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Affinity, Deborah, and Jacqueline
enjoying a moment at San Diego's Balboa Park

From the Publisher

A Tour of Klaire Laboratories

In the midst of a family vacation in San Diego, I broke away from our toddler granddaughter, Jacqueline, her mother, Affinity, and my wife, Deborah (pictured here) to take a field trip to Klaire Laboratories facilities in Reno, Nevada. Klaire is part of SFI, a company that originated as an herbal apothecary in the early 1800s. It now has production facilities in England, Switzerland, South Africa, South Korea, and is headquartered in Australia. SFI directs its researchers to develop high-quality natural products promoting health maintenance, avoiding inclusion of pharmaceuticals and chemicals. Its Reno division is focused on the production of innovative probiotics that adhere to structure and function

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From the Publisher

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regulations of supplements as imposed by the FDA. Supplement manufacturing previously labelled as ProThera will now carry the Klaire Labs label produced to meet the same quality control required by the FDA for pharmaceutical manufacturers.

Reno calls itself the "Biggest Little City in the World" and is located very close to the wonderful natural attractions of Lake Tahoe and Squaw Valley ski resort. Klaire Labs is very near downtown and its facility, only recently completed, includes all the features necessary to ensure both product composition accuracy and non-adulteration. All workers in the production side are obligated to be gowned up like surgeons and do not have free access to receiving and shipping. All raw materials

The publisher and guests touring SFI's Klaire Laboratories' facility in Reno, Nevada. Surgical attire is required ensuring minimal contamination from the outside.

are quarantined until they undergo quality control testing both within the facility itself and also by independent lab testing. Once a container of raw material is certified, the container is sealed and affixed with labelling that is digitally coded; monitoring devices ensure that the container may not be moved or tampered with until authorized.

When a raw material is ready to use in the production of a product, for example, a probiotic with several different bacterial strains, the first step is precise adherence to the product's formulation. There should be neither too little nor too much of the bacterial strain in the product. For this work, manufacturing pharmacists carefully examine the raw material microscopically and then digitally weigh it, ensuring a very specific amount of it is put in a container with labelling that is digitally monitored. Once the ingredients are all weighed, they are set aside for mixing. In a unit that looks much like a miniature concrete truck mixer, the raw materials are thoroughly blended in preparation for encapsulation. Mixers are thoroughly washed after each run. The weighing and mixing rooms have air flow hooding to ensure dust and other particulates do not contaminate the processing. In addition, air is maintained at higher than 1.0 atmosphere to ensure that ambient air flows out, again ensuring no dust contamination.

After confirming quality mixing of the product, the mix is introduced into an encapsulating device. Capsules are dropped

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into supplement bottles that are capped and labelled and then prepared for distribution. All products are digitally monitored once they have been labelled and then are prepared for stocking and/or shipment. Needless to say, such intense mechanical operations need regular maintenance and on-site technicians repair equipment as needed. The overall impression is that the manufacturing facility for Klaire Labs not only meets quality control standards but sets the standard that other facilities should meet.

Just because a company's label states that it is manufactured with highest quality standards does not mean that this is true. We should be able to ask the supplement manufacturer to provide information about its quality control and manufacturing process. Inexpensive supplements (and some expensive supplements) undoubtedly are not produced with reputable quality control and may be adulterated with heavy metals and chemicals.

Klaire Laboratories will permit interested individuals to take a tour of its facilities if permission is requested in advance. All supplement manufacturers should offer similar tours of their manufacturing sites. Why not request a tour and assess the company's quality standards?

A Probiotic Support for Depression?

Alcock, Maley and Aktipis review how eating behavior can be manipulated by the gastrointestinal microbiota.[1] They postulate that microorganisms have two potential mechanisms for how microorganisms might alter our eating behavior: (1) the organisms create cravings for eating foods that might suppress survival of competitive microorganisms; (2) the microbiota might elicit "dysphoric" emotions until we eat food that benefits their survival. Alcock et al. point out that a diverse microbiome composed of a large number of differing microorganisms has a greater ability to mutually provide for nutritional needs compared to a microbiome with less diversity. When the microbiome has less diversity, there is greater neurochemical signaling to eat more to provide nutritional needs; obese hosts tend to have limited microbiome populations. Numerous studies are cited of how microorganisms can play an important role in host eating behavior, including how their metabolic activity can modify the host's mood. Lactobacillus in breast milk is observed to increase tryptophan metabolism and have a respective calming effect on the suckling infant. When microbiota was transferred to "germ-free" mice from anxious mice, the cohorts were notably more agitated than prior to the transplant. On the other hand, stressed mice fed *Lactobacillus rhamnosus* had observable reduction in cortisone levels accompanied with calming behavior. Alcock et al. review neural mechanisms, particularly involving the vagal nerve, of how microbiota can alter eating behavior.

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From the Publisher

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Organisms of the microbiome have adapted to produce neurochemicals that closely mimic the human neurochemicals directly influencing emotional response. Alcock notes that the microbiome can be modified by the use of prebiotics and probiotics, microbiota transplantation, antibiotics, and other methods. The authors posit that these approaches may be used to modify our psychiatric state as well as cognitive functioning.

Dr. Collin enjoying the park in San Diego with his family.

Steenbergen, Sellaro, van Hemet, Bosch, and Colzato, researchers in the Netherlands, have demonstrated the efficacy of multispecies probiotics in a randomized control trial on sad mood.[2] As noted by Alcock, it has been hypothesized that probiotics may have a direct impact on depression. However, human studies of the effectiveness of probiotics on depression have been limited. The Dutch investigators tested a probiotic blend containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacilus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, and *Lactococcus lactis* (W19 and W58).

Forty healthy individuals were studied: 20 received the probiotic mixture for one month, while 20 received a placebo mixture in a triple-blinded, randomized trial. Sad mood was assessed using the Leiden index of depression sensitivity. Compared to control, treated individuals revealed a significant reduction of sad mood thought to be manifested by less violent thoughts and worrying. The authors affirm that this is the first evidence that probiotics have a significant effect on diminishing sad mood and suggest that it may be a helpful adjunct for depression.

Elsbeth Pekelharing on Probiotics Science

At the Reno Klaire Lab tour, Elsbeth Pekelharing, Science Liaison for Winclove Probiotics, presented a primer on probiotics science; her lecture serves as the basis for the following editorial notes. Winclove is a private, business-only probiotic manufacturer providing more than 70 probiotic strains to 80+ commercial manufacturers in 35 countries. Strains of microorganisms are specific and represent a subspecies of the designated organism. For example, *Lactobacillus acidophilus* only names the species, but *Lactobacillus acidophilus* W37 is the strain. Different strains can have very different properties; it cannot be assumed that a product labelled as *Lactobacillus acidophilus* either contains *Lactobacillus acidophilus* 37 or functions in the same manner. As a general rule, formulations with multiple species will function better than ones with fewer probiotics species. It is not clear that having a preparation with very high numbers of multi-species that have not been strain identified will provide ideal clinical applications. Furthermore, there is the significant possibility that poorly manufactured formulations will not survive adequately to interact with the gastrointestinal microbiome.

Probiotic microorganisms have at least three major functions within the GI tract: (1) microbe-microbe interaction, for example, growth inhibition of the microbiome organisms; (2) local barrier effects of the gastrointestinal mucosa by microbe-barrier interaction, for example, mucous production; and (3) systemic internal effects, for example, changes in hormone and cytokine production. These functions establish the two-way communication between the gut and brain. The question is how effective the probiotic formulation is to optimize the gut-brain communication.

Intestinal permeability, a gastrointestinal dysfunction, is largely dependent on disruption of the intestinal cell barrier. At a cellular level there is an absence of a "thick" mucous layer, "strong" tight cellular junction, and epithelial cells in "good condition." Ideally the probiotic microorganisms should counter intestinal permeability in three ways: (1) stimulate regulatory response by increasing the production of IL-10; (2) inhibit pro-inflammatory response by decreasing mast cell activation and increasing LPS breakdown; and (3) strengthen intestinal barrier function through increasing trans-epithelial electrical resistance (TEER). These functions can be studied for individual microbial strains; an effective strain will demonstrate improvement of TEER, for example, while an ineffective strain will not. Assessment of barrier function is necessary to understand the effectiveness of a probiotic preparation. For example, clinical testing has demonstrated optimization of TEER with *Lactococcus lactis* W19 and W58 but no other strains. GI survival of the microorganism is another important criterion in selecting strains.

Our patients inform us that they are using a probiotic. We can no longer just accept the fact that the preparation they are using containing over 100 billion organisms means that an effective probiotic is being used. We will need to understand its quality control, strains delineated, and whether it is addressing the applications required.

Bonnie Nedrow, ND, on Non-Alcoholic Fatty Liver Disease

While we associate fatty liver disease with alcoholism, non-alcoholic fatty liver disease (NAFLD) has become a highly prevalent problem. Associated with obesity it is estimated that as little as 15% and as much as 52% of the population has NAFLD. As reviewed in this issue by Dr. Bonnie Nedrow, much of the same factors that bring about metabolic syndrome with obesity, dyslipidemia, and hypertension are involved directly in damaging the liver and causing NAFLD. Insulin resistance is associated with diabetes and pre-diabetes, but it is the key mechanism for insulting the liver, bringing about fatty deposition

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From the Publisher

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in the liver. While we are counseling our pre-diabetic patients about the hazards of inadequate glucose control, we need to bring fatty liver disease into the discussion because this is not a process that will happen in the future—it is currently underway and progressing. While many of the strategies we need to employ for insulin resistance are applicable to managing NAFLD, there are biochemical mechanisms impacting the liver that we don't associate with diabetes. Nedrow's review offers some innovative approaches ready to use in the office immediately.

Jenna Henderson, ND, on Myths Related to Treating Kidney Disease (Cover Story)

Patients seeing us for fibromyalgia, cardiovascular disease, autoimmune disease, or cancer are generally treated vigorously, asked to modify their diet, implement an exercise program, and initiate an extended herbal, nutraceutical, and homeopathic supplementation regimen. In many circumstances prescription medications may be added or reduced, and intravenous or parenteral medication or nutraceuticals are frequently implemented. However, all of this regimentation is called into question with patients who have chronic kidney disease (CKD). The one major contraindication for proceeding with intravenous chelation therapy would be a reduced eGFR (estimated glomerular filtration rate) and elevated creatinine. Despite some commentary that chelation improves kidney function, this is rarely the case; patients with CKD will trend to increasing creatinine levels if routine chelation protocol is followed. And, much the same, a robust supplementation regimen, liver cleanses, and detoxification treatment will likely worsen kidney functioning. So, what is the integrative and naturopathic practitioner to do with the CKD patient?

In this issue Dr. Jenna C. Henderson, a CKD patient herself, tackles this question. Henderson wants practitioners to confront the major misconceptions of kidney disease. At the very least, she would like doctors to become knowledgeable about the myths plaguing the internet. Herbal diuretic? Alkalinize the urine? Lower protein in the diet? Fasting? "Yes" and "no." These strategies cannot be employed "automatically" without evaluating and monitoring the patient. Avoidance of dialysis for severe Stage 5 chronic kidney disease should never be the advice of an integrative practitioner; we should be looking for supportive treatments to complement dialysis.

Jonathan Collin, MD

1. Alcock J, Maley C, Aktipis C. Is eating behavior manipulated by the gastrointestinal microbiota? Evolutional pressures and potential mechanisms. *Bioessays*. 2014 Oct; 36(10): 940-49.
2. Steenbergen L, Sellaro R, van Hemert S, Bosch J, Colzato L. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity tos ad mood. *Brain Behav. Immun.* 2015. http://dx.doi.org/10.1016/j.bbi.2015.04.003

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Shorts

briefed by Jule Klotter
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Gut Microbiota in Liver Disease

Gut microorganisms have a direct effect on liver health, according to an article by David A. Brenner and colleagues. While chronic alcohol consumption is known to damage the liver, what is less recognized is alcohol's effect on microbes in the GI tract and how these changes affect the liver. Chronic alcohol consumption boosts intestinal bacterial overgrowth by reducing intestinal antibacterial peptides (particularly Reg 3g) and changes the composition of the gut microbiome. People with cirrhosis have bacterial overgrowth in the small intestine, increased bacteremia, and increased intestinal permeability.

In studies in which mice were given alcohol, Lactobacillus decreased markedly, as did bacterial synthesis of long chain fatty acids, the primary fuel for Lactobacillus. Firmicutes and Bacteroidetes also declined. As the populations of these anti-inflammatory bacteria declined, intestinal inflammation and gut permeability increased, allowing bacterial products to enter portal blood and damage the liver. Alcohol-fed mice that were also given saturated long chain fatty acids showed less steatosis, lower ALT, and decreased oxidative stress, compared to controls. They also had a higher level of Lactobacillus and less intestinal permeability.

When bacterial products, such as lipopolysaccharide (LPS), travel to the liver via portal blood, they activate Toll-like receptors (TLRs) on macrophages, dendritic cells, and other immune cells, instigating innate immune responses. Brenner et al explain, "...different TLRs have been assessed for their roles of liver disease. For each TLR, the presumed ligand is a bacterial product from the gut microbiota. In particular, hepatic stellate cells (HSC) have TLRs 2, 4, and 9. Kupffer cells, the resident macrophage in the liver, have TLRs 2, 3, 4, and 9, and hepatocytes have TLRs 1-9." LPS from Gram-negative bacteria activate TLR4. CpG DNA from bacteria activate TLR9. Experiments with TLR4 knockout mice (no TLR4 receptors) and TLR9 knockouts have shown that TLR activation sets off a series of reactions that lead to liver inflammation, hepatic steatosis, and fibrosis.

In addition to dysbiosis and intestinal permeability, some gut microbiota can contribute to phosphatidylcholine deficiency by converting choline to TMA, rendering the choline useable for making phosphatidylcholine. Phosphatidylcholine is needed to prevent lipid accumulation in liver cells. Choline-deficient diets are known to produce non-alcoholic steatohepatitis (NASH). Also, some polymorphisms in the human PEMT gene result in less phosphatidylcholine production and are associated with non-alcoholic fatty liver disease.

Healing the liver cannot occur without addressing gut dysbiosis.

As an aside, FDA approved Heplisav®, a hepatitis B vaccine, in November 2017, and the CDC's Advisory Committee on Immunization Practices (ACIP) panel added the vaccine to its vaccine schedule at its February 2018 meeting (available on YouTube). Heplisav is the first approved vaccine to use the TLR9 agonist 1018 ISS as an adjuvant. Adverse effects in the Heplisav group, occurring within seven days of vaccination, were reportedly similar to adverse effects reported in the "control" group, which received the aluminum-adjuvant hepatitis vaccine Engerix B. A case of autoimmune Wegener's granulomatosis, two cases of hypothyroidism and one of vitiligo occurred in the Heplisav groups, and no autoimmune diseases were reported in the aluminum-adjuvant groups: "... although due to small numbers and 4:1 randomization ratio this difference was not significant," Nikolai Petrovsky writes. At the ACIP hearing, panel members voiced concern about reports of myocardial infarction in Heplisav recipients. Heplisav is the first approved vaccine in the world to use a TLR agonist as an adjuvant.

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Vagus-Nerve Stimulation

Vagus-nerve stimulation (VNS) using an implanted device that emits electrical pulses is an FDA-approved treatment for drug-resistant depression and epilepsy. VNS may also be

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Shorts

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therapeutic for autoimmune and inflammatory disorders, such as rheumatoid arthritis and Crohn's disease, in which the inflammatory protein tumor necrosis factor-alpha (TNFα) is a key factor, according to a review by Bruno Bonaz, MD, PhD, and French colleagues. Gold standard treatments for these conditions aim to counteract TNFα's effects. VNS aims to prevent TNFα's release in the first place.

Bonaz et al say that recent investigations show that the vagus nerve has an anti-inflammatory role in addition to homeostatic regulation of organs. Vagal nerve fibers mediate the cholinergic anti-inflammatory pathway in which acetylcholine is released at synaptic junctions with macrophages. The acetylcholine inhibits macrophage release of TNFα. Vagal stimulation of the splenic nerve's anti-inflammatory pathway may be another route by which macrophage release of TNFα decreases.

Yaakov Levine told *Nature* journalist Douglas Fox that macrophages are unable to produce TNFα for up to 24 hours after being exposed to acetylcholine. In animal studies, Levine found that just 250-millionths of an amp – "one-eighth the amount often used to suppress seizures" – is enough vagus-nerve stimulation to reduce inflammation. Levin works for SetPoint Medical, a company founded to develop and market vagus-nerve stimulation as a medical treatment.

The first VNS clinical study for inflammation began in 2011 when 18 people with rheumatoid arthritis agreed to be implanted with stimulators. Twelve of the participants experienced symptom improvement at six weeks. Also, their blood levels of TNFα and inflammatory IL-6 decreased. These improvements disappeared when the device was deactivated for 14 days and returned with VNS (Koopman FA et al. *Proc Natl Acad Sci USA.* 2016;113:8284-8289).

