold per square inch
12-Hours Post-Exercise	+100,000 Aerobic bacteria per square inch	No Yeast-Mold per square inch

to apocrine sweat whose contents they consume, then break down into acids, resulting in offensive body odor. A variety of bacteria, mold, and yeast colonies rapidly proliferate in an enclosed space where evaporation is restricted by clothing.

Methods

A novel aromatic-oil compound was previously shown to effectively inhibit aerobic bacteria, yeasts, and mold spores located in dark, moist human body recesses, where odor-causing microbes tend to proliferate rapidly.[3] A single subject wore a pair of professional cycling shorts with a padded chamois seat-cover for 24-hours with no cream applications to determine base number count per square inch of aerobic bacteria, yeast, and mold on bilateral ischial tuberosities with no creams or solutions following a 90-minute aerobic workout. Then the following day the subject was instructed to take a shower and to wear a clean set of professional cycling shorts with the chamois; the subject's bilateral ischial-tuberosities were covered with a light layer of the new proprietary Botanix Plus cream.

This product was selected to measure its efficacy for suppressing irritational friction, aerobic bacteria, yeast, and mold cultures proliferating inside a warm, dark, moist, confined area (professional cycling shorts with chamois) specifically on the bilateral surfaces of 1" square of the subject's bilateral ischial tuberosities. All aerobic bacteria (AB) sample counts were determined, following 24-30 hours incubation at 25-30 degrees centigrade. All yeast-mold (YM) counts required 72-hours incubation at 25-30-degrees centigrade. The Biosan Laboratories' Sani-Check AB and YM test systems were utilized for accurately counting aerobic bacteria and yeast mold samples.

A male athlete (age 81 years) submitted swab samples taken after wearing professional cycling shorts for 24 hours, then added 90-minutes aerobic exercising to measure AB and YM counts per square inch. Then the same subject showered, changed to clean professional cycling shorts, and applied the new proprietary Botanix Plus Cream prior to a 90-minute aerobic workout. The subject's AB and YM counts per square inch test samples were taken immediately, four hours after, eight hours after, and 12 hours after exercise to determine the commensurable microbes collected during five test periods, described in Table 1.

Conclusions

On the first day a single subject with no gluteal lubricant on his cycling shorts chamois completed 90-minute aerobic exercise, then presented with 1,000,000 aerobic bacteria count per square inch and 100 yeast-mold count per square inch. On the second day same protocol was repeated to compare aerobic bacteria and yeast-mold counts after application of Botanix Plus cream to one-inch squares of the subject's bilateral ischial tuberosities. On day two the aerobic bacteria proliferation was remarkably inhibited to 100,000 per square inch representing only one tenth of the original 1-million aerobic bacteria per square inch. The Botanix Plus' proprietary cream inhibited yeast-mold proliferation completely for 12 hours. No yeast-mold was detected. It was concluded that this subject's 90-minutes aerobic exercise with Botanix Plus cream inhibited 900,000 aerobic bacteria and all 100 yeast-mold growths per square inch as compared to his previous day's exercise session with no chamois lubricant application.

Addendum: Whether topical application of this compound prevents issues associated with microbial proliferation or abrasion injuries in larger populations is unknown, nor is it shown here. This calls for more research collected from larger multiple populations exposed to a variety of elements that may increase their microbial proliferation resulting in skin infections and abrasive injuries.

Competing Interests

All work has been completed in accordance with guidelines governing such work with no financial relationships (including grants, honorarium, stipends, patents or patents pending, royalty agreements, board memberships) related to these findings. The author has no remunerative nor competing interests nor any commercial interests in this product. Collected data from a single subject case report is conclusively relevant to only the single subject participant in this study. The results describe what occurred in this single subject, and, therefore, may not reoccur in a larger cross population of subjects. In order for the controls to be precisely monitored, the single subject of this research required the author to be that subject tested in a strictly controlled environment for 48 hours.

Acknowledgements

The author acknowledges with appreciation to Biosan Laboratories (4722 N. Alameda Boulevard, Spokane, Washington 99205, Telephone 509-936-5645) for their generous donation of their new Botanix Plus proprietary cream. This strictly controlled test, following two sessions of 90-minute aerobic exercise first without application of lubricants then with Botanix Plus proprietary cream applications, required the author to be the single subject in this original case study research project.

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Bill Misner graduated from Indiana University, and later completed both his MS and PhD at the American Holistic College of Nutrition. He is an AAMA board-certified alternative medicine practitioner. He published papers in the American College for Advancement in Medicine (ACAM) journal, *Journal of the International Society of Sports Nutrition* (JISSN), and seven original research papers in past issues of the *Townsend Letter*. Misner wrote *Endurance Nutrition – Finding Another Gear,* Editions I and II of *What Should I Eat? A Food Endowed Prescription for Well Being*, and *Phytonutrition: Finding Fitness for Life!* Misner, age 81, continues to run races from one mile up to 13.1 miles to demonstrate "Practice (what he preaches) really works!"

My Personal Story of Mega-Dosing Vitamin C

by Allen Cohen

Orthomolecular Medicine News Service

I am 78 years old and have been taking 30,000 mg/day of vitamin C for over 40 years. And I do not get sick!

As a child and up until my mid-30s, I had to deal with many food allergies, such as dairy, nuts, strawberries, chocolate, and many others, which made going out with friends to restaurants sometimes an ordeal. The allergies would cause eczema or often asthma and greatly affected my life.

In my mid-30s I read a series of articles on Dr. Linus Pauling, and his two Nobel prizes, with particular emphasis on vitamin C. I decided to try it. I started with 1,000 mg twice per day, and each week, I would increase it by 1,000 mg, so that at the end of about five weeks, I was taking 5,000 mg, twice per day.[1-3] After doing that for a couple of months, one of my friends' wives made a strawberry pie and suggested I try it. I resisted out of fear of an asthma attack and/or severe eczema rash. However, I decided to try the pie, and much to my surprise nothing bad occurred. I was amazed, and at first did not even make the connection to vitamin C, which I was now taking at 10,000 mg per day. After a couple of days, I decided to purchase some fresh strawberries and have them with a glass of fresh whole milk. Again, nothing bad occurred. On the next day, I tried a handful of nuts, and again, no asthma, no eczema rash, no problems. I ran to the library and sought out a book by Dr. Pauling on vitamin C, and read it cover to cover.[4] Nothing else in my life had changed, except I was now taking 10,000 mg/day of vitamin C, at the rate of 5,000 mg with my breakfast, and 5,000 mg with my dinner.

I have continued with this protocol ever since, and I no longer suffer from any food allergies! [Editors' note: Individual need for vitamin C varies considerably. Each person must determine their own optimal intake level. Bowel tolerance (loose stool) indicates that too much C is being taken at one time.[1]]

A Woman with Ileitis

Some months later I was introduced to a woman in her mid-30s who was suffering from ileitis and was taking sulfa-based antibiotics at the rate of 6-8 tablets per day. Her skin actually had a slightly yellow/green tinge to it, and you could smell the sulfa. She was living on a diet that was 100% fiber free, so no fresh vegetables and no fresh fruits. She had constant diarrhea, stomach cramps, and generally felt sick. She was told that in due course she would have to have her lower bowel partially or completely removed, her rectum sealed, and would live with a colostomy bag, for the rest of her life. Needless to say, she was terrified.

I suggested she take plain yogurt 6-8 ounces twice per day, eat fresh fruits and vegetables, and take vitamin C 1,000 mg twice per day with meals, and increase it by 1,000 mg each week, so that in approximately five weeks, she would be taking 5,000 mg twice per day. After about three months she began reducing the sulfa antibiotics; and by the time six months went by she was eating normally, no longer taking antibiotics, taking a total of 10,000 mg vitamin C every day. Her internist called me and asked me to come into his office to explain what I had suggested, as she no longer showed any signs or symptoms of ileitis. I told him what I had suggested, and how well it obviously had worked. He told me he was going to send in this story to *JAMA* and that I would probably hear from them directly. I never did.

Shared Success

Over the course of more than 40 years, I have received referrals from friends and family who knew about my success using mega-doses of vitamin C and passed the information via word of mouth to associates who were having intestinal disorders of all types.[5] I would receive calls by phone and the people would introduce themselves and explain that they were friends or family members of those who knew how well I did with vitamin C and had simply passed the word. It's amazing how sometimes word of mouth gets passed around. So I continued to suggest to friends and family to use the same treatment. In all cases it worked, and they no longer suffer from these conditions.

I often do volunteer work at local senior citizens rehabilitation centers, where there are many sick patients. Accordingly, I have increased my vitamin C to 30,000 mg per day (10,000 mg, three times per day). I do not have diarrhea nor suffer from any side effects of a mega-dose of vitamin C. I do not become ill.

What I Did When Sickness Was Coming On

About three months ago I attended a medical lecture on osteoarthritis in the elderly. There was someone there seated near me, who was coughing during the lecture, but frankly I did not think much about it. Some days later, I awoke in the morning with a low-grade temperature, sneezing and coughing and felt that I had picked up an upper respiratory infection. I was not tested, nor did I go to the doctors or the hospital to be tested.

I took 10,000 mg of plain vitamin C (ascorbic acid), five times during the day. Yes, I swallowed 50,000 mg of vitamin C during the day from about 6 AM until about 10 PM that night. I awoke the next morning, feeling great, with no symptoms of an infection!

I can tell you many stories about people who take a minimum of 10,000 mg of vitamin C every day on my recommendation, and who all have told me that they are feeling great, and like myself, do not get ill and are not at all worried about their health in this coronavirus pandemic![3,6-8]

Pharmaceutical medicine does not like vitamin C. After all, vitamin C works, is not expensive, and has no side effects. But vitamin C has changed my life, and the life of everyone I know who will take the time to listen and to have an open mind on this subject.