Raul Coimbra and Todd Costantini at the University of California-San Diego have found evidence that some people are resistant to vagus-nerve stimulation, according to *Nature.* Humans, unlike other animals, have genome codes for an extra acetylcholine receptor protein: "...if the abnormal receptor is produced in sufficient quantities, it can disrupt signaling and render macrophages unresponsive to acetylcholine. They may then continue releasing TNF-α despite vagal stimulation."

Bonaz and colleagues report that non-invasive VNS devices are entering the market. Instead of requiring general anesthesia to implant an electrode around the left vagus nerve in the neck and a bipolar pulse generator subcutaneously in the left chest wall or axilla, new devices use an earphone-like device to stimulate the vagus nerve in the ear; or they transmit proprietary electrical signals through the skin. The Bonaz article also notes ways other than VNS to decrease TNF-α levels via the cholinergic anti-inflammatory pathway: fat nutrition, choline, ghrelin, acupuncture, hypnosis, meditation, and tai chi. Physical activity and exercise stimulate vagal efferent nerve fibers and the cholinergic anti-inflammatory pathway.

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Ben Lynch, ND

- ★ Dirty Genes: MTHFR and Genetics in Mental Health

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Shorts

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Treating Mitochondrial Dysfunction with Natural Supplements

Mitochondrial dysfunction, resulting in impaired cellular energy production, produces excess fatigue, making the simplest tasks feel onerous. It occurs in aging and in all kinds of chronic diseases: neurodegenerative, cardiovascular, metabolic, autoimmune, gastrointestinal, chronic infections, neurobehavioral, and cancers. Non-genetic, acquired mitochondrial dysfunction responds to treatment with natural supplements, writes Garth L. Nicolson, PhD, in a 2014 article. Dr. Nicolson is founder, president, and research professor at the Institute for Molecular Medicine's department of molecular pathology (Huntington Beach, California).

During the process of creating energy, mitochondria also produce damaging free radicals that cause oxidative damage to cellular and mitochondrial membranes. As a result, function is impaired and inflammation ensues. Nicolson explains that people with chronic fatigue typically show signs of excess oxidative stress in blood tests, including elevated peroxynitrite levels. He considers alpha-lipoic acid, L-carnitine, coenzyme Q10, and phospholipid therapy to be among the "most promising supplements" for improving mitochondrial function and reducing fatigue.

Alpha-lipoic acid is a necessary co-factor for important mitochondrial enzymes. In addition, it helps reduce oxidative stress by stimulating the production of glutathione. Alpha-lipoic acid has the added benefit of being able to remove excess metals associated with hemochromatosis, Parkinson's, and other chronic diseases. Although α-lipoic acid's effect on chronic fatigue had not yet been studied in controlled clinical trials (as of 2014), Nicolson said, "...its widespread use as a safe supplement (usually 200-600 mg/d) to support mitochondrial function and reduce oxidative stress has justified its incorporation into various supplement mixtures."

L-carnitine transports fatty acids into the mitochondria for oxidation and removes excess acyl groups. It also increases the rate of mitochondrial oxidative phosphorylation, which tends to decline with age. Reduced phosphorylation impairs energy production and increases damaging reactive oxygen species and reactive nitrogen species. Nicolson cites a study in which 70 centenarians who took L-carnitine for six months experienced significant improvement in physical and mental fatigue. They also showed improved cognitive function, increased muscle mass, and better endurance (Malaguarnera M, et al. *Am J Clin Nutr.* 2007;86(6):1738-1744). Studies involving L-carnitine, most of which have focused on insulin resistance and cardiovascular disease, indicate doses up to 2 grams per day are safe.

Coenzyme Q10 is vital for electron transport along the mitochondrial electron transport chain. It also affects the expression of genes associated with cell signaling and metabolism. Coenzyme Q10 has the added benefit of being a strong antioxidant in its reduced form. Nicolson says, "Clinically, it has been used in doses up to 1200 mg per day, but most studies used lower doses."

Lipid replacement therapy provides the molecules needed to replace damaged phospholipids in mitochondrial membranes, thereby improving mitochondrial function. Oral phospholipid supplementation, in doses ranging from 500 to 2000 mg per day, have decreased fatigue in people with Gulf War illness, chronic fatigue syndrome, fibromyalgia as well as fatigue associated with aging.

In addition to the supplements discussed by Nicolson, the pineal hormone melatonin is useful for mitochondrial dysfunction, according to Reza Sharafati-Chaleshtori and colleagues. Melatonin helps regulate mitochondrial function. It also stimulates antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase; and it inhibits lipoxygenase, an enzyme that takes part in oxidation of unsaturated fatty acids. The authors say melatonin is an inexpensive, safe medication with mild adverse effects. Drug interactions, however, have occurred with anticoagulants, immunosuppressants, anti-diabetes, and birth control pills.

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Actaminophen-Induced Liver Damage

Acetaminophen (Tylenol (US); paracetamol (Europe)) is widely used for headache and mild pain. While very safe if taken in limited doses, overdose leading to liver damage is common, as William M. Lee explains in his 2017 article. About 500 US deaths each year are due to acetaminophen dose-related hepatocellular necrosis. Acetaminophen overdose also is responsible for 50,000 emergency room visits and 10,000 hospitalizations.

People can have a hard time keeping track of dosage because acetaminophen is present in over-the-counter products like Nyquil and in opioid combination medications like Vicodin and Norco. In most cases, patients have ingested 6-10 grams per day for several days to relieve postoperative pain, low back pain, or other painful conditions before experiencing signs of overdose: nausea, vomiting, abdominal pain, and eventually drowsiness. In a 2005 study of patients with acute liver failure 275 of 662 (41.5%) had overdosed on acetaminophen; seven percent of them reported taking less than 4 grams. Lee reports that alcohol, starvation, or other factors that decrease glutathione may account for their increased sensitivity to the drug. "Current package labeling mentions severe liver injury as a possible outcome if one takes more than 4000 mg in 24 h or with other APAP-containing compounds or with alcohol," Lee writes. About two-thirds of patients with acetaminophen-related acute liver failure recover, with or without the recommended antidote, N-acetylcysteine. Patients who receive N-acetylcysteine within 12-18 hours usually avoid severe liver injury.

Because acetaminophen is such a common cause of acute liver failure, Constantine J. Karvellas, MD, and colleagues sought a more reliable means of assessing outcome. They conducted a study with 198 patients with acetaminophen-induced acute liver failure and focused on serum liver-type fatty acid binding protein (FABP1), which transports long-chain fatty acids in tissues with active fatty acid metabolism, including liver cells. Patients with liver damage due to alcohol or drug toxicity are known to show elevated levels of FABP1.

In this study, the researchers found that people who survived acetaminophen-associated liver failure had "significantly lower serum FABP1 levels early [day 1] (238.6 vs. 690.8 ng/ml, $p<0.0001$) and late [day 3-5] (148.4 vs 612.3 ng/ml, $p<0.0001$) compared with non-survivors." Patients with FABP1 levels greater than 350 ng/ml, either early or late, had a significantly higher risk of death. The authors recommend that FABP1 be studied further as a prognostic tool for acetaminophen-related liver injury.

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Lee WM. Acetaminophen (APAP) hepatotoxicity – Isn't it time for APAP to go away? *Journal of Hepatology.* 2017;67:1324-1331.

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Coffee and Liver Disease

by Steven Helschien, DC

Introduction

Drinking coffee has been enjoyed for generations, and there is good news for those who like drinking coffee. Recent studies have found that coffee is an antioxidant superfood rich in phytochemicals, polyphenols and other nutrients that reduce inflammation by neutralizing harmful free radicals, reducing the risk of diseases related to inflammation, including liver disease.

The liver is a major organ in the body that is responsible for the breakdown of food, nutrients, and drugs, the regulation of blood sugar and fats, and the detoxification of toxins in the blood. Any damage to the liver is a medical emergency and can have a significant impact on one's health.

Due to the rise in metabolic syndrome, type 2 diabetes, and obesity, there has also been a rise in liver disease. Liver disease consists of a number of conditions including cirrhosis, hepatitis, non-alcoholic fatty liver disease, and cancer. Liver disease statistics from the CDC and the American Liver Foundation are as follows:

- Cirrhosis and other chronic liver diseases are common disease-related causes of death in the US. Approximately 31,000 people in the US die each year from cirrhosis.
- The vast majority of cases of cirrhosis could be prevented by eliminating chronic alcohol abuse.
- Approximately 3.5 to 4.6 million people in the US are chronically infected with the hepatitis C virus. About 2,000 people die of hepatitis C annually in the US.
- Hepatitis B kills approximately 2,000 people in the US annually, and 85,000 to 2.2 million people in the US are infected with the virus.

Diabetes is also associated with a spectrum of liver diseases including nonalcoholic liver disease, steatohepatitis, and liver cirrhosis. According to the American Diabetes Association, in 2015 over 30 million Americans, or 9.4% of the population, had diabetes. Of the 30.3 million adults with diabetes, 23.1 million were diagnosed, and 7.2 million were undiagnosed.

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Coffee and Liver Disease

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There is a growing body of research on coffee consumption and liver disease that suggests that a moderate intake of coffee is associated with a reduced risk of liver disease.

The Roundtable Report by the Institute for Scientific Information on Coffee in Association with the British Liver Trust

In 2017, European experts from a variety of backgrounds, including academic research, medical practice and patient associations, met at the Royal Society of Medicine, London, to discuss and report on the latest research on coffee and liver disease.[1] The research concluded that regular moderate coffee consumption is associated with a reduced risk of liver disease

Liver disease causes inflammation that can lead to cirrhosis. Cirrhosis develops when scar tissue replaces healthy tissue in the liver**,** usually progressing over a period of many years and eventually preventing the liver from functioning properly. Cirrhosis is estimated to be the cause of death for around 1 million people each year and can be caused by excessive alcohol consumption, hepatitis, fatty liver disease (due to obesity and diabetes), and immune disorders. It can also lead to liver cancer.

The report cites studies that show that regular coffee consumption can reduce inflammation in the liver and the chances of developing cirrhosis by 25% – 70%. Other studies have shown that as little as two cups of coffee a day can reduce the risk of cirrhosis.[2] The greater risk reduction was observed in those patients with alcoholic liver cirrhosis. It's reported the damage cannot be reversed, but coffee may help protect against the onset of the disease.

Damage or inflammation of the liver can manifest as raised levels of liver enzymes. Coffee consumption has been inversely associated with the activity of the liver enzyme gamma-glutamyl transferase (GGT) in studies from Japan, Europe, and the USA. Global research also suggests that coffee consumption is associated with an approximate 40% reduction in the risk of elevated levels of the liver enzyme ALT.

The roundtable experts suggested that 'metabolic syndrome' (a combination of obesity, hypertension, and type 2 diabetes) is associated with liver dysfunction and a greater risk of liver cancer. Research suggests that a moderate intake of coffee is associated with a reduced risk of type 2 diabetes, as well as a reduction in insulin resistance, which in turn may improve outcomes for diabetes and liver health.

The Institute for Scientific Information on Coffee (ISIC) is a nonprofit, established in 1990, devoted to the scientific study of coffee and health for benefit of health professionals.

The British Liver Trust is a nonprofit UK organization for adults with liver disease. It provides current information on liver disease and prevention, as well as support for improved services and care.

The roundtable conference concluded that research consistently suggests that a moderate consumption of coffee (3-5 cups per day), is associated with a reduced risk of liver disease.

Dr. Steven Helschien (a.k.a. Dr. Coffee) is a coffee aficionado and believes that coffee is a powerhouse superfood. He is the founder of Level 1 Diagnostics (a cardiovascular testing program that uses advanced, noninvasive technology to detect and prevent cardiovascular disease), and Level 1 Therapeutics (a health and wellness program dedicated to supporting optimal health). Dr. Helschien is passionate about progressive health issues and encouraging people toward greater health and wellbeing.

Coffee Reduces the Risk of Cirrhosis

At the University of Southampton in the UK, researchers conducted a meta-analysis of nine long-term studies, involving half a million men and women, and found that an extra two cups of coffee per day may reduce the risk of cirrhosis by 44 percent, and it may nearly halve the risk of dying from cirrhosis. The study, which was published in the science journal *Alimentary Pharmacology and Therapeutics*, stated that coffee appears to have a number of protective effects on the liver.[3]

Drinking Coffee Shown to Reduce Risk of Liver Cancer

Liver cancers are largely avoidable through reduction of alcohol drinking, hepatitis B vaccination, and control of hepatitis C virus transmission. These measures could prevent more than 90 percent of primary liver cancer worldwide.

Liver cancer is the third most common cause of cancer death. Hepatocellular cancer (HCC) is the most common type of liver cancer, accounting for more than 90 percent of cases worldwide. Chronic hepatitis B and C are the main causes of liver cancer; but causes also include alcohol, tobacco, obesity, and diabetes.

Researchers from the University of Southampton and the University of Edinburgh examined the data of 26 studies with 2.25 million participants and concluded that the more coffee consumed, the greater the protection against HCC.[4]

The research found that drinking one cup more of caffeinated coffee a day was associated with a 20 percent reduction in the risk of developing liver cancer. Consuming two cups more of coffee showed a 35 percent reduction, and up to five cups halved the risk. Those who drank decaffeinated coffee also benefitted, though not as much as those who drank caffeinated coffee.

It is estimated that, by the year 2030, the annual number of new cases of liver cancer will rise by about 50 percent.

One of the researchers, Professor Peter Hayes of the University of Edinburgh, commented: "We have shown that coffee reduces cirrhosis and

also liver cancer in a dose-dependent manner. Coffee has also been reported to reduce the risk of death from many other causes. Our research adds to the evidence that, in moderation, coffee can be a wonderful natural medicine."[6]

A meta-analysis of 16 studies and 3,153 cases, published in the journal of the American Gastroenterological Association, *Clinical Gastroenterological and Hepatology*, showed coffee consumption reduces the risk of HCC, by about 40 percent. Further, data indicate that three cups of coffee per day may reduce liver cancer risk by more than 50 percent.[5]

Carlo La Vecchia, MD, the study's author from the department of epidemiology, Istituto di Ricerche Farmacologiche "Mario Negri," and department of clinical sciences and community health, Università degli Studi di Milan, Italy, asserts: "Our research confirms past claims that coffee is good for your health, and particularly the liver…. The favorable effect of coffee on liver cancer might be mediated by coffee's proven prevention of diabetes, a known risk factor for the disease, or for its beneficial effects on cirrhosis and liver enzymes."[6]

Not All Coffees Are Created Equal

The best quality coffee yields the greatest potential health benefits. The way coffee is grown, handled, and roasted has a direct effect on its quality. Where it is grown (high altitudes are best), how it is farmed (is it organic or are pesticides used?), and whether mold or mycotoxins (toxins produced by mold) are present, all affect the quality of the coffee. The healthiest brew also requires pure, good-quality water.

Coffee Antioxidant Boosters

Two sources of rich antioxidants that can be used to boost healthy coffee are EGCG and L-theanine. Epigallocatechin gallate (EGCG) is the major polyphenol and flavonoid in green tea. EGCG is high in antioxidants with many proven health benefits, especially for cardiovascular and metabolic health.[7] The extract, used as a supplement with coffee, produces the healthiest drink you can make. The combination of coffee and L-theanine boosts concentration, focus (it is being used to help with ADHD), creativity, memory, and relaxation. L-theanine is a non-essential amino acid that is found in the leaves of black, oolong, and green tea. The combination is a powerful antioxidant source, brain booster, and can also relieve coffee jitters.

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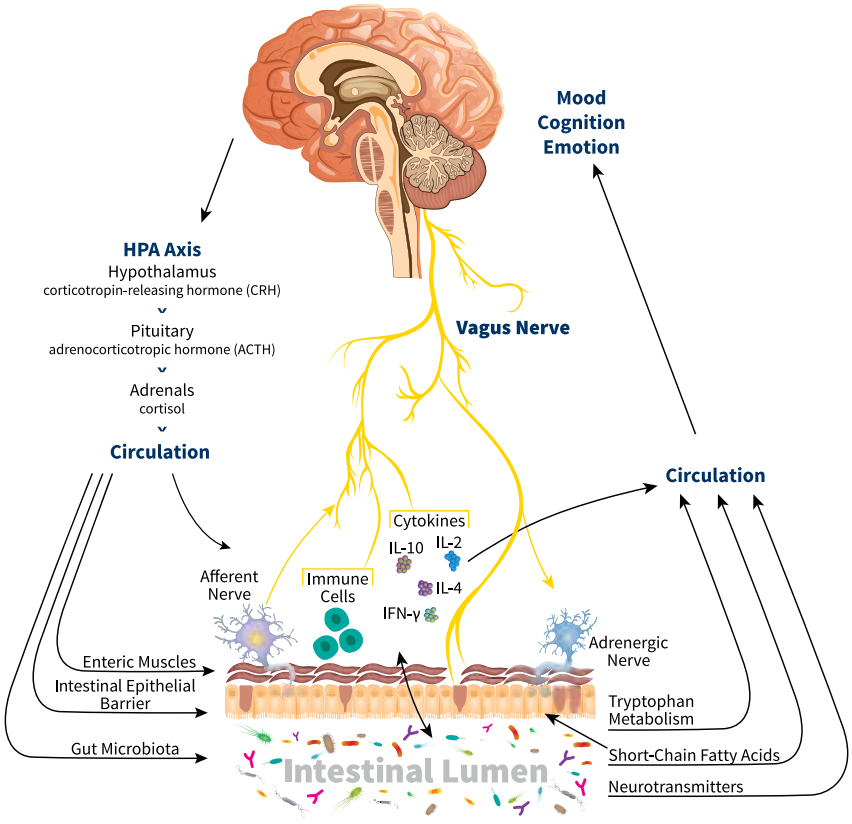
Introduction: the gut-brain axis

The gut-brain axis is a communication network that links the central nervous system (CNS) with the enteric nervous system. The anatomical network includes the brain and spinal cord, autonomic nervous system (ANS), hypothalamic-pituitary-adrenal (HPA) axis, and the innervation of the GI tract, or enteric nervous system.

Both neural and hormonal routes of communication allow the brain to influence intestinal activities, including activity of functional effector cells (i.e., immune cells, epithelial cells, enteric neurons, smooth muscle cells, interstitial cells, etc.). Gut microbiota also influence the CNS both directly and indirectly by supporting epithelial barrier function, modulating immune function, supporting healthy inflammation metabolism, and directly altering circulating neurotransmitter levels.



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Target gb-X research

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Clinical findings

Steenbergen and colleagues studied the effects of Ecologic BARRIER in a 2015 randomized, triple-blind, placebo-controlled trial (n=40, non-smoking healthy young adults, mean age 20 years) at a dose of 5 billion CFU per day. Consumption of Ecologic BARRIER significantly reduced overall cognitive reactivity to sad mood, in particular aggressive and ruminative thoughts, as assessed by the Leiden index (LEIDS-R).†[2] Heightened cognitive reactivity to normal, transient changes in sad mood is an established marker of vulnerability to more serious mood alterations in otherwise healthy individuals, and is therefore considered an important target for interventions.

Animal studies

In a 2016 laboratory study, 40 male rats were randomized to either a control or high-fat diet for 10 weeks.[3] After five weeks, the rats received either placebo or the Ecologic BARRIER probiotic blend. Forced swim test results demonstrated, independent of diet, Ecologic BARRIER significantly improved mood in the treatment group by 34%.†[3] In addition, the probiotic group had decreased levels of inflammatory cytokines and increased indole-3-propionic acid, a potential neuroprotective agent.

Conclusion

Target gb-X with Ecologic BARRIER is the first probiotic clinically shown to support healthy mood.† Supplied as convenient, single-serving, shelf stable sachets, Target gb-X is suitable for supporting the gut-brain axis through intestinal barrier integrity and healthy immune/inflammatory response.†

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The Oxidative Dried Blood Test in the Assessment of Metabolic Dysfunction and Inflammatory Conditions

by Professor Serge Jurasunas

In 1848 C.G. Hufeland, the first medical doctor of the King of Prussia, was a very popular doctor in Europe at that time. The mention of his book *Practical Medicine* showed that to know a disease was not only to know the name of the disease but to also know all the dysfunction and the causes of the disease. Otherwise, as he said, we can only cure the body superficially. This has always been my main concern since the beginning of my iridology practice, but it's not enough if you work with a disease such as cancer where to know the exact condition today and then again next week, for example, can be a problem. For this reason, 38 years ago, I was looking for something that would help me to assess my patients according to their disease. Since then, I have been using in my practice an original blood test that permits me to assess metabolic dysfunction and inflammatory conditions from acute to the degenerative stage that are associated with oxidative stress and deficiency or collapse of endogenous antioxidant enzymes. The idea of examining a drop of dried blood to diagnose a disease was not new. It was backed in Europe as early as 1920 by several medical practitioners from Germany and France, who were able to implement similar test observations. Also, in the USA by 1930, the head of surgery at Massachusetts General Hospital in Boston, L. Bolen, MD, introduced this technique, called the Bolen test.

Oxidative Dried Blood Test

This test known as the oxidative dried blood test or oxidative dried blood layers test (which I also call in my book the metabolic blood test) was initially called HLB when, in 1975, Dr. Robert Bradford, engineer and researcher became interested in this test and subsequently developed the theory of oxidative stress and reactive oxygen species to explain the differences existing between a normal blood pattern and various deviations.

My Implications and Own Research with This Blood Test

In Summer 1979, I flew to San Francisco to meet Bob Bradford and to learn more about this test. Why such a personal interest? I was intrigued after traveling to Germany some years before where someone told me about a curious test called the Aura-Blood Test, similar but different which I explain in my book together with its initial story. At that time, it was taught only in German language with many restrictions, thus I made no further contact. Returning to Portugal with some information and just having opened a new, large, three-story clinic, I decided with my team of doctors to systematically perform this test for most of our patients with diseases ranging from acute to degenerative condition. At that time cancer patients were already my main interest. But, of course, we assessed many other pathologies or organic disorders. We could really experiment with this dried blood test on many patients since, at that time with my team, we performed around 300-400 consultations per week. This opportunity really offered me a large range of diseases to learn what the oxidative dried blood test can really explain.

My Own Discovery

After working a couple of years with this test, for the first time I developed the theory correlating the segmented abnormalities in the drops of dried blood with the body's organ condition. This discovery is further explained in my book where I explain how I came to document how the oxidative dried blood test may offer some additional very useful information. This is why I called this test, in Europe and named it in my book, the metabolic blood test or MBT.

The Oxidative Dried Blood Test Technique

Roughly, the technique is to examine the coagulation of blood by taking a small amount of blood expressed from a fingertip looking like a ball which is transferred to a clean microscope slide in a series of eight sequential layers, then allowed to air-dry at room temperature for one minute which activates the intrinsic coagulation pathway. When the drop of blood remains on the fingertip for one minute, there is a split into various blood constituents. Light polymerized protein puddles (PPPs) may travel downward to the bottom

while heavy PPPs may only go down half way depending on the metabolic condition. The resulting fibrin web is then examined microscopically using a multi-phase contrast microscope at 200X essentially to monitor any deviation and morphological changes from a blood pattern. During the process of a degenerative disease, the blood carries toxins, by-products from free radical activity, and fragments from extra cellular matrix degradation. High oxidation inhibits proteases allowing for extra cellular matrix degradation, which releases soluble fragments in the blood. Other consequences are heavy metals, polymerized proteins, and fungal yeast invasion. Yeast as candida may deteriorate the layers of the dried blood and modify the fibrin, making a deviation from a natural healthy pattern.

How to Evaluate the Oxidative Dried Blood Test

Usually we classify deviation visible in the different layers of the dried blood in six stages from 0 (a normal pattern) to 6, according to the morphological changes such as a break in the fibrin web, the absence of a web, and the presence of white clots, which are mostly observed with different sizes and shapes, color, number and position according to the health condition – acute or degenerative disease, allergy, or even physical or emotional oxidative stress condition and low antioxidant status. In the past, the test was particularly useful for examining the effects of oxidative stress and other types of stress on the body at the cellular level.

The main observation is associated with white clots referred to as polymerized protein puddles (PPPs), which are the result of metabolic disturbing factors and protein residues circulating in the blood. Stressors include electromagnetic field radiation, and other physical aggression such as chemotherapy and radiation therapy,

The PPPs are not exactly clear holes but contain a white material that results from free radical activity, fungus, and other microorganisms, toxins, and trapped plasma proteins and fats in the lymph system. For instance, hydroxyl radicals and peroxynitrite bursts generated in some acute disease and more in degenerative disease create more and larger PPPs. Each white footprint represents an inflammatory condition and indicates an oxidative stress condition. The position of the white PPPs in the clot layers and their distance from center indicates what areas of the body are affected.

Sizes may vary from the smallest round PPP of 2 microns an indication of allergy sensitivity to a larger size of 20 microns, an indication of physical stress and other trauma. In the case of serious damage and disease, PPPs of 30 microns are visible but may vary on the inside edge. The larger the PPPs, the more serious the problem; 40 to 50 microns are visible in serious degenerative process (see Figure 1). Broken edges indicate major trauma and inflammation; while in cancer, PPPs appear with a dark-shaped inside edges, and some green coloration may also be visible. PPPs of 40 microns in great number show an advanced cancer usually under chemotherapy. PPPs tend to extend, look like lakes or rivers connected with each other. Bridges between one side and another indicate lung cancer or metastasis from primary tumor. I have been working for many years and have assessed over 28,000 cancer patients with this blood test, feeling that I have contributed greatly to the development of this system.

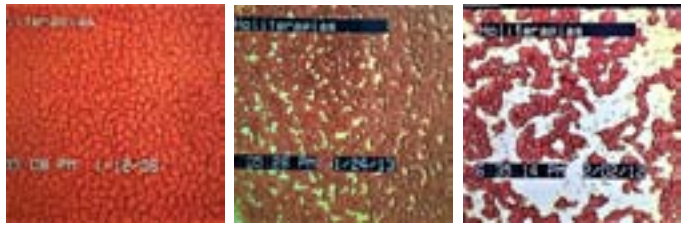

Figure 1. 1/12/06: Normal blood pattern; 1/24/13: Crohn's disease. 1.2.3. layers. PPPs of 20 microns, acute inflammation; 2/2/12: Lung cancer. 7-6 layers. Large PPPs of 40 microns formed like lakes.

This stage, and more with a condition of PPPs of 50 microns in all the layers, indicates chemotherapy is useless and even dangerous. Advanced cancers show a very poor fibrin concentration, large PPPs with debris necrotic tissues, a sialic acid bed, and spicules visible in all the layers of the drop of blood. We know that excessive chemotherapy induces a permanent oxidative stress and destruction of tissue, proteins, activating all the inflammatory mediators that in turn stimulate angiogenesis and inhibit apoptosis and immune activity. Therefore, the observation includes the size of the PPPs and the number on each layer of the dried blood, since each layer also has a particular significance.

PPPs may be visible in different areas of the layers taking 30% or 50% of the layer surface while the remaining 50% or 70% is filled with a network of fibrin.

The oxidative dried blood test can monitor the following conditions:

- Chronic vs acute conditions,
- Inflammation,
- Physical stress and localized trauma,
- Psychological stress,
- Hormonal disturbance,
- Toxicity from the polluted environment,
- Allergy,
- Vitamin C deficiency,
- Toxic colon, and
- Degenerative disease indication, and
- Localization of organ dysfunction in the dried layer segmentations.

Diseases that may correspond or associate with ROS activity include asthma, pulmonary fibrosis, emphysema, Crohn's disease, arthritis, inflammation of the gall bladder, diabetes, cancer, bacterial infection, candidiasis, atherosclerosis, and multiple sclerosis.

While this test is not a diagnostic and not a substitution for regular hospital diagnostic check-ups, it will provide some additional information in only a short time to present to the patient. More importantly, reversing the process from broken fibrin nets and the presence of PPPs of several shapes and sizes to a normal blood pattern is a real challenge. This test is advantageous since it can show, step by step, the result of the applied treatment and the reversal of the disease.

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Dried Blood Test

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The Method

After making the puncture on the finger to get the small red ball of blood on the finger, you have to wait one minute before transferring rapidly the blood in eight layers onto a glass slide. Why? The PPPs spin out into rings on the dried layers dependent according to their weight, indicating cellular disorganization in specialized areas of the body. During the time the drop of fresh blood waits to dry on the microscope slide, there will be a move from up to down within the drop with the separation of red cells, white cells, blood plasma and PPPs between light and heavy in weight. Therefore, organs near the center of the body produce light PPPs which don't spin out very far on the layers.

By contrast, breast or lung disease produce medium weight PP's which spin about one-third of the way out. Lymph or skin produce heavy PPPs which spin out around the outside and inside of the periphery of layers. Now, I have been mostly concerned with cancer and therefore have done research with explanation about what we observe and the type and stage of cancer.

If we observe PPPs all around the periphery within a specific ring, it indicates an active degenerative process, a localized cellular degeneration, and possibly a problem of cancer profile if not an early cancer. This is what we observe with breast cancer; PPPs of various sizes visible in rings 4 and 5 that include the lymphatic system are always implicated in

Figure 2. 12/22/06: Dark mass center. 1-3 layers. Large bowel dysfunction. Toxic Colon; 4/6/06: Lymphatic congestion. 3, 4 layers.

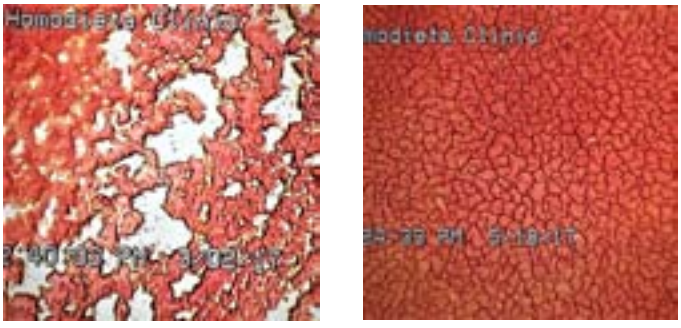

Figure 3. 3/2/17, 5/18/17: This is a case of stage 3 cancer of the larynx during chemotherapy, before and after. Here we can observe a great change after my treatment and diet. Note 100% modification of the blood status followed by a complete remission.

breast cancer, (See Figure 2). But again, we need to observe if it is PPPs related to cancer as explained before or only an inflammatory process.

At stage 2 cancer (early clinically detected disease) or stage 3, PPPs may be concentrated in ring 5 with visible small PPPs from adrenal stress and emotional stress, often associated with the disease of the patient. But under chemotherapy and intestinal and liver damage, PPPs are visible at the 5th, 6th, 7th, and 8th layers showing a major inflammatory process and damaged liver. (Also, see in my book for a toxic colon, page 82.)

Damage done to the bone marrow is visible on the second ring of the first and second layers. It is interesting to observe the dried blood of a cancer patient before chemotherapy and after chemotherapy especially after several sessions (see Figure 3). PPPs increase in size and appear to take up more space. For instance, in breast cancer PPPs increase their space and take over to fill up the lung ring, usually appearing like lakes communicating with each other. Usually with breast cancer, PPPs go all the way around the outside of the breast-lung ring, an indication of lymphopathy as well but also of lung metastases. I have developed several figures associated with the stage observed in the dried blood layers and the stage of cancer, and we realize that there is a limit not to cross before it become incurable for the patient.

Advanced Cancer

In an advanced cancer stage, large PPPs with different shapes are visible in the totality of most of the layers with poor fibrin concentration. Here the idea is to try to reverse the process which can be done with stage 3 or even 4 but hardly with stage 5, while stage 6 is near death. Cancer patients have low antioxidant levels and are mostly deficient in essential nutrients and proteins as they suffer from intestinal disorders and poor food absorption, which has an impact on fibrin interconnection in the dried blood layers with low concentration of the fibrin nets. In cancer stage 4, you may observe inside of the large PPPs a free radical footprint, denatured red cells, different colorations, and necrotic tissues. Of course, you need a microscope with higher amplification to see the necrotic tissues. Such examination permits us to tailor the best diet and treatment for the patient, especially using some antioxidant enzymes that can be easily absorbed by the body.

I use my own formula developed years ago consisting of a low-molecular antioxidant compound made from modified vegetables having therapeutic properties, which are active one hour after oral intake (Anoxe), or an injectable IM or IV such as glutathione, SOD, cysteine, live yeast cells preparation, or chlorella extract, or a rice bran arabinoxylan compound.

What is interesting with this blood test is that you can reverse the abnormal blood pattern, observe the diminution in the size of the PPPs and even come back to a stage 0 after treatment, which the patient can see for himself. Even using some different tests and even molecular markers, I still use the oxidative dried blood test, which I personally find very

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Dried Blood Test

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important to measure the exact condition of inflammatory process, degenerative condition, or other organic problems, telling us how to reverse the disease. The most powerful aspect of this particular blood test is to assess whether the patient is or isn't really getting better!

When a patient is improving by means of an applied treatment, the doctor knows definitively by means of a new blood examination; this is really unique when you may observe, in front of your patient, the diminution of the size and quantity of PPPs or even an almost normal blood pattern with new fibrin network. Now, in the case of a cancer profile, we have the same situation; if the blood testing shows an inside improvement, white puddles will begin to fill back in with red blood cells, but if the patient gets worse, the pattern will be present with more and more large white puddles (PPPs). As I have often told my patients, there is a limit not to cross with this blood test.

Intoxication with Heavy Metals

This dried blood test also permits us to assess heavy metal intoxication, which is essential today. By natural centrifugal action during drying, heavy metals spin out the furthest, causing coats around the layer displaying a darkened protein rim if mercury, aluminum, cadmium, etc, are present in the fatty tissues, brain, central nervous system, organs, and glands (see Figure 4 and also pages 86-87 of my book with dried blood test examination of heavy metal intoxication and the difference after treatment). This can lead to Alzheimer's, Parkinson's, multiple sclerosis, cognitive disorder, or even cancer.

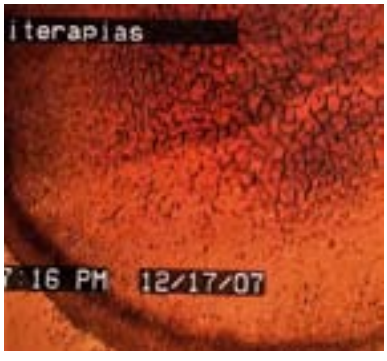

Figure 4. 12/17/07: Dark ring forming a rim around the periphery indicates intoxication with heavy metals.