My Vitamin and Mineral Protocol to Prevent Infection

For optimal health and to prevent infection by viruses, I recommend taking a multivitamin, along with additional vitamin C, vitamin D (5000 IU/d),[8-10] vitamin E (400 IU, mixed tocopherols),[11] magnesium (400 mg/d in malate, citrate, or chloride form),[12] and zinc (20 mg/d). To find your correct dose of vitamin C, learn about "bowel tolerance"—the daily dose just below the amount that causes a laxative effect.[1-7] Many people find that when they're not sick, a dose of 3000 mg-10,000 mg/day taken all at once will cause a laxative effect, but they can tolerate the same daily dose of vitamin C when taken in divided doses. However, when an infection starts, much higher doses[1-7] can prevent it from taking hold. Of course, I recommend healthy eating, and daily exercise, and not smoking or drinking alcohol to excess. You may want to discuss doses of vitamins and minerals with your doctor. You might indeed be doing your physician a favor.

Conclusion

So, this is my story of my experience with vitamin C over four decades. Vitamin C in mega-doses works wonders. I tell everyone, if you take only one vitamin, be sure to take vitamin C at a minimum of 10,000 mg/day.

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Vitamin C Pioneer Frederick R. Klenner, MD An Historic Interview

by Martin Zucker

Orthomolecular Medicine News Service

As a long-time health writer with great respect for the significant (but alas, largely overlooked) value of large doses of vitamin C, it has been interesting to me to see this foundational nutrient mentioned, studied, and even used therapeutically in the current battle against the COVID-19.

It has been well said that vitamin C is the ultimate immune-boosting supplement, equally vital for protecting against diabetes, cardiovascular disease, skin conditions, and much more.

Much more, indeed.

Beginning more than 40 years ago, I had the good fortune to interview a doctor in the US who applied large doses of vitamin C in his preventive and therapeutic protocols. And with great results. I became a devoted mega-user of vitamin C, a habit that continues to this day.

In 1978, I spoke in detail with Frederick Klenner, MD, of Reidsville, North Carolina. I am sharing my original notes with the *Orthomolecular Medicine News Service* because I believe the information is still very valid all these years later, and may be particularly informative for doctors today who practice integrative and preventive medicine.

Conversation with Dr. Fred Klenner on Pregnancy and Childbirth, Assisted by Vitamin C (June 1978)

Summary transcription of Dr. Klenner's comments:

For a consecutive series of 322 pregnancies, we gave vitamin C in similar doses to those recommended by Irwin Stone in his book, *The Healing Factor*.[1] We advised 4 grams per day in the first trimester, 6 gm/d in the second, and 10 gm/d in the last trimester. I've been involved with 2,500 pregnancies during my career... that gave me the basis for comparisons. All deliveries were at one hospital, the Annie Penn Memorial Hospital in Reidsville, North Carolina.

We always observed the vitamin C to be a helping factor – very definitely! The first thing I started to notice, 30 years ago (1948), that when I was giving vitamin C to some of the women, their blood counts remained better than those who weren't receiving it. That was the first thing we found that turned us on to giving high doses of vitamin C. We found that vitamin C, given over the course of the pregnancy, generally makes labor shorter and less painful. That's where the elasticity of the perineum comes in. Though ordinarily we saw labor take 24 hours, labor with vitamin C was reduced down to not more than six hours and most of the time they were in labor only three or four hours. When you reduce the time, you reduce the pain. Delivery was easy because the perineum would stretch so much more easily than in women who didn't receive the vitamin C.

Another thing you may sometimes get after the child is born is hemorrhaging. We had no hemorrhaging or excess bleeding in this series. Two-thirds of the non-vitamin C patients had some type of bleeding, but with vitamin C we had none whatsoever. So vitamin C, in the program of 4 to 10 grams daily, improved the elasticity of not only the perineum, but also the blood vessels themselves.

We seldom saw abdominal wrinkles – the "striae." *We never had a single stretch mark after we started on this regime of high-dose vitamin C.* Previously, we hit a quota which was about one out of three pretty bad, and another third would show some degree of striae. The abdomen stretches when the uterus enlarges rapidly, and the skin is damaged when it cannot expand fast enough. We noted this in the ones we delivered. We had one lady who delivered several babies in our program. Before she started in our program, she had a few striae from her first two pregnancies and labors. After that we had her on this protocol of vitamin C and she actually improved her abdominal skin. We found that in this program the perineum recovered quickly and completely.

Did we have any toxic manifestations? Hardly, in this group – we only had toxic manifestations in about one per cent of the cases. I found that on average the right amount was 10,000 mg/day. It's important to find and maintain the right level. Szent-Györgyi too in his recent experiments has proved that dose to be correct. That's just to keep the body normal. If you got the sniffles or something more serious (and you could get that even taking 10 grams), for example if you got a really potent virus, you would have to double that dose or more to compensate.

Any miscarriages? Not a single one.

The children were called "Vitamin C Babies" because they were so outstandingly healthy as compared to the other babies delivered in the hospital. They were strong babies. No resuscitation was necessary with any of them. As they were taken out of the delivery room in the so called "rolling bassinets," they were grabbing onto the sides. Some of them were even turning over.

The Fultz quadruplets were in this group. They are identical twins, coming from one egg. They are the only quads in the southeast USA that survive until this very day. Born in 1946, they are still doing very well.

Why are the mothers doing better with vitamin C? Because of its health-producing features. It's the number one anti-fatigue vitamin. We didn't have a single tooth cavity in a mother during this series, and that to me was very unusual. Vitamin C also helps in the metabolism of protein in the baby and the mother,

allowing her to maintain her strength. It is a prime factor in the building of collagen, the connective tissue in our bodies, and that is important in making the baby.

The key to the quicker childbirth with vitamin C is that it makes the perineum more elastic. Although no formal studies have yet documented that, we do know that the perineum does flex much more easily and more safely if the patient has been on high doses of vitamin C. That's the key.

The Fultz babies: 2 lbs each except for one, who weighed 3. We gave them 50 mg of vitamin C. They were born at midnight, and they got 50 mg the next morning. We gave that much although most people gave 25 mg. There were just no problems with sleeping.

If you ask most Ob-Gyns what they give, most don't give anything except a pregnancy tablet that has a little iron and minerals in it. We'd go with 50 mg/day of vitamin C for a while and raise it gradually so that by six months the babies were getting 500 mg/day, and by a year getting 1000 mg/day. We were giving it in the form of drops on the tongue.

We found that healing time after delivery was 50 per cent faster than those who didn't get vitamin C. Dr. Ringsdorf confirms this,[2] and most of the time those who weren't getting vitamin C just didn't heal. Vitamin C is the best pregnancy vitamin. No question about it. Of course, they need iron and the vitamin C tends to oxidize the iron, so it's important not to give too much iron. We gave our mothers vitamin C, a good iron preparation, and a quart of milk every day.

I began to realize that they were healing better because of the vitamin C. Evidently the collagen metabolism is much enhanced over the other women who were having lots of problems. My wife took vitamin C and didn't have more than an hour of labor with any of our three daughters. She was quick and she was up and around in a day or so. A lot of procedures that doctors do are developed in clinics – in their offices, with personal attention – not in medical schools or in big studies. This is the one-on-one situation.

So, we advised the women to take vitamin C starting at 3,000 mg/day, in divided doses. I suggest using ascorbic acid granules or crystals, which can be mixed in their orange juice or sprinkled on their cereal. Much less hassle than with tablets. Then we had them increase their dose slowly.

There are many problems associated with infants born in this country and we don't know why. We are beginning to think now that maybe nutrition, after all, has a great deal to do with it. Our lifestyle and diets may be a big factor here. We are a rich country, but unwittingly some have developed poor dietary habits and even malnutrition. So I put all my patients on a well-balanced diet with supplements of essential vitamins and minerals. And I think further that adequate dosage of vitamin C has a lot to do with it.

Most doctors run like ostriches when you mention the word "vitamin." It seems to me they can't get it into their heads that these chemicals are very safe. "Vitamin" is just a name. There is no injurious effect of taking ascorbic acid – there is only beneficial effect. In pregnancy it is important for the mothers' own good health and the baby's good health that they take it.

The actual process of pregnancy drains ascorbic acid from the mother. It's a stress on the body. A rat normally makes 3.8 grams (3800 mg) of ascorbic acid a day (in a 154-pound human body equivalent amount). If you put the rat under stress it will automatically start making 15,000 mg. Now, pregnancy is a major stress factor on the body and so therefore the requirements of vitamin C are multiplied by many times. That's why it is so necessary.

To go into these details of metabolism, since humans do not produce their own ascorbate, we must go out and get it. Mothers should follow up with ascorbic acid. That's just good medicine. Any good doctor will prescribe a vitamin preparation for the baby, and most of them contain some small amount of vitamin C; 6.25 mgs or a similar amount. But we have determined that you should give a child 1000 mg/day of vitamin C per year of life up to 10 years. We always recommend this. And we get a tremendous feedback; the babies who take it are so much healthier than those who don't take it. They eat better, they sleep well, no problems.

Dr. Irwin Stone, a biochemist who has researched vitamin C for decades, says the work of other doctors, going back 40 years, shows that vitamin C "is the best thing for pregnancy."[1] It also reduces the risk of hemorrhaging and miscarriages. Anyone who tends to lose babies after getting pregnant should be on these high levels of ascorbate to prevent the hemorrhages. The first symptom of scurvy is hemorrhaging, and vitamin C prevents that.

There were over a thousand patients on our vitamin C program, with no adverse reactions, and never a deformed baby when the mother was on this program. In post-natal consultation, I urged my patients to continue on high doses of vitamin C. When they began to notice the good effects like better healing and fewer colds, little by little they became convinced.

Author's note: I have interviewed several other doctors with practices contemporaneous with Dr. Klenner's practice, including Dr. Archie Kalokerinos,[3] Dr. W. Marshall Ringsdorf,[2] Dr. Robert Scott, and Dr. William J. Saccoman. All have recommended Dr. Klenner's high-dose vitamin C protocol.

To learn more about Dr. Klenner:
Saul AW. (2007) Hidden in plain sight: The Pioneering Work of Frederick Robert Klenner, MD. *J Orthomolecular Med*, Vol 22, No 1, p 31-38. http://www.doctoryourself.com/klennerbio.html

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My Expulsion from Medical Practice: Censorship and Economic Ruin Threaten Dissenting Physicians

by Dr. Albert Louis

Orthomolecular Medicine News Service

It's a very bizarre state of affairs when, as a doctor for over 30 years, I suddenly find myself completely isolated from people I know, and from humanity. In this situation, there seems to be no way to help with healing or caring or treating, because I have been expelled like a priest excommunicated from the church. I have been cancelled.

This happened because I was not conforming to the religion of medicine. I said things that were against the perceived modus vivendi. I was immediately suspended and completely and utterly cut off, as if I were a dangerous, evil person.

This sense of doing wrong eats into your guts. It is like you have done some kind of severe sin, where you have done something so bad and so awful, that you can never be recuperated or saved because you've gone against absolute authority.

Now, this authority is determined and written by AHPRA, the medical board of Australia which produces the code of behavior.[1]

This code of behavior was not something I had contradicted in public. I hadn't attacked or injured a patient. I had posted on Facebook statements that were inimical to the system because I criticized issues about the system, which were not good.

Looking outward into the world beyond medicine, I have learned that the best companies are run with their employees feeling a group spirit, where the team is heard, understood, and appreciated.

But over the past two to three years, when working in medical practices, I've seen no such thing as a team spirit. I found modern medical clinics in Australia to be like workhouses, where the doctors are consumed with input and output of patients. The only thing that the practice owners care about is a throughput of patients to give an indecent profit.

So doctors effectively become part of a cattle market that accepts as many patients as possible to be treated with a preset path of investigations, drugs, and referrals and are quickly released. Beyond that, the doctors must also have good marks on social media to make sure that the patients return.

This medical meat market lacks the previous dedication of the medical profession to treating or caring about patients. It seems that the whole system has become so computerized and automated that it has become the "fast-food" modernization of medicine.

Apparently, there is no such thing as medical practice in the absolute sense anymore. Caring goes out of the window. Nowadays, a patient arrives and it's in and out within five minutes; and all the patient gets is a drug - often an antidepressant!

Considering our modern world, I realized that this new concept of medical practice is part and parcel of what is happening in the larger society. It seems that we no longer have a society that even cares about itself.

In medical lectures and webinars, I see health professionals giving lip service to the need for patients to be looked upon with a certain sense of care by the doctors – the therapeutic agents. Yet this seems an utter hypocrisy because doctors nowadays are more concerned about the efficacious use of investigational processes and therapeutic agents than a direct relationship with the patient.

In fact, there's no such thing as a partnership in medicine anymore, even in functional medicine. This has gone out the window because society and particularly the medical system frown upon anything to do with mind, body, or with healing itself.

People are eating the wrong kinds of food because doctors have not been taught nutrition in medical school and have not learned that food is one of the most powerful therapeutic agents. People are eating themselves to death by the toxic foods that they get from their local stores.

Because of the COVID-19 pandemic, unemployment, marginalization, and alienation due to the need to keep separate have increased and have accelerated to the extent that there is a significant increase in mental illness.

This is because priority is placed on COVID-19 itself. In medical practices, other illnesses are being left behind and people are no longer being treated, to the extent they were previously, for chronic illness, heart disease, and cancer.

In this COVID-19 epidemic situation, the simple nutritional supplements that could prevent COVID-19, such as vitamin C, vitamin D, zinc, magnesium, and hydrogen peroxide sprays are looked upon by the medical establishment as

being useless and are banned. This is also the case with social media who rely on "fact checkers" who have not been educated in nutrition.

Hippocrates said, "Let food be your medicine and medicine your food." This applies to an excellent diet that provides the essential nutrients while avoiding excess sugar and processed foods with empty calories, as well as safe and inexpensive vitamin and mineral supplements. It can also apply to drugs that are effective against COVID-19 and do little harm such as hydroxychloroquine/zinc and ivermectin. If everyone would take the vitamin and mineral supplements (vitamin C 1000mg 3x/day or more, vitamin D 5000 IU/day, magnesium 400 mg/day, zinc 20 mg/day, etc.) we could end the pandemic in a month.[2-7] But any doctor who says these things in public will be cancelled.

This epidemic has been handled as if the governments in charge are following rules from some unknown puppet master. Each knows how to follow the rules, and the rules are such that every government is being taken for a ride and they don't even realize it. I am referring to individual governments who do not realize they are being taken for a ride by the profit-seeking medical establishment. Is it the WHO, the drug companies, or are we all responsible?

I started listening today about the need for sending vaccines to Africa, Egypt, and India. This was on the BBC and they were talking so eloquently about the need for vaccines, particularly for health workers. These vaccines have been put out in a rush without the full testing that should be done before a vaccine is given to large populations. The mRNA vaccines are quite new and may have unforeseen consequences and yet the medical authorities don't seem to care. Already many adverse effects are being reported and ignored.

And what could really help Africa and India is not being talked about. Even when hydroxychloroquine and ivermectin are being given, they're not being widely discussed. What they did talk about on this particular BBC presentation was the fact that over 2 billion people, particularly in Africa and India have sanitation problems. There are so few latrines that many people die from cholera. Also one billion people have no bathing facilities. If philanthropists really cared, instead of focusing on vaccinations and billions of dollars for drug companies, they should be providing education, latrines, clean water and bathing facilities, and excellent nutrition and vitamin supplements to the poor!

The international and USA media make no connection between the fact that people are going to get COVID-19 simply because they haven't got the immune strength to defend themselves against a virus, any virus! And what about the new COVID-19 variants that may be able to evade current vaccines? Virus variants are nothing new, that's how viruses propagate, and that's why the annual flu vaccines aren't universally effective. Bottom line – the immune system empowered with adequate nutrition and supplementation will likely provide excellent protection – as a strong immune system can generate new antibodies faster than new vaccines can be developed!

Most medical doctors and especially the media, or should we say the "propaganda industry," don't know about the social determinants of health – education, low psychological stress, good hygiene, excellent nutrition. They just think that the vaccine is a magical cure, which allows everyone to ignore other solutions. This will likely continue as long as the media suppress relevant information and medical professionals avoid learning about nutrition. This is utter absolute stupidity and hypocrisy.

(Editor's note from Andrew W. Saul: Normally I include a brief "about the author" statement here, but in this case, if I did so, Dr. Louis would be in even more hot water than he or she already is. Suffice to say that, as a journalist, I opt to protect my sources. To that end, Dr. Louis is a pseudonym. But the doctor, an Australian, is very real indeed)

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Letters to the Editor

Re: Mac and Cheese

Speaking of mac and cheese, abhorrent nutrient lack, and COVID susceptibility…the article "COVID-19 – A Wakeup Call for Our Love of Mac and Cheese" (www.townsendletter.com) is a no brainer, and I would think most in the *Townsend Letter* world have known this for at least 40 years.

Let's call the pandemic what it really is…genocide of the poor. After all, the other Mac and cohorts of the fast-food kingdoms have drugged the populations; and their mission is far and wide around the world.

When I lived in China in the 1980s, there was but one MacDonald's in Beijing...now there are countless, and the rate of diabetes has skyrocketed.

Alas, my friends, this is just the beginning of pandemics.

As fast-food restaurants can cheaply sell so-called foods to the masses that do not have healthy food security, there will never be a way to stop the pandemics from steadily killing off the poor and disenfranchised, African Americans, Latinos, and all poor White Americans. This is the frightening era we live in; and as the saying goes, the rich get rich and the poor get dead!

Unless all, of every stripe are committed to help getting nourishing foods to the poor, the entire population will be doomed. Not just the poor!

Barbara Kolodie

more letters ➤

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A Published Article Confirms Scientific Soundness of Energetic COVID-19 Vaccine and FCT®

My recent experience with attempting to publish an article on the subject of energetic vaccines in a medical peer-reviewed journal has only reaffirmed the dismal state of our commercialized medicine that is ultimately responsible for this crisis. The article was finally published.[1] The dismal state consists of ignorance in science, greed, and sociopathy. One would think that considering the catastrophically high number of dead and dying that the article – with the support of over 400 scientific references, endorsement of its principles by the three Nobel Laureates, zero scientific conflicts, and patient testimonials vouching for the efficacy of COVID-19 vaccine – would be readily accepted. Instead, it was rejected by over a dozen medical journals with offering bizarre "scientific" reasons. Among these, "due to space and typology," "not of interest to our readership," "not for this journal," while any imaginable and unproven drugs have been haphazardly used.

Yet, how open-minded our "progressive medicine" is to low-cost, non-pharmaceutical solutions can be concurred from the fact that the academician preferred to remain anonymous. This isn't new, as some vaccine researchers who disclosed the hidden side effects of vaccines requested the same. My multiple proposals to conduct clinical trials with the energetic COVID-19 vaccine fell on deaf ears, as the number of dead keep skyrocketing. Obviously, the main priority of our healthcare has never been people but on money, when an approach like this proposes a dollar worth of life savers that can be immediately used by everyone, instead of waiting forever for multibillion dollar nuclear submarines. The latter option invariably wins, where strictly speaking, the current COVID-19 pharmaceutical submarines, named vaccines, even hardly meet the criteria of vaccines since none of these contains the virus or its products. The correct name should be immuno-stimulating drugs.

Pfizer and Moderna's vaccines contain synthetic mRNA for stimulation of the immune system, and Oxford/AstraZeneca a different, attenuated adenovirus isolated from monkeys' feces – *bon appétit*. This is in contrast to an 100% specific homeopathic or other energetic vaccine that is prepared through a simple patented technology by a doctor of electro-engineering, Cyril Smith, and myself, in which such vaccines use the field of the virus itself. The field of microbes, as the cited studies in the article demonstrated, is as specific to a reception by the immune system as the virus molecular chemical structure because our bodies are primarily energetic systems, not chemical soups. Also, while the pharmaceutical vaccines cannot treat the already infected, sick, or dying, energetic vaccines can. Several immunologists also expressed a high risk of autoimmune reactions due to similarity of proteins in the conventional COVID-19 vaccines. These vaccines also contain a highly allergenic substance, polyethylene glycol (PEG) with its estimated allergy among Americans exceeding 16 million people. The rest of the population cannot be excluded from reacting adversely to PEG, either. The allergic reactions may include life-threatening anaphylactic ones, some of which have already occurred from the Pfizer and Oxford/AstraZeneca vaccines. But in the midst of this bloodbath and pulling at straws in the unsafe pharmaceutical kitchen, even the consideration of water-based vaccines – free of side effects and costing virtually nothing – still falls in "God forbid" land in our "progressive medicine."