Reading the Eight Layers of Dried Blood

"Layer" refers to each of the eight blood drop layers on the glass side to evaluate the oxidative dried blood test (Figure 5). The largest layer is layers #1 and #2 and the smallest being layers #7 and #8. PPPs of 20 microns from physical stress appear on layers 1-2-3, and PPPs of 20 microns from psychological stress appear on layers 4-5.

Layers 1-2. Readings on these layers allow for greater accuracy in conditions that are shallow, acute, and temporary and those that occur on the outside of the body, skin, head, neck, lymph, ears, nose, bone marrow, and connective tissue.

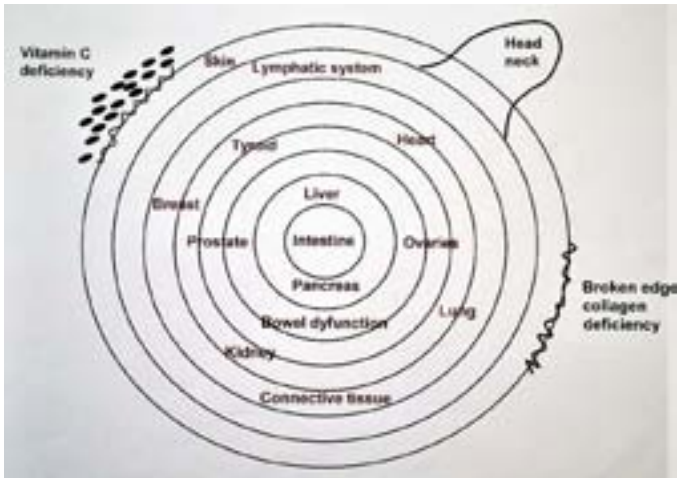

Figure 5. Correlation of blood morphology with body abnormalities

Layers 3-4-5 give more accuracy regarding lung, lymphatic system, breast, and harmonious conditions.

Layers 6-7-8 show problems with the colon, small intestine, kidney, liver, ovaries, pancreas, and spleen. These layers represent more accuracy in chronic long-term, deep-seated situations and conditions relating to organs and glands near the center of the body. The layers 6-7-8 will indicate a situation associated with an inflammatory condition of the colon or liver condition, especially after chemotherapy. Toxic colon is also quite visible (See Figure 3 and my book pages 81-82).

When I started to use the test by 1969-1970, I was already working with breast cancer; I rapidly made an association between the disease and emotional stress by observing the blood test.

What to Read in the Different Layers of Blood

Typically, the doctor is looking for the following elements:

1. Increase in number of PPPs and their sizes and color in the 8 layers.
2. Examination of the leaking fibrin nets.
3. Localization of the PPPs within the layers.
4. The presence of metabolic by-products into the white holes, Heinz bodies, necrotic tissue, degenerative red cells, spicules, free radical footprint or any additional coloration.
5. Specific localization and particular signs that may indicate organic disorders.

Conclusion

The widespread use of this test in Europe and other continents offers a very strong body of compiled empirical evidence which clearly points out consistent conclusions. However very little literature is available and practically no books were published about this blood test except a book by Robert Bradford, published about 20 years ago.

This very simple, fast, inexpensive test offers a large range of possibilities to immediately assess your patients directly in your office or clinic, thus permitting practitioners to use the appropriate treatment according to the observations made.

Excessive free radical activity, especially from very aggressive families such as hydroxyl radicals and peroxynitrite or the result of excess hydrogen peroxide, is very damaging to cells and tissues, where it corresponds to the number and size of PPPs on the dried blood layer glass. Many people have a poor endogenous antioxidant defense such as induction of SOD, glutathione, and catalase. Decreasing catalase and glutathione activity increases the level of hydrogen peroxide, which is toxic to cells and activates the enzyme sialidase that strips the negatively charged sialic acid protection off the blood fibrin protein, allowing it to unnaturally hook together and polymerize into a hole or a white pasty mass, named as PPPs. Also, a bad dietary style with poor intake of fruits and vegetables while living under high physical or emotional stress overtaxes the endogenous antioxidant enzyme defense mechanism. This is what this blood test can assess. It helps you improve your way of choosing the best therapy or compounds that can improve the patient's condition, visible during observation on the monitor of your microscope.

Of course, the purpose of this article is only to present and have a basic idea of what this oxidative dried blood test can do and offer, not being a complete explanation which is far too complex to fully understand and practice. The transferring of the eight layers must be a precise and exact technique. This article can be a beginning to start understanding and observing this technique. I will be happy to send additional information to those doctors who would like to inquire.

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Serge Jurasunas. Health and Disease Begin in the Colon. 2017; pp.66-88.

Serge Jurasunas is an internationally well-known practitioner and researcher in complementary oncology and molecular medicine. He is a professor of naturopathic oncology at Pan-Am University of Sciences and Natural Medicine and a former professor of integrative medicine at Capital University in Washington, DC. Dr. Jurasunas has delivered lectures in over 45 countries including Russia, Poland, Australia, and those in Asia. In recent years, Dr. Jurasunas has been invited several times to China to the World Congress of Molecular Medicine.

Professor Serge Jurasunas specializes in treating all types and grades of cancer in his clinic located in Cascais, Portugal, having devoted five decades developing innovative therapies and being a pioneer in several approaches to cancer including immunotherapy, stem cell therapy, and developed his own formula used exclusively in his clinic along with live blood analysis and oxidative dried blood testing. His field of interest includes nutrition and iridology.

He spent the past 10 years investigating, researching and putting into clinical application testing of the P53 tumor suppressor gene and reversal of P53 mutation in cancer patients using selective dietary agents. He is member of many professional associations, and academies, which include the New York Academy of Science.

He is a frequent *Townsend Letter* contributor and author of over 150 papers, lectures and articles translated into 13 languages. He is the author of seven books and his new one, *Health and Disease Begin in the Colon*, written in English is a most interesting textbook for both laymen and health professionals that reflects his 50 year professional career. He is now involved in the preparation of a new book on immuno-nutrition and the biological response modifier Biobran (Rice Bran Arabynoxylan Compound).

For those doctors who would like to inquire further, they may also read my new book, *Health and Disease Begin in the Colon* (Amazon) for further details, or contact me:

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Local and Systemic Consequences of Gut Inflammation

by Keegan Sheridan, ND

"All disease begins in the gut."
– Hippocrates

This often-referenced quote from the father of medicine is well-known, and with good reason. Over 2000 years of medical research and practice since the days of Hippocrates continues to confirm his observation that the health and function of the digestive tract profoundly influences overall health and the pathogenesis of disease. Particularly in the past decade, as investigation of digestive health and immune function has focused on the gut microbiome, this vast ecosystem has increasingly been recognized not only as an influencer of local digestive function, but as a part of the bidirectional communication network connecting the brain, immune, and endocrine systems.

We now understand that inflammation in the digestive tract is a critical link between digestive and many systemic inflammatory diseases, and data demonstrate that gut dysbiosis directly mediates this inflammation.[1] Thus, probiotics hold unique potential to influence this observed chain of events, correcting dysbiosis locally and thus influencing systemic inflammation and disease.

The Intestinal Barrier in a Healthy State

The digestive tract is the largest mucosal surface in the body, a selective interface between self and non-self, and a central hub of immune activity (the gut-associated lymphoid tissue, or GALT). The four primary components of the intestinal barrier are: 1) the gut microbiota, 2) a mucin layer that acts as a buffer between gut bacteria and intestinal epithelial cells, 3) a single-cell layer of epithelial cells connected by tight junctions, and 4) innate and adaptive immune cells that form GALT.[2] When functioning optimally, the gut microbiota is diverse and replete with beneficial, commensal bacteria that displace pathogens, while tight junctions strictly limit the passage of bacteria, metabolites, and other material from external to internal environments.

The Role of Gut Microbiota in Intestinal Inflammation

Diet, medications such as antibiotics, infection, and genetic susceptibility can dramatically shift gut microbial composition and alter barrier function.[3] Inflammatory diseases of the gut are associated with a significant decrease in microbial diversity and a shift from a predominance of Gram-positive bacteria to a state of Gram-negative dominance.[3] This dysbiotic composition disrupts the mucosal barrier, increasing intestinal barrier permeability and resulting in penetration of bacteria from mucosal biofilm in the gut lumen into direct contact with epithelial cells and tight junctions.[4] This direct contact triggers immune inflammatory responses, such as are seen in inflammatory bowel diseases (IBD). The cell walls of these largely Gram-negative bacteria express endotoxic lipopolysaccharides (LPS), which are highly pro-inflammatory.[5] That LPS contributes to the pathogenesis of many systemic inflammatory diseases has been well demonstrated in clinical and pre-clinical studies.

Intestinal Inflammation in Systemic Inflammatory Disease

Gut inflammation with resulting increases in intestinal permeability has consequences that extend beyond the digestive tract. A number of systemic inflammatory diseases, including those discussed below, are associated with, if not triggered by, inflammation in the gut.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, typically progressive disease in which lymphocytes of the immune system inappropriately mount an inflammatory attack of the myelin sheath around the brain and spinal cord. It has long been suspected that infection with bacterial pathogens could trigger MS. A growing body of research now implicates the gut microbiota as the primary inducer of autoimmunity, and it has even been proposed that MS patients may have characteristic alterations to their microbiome.[6,7] In one study, the microbiomes of MS patients revealed specific bacterial taxa, when compared with healthy controls, i.e., *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* were significantly associated with MS. Both of these organisms were found to induce proinflammatory responses in human peripheral blood mononuclear cells. In contrast, *Parabacteroides distasonis*, reduced in the microbiomes of MS patients, was found to stimulate an anti-inflammatory response.[8]

Alzheimer's Disease

Alzheimer's disease (AD) is another chronic, progressive illness where inflammation is an established etiologic element.[9] New research now demonstrates that gut dysbiosis contributes to the pathogenesis of dementia by triggering low-grade peripheral inflammation.[10] Cattaneo and colleagues assessed the role of gut microbiota in AD pathogenesis by studying the association of brain amyloidosis with specific gut microbiota taxa, pro- and anti-

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inflammatory activity, and occurrence of peripheral inflammation in cognitively impaired patients.[11] AD patients with amyloidosis showed higher levels of pro-inflammatory cytokines compared with both controls and with amyloid negative patients. In addition, patients with amyloidosis showed higher abundance of inflammatory Escherichia/Shigella taxa compared with both healthy controls and amyloidosis negative patients.

Obesity and Related Diseases

Evidence from human and animal models demonstrates plasma elevations of gut-derived endotoxin (LPS) as a driving factor behind the low-grade systemic inflammation associated with obesity, Type II diabetes, metabolic syndrome, and cardiovascular disease. The pro-inflammatory environment in obesity is well enough established to have earned its own name: "metabolic endotoxemia."[12] To directly study the influence of LPS on adiposity, Cani and colleagues injected low dose LPS (300 µg/kg/day) in lean mice on a normal chow diet.[13] These injected mice had similar outcomes to diet-induced obesity (i.e., weight gain, tissue specific inflammation, hepatic lipid deposition, and insulin resistance). However, lean mice lacking LPS co-receptors were resistant to these changes, indicating LPS is a mediating factor in obesity-related comorbidities.

Probiotics as Therapy

As previously noted, gut bacteria influence both local and systemic inflammatory processes. This suggests that beneficial probiotic bacteria might be useful in mitigating inflammation.[14] Investigations of this theory have focused primarily on inflammatory bowel disease (IBD). However, newer animal and human clinical data suggest probiotic influence on systemic disease as well.

In IBD, a meta-analysis of twenty-three clinical trials comparing probiotics with controls, administration of an eight-strain probiotic combination consisting of four strains of *Lactobacillus,* three strains of *Bifidobacterium,* and *Streptococcus thermophilus* with a total of 900 billion viable bacteria, significantly increased remission rates in patients with active ulcerative colitis compared to placebo.[15] In another clinical trial, this same probiotic mixture was shown to lower levels of mucosal inflammatory cytokines compared to placebo when given to patients with Crohn's disease within 30 days after ileocolonic resection surgery.[16]

In a clinical trial, 54 diabetic patients were randomly assigned to take either a multispecies probiotic consisting of *Lactobacillus acidophilus* (2×10^9 CFU), *L. casei* (7×10^9 CFU), *L. rhamnosus* (1.5×10^9 CFU), *L. bulgaricus* (2×10^8 CFU), *Bifidobacterium breve* (2×10^{10} CFU), *B. longum* (7×10^9 CFU), *Streptococcus thermophilus* (1.5×10^9 CFU), and 100 mg fructo-oligosaccharide or placebo for eight weeks.[17] Group comparisons revealed that probiotic consumption prevented a rise in fasting plasma glucose and that mean changes in serum high-sensitivity C-reactive protein were significantly different between the two groups. From these data, the researchers concluded that multispecies probiotic supplementation directly and positively impacts the endocrine and inflammatory mechanisms underlying diabetes.

Although inflammation is a normal and important response to the presence of damaged and/or harmful cells, pathogens, or toxins, an excessive or prolonged inflammatory response can cause or exacerbate disease. Dysregulated inflammatory responses originating in the gut due to dysbiosis and resulting increases in intestinal permeability are now recognized as being determinative of disease pathogenesis. An increasing number of clinical trials now demonstrate probiotics as an effective therapeutic intervention. Further controlled clinical trials are urgently needed to clarify organisms, dose, mechanisms of action, and therapeutic targets. Restoring homeostasis in the digestive tract through multispecies probiotic supplementation should be considered a primary therapeutic intervention for both local and systemic inflammatory diseases.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Fructose as a Cause of Fatty Liver

Forty-one obese children (aged 9-18 years) with habitual sugar consumption of more than 50 g per day had all of their meals provided for nine days with the same energy and macronutrient composition as their standard diet, but with starch substituted for sugar, yielding a fructose content of 4% of total energy (as compared with 12% of total energy at baseline). Median liver fat concentration (determined by magnetic resonance spectroscopy and imaging) decreased from 7.2% at baseline to 3.8% on day 10 ($p < 0.001$). *De novo* lipogenesis (the conversion of fructose to fat in the liver) and visceral adipose tissue also decreased significantly.

Comment: Studies in experimental animals and observational studies in humans suggest that excessive consumption of fructose can promote the development of nonalcoholic fatty liver disease (NAFLD), which has become a major epidemic over the past few decades. Intake of large amounts of fructose (usually in the form of high-fructose corn syrup) can contribute to obesity, which is a risk factor for the development of NAFLD. However, the results of the present study and of other research indicate that, even in the absence of increased caloric intake, fructose consumption can increase liver fat deposition. The increase in the prevalence of NAFLD during the past 30 years has coincided with the widespread replacement of sucrose with high-fructose corn syrup in soft drinks and other sweets.

Schwarz JM, et al. Effects of dietary fructose restriction on liver fat, de novo lipogenesis, and insulin kinetics in children with obesity. *Gastroenterology*. 2017;153:743-752.

Vitamin C for Dialysis Patients

Twenty-two stable patients on hemodialysis who had functional iron deficiency (defined as transferrin saturation less than 30% and serum ferritin greater than 100 µg/L) and an erythropoietin requirement of at least 4,000 U per hemodialysis session received oral vitamin C (250 mg per day) for three months. Iron supplements were not given. Among the 15 patients who completed the study, the median erythropoietin dose requirement fell by 15% ($p = 0.01$) and the mean hemoglobin concentration increased from 10.1 g/dl to 10.7 g/dl ($p = 0.03$). No adverse effects of vitamin C were observed.

Comment: Functional iron deficiency is a major cause of persistent anemia in dialysis patients and also contributes to a suboptimal response to erythropoietin. Erythropoietin is an expensive drug that contributes to the high cost of treating end-stage renal disease. Vitamin C enhances mobilization of iron to transferrin, thus increasing iron bioavailability. In previous studies, high-dose intravenous vitamin C decreased erythropoietin requirements and improved hemoglobin levels. The results of the present study suggest that low-dose oral vitamin C can also reduce erythropoietin requirements in hemodialysis patients with functional iron deficiency. Low-dose vitamin C is preferable to higher doses, because high-dose vitamin C can lead to soft-tissue oxalate deposition in patients with end-stage renal disease.

Sultana T, et al. Oral vitamin C supplementation reduces erythropoietin requirement in hemodialysis patients with functional iron deficiency. *Int Urol Nephrol*.2016;48:1519-1524.

Maintaining Balance Between Alpha-Tocopherol and Gamma-Tocopherol

Ten healthy volunteers (aged 18-45 years) ingested 1,200 mg of gamma-tocopherol every 12 hours for three doses. The mean serum concentration of alpha-tocopherol decreased significantly from baseline to 30 hours, while the concentration of its main metabolite (alpha-CEHC) increased significantly.