In the meantime, using energetic COVID-19 vaccine since the onset of this pandemic, I had several patients with typical COVID-19 symptoms that were promptly resolved, and some 70 patients taking it prophylactically who never developed COVID symptoms. None of my patients has been hospitalized or even visited an ER with COVID. Yet, multiple proposals for the clinical trial continue to fall on the same sociopathic ears that run the medical journals and our healthcare – even as formal scientific support has been presented. The demonstrated research that such vaccines can be produced to fill the size of a lake in minutes and constitute a money saver, if anything, feeds their rejections. The bottom line is that the more scientific evidence you show them, the faster the sociopaths run from it.

The hope is that as we know from *Schindler's List*, even among the Nazis, there were a few decent people. Perhaps we can find them in our healthcare system, too. So, if anyone knows such white elephants, please make them aware that cheap lifesavers still work.

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[1] *The Journal of Infectious Diseases and Therapy* Volume 8 • Issue 6, Can Energetic Vaccines, Based on Physics, Be the Sound Options for COVID-19 and Other Pandemics, in the Absence of Pharmaceutical Vaccines?

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Is It Possible to Reduce the Toxic Elements We Consume?

review by Craig Soderberg

Food Forensics: The hidden toxins lurking in your food and how you can avoid them for lifelong health by Mike Adams
BenBella Books, Inc., Dallas, Texas; www.benbellabooks.com
2016, 368 pages, $16.95

This book is unlike any other book I have ever read. It lists and describes the toxic elements that we are unknowingly consuming every day. There are three broad categories of toxic elements that are getting into our bodies: heavy metals, chemical contaminants, and certain food ingredients as contaminants.

The first section of the book discusses the origins of toxic heavy metals, how we are absorbing these contaminants, and the harm that they cause to our bodies. Adams covers seven toxic heavy metals: arsenic, mercury, lead, cadmium, aluminum, copper, and tin.

The first toxic heavy metal discussed was **arsenic**. This toxin is found in some medical treatments, wood preservatives, and pesticides. Unfortunately, it is also found in drinking water. The biggest source of arsenic found in food comes from seafood, including fish, crustaceans, and seaweed. Drugs used in animal feed for chickens to control internal parasites have long contained high levels of arsenic. Arsenic has been linked to tumors formed in the skin, lungs, bladder, kidneys and digestive tract. Arsenic can also lead to diabetes, heart disease, cardiovascular issues, respiratory diseases, impaired neurological development, and even depression. Several studies have linked the use of garlic to decreased effects of arsenic toxicity on cells.

The second toxic heavy metal discussed was **mercury**. Mercury is one of the most toxic elements on the planet. Miners, gilders, and mirror makers in the Middle Ages were exposed to the harmful effects of mercury. Today, mercury is found in thermometers, batteries, pesticides, fluorescent light bulbs, coal-burning plants, and dental fillings. High-fructose corn syrup (HFCS) (in sodas, fruit drinks, candy, ice cream, bread, chips, soups, jellies, deli meats and many other products) generally contains mercury. HFCS has been linked to obesity, diabetes, heart disease, fatty liver, and early death. Mercury is even used in vaccines given to children. Flu shots typically contain 50,000 ppb of mercury. This level is about 25,000 times the concentration limit of mercury allowed by the EPA in drinking water. Methylmercury, as found in tuna and other large fish, is the primary source of dietary mercury consumed today. Even low-level mercury poisoning can cause rashes, inflamed gums, mood disturbances, insomnia, anxiety, and depression. Strategies for chelation and removal of mercury include avoiding or limiting fish intake, consuming raw fresh strawberries that bind and capture over 90% of the mercury during digestion, consuming activated charcoal, and consuming propolis (the resinous botanical mixture honey bees mix with their beeswax to glue their hives together). Registered pharmacist and nutritionist Barbara Mendez also recommends a diet that helps optimize liver function, including garlic, cilantro, Brazil nuts, pumpkin seeds, and ground flaxseed. Seaweed also tends to have a high efficiency in capturing free mercury. Foods containing natural fibers can capture elemental mercury. Strawberries were the most effective.

The third toxic heavy metal discussed was **lead**. Lead is a shiny, bluish-white metal that dulls to gray when it comes into contact with air. It is used in water-carrying pipes, glazed pottery, cooking utensils, and even in the preservation of wine by the ancient Romans. Other sources of lead included leaded gasoline, lead-tainted paint chips, pesticides, cosmetics, bullets, batteries, pipes, and industrial practices such as mining, and smelting. Lead is unsafe at any level and is poisonous to every bodily system. There are no EPA limits on the concentration of lead allowed in food sold in the United States. Whole Foods continues to sell vegan, organic protein powder in its stores that show alarming concentrations of lead contaminants because the raw materials are sourced from China. Lead is found in the roots and shoots of wheat and other grains sold in America. Of over 400 lipsticks, including the most popular brands purchased in retail stores, every single one contained lead –all of them. Lead exposure can cause significant memory impairment, dementia, and other negative mental health issues. Lead has been linked to heart disease, impaired metabolism of antioxidants, disrupted hemoglobin synthesis, damaged kidneys, decreased sperm motility, miscarriage, infertility, gingivitis, periodontitis, decay and missing teeth. Lead can remain in the bones for up to thirty years. But several foods and vitamins can help rid the body of toxic lead deposits. These include vitamin B1 (thiamine), B6 (pyridoxine), vitamin C, garlic oil, and bioflavonoids such as quercetin (found in grapefruit, onions, apples, and red wine). Sesame seed oil contains the natural antioxidant sesamol, which can be a chelator against liver and kidney lead poisoning. During digestion, dehydrated seaweed and seawater extract can be efficacious in binding free lead.

The fourth toxic heavy metal discussed was **cadmium.** Cadmium is used in rechargeable nickel-cadmium (Ni-Cd) batteries, metal plating, pigments, as a stabilizer for PVC pipes, in phosphate fertilizers, in sewage sludge. Even at

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low concentrations, cadmium is toxic, killing off egg cells, significantly slowing the ability to produce sperm, lowering bone density, and causing demineralization in the body. The author's lab testing consistently found cadmium in coffee products. But there is some evidence that high doses of antioxidant-rich spirulina may help protect the body from the most harmful effects of cadmium.

The fifth toxic heavy metal discussed was **aluminum.** Aluminum is found in airplane parts, building materials, baseball bats, soda cans, kitchenware, foil, cosmetics, antiperspirants, antacids, vaccines, and many more consumer goods. Aluminum is everywhere and can be inhaled, absorbed through the skin, and imbibed in contaminated liquids. Some foods such as flours, breads, cakes, pastries, certain vegetables (such as spinach, radishes, and lettuce), dairy products, sausages, and shellfish contain higher-than-average levels of aluminum. The highest concentrations are found in cocoa, tea leaves, herbs, and spices. Aluminum in the water supply has been linked to dementia. Aluminum in antiperspirants has been linked to breast cancer. Canadian researchers published a study in *Current Medical Chemistry* noting that aluminum in vaccines put everyone, including infants, at risk for long-term brain inflammation and other neurological complications in addition to autoimmune disorders. These same researchers published another study in the *Journal of Inorganic Biochemistry*. This second study concluded that vaccines may share a causal relationship with the rise of autism. In January 2016, the American College of Pediatricians issued a warning statement about the toxic effects of the Gardasil vaccine, citing that aluminum and polysorbate 80 (in that vaccine) could possibly be associated with the rare but serious condition of premature ovarian failure. Aluminum hydroxide in antacids has been shown to cause phosphate depletion syndrome. The most important sources of aluminum to avoid are vaccine injections, aluminum-containing medicines, and any liquids or beverages that may contain aluminum. Green algae chlorella has been found to be very effective at safely removing concentrations of several heavy metals from wastewater, including aluminum.

The sixth toxic heavy metal discussed was **copper.** Copper is essential for maintaining good health, but it must be in balance with zinc, iron, and other essential minerals, otherwise it blocks necessary enzymatic activities and may contribute to detrimental health effects. Copper toxicity typically occurs through multivitamins that contain high levels of this heavy metal. Too much copper impairs the thyroid, decreases liver and kidney function, can cause brain damage and lead to death. A copper imbalance can also cause Graves' disease which can lead to hyperthyroidism. A copper imbalance is also closely associated with mental deficiency, neurological dysfunction, and psychological disorders. Overexposure to copper in drinking water could lead to Alzheimer's disease. Sulfur binding blocks copper retention in the body. Therefore, it is important to make sure your diet includes a healthy dose of food-based sulfur compounds like those found in garlic and whole eggs.

The seventh toxic heavy metal discussed was **tin**. Tin vapors can cause headaches, nausea, and general fatigue. Animal studies involving tin fluoride and tin chloride have been shown to reduce or inhibit the natural function of the liver. Animal studies have also shown that tin tartrate can lead to liver damage. Some 90 percent of canned foods use tin compounds. Tin may leach into the food stored inside those cans. Trace amounts of tin can be found in the water supply. Stannous fluoride – composed of tin and fluoride – is one of the most common types of fluoride applied in dentistry to prevent cavities. It has been used in brands such as Crest and Oral B. Stannous fluoride can lead to osteosarcoma, osteoporosis, and fluorosis. Stannous fluoride has caused death in at least a few cases. One way to remove tin in the body is through the chelation properties of quercetin, a flavonoid found in many fruits and vegetables.

There are many foods that naturally have some limited chelation properties. Cilantro, chlorella, and lemons have all been identified as agents with some effectiveness for reducing heavy metal toxicity, while foods like garlic can reduce oxidative stress. Activated carbon (charcoal) is also very effective at neutralizing and removing metal toxins. Exercise and sweating have been shown to remove heavy metals in much higher quantities than through urination.