Comment: In previous research, supplementation with large doses of alpha-tocopherol decreased serum concentrations of gamma-tocopherol, apparently by increasing the metabolism of the latter. Circumstantial evidence suggests that alpha-tocopherol-induced depletion of gamma-tocopherol may blunt some of the beneficial effects of alpha-tocopherol and might be responsible for the reported increase in prostate cancer and heart failure in people taking large doses of alpha-tocopherol. Conversely, the results of the present study suggest that taking large doses of gamma-tocopherol can deplete alpha-tocopherol, an effect that also could have adverse consequences. Thus, supplementing with mixed tocopherols would in most cases be preferable to using pure alpha- or pure gamma-tocopherol.

It has been my practice to recommend products that contain 50-100 mg of gamma-tocopherol per 400 IU (268 mg) of D-alpha-tocopherol. That ratio is in line with the ratio of gamma- to alpha-tocopherol in the European diet, although it is lower than the ratio in the American diet. Some commercially available vitamin E products contain a higher ratio of gamma- to alpha-tocopherol than that mentioned above. The optimal ratio of these compounds is not known.

Burbank AJ, et al. A short course of gamma-tocopherol mitigates LPS-induced inflammatory responses in humans ex vivo. *J Allergy Clin Immunol*. 2017;140:1179-1181.

Taurine for Portal Hypertension

Twenty-two patients (mean age, 52 years) with cirrhosis, clinically significant portal hypertension (hepatic venous pressure gradient [HVPG] of 12 mm Hg or greater), and esophageal varices were randomly assigned to receive, in double-blind fashion, 6 g per day of taurine or placebo for four weeks. Mean HVPG fell in the taurine group from 20 mm Hg at baseline to 18 mm Hg after four weeks ($p < 0.01$) and increased in the placebo group from 20 mm Hg at baseline to 21 mm Hg after four weeks ($p < 0.01$ for the difference in the change between groups). Treatment-related adverse events included gastrointestinal discomfort and fatigue and were usually mild and comparable between treatment groups.

Comment: Portal hypertension, which is a complication of cirrhosis of the liver, can increase the risk of ascites, hepatic encephalopathy, and potentially life-threatening bleeding from esophageal varices. Beta-blockers are commonly prescribed to lower portal pressure in patients with portal hypertension. The results of the present study indicate that taurine can also produce a modest improvement of portal hypertension in patients with cirrhosis, which could potentially reduce the risk of severe complications. The mechanism of action of taurine is not known; nor is it known whether taurine could augment the effect of beta-blockers.

Schwarzer R, et al. Randomised clinical study: the effects of oral taurine 6 g/day vs placebo on portal hypertension. *Aliment Pharmacol Ther*. 2018;47:86-94.

Probiotic for *Clostridium difficile* Infection

Thirty-three patients with an initial episode of mild-to-moderate *Clostridium difficile* infection were randomly assigned to receive, in double-blind fashion, one capsule per day of a four-strain probiotic or placebo for 28 days, in addition to standard antibiotic treatment (vancomycin or metronidazole). The probiotic contained *Lactobacillus acidophilus* NCFM, *L. paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07 and *B. lactis* Bl-04 (1.7×10^{10} total colony-forming units per capsule). The median number of days with diarrhea was significantly lower in the probiotic group than in the placebo group (3.5 vs. 12.0; $p = 0.005$).

Comment: *Clostridium difficile* is a Gram-positive bacterium that is a common cause of antibiotic-associated diarrhea and pseudomembranous colitis. *C. difficile* infection usually manifests as mild-to-moderate diarrhea, but severe colitis culminating in colectomy or death may also occur. Since around the year 2000, there has been a marked increase in the incidence of *C. difficile* infection. Increases in disease severity and mortality rates have also been observed, apparently because of the emergence of a more virulent strain of the organism. Treatment with vancomycin or metronidazole is usually effective, but the infection recurs in approximately 20% of patients after treatment with these antibiotics. Several double-blind trials have found that administration of various probiotic organisms can prevent the development or reduce the recurrence rate of *C. difficile* infection.[1] The present study demonstrates that probiotics can also be used as an adjunct to antibiotic therapy to accelerate recovery from *C. difficile*-associated diarrhea.

Barker AK, et al. A randomized controlled trial of probiotics for Clostridium difficile infection in adults (PICO). *J Antimicrob Chemother*. 2017;72:3177-3180.

Thiamine Deficiency and Septic Shock

A retrospective cohort study was conducted on 53 patients with septic shock at a tertiary care center who also had a diagnosis of alcohol-use disorders. Ten other patients with alcohol-use disorders who received thiamine more than 48 hours after the onset of sepsis were excluded. Of the 53 patients analyzed, 34 (64%) received thiamine. The median time to thiamine administration was nine hours. The mortality

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rate was significantly lower in patients who received thiamine than in those who did not receive thiamine (44% vs. 79%; p = 0.02).

Comment: Alcohol-use disorders are associated with both thiamine deficiency and increased sepsis-related mortality. In a recent double-blind trial, intravenous administration of thiamine (200 mg twice a day for seven days or until hospital discharge) to patients with septic shock had no significant effect on mortality. However, among the 35% of patients who were thiamine-deficient at baseline, treatment with thiamine significantly decreased mortality compared with placebo (15% vs. 50% [data estimated from Figure 3 in the paper]; p < 0.05). The present study also found that thiamine treatment can reduce mortality in patients with septic shock who are likely to be thiamine-deficient. At most hospitals it is standard practice to administer thiamine parenterally to patients with chronic alcoholism, in order to prevent or reverse Wernicke's encephalopathy. It is noteworthy that more than one-third of alcoholic patients in the present study did not receive thiamine. The study should serve as a reminder of the importance of timely thiamine treatment in this patient population.

Holmberg MJ, et al. Thiamine in septic shock patients with alcohol use disorders: An observational pilot study. *J Crit Care*. 2017;43:61-64.

Xylitol Prevents Dental Caries in Adults

One hundred seventy-nine adults (aged 30-45 years) who were considered at high risk of dental caries because of the presence of one to three caries and a high salivary concentration of *Streptococcus mutans* (the main cariogenic microorganism) were randomly assigned, in double-blind fashion, to chew xylitol chewing gum or a sugar-free placebo gum for 12 months. Participants chewed two pieces of gum for five minutes in the morning, two after lunch, and one in the afternoon. The total daily xylitol dose was as 2.5 g. The participants were followed for a total of 24 months. At 24 months, the mean incidence of new caries was significantly lower by 31% in the xylitol group than in the placebo group (1.25 vs. 1.80; p < 0.01). The concentration of *S. mutans* decreased significantly in the xylitol group (p < 0.01) but did not change in the placebo group.

Comment: Xylitol is a sugar alcohol that inhibits the growth of *S. mutans* or promotes the growth of an *S. mutans* strain that may be less cariogenic than other strains, because it adheres less well to tooth surfaces and produces less acid. Numerous clinical trials in children have shown that regular use of xylitol chewing gum reduces the incidence of dental caries and is as effective as application of occlusal sealants. For xylitol gum to be maximally effective in children, it should be started at least one year before permanent teeth erupt. The results of the present study suggest that xylitol chewing gum is also effective for caries prevention in high-risk adults.

Cocco F, et al. The caries preventive effect of 1-year use of low-dose xylitol chewing gum. A randomized placebo-controlled clinical trial in high-caries-risk adults. *Clin Oral Investig*. 2017;21:2733-2740.

Interaction Between Diets and Valproic Acid

One hundred thirty-nine children (median age, 2.9 years) with epilepsy who were treated with the ketogenic diet, a modified Atkins diet, or a low-glycemic index diet for more than 30 days (median, 5 months) were studied. After diet therapy, the mean serum concentration of valproic acid decreased significantly. No significant changes were seen in the serum concentrations of carbamazepine, lamotrigine, levetiracetam, topiramate, or phenobarbital.

Comment: The ketogenic diet is an extremely restricted diet that is sometimes used to treat refractory cases of epilepsy. The Atkins diet is a very-low-carbohydrate diet that is widely used to lose weight and less frequently as an alternative to the ketogenic diet in patients with epilepsy. A low-glycemic index diet is useful for preventing and treating diabetes and is also used as an alternative to the ketogenic diet in patients with epilepsy. Valproic acid is an anticonvulsant medication that is used not only for epilepsy, but also for migraine prophylaxis and to treat manic episodes associated with bipolar disorder. Consumption of any of the diets listed above might result in decreased effectiveness of valproic acid. In cases where initiation of these diets is followed by clinical deterioration, measuring the serum valproate level might be useful to determine whether a dosage adjustment is needed.

Heo G, et al. Effect of ketogenic diet and other dietary therapies on anti-epileptic drug concentrations in patients with epilepsy. *J Clin Pharm Ther*. 2017;42:758-764.

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Correction Notice

Below is an updated bio for Gary Huber, DO, whose article "Testosterone's Role in Cardiovascular Health: A Review of the Literature" appeared in last month's issue. The bio printed with the article was severely out of date. We apologize for the error.

Dr. Gary Huber spent 20 years as an emergency medicine physician before evolving his practice to integrative medicine. He is currently the Medical Director at Huber Personalized Medicine (www.huberpm.com) in Cincinnati Ohio. Dr. Huber is a professor for the American Academy of Anti-Aging Medicine as well as George Washington University's Metabolic Medicine Institute for integrative medicine. Dr. Huber serves as adjunct clinical professor teaching integrative medicine to medical students and residents at Ohio University's medical program as well as the University of Cincinnati College of Pharmacy.

He lectures nationally on hormone replacement therapies, cardiovascular care, sports medicine and other integrative medicine topics. Dr. Huber was honored with the "Best In Medicine" award from the American Health Council in 2017, awarded for his contributions to the advancement of integrative medical care and active education role.

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Bastyr University San Diego Clinic: Student Case Reports

edited by Baljit Khamba, ND, MPH

Fourth-year interns at Bastyr University are actively developing their clinical skills through treating patients at the school's clinic. They engage their didactic skills in rigorous case taking, examinations, evaluation, and a naturopathic-focused treatment plan under the supervision of their attending doctor. The interns are able to gain experience in areas such as mental health, mind-body medicine, oncology, hydrotherapy, physical medicine, out-reach community care, IV treatment, biofeedback, and so on. Each one of these opportunities presents a prime opportunity for the students to enrich their knowledge about conditions and approaches to care. In efforts to salient their understanding, the students write case reports under the supervision of Dr. Baljit Khamba in their course "Advanced Case Studies." By completing these reports, future practitioners gain a valuable skill that they can then utilize once they graduate.

A Case of Gastroesophageal Reflux (GERD) and Hiatal Hernia

by Anna Feagan

Abstract

Gastroesopageal reflux disease continues to be a growing health concern in the Western world. The physiological mechanisms behind the etiology of the disease and their relationship to other pathologies have been debated for decades. The purpose of this case report is to evaluate the current knowledge on the most common mechanism of gastroesophageal reflux disease and how it pertains to treatment. It aims to explore the literature, or lack of literature, that supports popular natural treatment options for this disease and discusses potential dangers of conventional standards of treatment. The goal of this literature review is to relate the findings on current literature surrounding GERD to a specific case.

It is the current consensus that a transient lower esophageal sphincter (LES) is the main physiological defect contributing to acid reflux.[1] This is particularly significant for patients with hiatal hernias, as this pathology has been found to decrease the pressure in the LES. The relationship between hiatal hernia and GERD will be discussed further throughout this report. Given this research on the etiology of GERD, treatments that aim to soothe tissues, such as demulcents, and treatments that target a decrease in acid production are mostly palliative and work to prevent further tissue damage. Curative treatment should be targeted at strengthening the integrity of the LES and this report discusses treatments that are thought to do so, particularly the herb *Fumaria officinalis*.

Introduction

Proton pump inhibitors (PPIs) are a main choice for the treatment of gastroesophageal reflux disease and continue to be one of the most prescribed drugs in the United States. It is estimated that 44% of Americans experience GERD symptoms at least once per month with 20% experiencing them as much as once per week.[2] While this drug is indicated for short term use in the treatment of GERD, evidence shows that chronic use with no documented clinical indication is prevalent.[3] Although PPIs are considered to be safe and relatively well tolerated, they are associated with several adverse outcomes. These include diarrhea, impaired B12 absorption, and hypomagnesemia. Increased risk of developing *Clostridium difficle* infection, hip fractures, and pneumonia is a concern in older patients taking PPIs as well.[3] After four to eight weeks of PPI therapy, in the absence of Barrett's esophagitis or erosive esophagitis, the use of this medication should be reassessed. Lowering the dosage of PPI and discontinuing the medication while switching to on-demand use are equally effective methods of tapering and the choice should be based on patient preference.[3]

In many patient populations, especially the elderly, there is a need for alternative therapy for GERD since the risks of PPI use are increased. Considering the known mechanisms underlying GERD, there are several natural therapeutic options that offer promising choices for the management of this disease and pose little to no additional health risks. Aloe

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vera gel, in particular, has been shown to have anti-ulcer, wound healing, and anti-microbial effects, all of which are of particular interest in treating GERD.[2] There has been little research on the efficacy of natural therapies such as *Aloe vera* in the treatment of GERD, though the few evaluations have shown promising results. *Aloe vera,* in particular, has shown efficacy in comparison to both PPI therapy and histamine receptor antagonists in pilot studies. With no adverse side effects, aloe vera gel is a potentially safer long-term option for the management of reflux.

In addition to aloe vera gel as a potential natural therapy for the treatment of many of the consequential pathologies of GERD (ulcerations, esophagitis, infection, experience of burning sensation), there is also a need for therapies that are more targeted toward treating the actual cause of GERD. Symptoms of GERD tend to occur when there is an imbalance between defensive and aggressive factors in the gastric system. Defensive factors are the gastroesophageal junction (including the lower esophageal sphincter), resistance to tissue damage, and acid clearance. Aggressive factors include acid secretion and impaired digestion (i.e. delayed gastric emptying). Since the LES is the first barrier between stomach acid and the esophagus, problems in this region are the source of GERD often. The LES is the distal 3-4 cm of the esophagus and is considered to be the primary reflux barrier. This region is tonically contracted at rest and maintains its tone intrinsically by the integrity of the muscle itself and extrinsically by cholinergic innervation.[1] There is significant variability in the tone of this region with it being lowest after meals to allow the entry of food and highest at night. If gastroesophageal incompetence is the source of reflux, there are three main reasons this could be happening. The first, and most common mechanism in cases of mild GERD, is that the LES is transiently relaxing. The other two mechanisms which tend to have a more severe presentation of disease state include a hypotensive LES and anatomical defect such as hiatal hernia.[1]

The relationship between the hiatal hernia and LES is of particular interest in cases of GERD considering the high association between the anatomical defect and disease. Studies have shown that over half of patients in Western countries that have reflux esophagitis also have hiatal hernias.[1] Normally the LES and crural diaphragm are superimposed, and the tone of the LES with the extrinsic pressure from the crural diaphragm create a resting LES pressure that is between 10-45 mmHg. This pressure is compromised in the case of hiatal hernias as the defect causes the LES to be proximally displaced.[1] The knowledge of this relationship between LES pressure and hiatal hernias in congruence with the knowledge of the importance of the LES in controlling reflux leads to the logical treatment for GERD being focused on improving the integrity of the LES. Certain botanicals including *Atropa Belladonna* and *Fumaria officinalis* have shown efficacy in regulating spasmodic muscle issues in the gastrointestinal system and therefore show promise in use for the treatment of compromised LES integrity leading to GERD.[4]

Case Description

The patient in this case is a seventy-five-year-old Caucasian male. He originally presented to clinic with a chief complaint of tingling sensation in his lips and an ulceration in his mouth. Under his year of care at the Bastyr University Clinic, California, reflux has been an ongoing complaint. He experiences a non-radiating burning sensation in his chest and throat that is worse when he lays down to sleep at night. He does not notice any increase of symptoms in relation to meals. Under the care of BUC, he has been recommended many different therapies. Mainly, apple cider vinegar, demulcents such as *Althea officinalis*, aloe vera gel, and de-glyccerinated licorice, and bitters such as gentian. The patient is seeking natural care for his reflux because he has been taking proton pump inhibitors for over twenty years and would like to taper off of this medication.

His past medical information reveals an ongoing history of GERD and related pathologies. Imaging esophagogastroduodenoscopy (EGD) from 2010 and 2014 revealed a 5 cm hiatal hernia and an area at 34 cm of suspected Barrett's esophagitis. His most

recent EGD, in April 2017, revealed no suspicion of Barrett's but a 7 cm hiatal hernia and distal esophageal ulcerations at 28-31 cm. DEXA imaging of his hips in April 2017 has revealed a T score of -3.3 of his right hip, giving him the diagnosis of osteoporosis. His most recent CBC revealed a pernicious anemia as his mean corpuscular volume was elevated at 95.1 fL. Other ongoing concerns for this patient include gout and lower back pain, for which he is being managed at BUC on a physical medicine shift.

A review of systems was completed during his first visit with me to rule out any serious complications and differentials of his conditions. He reports no cardiac signs or symptoms and no muscle weakness or tingling, although the tingling sensation on his lip is still present periodically. He did, however, report that he has been experiencing a cough and some difficulty breathing for the past two or three years. The cough produces a small amount of clear sputum in the morning but persists throughout the day. A physical examination reveals a red and enlarged tongue, lungs that are clear to auscultation with normal breathing rhythm and slightly decreased rate, regular rate and rhythm of the heart with no murmurs, gallops, rubs or abnormal heart sounds, and intact deep tendon reflexes.

Given the patient's most recent imaging revealing a hiatal hernia with esophageal ulcerations in concurrence with his primary symptom complaint of burning sensation in the chest, a primary diagnosis of hiatal hernia with GERD and esophagitis was made. In addition, his most recent complete blood count revealed low MCV, indicating a diagnosis of macrocytic anemia while his DEXA scan revealed a diagnosis of osteoporosis. Treatment of his condition involved removing redundant therapies that are not addressing the cause of his symptoms, which is a hypotonic LES due to hiatal hernia. This led to the discontinuation of DGL, *Althaea officinalis*, gentian, and apple cider vinegar. The addition of *Fumaria officinalis*, five droppers full three times per day was made and he was instructed to continue the use of aloe vera gel prior to meals. Follow up with the patient two weeks later revealed no symptoms since beginning this new therapy despite the continuation of tapering his PPI medication.

Discussion

Gastroesophageal reflux disease is typically diagnosed on clinical symptoms alone. Further diagnostic tools such as endoscopies are invasive and are not typically necessary to diagnose GERD, especially if it is not complicated. According to the American Gastroenterological Association, endoscopy with biopsy should only be performed on patients with GERD if they have a troublesome dysphagia, suspected GERD related esophageal syndromes, or have not responded to PPI therapy.[5] Esophagitis is one of the most common complications of GERD, and the Los Angeles classification is the most widely used grading system to assess it. This system grades the lesions based on number, size, and level of involvement of the luminal circumference. Further complications that may result from GERD include esophageal ulceration, laryngeal irritation resulting in chronic cough, teeth erosion, and Barrett's esophagitis. Barrett's esophagitis is considered a more serious complication, happening in about 10% of patients with chronic GERD with under 1% of those patients developing adenocarcinoma.[5]

In this particular case, diagnosis was made using a combination of symptoms and imaging. The most recent imaging report indicated an endoscopy that showed small esophageal ulcerations and a hiatal hernia. In conjunction with the patient's self-report of burning sensation in the chest and throat, a diagnosis of GERD with esophagitis and hiatal hernia was made. Considering the association between decreased B12 absorption and PPI use, together with macrocytic anemia findings on his CBC and the physical exam findings of enlarged tongue and lip tingling, it is likely this patient also has a B12 deficiency. Other conditions, such as chronic cough, that the patient displayed may also be related to his chronic reflux as laryngeal irritation from the acid can lead to this condition. Additionally, osteoporosis is a condition associated with chronic PPI use that the patient also has, as indicated on his most recent DEXA scan.

Although GERD is usually considered a benign condition, treatment can prevent the more complicated conditions previously discussed. Inhibiting acid production is the main allopathic treatment modality and is accomplished using four to eight weeks of therapy with a proton pump inhibitor. PPIs have demonstrated excellent efficacy in the treatment of GERD, with a 90% healing rate in erosive esophagitis and an 80% healing rate in Barrett's esophagitis.[6] In non-erosive reflux, PPI therapy has been shown to have 50-65% healing rates, which is the highest among all pharmaceutical anti-reflux therapies.

Studies demonstrating the efficacy of herbal demulcents in treating reflux and preventing further complications of GERD are not as prevalent as pharmaceutical therapies; however, aloe vera gel has shown efficacy and indication in several trials. In one study this species was shown to reduce gastric juice, acid and pepsin, and inhibit acute gastric lesions in rats.[2] Other studies have shown reduced TNF-alpha as well as reduced gastric inflammation and ulcer size, with protective effects being comparable to the drug sucralfate. *Aloe vera* has also demonstrated efficacy in treating other gastric conditions such as *H. pylori*. In comparison to PPI therapy and H2R antagonists in the treatment of GERD symptoms, aloe vera gel is comparable in efficacy.[2] *Aloe vera* is a promising medication as both a supplement in the conventional treatment of GERD and as mono therapy for symptom management. However, additional studies that directly compare this therapy to conventional management are needed. In addition, studies on the use of aloe vera gel in conjunction with as needed pharmaceutical intervention are non-existent and could be extremely useful in reducing the number of individuals on chronic PPI therapy.

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As previously discussed, there is a need for therapies that are directed at the actual cause of GERD, which is transient LES. None of the common pharmaceuticals used in the treatment of GERD have mechanisms of action that address this issue. However, certain anti-spasmolytic herbs have demonstrated ability to regulate the pressure in the LES and thus improve symptoms of GERD. In particular, *Fumaria officinalis* has incidentally shown to improve symptoms of GERD while being used to treat gallbladder spasms.[4] The efficacy of this treatment is incidental, and more studies need to be done that directly investigate the effect of *Fumaria* on the LES. However, with a lack of other treatment modalities, and the overall safety of this herb, it can be considered as a liable treatment in concurrence with other medications.

In regard to examining the treatment of this particular case report of GERD, there are several inherent limitations. The most prevalent one is the limitation on time and follow up with the patient. As the primary student clinician, I will only follow this patient for a 12-week period of time. This is insufficient to properly evaluate the efficacy of treatments and to follow up with post-treatment imaging. However, he had been seen at BUC for over one year during which time he had been treated with demulcent therapies (including aloe vera gel) as part of his GERD management. His endoscopy in April of 2017 did show some improvements in the amount of ulceration present in the esophagus from the previous imaging done in 2010. Additionally, in just two weeks of therapy with *Fumaria* the patient reported a resolution of symptoms, despite continuing to taper from his PPI medication. This has motivated me to continue this course of treatment with the hopes of absolving GERD complications such as esophagitis with the *Aloe vera* and to improve the integrity of the LES by adding the *Fumaria*. If his symptoms continue to dissipate, and considering his esophagitis is not classified as severe according to the small size of the ulcerations, he should be able to completely stop his PPI medication which is putting him at risk for developing other severe health complications.

Conclusion

The goal of this case report was to discuss the research on the etiology of GERD and how current treatments, both natural and synthetic, do or do not address this etiology and how these treatments have affected one particular case of GERD. Adverse side effects of PPI therapy has prompted need for natural therapies to address reflux, particularly when it is uncomplicated. Research on the efficacy of natural therapies in treating this disease is lacking, although preliminary investigations show promise. In the case of GERD discussed here, a hiatal hernia is present, indicating that lack of LES integrity is most likely the etiology of the symptoms. This has prompted a treatment approach that includes both strengthening the LES as well as protecting the esophagus from further inflammatory damage.

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Anna Feagan is a naturopathic medical student at Bastyr University in San Diego, California. After studying psychology and pre-medicine at the University of Miami, she moved to Boston, Massachusetts, where she worked for a psychologist specializing in neurofeedback. While there, she learned how integrative medicine can be used to treat mental health disorders and was inspired to pursue a degree in naturopathic medicine. After graduating in the spring of 2018, she plans to open a private practice in San Diego. She looks forward to utilizing her knowledge of holistic medicine in combination with her experience and training in neurofeedback to provide patients with the best possible treatment outcomes. Besides medicine, Anna fuels her life with passions for cooking, hiking, yoga, traveling, surfing, and the constant pursuit of new knowledge and adventure.

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On the cover

Myth Busting Common Misconceptions of Kidney Disease

Dr. Jenna C. Henderson

The kidneys may well be the most misunderstood of all the major organs. Patients often fail to grasp the seriousness of their condition and, without a proper understanding, cannot take appropriate steps to ameliorate their condition. Part of the reason for this is the very nature of kidney disease. Most of the damage of kidney disease has already taken place by the time the patient becomes aware that there is a problem. The "silent killer" is easy to ignore; and by the time some patients are roused into action, it is in a last-ditch effort to avoid dialysis.

When attempting to properly treat kidney disease, patients usually first look to their nephrologists who typically use anti-hypertensive medications as a first line of defense. Only very rarely do they give patients any advice about diet. When patients press for further options they are offered more medications and are told that if they are lucky, eventually they will be transplanted.

Those patients who venture outside of mainstream medicine in search of other options are confronted with confusing and often contradictory information, much of which is inappropriate to their situation. When there is a vacuum of sound medical advice, the internet often fills in the gaps. The patient at least feels they are doing something and not just passively waiting to go on dialysis. However, some good advice is usually mixed with a lot of bad advice. When cranberry juice and herbal diuretics don't stop the progression of chronic kidney disease, the patient often feels they have run out of options.

Patients who turn to alternative practitioners for advice on treating kidney disease often have high expectations and end up disappointed. The gaps in knowledge of nephrology among holistic doctors becomes apparent, particularly with advanced kidney disease. Without a clear understanding of chronic kidney disease, unfortunately patients and practitioners alike often default to many of the prevailing myths surrounding kidney disease. In this article we will look at some of the common misconceptions around kidney disease and how holistic physicians can better serve their renal patients.

Not Using Proper Terminology

Kidney patients experience a huge gap between their experience with their nephrologist and their holistic practitioners. Not only do they operate from different paradigms, they don't even seem to speak the same language. This leaves the patient confused but also contributes to a sense of mistrust from mainstream medicine. How can another practitioner address the kidney patient's concerns if they misuse common terminology?

Kidney function refers to the kidney's filtration ability and only this. The kidneys have many functions including regulating blood pressure, regulating the pH of the blood and producing erythropoietin, but the term kidney function refers only to the ability of the kidneys to filter out uremic wastes. A patient could have any type of kidney ailment from nephrotic syndrome to polycystic kidney disease to chronic kidney infections, and these conditions are serious, but if the kidney's ability to filter wastes has not been compromised, they have 100% kidney function.

Kidney failure refers only to stage 5 chronic kidney disease. There is no such things as stage 3 or stage 4 kidney failure. There is chronic kidney disease which comes in stages, where the kidneys are gradually deteriorating and losing function. If chronic kidney disease continues to

progress, it leads to kidney failure. Kidney failure is the state in which the kidneys have lost the ability to filter uremic wastes to the point where lifesaving measures are necessary. If creatinine is normal or just mildly elevated, the patient is not in kidney failure.

Patients in kidney failure may retain some **residual function** and produce some urine, but if the filtration rate is not high enough to sustain life, they are in renal failure. Residual function may include a high volume of urine, as the kidneys lose the ability to concentrate urine. But this urine is mostly water as the uremic compounds are not being filtered out and remain in the bloodstream.

Not Understanding How Calculations of Kidney Function Work

The most common measurement of kidney function used is eGFR (estimated glomerular filtration rate). This is often taken as what percentage from out of 100% the kidneys are currently operating. It is also used to grade chronic kidney disease. Stage 5 is an eGFR under 15 and considered not enough activity in the kidney to sustain life. Intervention in the form of dialysis or a transplant will be necessary at this point.

However, one should consider how eGFR is calculated. Four values are plugged into a formula that includes creatinine, age, gender, and race. Creatinine is one uremic waste product that the kidneys need to clear. There are more than 3,000 different uremic waste products that the kidneys handle, but creatinine tends to be the most stable.[1] Creatinine is a waste product that comes from muscle tissue and since muscle mass does not shift significantly from one day to the next, creatinine tends to be more reliable than other potential markers. BUN (blood urea nitrogen) is also a uremic waste product, but BUN comes from dietary protein and can shift rapidly based on protein intake.

Age is also a factor in calculating eGFR. Some loss of kidney function is part of the aging process, and age-related kidney decline can lead to kidney failure in an otherwise healthy individual. However, it is important to know that *anyone over age 60 will have a low eGFR no matter how healthy they are*. This is simply how the formula is designed.[2] Many elderly patients have consulted the author in a panic because their eGFR is low. It is important for practitioners to keep this in mind and look to the creatinine level directly to judge the patient's situation.

Since men have a greater muscle mass than women, their creatinine will run higher. This is why gender is factored into the calculation for eGFR. Race is also factored in as those of African descent tend to have a higher baseline creatinine. However, many practitioners encounter the extremely fit young man who has a high creatinine and low eGFR. This is due to the increased muscle mass and may not be indicative of kidney weakness. For these people, it is good to run Cystatin C, an altogether different indicator of kidney function that is not affected by muscle mass.[3]

Misinterpreting Wide Fluctuations

With healthy kidneys, measuring function is often straightforward: the amount of the waste product creatinine present per volume unit of blood. A creatinine under 1.0 or under 1.3 is a healthy kidney, and whether the patient drank water the day before will have little impact on the creatinine. As the creatinine creeps up above 1.3 toward 2.0 and beyond, small changes in hydration can result in wide readings. Dehydration will cause the creatinine to be more concentrated. While a healthy kidney tightly regulates the water balance, advanced kidney disease often brings large shifts in the numbers. This is not necessarily reflective of an actual shift in the kidney filtration.

It is not always straightforward whether or not the patient is dehydrated and if dehydration is shifting the serum creatinine. Dehydration may be apparent from the specific gravity on the urinalysis or a pH that is more acidic than usual. A high hemoglobin/ hematocrit may also indicate dehydration, but since these numbers tend to be low with chronic kidney disease, it may be difficult to tell.[4] It is also important to know if the patient has been warned against drinking too much water due to concerns over cardiac stress with fluid overload.

Underestimating the Relationship Between Filtration and Blood Pressure

Hypertension is easy for many patients to ignore, but once the damage to the kidneys becomes apparent, patients want to get on track. Now they're ready to get serious, take their blood pressure medications and do holistic interventions to keep their blood pressure down. But much to their dismay, their kidney function doesn't get better, it actually gets worse. The patient may interpret this as a side effect of their medication and blame the toxicity of the drug. They stop the blood pressure medication and their kidney function gets better, so in their mind clearly the drugs were the problem. And since their listlessness and fatigue seems worse with an alpha blocker or beta blocker, who can blame them?

Convinced that blood pressure medications are the biggest issue, the patient may want to leave well enough alone and think that out-of-control blood pressure is really not all that bad. Or if they're seeking out alternatives, they believe that If only the blood pressure were managed naturally instead of with medications, it would be different. But much to their dismay, natural agents like Rauwolfia, celery seed, hibiscus, and magnesium don't seem to help the kidney function either.

This is often a difficult situation and it can be hard to convince these patients that blood pressure management is essential. As the kidneys filter the blood across a pressure gradient, the more internal tension there is in the kidney, the better it will filter the blood. It's often useful for the patient to compare this to cleaning with a sponge. The tighter one squeezes a sponge, the better it cleans. When the kidneys are weak and not filtering the blood well, the

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blood pressure goes up. This helps the kidneys filter out the waste products. A healthy kidney does not need elevated blood pressure to sustain normal filtration. Correcting the blood pressure did not damage the kidneys, it simply revealed how much damage had already taken place. And like a sponge that is squeezed too vigorously and becomes worn out, the extra wear and tear of uncontrolled blood pressure will make the situation worse in the long term, even if it temporarily makes the serum creatinine better.[5]

Patients coming to alternative practitioners often hope to be able to discontinue their prescription medications. They need to understand that with weak kidneys there will be a need for intervention to manage blood pressure most likely from this point forward.[5] At best they may be able to reduce the dosage or switch to some agent with fewer side effects. The worst course of action would be to abruptly stop blood pressure medication, especially since there is the possibility of rebound hypertension making the situation much worse.

It is important for the patient and the practitioner to anticipate that once out-of-control blood pressure is brought under control, there may be a sudden elevation in serum creatinine. Understanding the relationship between blood pressure and kidney filtration is necessary to understand the patient's situation. Once the blood pressure is normalized, then evaluating the serum creatinine will give a better picture of the kidney's filtration.

This is true not only for hypertension but also for hypotension and bradycardia. If an elderly patient exhibits low blood pressure and a slowed heart rate, do not jump to the conclusion that high creatinine means kidney dysfunction. There may simply be not enough pressure for filtration to take place. Normalize the blood pressure and heart rate first, and then see if the creatinine goes back down to an acceptable baseline.

Using Diuretics to Build Kidney Function

A diuretic is a stimulant. It temporarily pushes the kidney to expel more water and nothing more. It does not address the root cause of chronic kidney disease or protect the parenchymal tissue of the kidney from damage. One would not use a stimulant for other chronic conditions. One would not prescribe large doses of coffee for adrenal fatigue, and yet herbal diuretics are used as a panacea for all renal problems.

While anuria and oliguria are a problem in advanced kidney disease, as the kidneys break down and lose the ability to produce urine, herbal diuretics are not a solution. Like flogging a dying horse, demanding that it go faster, diuretics only serve to push an already weakened state. This is often difficult for the patient to accept as they believe that kidney cleanse products they purchased from the health food store are helping and they take the increased urine volume as evidence.

This is not to say that diuretics don't have a place. When water retention is a serious issue, diuretics – either natural or by prescription – can provide relief. Diuretics can also be an important line of defense against persistent hypertension. Just don't expect uva ursi, juniper, or parsley to help the kidneys filter wastes any better. The urine will be in a greater volume, but the kidneys are not any stronger.