The second section of the book discusses the origins and dangers of toxic chemical compounds, how we are absorbing these contaminants, and the harm that they cause to our bodies. Adams covers three chemical contaminants: bisphenol A (BPA), hexane, and pesticides.

Bisphenol A (BPA) is used in household appliances, construction, electronics, medical equipment, dental sealants, eyeglasses, and especially, food containers. Some tin-containing food cans are lacquered with a bisphenol A lining. BPA leaches from these cans into food, particularly from acidic fruits and vegetables such as tomatoes and tomato-based foods. BPA is linked to hormonal disruption and reproductive dysfunction, including infertility, birth defects, developmental issues, autism, diabetes, obesity, cancer, irregular heartbeat, and a host of other health problems. BPA has also been demonstrated to be a possible carcinogen, triggering prostate and breast cancers in animal studies. The French parliament voted to ban the use of all BPA in *all* food containers by 2015, making France the first country to do so. In order to minimize the risk of consuming BPA, avoid consuming hot foods in plastic containers and avoid putting such containers into the microwave to heat foods. Also try to limit canned goods as much as possible, opting for fresh or frozen food instead when possible. Leafy green vegetables, herbs, clean-sourced animal livers, and especially probiotics and fermented foods provide ample folate (or B-9 or folic acid) to the body and help eliminate BPA while boosting body function and immunity.

Hexane is a volatile, flammable petrochemical solvent. Hexane is also listed as a hazardous air pollutant and its dangerous neurotoxic effects are noted on the EPA's Technology Transfer Network. Long-term hexane exposure

via inhalation causes polyneuropathy, weakened muscles, blurred vision, fatigue, headaches, nausea, and numbness in the arms and legs. Chronic hexane exposure can also lead to dermatitis, confusion, jaundice, and coma. Unfortunately, the food industry uses hexane to extract proteins from soybeans and oils from other crops such as canola and corn. Many soy food additives are derived from a process that uses hexane. In addition, cornmeal and soybean meal are extracted using hexane, and this extract is given to all grain-fed livestock in America, including cows, poultry, hogs and even farmed fish that are raised on completely unnatural grain diets. The CDC noted that when female mice were exposed to commercial hexane for two years, they had an increase in liver cancer. The Cornucopia Institute found nearly one hundred adverse reactions to infants fed formula with hexane-extracted DHA/ARA oils added. Just because something is labeled "organic" does not mean that it is hexane-free.

Adams discusses various pesticides that most people are regularly consuming with the foods that they eat. In addition to pesticides, at least 60% of the herbicides used in global agriculture have been demonstrated to interfere with the endocrine system and reproduction. Glyphosate, patented by Monsanto, is the most widely used herbicide in agricultural production. Neither the FDA nor the USDA test for glyphosate residue on food. But MIT researchers have found that glyphosate enhances the damaging effects of other food-borne chemical residues and environmental toxins by interfering with certain enzymes and healthy gut bacteria. By doing so, glyphosate contributes to a wide range of ailments including gastrointestinal disorders, obesity, diabetes, heart disease, autism, Alzheimer's disease, infertility and cancer. Adams discusses about seven other dangerous pesticides and herbicides in his book, but those will not be discussed here.

Food Forensics Review

Aspartame, known by its brand names Equal®, NutraSweet®, and AminoSweet®, is one of the most widely used artificial sweeteners on the market today. Aspartame can be found in candy, yogurt, desserts, sports and energy drinks, coffee drinks, instant breakfast shakes, diet sodas, vitamins, over-the-counter medicines and so much more. Aspartame is being consumed by two-thirds of the population in over six thousand products in one hundred countries worldwide. It's also one of the most addictive neurotoxins in the food supply. An overdose of aspartame can cause all kinds of awful symptoms, including headaches, blindness, difficulty breathing, convulsions, seizures, low blood pressure, coma, liver dysfunction, nausea, vomiting, abdominal pain, and leg cramps. The EPA has listed aspartame as a "chemical with substantial evidence of developmental neurotoxicity." Rats fed low doses of aspartame developed significantly more leukemias and lymphomas.

Monosodium glutamate (MSG) is found in chips, sauces, salad dressings, fast food, frozen dinners, TV dinners, marinated meats, baby foods, formulas, and vaccines. But the toxicity from MSG can induce not only brain damage and neurodegenerative disorders, but also endocrine disruption, irritable bowel syndrome, weight gain, reproductive issues, behavior disorders, and cancer. To prevent the problems associated with MSG, avoid processed foods and preserved foods. Magnesium also helps play a role in modulating MSG's toxic effects.

Adams also had helpful information about artificial colors, chemical preservatives, emulsifiers, thickening agents, and nitrites. But due to size constraints on this book review, these will not be discussed here.

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Healing with Homeopathy

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

Homeopathy for OCD: A Deep and Lasting Cure

Claudio's Incapacitating OCD (Obsessive-Compulsive Disorder)

Claudio, in his mid-forties, had his first appointment with me in late 2014. Married with two children, he described himself as "outgoing, happy, and very strong about getting what I want." He enjoyed a challenge and was considered very successful: "I was bold coming to the US from Mexico. I had a degree in computer science, and one of my first jobs was equivalent to a master's degree in manufacturing. That began a two-year process with lawyers to try to convert my US visa into residency. That's when the uncertainty started. There was a drastic increase in gang activity in Mexico, and I was afraid for my family to go down there. What if they denied me the visa? Just before the date of immigration review, I began to experience anxiety on a daily basis. I didn't want to eat. I worried constantly that I would arrive late to the interview. And, if it were denied, what about my responsibilities? How would I pay my rent? What if the visa were denied? Would my family have to move back to Mexico with my parents?"

The tremendous stress started to take a toll on Claudio's work life: "Since it was my job to double check the computer backups for the entire organization, it occurred to me that a mistake on my part could cause anguish to hundreds of people, all of whom depended on my backups being accurate…. Then I began to feel anguish that someone would break into our house because I forgot to lock the door. So, I began to go back three to four times to check. Then I started to double- and triple-check the car. Did I really put it in park? Lock it? Set the emergency brake? Then came worrying about leaving on the stove burners.

"At work I started obsessing about whether I needed to lock my computer when I walked away from my desk. Then I wasn't pacified even when the screen read 'locked.' What if I created a new program and it accidentally deleted important files? I'm afraid I'm gonna harm someone, then I will feel responsible for it. I'd lose sleep at night trying to figure out how to test and retest, make the system foolproof… at home I am afraid that someone will go through the paper shredder and use my information, even though it's not even sensitive data. What if I get contacted by the police, lawyers, immigration officers? They might send me to jail!

"I also have a problem with germs. When I wash the dishes, I get concerned that I didn't wash them right. That it will contain something that may harm my children or my wife. When I take money, I have to wash it once or twice, in case it might hurt someone else… I'm afraid to put pesticides into the garden because it will drain into the drinking water."

"Tell Me More"

Patients often complain that their conventional medicine docs seemed rushed – the hand reaching for the doorknob after five or ten minutes. Homeopaths are definitely not like that. In order to choose the one best remedy (*simillimum*) out of 8000+ (!) takes a lot of listening and individualizing the possibilities. Claudio continued, "I get restless. A fear of being on the edge. Let's say you were just scared by a dog who was very close to you and barking. That's how I feel every morning when I wake up. My heart is beating fast. I feel anguished. In alert mode…. Say your father is in a life-or-death duel and you know someone will be killed, die."

Claudio woke regularly at 3 or 4 AM with anxious thoughts. "Anguish. A fear of danger, of getting hurt, of not living anymore." As a child, Claudio was the victim of bullying. It had taken much time and great effort for him to develop the boldness that he had referred to early in our conversation. "Fearless, secure… knowing that everything will be fine."

Persistence on the Part of Both the Patient and the Homeopath

Using Rajan Sankaran's *Sensation Method*, Claudio clearly had the qualities of a mineral: organized, structured, responsible, performance, identity. But I didn't find the remedy that ultimately resolved the OCD initially. *Kali bromatum* (Potassium bromate) helped quite a bit over a three-year period, but not completely.

Kalis are all about keeping things safe, sure, and invulnerable to attack. You can see how that fit Claudio quite well. Claudio had a great deal of faith in homeopathy (I use that word instead of "confidence" intentionally.) He was willing, unfailingly, to hang in there until I found the right remedy to cure his OCD: Not only was it my unswerving belief that there is, indeed, a *simillimum* (perfect remedy match) for each person, but his confidence, and my simply wanting to help him because he was such a sincere, heartfelt, caring individual.

So, as I do when I feel stuck on a case, I carefully revisited Claudio's case from the beginning, open to a new remedy from understanding the patient in a fresh way. I believe it is partially the intention of the homeopath, patience, and the belief that the *simillimum* does exist and can be found. So, two and a half years ago, I looked carefully again at what were the core issues of Claudio's case, and found homeopathic rubrics that matched more precisely: "*Delusion that he has neglected his duty*;" "*Ailments from responsibility;" "Compulsive disorders;" "Remorse/repentance;" "Praying;" "Fear something will happen to his family or to him;"* and *"Washing one's hands."*

The remedy that came up was one that fit Claudio so perfectly that I was amazed I had not come upon it earlier: *Aurum arsenicum. Aurum* (gold) has more of a nobility, responsibility, and duty than the *Kali's*. They are able to withstand considerable pressure, often find themselves in positions of leadership and management, and feel personally responsible for the welfare and wellbeing of others. They are quick to blame themselves, as did Claudio: and the remedy, found under the very appropriate rubric "conscientious," was so descriptive of Claudio, who fits *Aurum* much more than the *Kali's.* As does the tendency to self-reproach. There are so many features of *arsenicum* in this case: the anxiety about the future, obsessive-compulsive checking, worries about safety of oneself and one's family, and loss of sleep due to anxiety, just to name a few. There are a few uniquely *Aurum arsenicum* symptoms in the homeopathic literature, which I have seen before but which did not fit Claudio: "*Indifference to domestic duties"* and "Neglects her children." In fact, the opposite was true in Claudio's case: an obsession about washing dishes and cleaning.