Treating All Kidney Problems the Same

It is amazing that so many natural kidney support formulas try to be all things to all people. Herbs for treating kidney stones, urinary tract infections, glomerulonephritis, and hypertension are often thrown together in one formula. While kidney stones may lead to chronic kidney disease, these conditions are not interchangeable. Some lay people are under the impression that renal lithiasis is rampant, and all people would benefit from a purification program to push these kidney stones out. This, however, is not the case with a prevalence of kidney stones in the United States at only 8.8% of the population.[6]

Formulas for kidney stones often contain an agent like *Chanca piedra* or *Hydrangea arborescens* to address the issue, as well as a demulcent like slippery elm and a diuretic. Formulas for urinary infections will typically have D-mannose, cranberry and also maybe a diuretic. Formulas to support kidney filtration may have cordyceps or rehmannia included. *Hibiscus sabdariffa* is an herb with multiple benefits as it may inhibit the formation of kidney stones,[7] inhibit urinary tract infections,[8] and support kidney function.[9] But this is an exception. For most kidney patients, clarifying the problem is important for individualized treatment. A one-size-fits-all formula will have items they don't need and probably won't give an adequate dose of what they do need.

Expecting Water to Cleanse All

Clinical dehydration is certainly bad for the kidneys. Dehydration can also elevate creatinine on a blood draw, making kidney function appear worse than it really is. For many patients not drinking water is just a habit and their sense of thirst may be off. However, going to the opposite extreme brings its own problems.

This was one area where as a kidney patient, the author found agreement working with both a nephrologist and an OMD (Oriental Medical Doctor). The nephrologist was adamant that excess fluids would not help the kidneys get rid of more uremic waste. The same waste is passed but the urine is simply more dilute. The OMD for his part concurred. By the tenants of his practice, all things must be in balance including water.

It was the holistic doctors the author encountered who were of the mindset that if a little is good more must be better. For kidney patients in an early stage, an excess of water can cause an electrolyte disturbance. For patients with kidney failure, fluid overload can lead to congestive heart failure and shortness of breath.

For the holistically minded who have been told over and over that water is cleansing, the situation for those with kidney failure can be shocking. Fluid restrictions would seem counterintuitive when one is full of uremic toxins. However, producing urine is an active process on the part of the kidneys, and this production stops with kidney failure. The patient may be anuric with no urinary output or oliguric with very little output. The author has encountered holistic practitioners who questioned whether they should try to shift the urinary pH to a more acidic or alkaline balance in a patient with kidney failure. The fact that there is no urine and an entire bodily function has shut down did not immediately register.

Inferring Too Much from an Urinalysis

The urinalysis should be a complement to the blood work to provide a more complete picture. Patients often read online that cancer thrives in an acidic body, and therefore they must alkalize their system. The author has encountered many patients who decide that since their urine has an acidic pH, their body is too acidic. They will then set up the goal of a neutral urinary pH to alkaline the body.

It is actually a healthy kidney that is able to expel metabolic acids. A weak kidney unable to filter out uremic wastes will pass mostly water, with a neutral pH. Also, certain bacteria and UTI may be associated with a high pH. In order to achieve a more alkaline urine, the patient usually needs to severely cut back on protein, a diet that will ultimately be unsustainable.

Going to Extremes in Diet

Protein increases the workload of the kidneys and a high protein diet will lead to higher levels of BUN. And when patients are afraid of kidney failure they're willing to go to extremes to cut the protein out of their diet. They may cut protein out or even take up fasting to help their kidneys. But although this self-imposed marasmus or kwashiorkor will improve their BUN, it often comes at a price.

As the body strives for homeostasis, self-correcting mechanisms kick in. Blood albumin must be maintained; and without dietary protein, the body will take protein out of the muscles. Although protein deprivation may temporarily alleviate some kidney stress, the resulting sarcopenia will ultimately be to the patient's detriment.[10]

Protein deprivation can bring a host of issues for many types of kidney patients. This is especially true with diabetic kidney issues. The patient is careful to avoid carbohydrates but doesn't want to do too much protein either.[11] Often the patient feels there are no acceptable options. For the pediatric patient, protein is necessary for growth; and for the kidney patient also fighting infections, protein is necessary for the immune system.

Slightly lower protein may be helpful, but moderation is key. In general, between 0.8 and 1.0 grams of protein per kg of body weight may work. For patients with very low filtration 0.6 grams of protein per kg of body weight may be used for a short time. This calculation may need to be adjusted if the patient has more adipose tissue. Greater body fat would not allow for greater protein consumption. In that case, calculations can be made using ideal weight for height and build rather than the actual weight.

Demonizing All Dairy

Protein puts stress on the kidneys, but is dairy protein really worse than other types of protein? Kidney patients are often under the impression that all milk products are especially detrimental to kidney health, but is that really the case? Kefir has actually been shown to be helpful for diabetic nephropathy,[12] and there is evidence that whey and casein decrease kidney inflammation and renal damage.[13] While red meat, poultry, and seafood raise uric acid, dairy products will not. Some dairy products are more concentrated in phosphorus than others, but it is not the case that all dairy must be eliminated for every kidney patient.

Going to Extremes Cutting Out Minerals

When patients first learn that they have kidney trouble, the initial response is often to cut way down on sodium intake. Cutting out processed foods, canned soups, and preserved meats and eating in restaurants less often is a good first step. Drastically reducing sodium will also greatly improved edema. However, the body tightly regulates sodium in the blood and there will be diminishing returns if the patient goes to an extreme cutting out sodium. Blood pressure will only decrease a limited amount, as other factors besides sodium are driving the hypertension.[14] Depending on the circumstances, foods naturally high in sodium like celery, tomato, or spinach may be beneficial. Whether the patient consumes 1,000 mg of sodium or 1,200 or 1,500 a day is usually not of great consequence. As long as the patient is not well over 2,000 mg of sodium, they do not need to be continually counting the mg of sodium in all of their food.

Kidney patients may also be mindful of potassium consumption. Unlike sodium, there are no hormonal regulators keeping potassium in homeostasis. Under normal circumstances a healthy kidney will expel potassium every time the patient urinates. Problems come with late stage kidney disease when the kidneys no longer pass potassium through the urine, potentially leading to a dangerous state of hyperkalemia. But this danger comes only from late stage kidney disease (or potentially from potassium sparing diuretics). The problem comes when the patient starts a low potassium diet prematurely. If the kidneys are still healthy enough to excrete potassium, there is no benefit to a low potassium diet. It does not reduce stress on the kidneys and cuts the patient off from many healthy fruits and vegetables.

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Ignoring Phosphorus

Phosphorus is a mineral that puts more stress on the kidneys, but one can only go so far in eliminating phosphorus from the diet. Some phosphorus in the diet is unavoidable as phosphorus naturally occurs with protein. That is unless the patient completely eliminates protein and takes amino acid supplements, a drastic measure that few patients are able to sustain for an extended period of time. Some dietary measures can minimize the patient's phosphorus intake. Whole grains like quinoa and whole wheat are high in naturally occurring phosphorus. However, naturally occurring phosphorus is usually bound and not fully absorbed. Added phosphorus like phosphoric acid in soft drinks, however, are absorbed at virtually 100%. Many processed foods and fast foods also contain phosphate-based additives.[15] This may even be present with food considered healthy like rice milk fortified with tricalcium phosphate.

Often unconsidered are sources of phosphorus from dietary supplements. Sometimes the presence of phosphorus is obvious from the name such as phosphatidylserine or phosphatidyl choline. It may also be added to the supplement as dicalcium phosphate. Krill oil, which is a phospholipid, is also a potential source of phosphorus. With late stage kidney disease, it is often necessary to take a phosphorus binder; but eliminating extra sources of phosphorus will make the situation easier to manage.

Processing natural vitamin D is normally handled by a healthy kidney, and many kidney patients have chronically low levels of vitamin D. But patients and holistic practitioners may be overzealous in correcting low vitamin D, as vitamin D increases the uptake of phosphorus. Some patients unable to manage their phosphorus do well to reduce their intake of vitamin D. If the nephrologist has prescribed calcitriol, additional vitamin D supplementation may be unnecessary. Continual monitoring of blood work will help clarify the patient's needs. It is often good to have a target within normal range but on the lower side of normal.

Being Afraid to Use Magnesium

Many people group electrolytes together and assume that since too much potassium is dangerous, magnesium is also dangerous. But high magnesium does not disrupt the heart the way high potassium does. At worst the patient might experience a loose bowel with too much magnesium.

There are multiple benefits of magnesium for the kidney patient and, like the population at large, magnesium levels may be low. Magnesium is a natural calcium channel blocker, and it also helps balance blood sugar. Even dialysis patients, who don't eliminate magnesium in their urine, benefit from magnesium supplementation as it reduces calcification of the blood vessels.[16]

Expecting Too Much from Diet Alone

Diseases of the kidney such as IgA nephropathy, FSGS or polycystic kidneys are complex and multifactorial. In practice the author uses a combination of supplements, dietary strategies, and lifestyle changes (mild exercise, hydrotherapy and addressing sleep habits) to address chronic kidney disease. This is especially true with advanced kidney disease where decreased kidney filtration can impact a broad range of issues from cardiovascular health to bone density. Yet a surprising number of kidney patients want to address their issues with diet alone.

Many patients are under the impression that if only they can eliminate the offending food that's triggering their inflammation, the kidney problem will resolve. This is usually perceived as getting to the root of the problem, but in practice after a long series of tests and elimination diets, not much shifts. The etiology of many renal conditions may involve a genetic predisposition but many times the condition is considered idiopathic, probably involving a variety of factors. And while many patients are busy sorting out the fine details of their diet, their kidneys are continuing to break down.

Unrealistic Expectations of the Kidney's Capacity to Heal

Patients looking to alternative medicine sometimes believe that the body has an unlimited ability to regenerate. While some tissues of the body do have a great regenerative potential, the kidneys are not one of them. TCM acknowledges this as a weakening of the *Jing* with advancing years. Even without kidney disease, our nephrons are breaking down with the passing years, starting in our twenties.

Young children may outgrow conditions such as minimal change nephrotic syndrome. The kidneys are generally proportionate in size to one's fist, and as children grow their kidneys grow. New kidney cells are still forming as there is active mitosis in a growing kidney. Once the individual is full grown, there is a limited capacity for the kidneys to regenerate. For adult kidney disease, we are maintaining the kidneys and preventing further decline.

Aggressive Liver Detox

The liver and the kidneys are both organs of elimination, and there are some conditions that effect both such as heptorenal syndrome and cystic kidneys that also involve liver cysts. Many traditional liver herbs are also beneficial to the kidneys. Silymarin can protect the kidneys from toxicity,[17] and curcumin can support kidney filtration.[18] Berberine can also help the liver and protect the kidneys.[19] However, sometime patients and practitioners have unrealistic expectations of healing the kidney by correcting the liver. Aggressive liver detoxification will not be helpful if it pushes too much too fast.

Heavy metals, environmental toxins, and occupational exposure can tax the body's detox systems; but if the kidneys are struggling to eliminate basic metabolic wastes

like creatinine and BUN, it is important not to push too hard. The liver processes toxins through phase I and phase II detoxification and after these lipid soluble toxins become water soluble, they are handled by the kidneys. Often kidney patients are eager to detoxify, and they find that mainstream nephrology doesn't even acknowledge their concerns. However, liver detox should be a gradual process for kidney patients.

Aggressive Use of Colonics

When a major organ of elimination is taxed, it makes sense to support the body's other channels of elimination. Constipation is certainly a problem to be avoided, but aggressive use of colonics may be more fluid than the patient can handle. It could also make it difficult to manage electrolytes with a dramatic sudden shift. Some patients are given prescription laxatives like Kionex to help the body eliminate potassium. Patients could also use a distilled water enema to lower potassium, but the volume of fluid with a colonic can be problematic.

Avoiding Dialysis at All Costs

Traditional Chinese medicine states that fear is detrimental to the kidneys; and for most patients, there are few things more fear provoking than the thought of dialysis. Like most fears looming large in one's mind, the thought is often worse than the reality. The author writes this having experienced fourteen years of hemodialysis.

Avoiding dialysis can be a good motivation for change, and natural therapies can be an important part of slowing the progression of chronic kidney disease. But when the kidney filtration is not strong enough to sustain life, it's time to be realistic about the patient's options. Some patients fear the machine more than the damage of kidney failure itself and need to understand that they will be better off having toxins mechanically removed from the body. The author has seen patients with creatinine as high as 18, holding out for a transplant, unwilling to face the dialysis machine. These patients need to understand just how dangerous it is to avoid dialysis at any cost.

Working with a TCM practitioner, the author was urged to watch comedy on a regular basis. Fear is the body's fight or flight responses, while laughter is the opposite state, breaking up the internal tension of fear and giving the body the message, 'danger averted'. Interestingly, a study on survival rates for dialysis patients found scoring high on sense of humor in self-assessment was a huge predictor of long term survival.[20] Holistic practitioners may have their own strong feelings against dialysis, but it will ultimately be for the patient's best interest to maintain a positive attitude.

A holistic approach to kidney disease can dramatically improve a patient's overall health and well-being, but patients and practitioners alike often hold notions that are at odds with the reality of their situation. With a balanced approach, it's possible to address the concerns of chronic kidney disease and avoid the common pitfalls. A better understanding of nephrology will allow natural medicine to offer more targeted therapies.

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Dr. Jenna Henderson's practice, Holistic Kidney, is dedicated to the unique needs of renal patients with an international clientele and patients on six continents. A kidney patient herself for over 25 years, 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 *Townsend Letter*, *Natural Medicine Journal*, and *NDNR*. She has lectured extensively across the US to naturopathic doctors, kidney patients and kidney professionals, and co-hosted the radio show *Improve Your Kidney Health*.

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. She holds a naturopathic license in the state of CT and has recently relocated to New Paltz, NY. For more information www.holistic-kidney.com.

Non-Alcoholic Fatty Liver Disease – A Metabolic and Inflammatory Chronic Illness

by Dr. Bonnie Nedrow, ND

Non-Alcoholic Fatty Liver Disease

Non-Alcoholic fatty liver disease (NAFLD) has been cited in the medical literature for over 100 years. However, in the past 20 years the prevalence of NAFLD has increased progressively, and the number of peer-reviewed studies regarding the etiology and natural history of NAFLD has followed suit. The growing incidence of hepatic steatosis parallels the rising obesity epidemic in the United States and worldwide. Current estimates for NAFLD, which is under-diagnosed, range from 15-52% in the US,[1] while roughly 30% of adults are obese. Although not all people with fatty liver are obese, nor do all obese subjects present with fatty liver, the overlap is significant and should not be clinically overlooked. Of note, the most common morbidity associated with NAFLD is cardiovascular disease, the number one cause of mortality in the United States.

Fat accumulation in hepatocytes, in the absence of liver damage from alcohol, viral infections and autoimmune disease, can be best understood as the manifestation of metabolic syndrome in the liver. When carbohydrate consumption exceeds cellular glucose expenditure, glucose is converted to fatty acids that are stored in adipocytes through insulin signaling. Dietary fat also contributes to fat storage when a carbohydrate-rich diet is consumed, due to insulin suppression of fatty acid oxidation. Excess accumulation of fat expands adipocyte tissue, resulting in the production of proinflammatory adiponectins and cytokines that promote insulin resistance. As fat cells become resistant to insulin, serum free fatty acids increase, which are then sequestered by the liver. When the liver is unable to clear excess fat via fatty acid oxidation and triglyceride production, triglycerides move into storage in hepatocytes. Eventually, hepatocytes also become insulin resistant, which triggers gluconeogenesis and de novo lipogenesis (DNL), further fueling insulin resistance and hepatic steatosis.[2]

In this milieu of insulin excess, hepatic steatosis, and inflammation, hepatocytes become vulnerable to additional insults, namely environmental chemicals and microbial dysbiosis. Endocrine-disruptive chemicals and some prescription drugs are frequently obesogenic, driving the same pathways associated with insulin resistance and metabolic syndrome.[3] Some of the well-recognized and extensively studied obesogens include phthalates, bisphenols, PCBs, PBDEs, tributyltin, dioxins, DDT and DDE, nonylphenol and parabens. Many drugs, including the anti-diabetic drugs, glyburide and tolbutamide, are also known obesogens. These endocrine disruptors interfere with peroxisome proliferator-activated receptors, alter estrogen metabolism, and impact satiety and food preferences. The end result is an altered fat metabolism favoring storage over fatty acid oxidation.[4] In addition, there are many common foods that act as obesogens, with high fructose corn syrup having the most dramatic effect, particularly on the obesity epidemic in children.