What Is a Homeopathic Mineral Salt and When Is It Needed?

A homeopathic mineral salt is a remedy made from more than one macro-element (such as calcium, phosphorus, magnesium, sodium, potassium, and chloride) and either a microelement (such as iron, copper, zinc, fluoride, iodine, selenium, chrome, cobalt), or a trace element (bromine, chrome, nickel, lithium, silicon, tin, and others). The idea is that such a remedy contains the qualities of *both* minerals. In many cases, especially for homeopaths who are not so experienced in differentiating these remedies, the patient will experience a partial, but not complete, amelioration from the prescribed remedy. Then, upon restudying the case, it becomes clear that the patient exhibits characteristics or symptoms of the other element as well.

One of the fairly common mineral salt combinations is *Kali bromatum*, potassium bromate. *Kali carbonicum* (the main potassium remedy) is a by-the-book, rule-oriented, family-oriented, responsible type of person. *Kali bromatum* adds the bromate characteristic of guilt, hence the classic "Delusion: brother fell overboard in her sight." Years ago, in our depression book, I included a case of a woman whose toddler had, tragically, drowned in their backyard while she and her husband were elsewhere in the house. *Kali bromatum* helped her dramatically. I recently gave *Kali muriaticum* to a very *Kali*-like woman with a number of children whose whole life and world revolved around caring for them. However, it is not, of course, just the situation of the patient that calls forth a mineral salt, but the *symptoms* and *nature* of the individual.

I have many cases of these mineral salts being used in my practice. In Claudio's case, I had given him a number of remedies. His anxiety was very typical of *Arsenicum*, and his high degree of responsibility could have indicated either *Kali* or *Aurum.* It is easy to confuse the two. So, I did not arrive at *Aurum arsenicum* for a while. Claudio was a very loyal and determined patient and had a great of confidence in homeopathy, in my ability to help him, and in the process. So, he was willing to stick with it until we both knew that I had found the *simillimum* (one best remedy) for him. And we both knew when I had.

Claudio's Response to the Remedy

Ten Weeks Later: "I'm surfing life! I think this remedy is one of the best I've had. I'm able to let go of my obsessions more easily than before. 80% of the time I can let them go… I think this is the remedy we've been looking for…. This is it!"

Five months: "This is a good remedy… I'm more able to manage my anxiety and obsessiveness. I'm able to let the thoughts go easier."

Seven months: "I'm fine. This remedy is the right one. I feel very good…. I'm able to let a lot of things go that I would obsess about. Like before I didn't want any soap remaining on the dishes I'd washed. Now, 'too bad.' I'm able to let go of a lot regarding responsibility and security. I've lost 20 pounds, too!"

One year seven months: "We haven't talked in a year. My remedies have kept me going. I'm back into sports big-time. I've done some therapy to heal my childhood wounds. I still take the remedy when I need to – the last time was two and a half months ago. I still have to remind myself that it's okay to make mistakes. To accept others. Put myself in their shoes. In some ways, I have the tools I need to deal with the quarantine.

Twenty-five months: In response to my email asking how he was doing: "I never took the last dosages that you sent me. I have them in case I feel I need them… How can I ever forget you who helped me for so long? I am so grateful for all that you have always done for me. You are in a very special place in my heart. My best regards, Claudio."

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

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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True or False: Antibiotics Cause Dysbiosis

It has been suggested that what sets humans apart from other arthropods is our superior pattern processing (SPP). This talent has been suggested "… as the fundamental basis of most, if not all, unique features of the human brain, including intelligence, language, imagination, invention, and the belief in imaginary entities such as ghosts and gods."

Somewhere along the evolutionary trail, our pattern processing capability became quite sophisticated as our cerebral cortex, in particular, the prefrontal cortex, expanded.

We became better and better at recognizing patterns in the world and making generalizations based on these observations. We have a talent for it and in many instances, this ability has proven advantageous.[1]

If you haven't noticed by now, my particular version of the human brain finds particular delight in finding exceptions to these generalizations and pointing them out. The good editor of this journal, Dr. Jonathan Collin, has chosen the term 'curmudgeon' to describe my peculiar tendency, a description that many have agreed with. If given a choice, I might have settled on a term more complimentary; but it's his journal, and he gets to make the rules.

One rather interesting study from November 2018 caught my attention. Bodogai and colleagues reported that treating old but healthy mice and macaques (a kind of monkey) with an antibiotic called enrofloxacin was a useful strategy to prevent aging.

Enrofloxacin (ENR) is a fluoroquinolone antibiotic sold by the Bayer Corporation under the trade name Baytril. It's only approved for animal use at this time. Fluoroquinolones are popular antibiotics used to treat a variety of illnesses such as respiratory and urinary tract infections. This family includes ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), and ofloxacin (Floxin). In general, we naturopathic doctors are not big fans of these drugs for a long list of reasons that I have enumerated elsewhere.

Enrofloxacin is a particularly potent bactericidal agent; its activity is concentration-dependent, and susceptible bacteria die within 20–30 minutes of exposure.

A circuitous route led these researchers to give their test animals this drug. They knew that aging in "… humans is associated with increased hyperglycemia and insulin resistance (collectively termed IR) and dysregulation of the immune system. However, the causative factors underlying their association remain unknown. Here, using "healthy" aged mice and macaques, we found that IR was induced by activated innate 4-1BBL+ B1a cells. These cells (also known as 4BL cells) accumulated in aging in response to changes in gut commensals and a decrease in beneficial metabolites such as butyrate. We found evidence suggesting that loss of the commensal bacterium *Akkermansia muciniphila* impaired intestinal integrity…"

Most of us can keep up with this theory that insulin resistance is a major boondoggle in living a long and healthy life and the blame is somehow related to gut biome stuff. We've subscribed to this idea pretty much since Elie Metchnikoff wrote his 1907 book, the *Prolongation of Life*,[2] though some of us might turn to Wiki to read up on these 4BL cells as they weren't discussed all that thoroughly during our education.

Most of us are aware that impaired intestinal integrity, aka leaky gut syndrome, is not a good thing. Decreased *Akkermansia* populations allow leakage of bacterial endotoxins into the body activating the conversion of B1a cells into those 4-1BBL+ B1a cells that in turn induce insulin resistance.

Now here's the line in the study that got my attention: "This pathway and IR were reversible, as supplementation with either *A. muciniphila* or the antibiotic enrofloxacin, which increased the abundance of *A. muciniphila,* restored normal insulin response in aged mice and macaques.[3]

Where do we start with this?

First, insulin resistance is reversible.

Second, that two relatively simple approaches might reverse it, both focused on increasing *Akkermansia* populations in the gut. At this point in our growing understanding of insulin resistance and type 2 diabetes, this isn't surprising. That glycemic regulation is impacted by gut bacterial populations is widely accepted. That increasing *Akkermansia* is a good idea has slowly taken hold these last few years. Yet this last bit of news, that taking an intense fluoroquinolone antibiotic might trigger changes in the gut that we should appreciate, comes out of left field.

After all, our general view is that antibiotics are bad for a multitude of reasons, but one of the most quoted reasons is that these drugs will disrupt our ever-so-important bowel flora. But, lo-and-behold, this study argues that fluoroquinolones may shift the biome in a favorable direction that may slow aging.

This idea should give all of us pause. Avoiding antibiotics and thinking of them as dangerous has become an article of faith, even among our medical colleagues. These results suggest that an occasional dose of Cipro may favorably impact mortality. Chew on that for a moment or two.

Now, of course, I'm lucky to live in Colorado where prescribing any antibiotic is outside my legal scope of practice. This information is all theoretical for me. I am left to translate these data and ask myself, "Are there other ways to increase *Akkermansia m.* populations?"

There is already a long and varied list of supplements associated with increasing *Akkermansia* populations that includes rhodiola,[4] algae,[5] flaxseed,[6] garcinol,[7] melatonin,[8] lactobacilli,[9] grape polyphenol extracts,[10] and berberine.[11] Note that this last supplement, berberine, has a synergistic action with some fluoroquinolone antibiotics against drug-resistant infections strains of Klebsiella bacteria.[12]

We live in a big, busy and complicated world. Being able to see patterns in this cacophony of a world allows us to move with some semblance of direction and advance our endeavors. The problem is that sometimes we forget that these generalizations do not apply under all circumstances. Whatever rules we attempt to adhere to to make sense of things will have their exceptions. Life is complex and will do its best to outsmart us.

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CALENDAR

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/

SEPTEMBER 29-OCTOBER 3: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE (ICIM) FALL MEETING – Vaccines and Immunology: Truth and Fiction in Fort Worth, Texas. CONTACT: https://icimed.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

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Women's Health Update

by Tori Hudson, ND
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Herbs with Strong Track Records: Research in Use and Therapeutic Effects

Ginseng Powder and NAFLD

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease. Many studies have reported on larger numbers of men with NAFLD than women; however, recent studies investigating the role of gender and NAFLD have reported the contrary. In a study reported online in 2017, women had a higher prevalence of NAFLD than men in all age groups; and the largest difference was found in those aged 56-60 years (prevalence = 27.4% versus 21.2%. (Verstion 2. F1000 Research 2017;6:1630.) In a 2015 study, the prevalence of NAFLD was studied in 2010-2011 among 9,360 women in Wuhan, China. The prevalence of NAFLD increased from 5.3% to 18.8% in women younger than 45 years versus women aged 45 to 55 years and rose to 27.8% in women older than 55 years. In obese women, the prevalence of NAFLD was 48.4%. Women older than 45 years and obese women with NAFLD had more unfavorable metabolic risk factors. The rising prevalence of nonalcoholic steatohepatitis (NASH) was also noted in women older than 55 and obese women with NAFLD. To put it simply, obese and postmenopausal women have a high prevalence of NAFLD and severe metabolic disorders. The prevalence of NASH seems to be considerably higher in obese and postmenopausal women with NAFLD and should be considered a primary concern in the care of postmenopausal women in particular. (*Menopause* 2015;June;22 (6):667).

In the search for botanicals to assess their therapeutic use in liver disease, a randomized, double-blind, placebo-controlled study was conducted to evaluate the effects and safety of fermented Asian ginseng powder on liver function and in the treatment of fatigue in patients with liver dysfunction.

This 12-week study was conducted between July 2016 and October 2017 in South Korea. Participants included were those between the ages of 19 to 70 years with a serum alanine aminotransferase (ALT) level of 35-105 IU.

Ninety participants were randomized to receive a placebo (n = 30), 125 mg of Asian ginseng powder, or 500 mg of the same Asian ginseng powder. Participants took two tablets once per day for 12 weeks. Individuals continued their usual physical activities but were asked to avoid functional foods or dietary supplements throughout the study. Overall, 28 in the low-dose group, 30 in the high-dose group, and 26 in placebo group completed the study and were included in analysis. The majority were men (80%) with a mean age of 43.5 years.

Liver function, lipids, high sensitivity C-reactive protein (hs-CRP), total antioxidant capacity (TAC), CBC and multidimensional fatigue scale (MFS) score were assessed at screening, baseline, and study completion. Dietary intake was evaluated using a self-reported food diary.

Results: No significant difference in ALT was found between the three groups. A decrease in gamma glutamyl transferase (GGT) levels was found in the ginseng low-dose group, but the difference compared with placebo was not significant. In men, the decrease in GGT in the low-dose group was significant compared with the placebo group. Levels of hs-CRP decreased with low dose ginseng, but this was not significant compared with placebo. In the men who had no known alcohol overuse, there was a significant decrease in hs-CRP with the low-dose ginseng group compared with placebo. There were no significant differences in TAC, AST, TC, TG, HDL-C, and LDL-C among the three groups. The MFS score decreased significantly with high dose ginseng when compared with placebo and low-dose ginseng. In men, this effect was seen after 12 weeks. There were no adverse effects observed over the course of this study.

Commentary: Low-dose ginseng for 12 weeks is safe, and it appears that it may improve liver function in patients with liver disease; high-dose may also improve their fatigue. These results were evident in those without alcohol abuse, and it is not yet clear if ginseng will lower GGT and hs-CRP in individuals with acute or chronic liver disease due to alcoholism. In addition, abnormal liver function tests may not always indicate liver disease. Still, there is a large patient population with NAFLD for whom ginseng should be offered as part of a whole person, multi-faceted strategy. While the majority of individuals in this study were men, I see no reason why not to include this strategy for women with NAFLD.

Jung SJ, Hwang JH, Park SH, et al. A 12-week, randomized, double-blind study to evaluate the efficacy and safety of liver function after using fermented ginseng powder (GBCK25). *Food Nutr Res*. April 6, 2020;64:10.29219/fnr.v64.3517.

Lavender Essential Oil for Renal Colic

My primary experience with lavender extracts is its use in general anxiety disorder. The research is compelling, and my clinical observations yield consistent, although not perfect results. There are other uses, of course, and here is a study on lavender essential oil and renal colic. Not something I see frequently but can be oh so painful when it occurs. Renal colic can be severe in the acute pain and sends individuals to the hospital about half the time. The back pain and/or abdominal pain is secondary to a stone in the ureter. Nonsteroidal anti-inflammatory drugs (NSAIDS) are the first-line treatment; and if that does not work, then opioid analgesics are used.

The goal of this double-blind, randomized, placebo-controlled, interventional study was to evaluate the effects of lavender essential oil on renal colic. The study was conducted in Turkey, and included 59 men and 41 women aged 19-64 years. Patients in group 1 (29 men and 21 women) received 75 mg intramuscular diclofenac and a placebo in an electronic vaporizer. Patients in group 2 (30 men and 20 women) received 75 mg intramuscular diclofenac and aromatherapy consisting of 2% lavender oil dispersed in an electronic vaporizer. The degree of pain was evaluated by patients before treatment and at 10 and 30 minutes after treatment using a visual analog scale (VAS).

While VAS scores before treatment and at 10 minutes after treatment did not differ significantly between the groups, in group 2, VAS scores at 30 minutes after treatment were significantly lower than group 1. VAS scores for men and women were analyzed separately and there was no difference between group 1 and group 2 for men, at 10 or 30 minutes; however, VAS scores for women at 30 minutes after treatment in group 2 were significantly lower than those of women in group 1.

Commentary: This study surprised me as I have been focused on the use of lavender essential oil for general anxiety disorder as well as cases of anxiety in conjunction with insomnia or depression.

It is thought that the linalool and linalyl acetate found in lavender essential oil are responsible for this analgesic property exhibited in this study. Linalool inhibits prostaglandin production. In addition, olfactory pathways are connected to the limbic system; and when it is stimulated, emotional changes may be effective in reducing pain. It would also be of interest to see if taking an oral dietary supplement of lavender essential oil might lead to similar or even better results for renal colic than the aromatherapy. With the option of lavender essential oil for acute pain, in addition to topical heat and wild yam tincture for it's antispasmodic effect on the ureter, I believe we have a good shot at providing relief. Then, we can set about the business of correcting the underlying cause and preventing future events.

Irmak Sapmaz H, Uysal M, Taş U, et al. The effect of lavender oil in patients with renal colic: a prospective controlled study using objective and subjective outcome measurements. *J Altern Complement Med*. October 2015;21(10):617-622.

Green Tea with Antibiotics for Simple Bladder Infections

Bladder infections in otherwise healthy pre-menopausal and non-pregnant women tend to be uncomplicated and are classified as lower urinary tract infections (UTIs). UTIs are amongst the most common infections in women, and *Escherichia coli* (*E. coli*) is the organism that is responsible for about 75-95% of uncomplicated UTIs.

Trimethoprim-sulfamethoxazole (TMP/SMX), aka co-trimoxazole and brand names Bactrim or Septra, is an inexpensive antibiotic and generally well tolerated and effective. However, due to its common use, resistance to *E. coli* strains with this antibiotic has increased significantly; and as many as 20% of cases will be resistant, which is why other first line antibiotics are often chosen.

The genesis of this current study is that there are laboratory studies that have shown antimicrobial effects of green tea catechins against *E. coli* as well as synergistic effects between the catechins and antibiotics, such as co-trimoxazole, against *E. coli*.

This randomized, blinded, placebo-controlled trial was conducted in Iran. Healthy premenopausal, non-pregnant women ages 18-50 with acute uncomplicated cystitis were included in the study. After urine collection, women were given four 500 mg capsules of green tea extract or placebo before bed, daily for three days. All of the patients also received the TMP/SMX at two 480 mg tablets twice daily for three days. Each gram of the green tea contained approximately a total phenol content of 283 mg and 65 mg of epigallocatechin gallate (EGCG). The urine was then tested again in each group, on the fourth day.

Results: Among the 107 eligible women patients, 70 completed the trial. Women in the green tea group showed a statistically significant decrease in the prevalence of cystitis symptoms at each time point (recorded daily). The presence of symptoms were as follows:

Baseline:	Green tea 68%; placebo 75%
After 1 day	Green tea 61%; placebo 74%
After 2 days	Green tea 34%; placebo 67%
After 3 days	Green tea 2%; placebo 63%

In addition, the addition of the green tea resulted in a statistically significant improvement in the urinalysis in terms of color, bacteria, and white blood cells. No patients, in either group, had a recurrence of their UTI after two weeks. After four weeks, one in the green tea group had a recurrence and after six weeks, two in the TMP/AMX only group had a recurrence.

Commentary: One of the unique things in the study design was that the green tea extract was given in a bolus, all four capsules at once, and in the evening. The rationale of the researchers was that the EGCG was better retained in the bladder all night, noting that more than 90% of the urinary EGCG is excreted in the first eight hours of administration; therefore all at once and in the evening before bed would theoretically enhance its effectiveness, if they did not urinate until morning.

A word of caution about green tea extracts: You might be interested in a report on green tea extracts that came to my attention in 2020 and was recently pointed out to me again, to be included for this column. (Ouyang J, et al. Prooxidant Effects

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of Epigallocatechin-3-Gallate in Health Benefits and Potential Adverse Effect. *Oxid Med Cell Longev*. Published online Aug 12, 2020)

It pointed out the susceptibility of green tea extracts to generate reactive oxygen species (ROS) via autooxidation and exhibit prooxidant effects. This leaves us with a dual role of epigallocatechin-3-gallate (EGCG), the major polyphenolic compound present in green tea. While most of us are familiar with antioxidant properties of EGCG, under certain conditions, it can act as a proxidant, with the subsequent benefits and harms of prooxidants. There may be a dose limit to EGCG such that harm, toxicity, and in particular liver damage can be avoided.

In a safety study of EGCG in humans, the no-observed adverse effect level (NOAEL) was reported to be 600 mg/day, and the acceptable daily intake of EGCG for humans was reported to be 322 mg EGCG/day (Yates AA, et al. Bioactive nutrients - time for tolerable upper intake levels to address safety. *Regulatory Toxicology and Pharmacology.* 2017;84:94–101).

Some European regulatory agencies proposed that the tolerable upper intake level of EGCG should be 300 mg per day for humans. (Yates A. A., Erdman J. W., Jr., Shao A., Dolan L. C., Griffiths J. C. Bioactive nutrients - time for tolerable upper intake levels to address safety. *Regulatory Toxicology and Pharmacology.* 2017;84:94–101). After reviewing the evidence from interventional clinical trials, The European Food Safety Authority (EFSA) concluded that an intake of 800 mg or more of EGCG/day could lead to elevated transaminases based on a review of interventional clinical trials. (Younes M et al. Scientific opinion on the safety of green tea catechins. *EFSA Journal.* 2018;16(4))

In a review of EGCG safety date and human adverse events, authors advised a safe level to be 704 mg per day EGCG in beverage form and 338 mg per day in bolus form: 100 g dry weight of green tea contains about 7000 mg EGCG, and 100 g of green tea infusion contains approximately 70 mg EGCG. (Hu J, et al. The safety of green tea and green tea extract consumption in adults - results of a systematic review. *Regulatory Toxicology and Pharmacology.* 2018;95:412–433)

In my experience, 49 out of 50 premenopausal non-pregnant women with uncomplicated UTIs can be successfully treated with a combination of herbal ingredients if dosed aggressively (formulas typically would contain cranberry extract, bucchu leaf, Oregon grape root, pipsissewa, uva ursi and marshmallow root); occasionally I might add mannose powder, along with a robust intake of water. On the atypical occasion that I prescribe an antibiotic, I will consider adding the dosing of green tea extract for three days used in the current study, whether the antibiotic is TMX/SMP or another.

Kheirabadi K, Mehrabani M, Sarafzadeh F, et al. Green tea as an adjunctive therapy for treatment of acute uncomplicated cystitis in women: A randomized clinical trial. *Complementary Therapies in Clinical Practice.* 2019;34:13-16

Turmeric and Cirrhosis – Yet Another Use for This Remarkable Medicine

Turmeric and its main bioactive component, curcumin, has previously reported benefits in liver injury and cirrhosis. The current randomized, double-masked, placebo-controlled trial investigated the effects of curcumin supplementation on health-related quality of life in patients with liver cirrhosis.

The study included 70 patients, ages 20-70, from a gastroenterology outpatient clinic in Iran. The patients had a score >11 (with a test range of 6 up to 40) on the Model for End-stage Liver Disease (MELD) and arterial oxygen pressure >60 mm Hg. The highest score of 40 represents the greatest severity of liver disease.

Thirty-five patients took 1,000 mg (two 500 mg capsules) daily of curcumin for 12 weeks and 35 patients took placebo capsules. The curcumin capsules contained 95% curcuminoids. Patients were instructed to eat their usual diet and maintain usual physical activity during the study.

Patients were assessed at baseline and after 12 weeks of treatment, using the Chronic Liver Disease Questionnaire (CLDQ), Liver Disease Quality of Life Questionnaire (LDQOL), Liver Disease Symptom Index 2.0 (LDSI), and 36-item Short Form Health Survey (SF-36). Both the curcumin and placebo groups were similar at baseline in primary causes of liver cirrhosis and scores on the questionnaires. The mean duration of cirrhosis was 4.25 ± 2.98 years.

In the final analysis there were 28 patients in the curcumin group and 30 in the placebo group. Compared with baseline, there were significant improvements in the curcumin group in the total CLDQ score and in the individual scores for fatigue, emotional function, worry, abdominal symptoms, and systemic symptoms ($P < 0.001$). Compared with baseline, there were significant decreases in the scores, i.e. worsening of symptoms, in the control group for all of the parameters above. In the curcumin group, there were also significant improvements in the LDSI domains of itching, bodily pain, decreased appetite, depression, fear of complication, jaundice, decreased sexual interest and more, with worsening of these same issues in the control group.

Improvements in the scores for SF-36 significantly improved in the curcumin group for total physical and mental health, physical functioning, bodily pain, vitality, social functioning and mental health while significant decreases in scores, indicating decreased quality of life, were seen in the control group for all these same domains except for emotional and mental health.

Commentary: The broad range of curcumin's clinical effects continues to be impressive, from simple issues such as hot flashes to serious health care issues, including cancers. Liver cirrhosis is serious as well and a life-threatening disease. While this study did not assess the improvement of liver disease with physical exams, blood tests, liver ultrasounds or liver biopsies, improvement in the quality of life and liver disease symptoms in those with liver cirrhosis is welcomed.

Nouri-Vaskeh M, Afshan H, Mahdavi AM, Alizadeh L, Fan X, Zarei M. Curcumin ameliorates health-related quality of life in patients with liver cirrhosis: a randomized, double-blind placebo-controlled trial. *Complement Ther Med*. March 2020;49:102351.

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Editorial

➤ *continued from page 80*

duration of pain was also significantly greater with the green LED than with the white LED ($p < 0.001$ for each comparison). The effect of the treatments on health-related quality of life was assessed by the Fibromyalgia Impact Questionnaire (FIQ). The FIQ is a 100-point scale where 0 indicates no impact from fibromyalgia and 100 indicates the worst possible impact. During treatment with the white LED, the mean FIQ score improved by 13.6%, from 76.5 to 66.1. During treatment with the green LED, the mean score improved by 40.4%, from 71.6 to 42.7 ($p < 0.05$ for the difference in the change between treatments). No side effects were reported during either treatment period.

The second study recruited 27 women and two men (mean age, 52.2 years) with recurrent migraines who were dissatisfied with their current treatments.[3] They underwent the same protocol with the white and green LEDs as in the fibromyalgia study.[2] During white LED treatment, the mean number of headaches days per month decreased significantly by 9.3%, from 18.2 to 16.5. During green LED treatment, the mean number of headaches days per month decreased significantly by 69.8%, from 18.4 at to 7.4. Mean headache severity decreased by 7.1% during white LED treatment and by 60% during green LED treatment. The beneficial effect of the green LED was similar in participants with episodic migraine (defined as less than 15 migraine days per month) and in those with chronic migraine (defined as 15 or more migraine days per month). No side effects were reported.

This research offers new hope for the millions of people who suffer from fibromyalgia or migraines. Green LED therapy is simple, inexpensive, and apparently safe; and it produced substantial benefit for both of these conditions. It should be noted that two of the authors of these studies have a patent pending through the University of Arizona for the use of green light therapy for the management of chronic pain. Confirmatory studies by a different research group would therefore be worthwhile.

Alan R. Gaby, MD

References

1. Martin L, et al. Green light exposure improves pain and quality of life in fibromyalgia patients: a preliminary one-way crossover clinical trial. *Pain Med*. 2020;22:118-130.
2. According to a personal communication from one of the study authors (Ibrahim MM) the LED protocols were identical in the fibromyalgia study and the migraine study. The protocols were described somewhat differently in the two studies because a reviewer of one of the papers asked for more details.
3. Martin LF, et al. Evaluation of green light exposure on headache frequency and quality of life in migraine patients: A preliminary one-way cross-over clinical trial. *Cephalalgia*. 2021;41:135-147.

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Shedding Light on Fibromyalgia and Migraine: A Natural "Green New Deal"

Fibromyalgia and migraine are two common chronic conditions that cause a great deal of pain and suffering. They affect both sexes, but they occur much more frequently in women than in men. Various medications are available to help manage these conditions, but the results are often less than satisfactory. Fibromyalgia and migraine respond well in some cases to nutritional therapies, such as identifying and avoiding allergenic foods, avoiding aspartame and monosodium glutamate, and supplementing with magnesium and coenzyme Q10. In addition, intravenous administration of magnesium (or the combination of magnesium, calcium, B vitamins, and vitamin C – the Myers cocktail) can rapidly abort acute migraines in a large proportion of cases, and appears to be effective for relieving symptoms in about half of fibromyalgia patients.

However, despite the best that conventional medicine and integrative medicine have to offer, many patients with fibromyalgia or migraines continue to experience symptoms, which are sometimes debilitating. New approaches are therefore needed.

Recently, researchers at the College of Medicine of the University of Arizona began investigating the effect of green light exposure on these two chronic painful conditions. The potential benefit of green light was suggested by an earlier study by this research group, in which exposure to a green light-emitting diode (also known as an LED or LED light) decreased experimentally induced pain (including neuropathic pain) in rats, without producing any noticeable adverse effects. The investigators followed up this animal study with two clinical trials: one in patients with fibromyalgia and the other in migraine sufferers.

In the first study,[1] 21 adults (mean age, 53.3 years; 20 women and 1 man) with fibromyalgia were exposed to a white LED every day for 10 weeks. After a two-week washout period, they switched to a green LED for another 10 weeks. Each treatment was provided as an LED flex strip that was 2 meters long. The strips were purchased from ledsupply.com. The white LED was listed as #LS-AC60-66-WH, and the green LED (wavelength, 525 nm) was listed as #LS-AC60-6-GR. Two of every three light bulbs across the entire 2-meter strips were covered with electrical tape, in order to achieve a light intensity of 4 lux at a distance of 2 meters and 100 lux at a distance of 1 meter. With each treatment, the participants were instructed to take the LED into a dark room and to use it as the only source of light for a minimum of one hour per day, with the option to increase exposure time to a maximum of two hours per day. The LED was placed between 1 and 2 meters from the eyes, to achieve an intensity that suited them best. The participants were instructed to keep the LED strips in their field of vision, but not to stare directly at the lights. With this protocol, the minimum intensity of the light was 4 lux, and the maximum intensity was 100 lux. During the periods of LED exposure, the participants were advised not to fall asleep and not to engage in activities that required other sources of light, such as watching television or using a computer or mobile phone. They were also asked to undergo the light therapy at the same time each day, all at one time.[2]

During treatment with the white LED, mean pain severity on a 10-point scale (with 10 indicating the worst pain and 0 indicating no pain) improved nonsignificantly by 6.6% (from 8.71 to 8.14). During treatment with the green LED, mean pain severity decreased significantly by 42% (from 8.38 to 4.86; $p < 0.001$ for the difference in the change between treatments). There was a nonsignificant trend toward greater pain reduction in those who were exposed to the green LED for more than 1.5 hours per day (as compared with less than 1.5 hours per day). The mean reduction in frequency and

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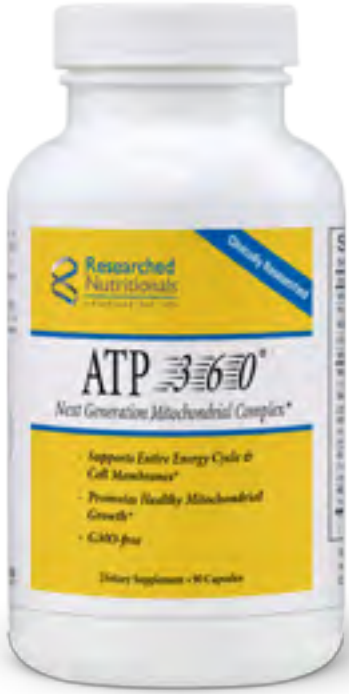

1) Hamilton, D., Jensen, G., Nutraceutical support of mitochondrial function associated with reduction of long-term fatigue and inflammation. *Altern Ther Health Med. Alternative Therapies May/Jun 2021 Vol. 27 No. 3*

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