Microbial dysbiosis has been identified as both an initiator and a significant contributor to both obesity and NAFLD. In a state of obesity, there is an increase in microbes that break down indigestible fiber into carbohydrates, leading to over-harvesting of fuel from fiber. This increased carbohydrate load contributes to insulin resistance and associated hepatic steatosis. More importantly, obesity-associated dysbiosis causes intestinal inflammation, barrier defects, and sets off a cascade of inflammatory molecules including lipopolysaccharides, lipoprotein lipase, interleukin-1 (IL-1), and tissue necrosis factor-alpha (TNF-α) in hepatic tissue. This is the pathway by which pathological intestinal permeability and endotoxemia produce toxic byproducts that are sequestered by the already over-burdened liver.[5]

It should be noted that while alcohol is not the prime inducer of NAFLD, it is a hepatocellular insult compounding the disease process. A diagnosis of alcoholic steatosis requires a significant and regular consumption of alcohol somewhere between 1-4 alcoholic beverages per day.[2] The added exposure to obesogenic and oxidative toxicants including alcohol, and endotoxemia from dysbiotic flora, overwhelm the natural detoxification and metabolic regulation seen in a healthy liver. As we begin to weigh in on this array of proinflammatory factors, pathogenesis of NAFLD is best explained as a multiple-hit model with metabolic dysregulation increasing the vulnerability of hepatocytes to exogenous and endogenous toxicants.[2]

Biomarkers for NAFLD

Liver biopsy has long been the gold standard for the diagnosis of NAFLD and nonalcoholic steatohepatitis (NASH), a more progressed form of fatty liver with significant liver injury due to advanced inflammation. More recently, proton magnetic resonance has become the noninvasive gold standard test to quantify liver triglyceride levels. With the rising increase in NAFLD, there is a need for less expensive, non-invasive screening tools. Proposed biomarkers are the liver enzymes ALT, AST, and GGT, triglycerides, HDL, adiponectin, fasting insulin and the homeostatic model assessment of insulin resistance (HOMA-IR). While all of these markers demonstrate a correlative relationship with NAFLD, ALT stands out as the most reliable single test when the upper range of normal is reduced to less than or equal to 23 IU/L. Further adjustment for sex indicates that women should have an ALT no higher than 21 IU/L, while the upper limit of 24 IU/L may be used for men.[7] In other studies, GGT has been shown to be a reliable marker.[8] Because all these biomarkers, with the exception of adiponectin, are relatively inexpensive, it would be prudent to monitor them as a group for optimal clinical outcomes.

Uric acid is another biomarker commonly elevated in both metabolic syndrome and NAFLD. A 2015 rodent and cell line study demonstrated that not only is uric acid a biomarker for fatty liver, it is also a causative factor. Uric acid was shown to induce NLRP3 inflammasome (also known as NRLP3, cryoprin and NALP3). NRLP3 is a signaling molecule for both hepatic steatosis and insulin resistance. The researchers documented that lowering uric acid with allopurinol improved glucose metabolism and insulin sensitivity in mice. Other potential mechanisms of cellular metabolism disruption from elevated uric acid include mitochondrial and endoplasmic reticulum injury.[9]

Carbohydrate Restriction as a Prime Therapy for NAFLD

A 2018 study on a low-carbohydrate diet illustrates three independent mechanisms explaining why this dietary approach has been so successful in treating fatty liver. In this small (n=10) and brief (14 day) human study, biomarkers for metabolic syndrome and fatty liver improved, including lowering of AST, ALT, insulin, HOMA-IR as well as a decrease in DNL and hepatic steatosis as measured by liver biopsy. The first observation was that restricting carbohydrates significantly and rapidly reduces hepatic de novo lipogenesis. Secondly, a very low-carbohydrate diet stimulates fatty acid oxidation, causing metabolism to shift from fat storing to fat burning. This combined effect of reducing fatty acid production and increasing fat oxidation lowers hepatic fat content within the first few days of a ketogenic low-carb diet. The researchers demonstrated the third contributing factor from this nutritional approach being a shift in the microbiota that favors liver fat metabolism.[10]

It is important to note that a high-fat diet is not the same as a low-carb diet. In fact, the research term "high-fat diet" lacks consistent parameters and often consists of a standard carbohydrate-rich diet with the addition of fat. A moderate to high carbohydrate diet, with the addition of fat, will cause increased fat storage, and over time will produce inflammation, insulin resistance, and fatty liver. Conversely, a low-carbohydrate diet will lower insulin and shift metabolism to fatty acid oxidation, which will reduce fat stores and reverse fatty liver. The addition of fat to a very low-carbohydrate diet produces satiety, making this dietary approach satisfying and sustainable. In the aforementioned study, carbohydrates were limited to < 30 grams per day and the ketone beta-hydroxybutyrate (BHB) was significantly elevated, demonstrating the effectiveness of the diet to produce ketosis.

There are two main goals when applying a ketogenic diet for NAFLD reversal. One is weight loss, as reducing triglyceride stores from visceral adipose tissue reverses the pro-insulin, inflammatory cascade produced by adipocytes. The second is the reestablishment of metabolic flexibility, the ability to utilize either fatty acids through beta-oxidation or glucose through glycolysis for energy production. Meeting both these goals will in turn reverse insulin resistance and create a hormonal and cytokine environment more amenable to weight stabilization and sustained reduction of inflammation.

There are several essential considerations when choosing a ketogenic diet as a therapy for metabolic syndrome and NAFLD. The first is the management of uric acid, which will be discussed below. The second is the need to address both exogenous and endogenous sources of fat-soluble toxicants. As previously noted, many drugs and environmental chemicals have been shown to increase inflammation, are obesogenic, and significantly contribute to metabolic syndrome and fatty liver. A ketogenic diet is very successful at stimulating fat burning; with the side effect of mobilizing fat-soluble toxicants from adipose storage. It is therefore crucial to assess your patients for environmental toxicity and incorporate appropriate depuration practices to protect them from mobilized endogenous toxicants. In addition, education on avoidance of common exposure sources from harmful exogenous compounds will lower the obesogenic toxicant effect. The third consideration is support for the microbiome. A low-carb diet is by design a low-fiber diet, and dietary fiber is crucial for microbial fermentation of short chain fatty acids (SCFAs) and overall intestinal health. For obese subjects with dysbiosis, the microbiome requires restructuring to reverse endotoxemia and over harvesting of fiber. An often-effective approach to correcting obesity associated dysbiosis is avoidance of processed food, consumption of a phytonutrient dense diet, and supplementation with fiber and a broad-spectrum probiotic.

Uric Acid, NLRP3 Inflammasome, and Flavonoids

A prolonged ketogenic, low-carb diet stimulates a series of metabolic changes in nearly every organ system; this metabolic restructuring is referred to here as keto adaptation. Most people

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can achieve keto adaptation within 6-12 weeks. Within the first few days of significant carbohydrate restriction, the liver upregulates fatty acid oxidation and ketone body production. Once ketosis is sustained, the brain and the muscles also increase fatty acid oxidation, shifting predominant fuel use to BHB in the brain, and various ketones and free fatty acids in muscle tissue. In the first few weeks of keto adaptation, ketone production by the liver transiently exceeds fatty acid oxidation capacity, and excess ketones are excreted in the urine. The renal pathway for excretion of ketones is the same as for uric acid, leading to temporary uricemia due to competition with ketones for excretion. This is not a concern for people who start adaptation with normal uric acid blood levels. Ketosis prior to renal adaptation will cause a slight elevation of uric acid, however levels remain non-pathogenic when uric acid is less than or equal to 5 mg/dL prior to initiating a ketogenic diet. For the subset of patients with high uric acid prior to keto adaptation, additional therapies are indicated to reduce the risk of significant side effects.

As noted earlier, uric acid at high blood levels can stimulate NLPR3 inflammasome, which in turn promotes insulin resistance and hepatic steatosis. Since uric acid associated inflammation drives metabolism away from fatty acid oxidation, your patient with uricemia may be unable to adequately produce and burn ketones. In addition, the risk of gout flare-up is greatly increased by the transient uricemia. Not only will this cause pain and suffering for your patients with gout, it will potentially limit exercise, an important component of any program that supports metabolism and weight loss. Finally, risk of developing uric acid kidney stones will be very high for susceptible individuals.

Patients with uric acid elevation over 5 mg/dL should be treated with uric acid lowering and NRLP3 modulating therapeutics prior to and during keto adaptation. Flavonoids including quercetin, resveratrol, epigallocatechin gallate, rutin and catechin, have demonstrated effective reduction of uric acid and blockade of NRLP3 inflammasome.[11] Resveratrol has been shown to increase adiponectin and improve HOMA-IR, serum triglycerides, and hepatic fat content. These significant improvements were associated with suppression of NRLP3 inflammasome activity by resveratrol.[12] Moderately low dosing with resveratrol may be adequate to reduce NRLP3 and achieve positive metabolic effects. However, for a patient with active gout, high dose may provide additional benefits through mitochondrial ROS amelioration.[13]

Quercetin is another flavonoid that shows promise as an effective therapeutic agent in the treatment of NAFLD. It positively impacts three areas of pathogenicity: inflammation, oxidation, and dysbiosis of the microbiota. One of the ways in which quercetin can prevent or reverse steatosis is by altering the genes involved in de novo lipogenesis. In particular, quercetin has been shown to be effective at suppression of CYP2E1, a significant player in fatty liver induction and a contributor to endoplasmic reticulum stress. As a prebiotic, quercetin stimulates increased production of SCFAs, a substrate for colonocytes that protect the intestinal barrier and prevent endotoxemia. Quercetin's effectiveness as an antioxidant is seen in its ability to significantly reduce pathological levels of IL-6, TNF-alpha, and hepatic NLRP3 inflammasome.[14]

Phosphatidylcholine

Choline deficiency is associated with fatty liver; low levels increase de novo lipogenesis, decrease hepatic triglyceride excretion, and lead to an increase in large lipid droplets. Aberrant microbes associated with obesity can further exacerbate these effects by metabolizing choline and decreasing host stores. Because choline is a substrate for lipid metabolism, essential to cell membranes, and a precursor for methylation metabolism, deficiency can negatively impact NAFLD progression in several ways.[15]

However, caution must be taken when prescribing choline and phosphatidylcholine (PC) because they are precursors for trimethylamine (TMA). TMA is then oxidized to trimethylamine *N*-oxide (TMAO), a potent vascular oxidant linked to significant atherosclerosis.[16] Many of the staple foods of a ketogenic diet are high in choline, including chicken, dairy, eggs, spinach, cauliflower, sunflower seeds, fish and beef. As choline is an effective agent against fat accumulation in hepatocytes, increasing choline may be one of the factors for the effectiveness of a ketogenic diet. It is important to note that conversion of choline to TMA/TMAO only occurs in a setting of intestinal dysbiosis, where there is a prevalence of TMA-producing bacteria. Bacteria that produce TMA/TMAO include *Anaerococcus hydrogenalis*, *Clostridium asparagiforme*, *C. hathewayi*, *C. sporogenes*, *Escherichia fergusonii*, *Proteus penneri*, *Providencia rettgeri*, and *Edwardsiella tarda*. This once again underscores how crucial it is to support a healthy microbiome when treating metabolic syndrome.[17]

Melatonin

Melatonin is a promising therapeutic for NAFLD due to its anti-inflammatory and regenerative properties. A 14-month human study with an n of 74 combined phosphatidylcholine 300 mg TID, with either melatonin 10 mg daily, or tryptophan 1000 mg daily. The control group was PC alone. Several biomarkers were significantly reduced in the treatment groups including reduction in GGT, LDL, TG, IL-1, IL-6 and TNF-alpha, which were non-significant in the control group. While liver biopsy was only performed pre and post for nine patients, a significance reversal of NASH to NAFLD was seen in all the subjects of the melatonin or tryptophan group, while liver biopsy in the control group demonstrated no change.[8] It is important to note that participants of this study had significant liver disease and also that dosing for tryptophan and melatonin were higher than is commonly prescribed.

When treating NAFLD with a ketogenic diet, one of the factors that will prevent fasting ketosis is poor quality sleep due to adrenal dysfunction. Middle of the night insomnia is often due to a breakthrough cortisol surge. Such a surge has the negative side effect of gluconeogenesis, which in turn will suppress ketosis. Since melatonin is effective at cortisol suppression, improved fasting ketosis is a likely positive side effect. Stress in general has a negative impact on metabolic syndrome progression. Improving both quantity and quality of sleep is foundational in stress reduction. Utilizing melatonin in conjunction with reestablishment of healthy circadian rhythms can be a cost effective component of any treatment plan for NAFLD.

Putting It All Together

The current leading cause of mortality is cardiovascular disease (CD); CD is the most common morbidity associated with NAFLD, and upward of half of Americans are suspected to have NAFLD. These stats move the diagnosis and treatment of hepatic steatosis nearer to the top of the list of chronic illness managed by clinicians today. When we consider NAFLD as one more manifestation of metabolic syndrome, and when we establish clinically relevant biomarkers, recognition and treatment of this under-diagnosed condition will undoubtedly increase.

Treatment of NAFLD must address both metabolic dysfunction and inflammatory insults. There is an imperative for weight loss and permanent reversal of obesity. There is also a need for restoration of metabolic flexibility, allowing fatty acid oxidation, in addition to glycogenolysis. Lifestyle interventions involving nutrition, exercise, and stress reduction with normalization of circadian rhythms should be at the core of treatment. Both a ketogenic diet and a Mediterranean diet have been used successfully for the treatment of metabolic syndrome. A Mediterranean-ketogenic diet may be the best nutritional intervention for NAFLD, particularly for patients with cardiovascular comorbidity.

It is essential to identify and avoid obesogenic and oxidative chemicals, drugs, and foods; while specific depuration protocols can be applied as indicated for each patient. Restriction, or better yet, elimination of alcohol is also prudent. Application of food-based antioxidants and phytonutrients can assist both the safety and efficacy of treatment protocols. While I have mentioned a few here, there are many other compounds that are effective and may be specifically indicated for comorbidities being treated. Utilization of nutraceutical and pharmacological agents should be considered to reduce unwanted side effects from treatment. Microbial dysbiosis and associated endotoxemia must also be assessed and remediated. Finally, individualizing treatment for genetic susceptibilities and concomitant chronic illnesses will reduce risks associated with specific therapeutics in subsets of patients.

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Insulin: The Life-Span Hormone for Healthful Aging

by Majid Ali, MD

Introduction

The core message of this article: Insulin is the life-span hormone of human biology. To make his case for it succinctly with simple words, the author introduces three terms: (1) "oxygen-insulin signaling matrix"; (2) "oxygen-insulin matrix model of health and disease"; and (3) "insulin as the life span hormone." The term "oxygen-insulin signaling matrix" refers to a complete bioenergetics and clinical integration of molecular biology of oxygen and insulin homeostasis. "Oxygen-insulin matrix model of health and disease" refers to a unifying model of health/disease/disease continuum, which has a strong explanatory power for understanding the pathogenesis and mechanism of healing for treating chronic diseases. The term "insulin as the life-span hormone" is intended to meaningfully counter the wholly inadequate "diabetes view of hyperinsulinism," which, in the author's view, is the principle folly in treating metabolic disorders in the prevailing medical model. It completely ignores the core issue of insulin dysregulation and allows hyperinsulinism-to-Type 2 diabetes (T2D) transition to occur undetected and untreated.

Unmasked hyperinsulinism is permitted to inflict cellular damage of varying degrees in all cellular populations of the body for five to ten or more years before the diagnosis of T2D is made by the prevailing glycemic criteria. To underscore this crucial issue, a series of sets of insulin and glucose profiles obtained with five timed blood samples (fasting, ½-hour, 1-hour, 2-hour, and 3-hour) obtained after a 75-gram glucose challenge, are presented. For children, the glucose challenge is reduced to 50 grams. Brief clinical notes concerning individual patients are included to provide clinical context for interpreting sets of insulin and glucose.

What Is Optimal Insulin Homeostasis?

What is optimal insulin homeostasis? Most regrettably, this crucial question has been almost totally ignored in endocrinology, diabetology, bariatrics, internal medicine, and family practice. On September 11, 2017, a Google search for optimal insulin homeostasis revealed only seven entries that listed the three words in that order; all of them by the author. Notably missing were websites of the American Diabetes Association, the European Foundation for the Study of Diabetes, Diabetes Ca (Canada), the American Congress of Obstetricians and Gynecologists, and the World Health Organization.

In the context of healthful aging and life span, an evolutionary bioenergetic optimum of human metabolism requires that (1) the lower the blood insulin concentrations following a glucose challenge accompanied by unimpaired glucose tolerance, the greater the efficiency of insulin; (2) the greater the efficiency of insulin, the closer the insulin homeostasis to its ideal; (3) hypoinsulinism by itself is of no clinical consequence since there are no known adverse effects of very low blood insulin concentrations when accompanied by unimpaired glucose tolerance; (4) hyperinsulinism sets the stage of metabolic overdrive in all cellular populations of the body; (5) insulin in excess has hepatic, endothelial, myocardial, neural, ovarian, renal, and other adverse effects; (6) the growth factor roles of insulin intensify and perpetuate inflammatory, autoimmune, and neoplastic processes. Tables 1 and 2 display two sets of insulin and glucose profiles that meet the criteria for optimal insulin homeostasis by criteria outlined here.

Optimal Insulin Homeostasis

Table 1. Insulin and Glucose Profiles of A 51-Yr-Old 5'1" Female Weighing 160 Lbs. Indicating Optimal Insulin Homeostasis. The patient presented with chronic constipation.

Patient	Fasting	1 Hr	2 Hr	3 Hr
Insulin uIU/mL	<2	17	15	6
Glucose mg/mL	75	61	72	71

Table 2. Insulin and Glucose Profiles of A 58-Yr-Old 5'11" Male Weighing 218 Lbs. He had undergone radical prostatectomy for prostate cancer two years earlier when he weighed 300 lbs.

Insulin uIU/mL	3.0	22.0	13.0	<2
Glucose mg/mL	82	75	63	60

In a survey of insulin homeostasis in 684 patients (506 of them with known T2D, (Table 3) in the general New York metropolitan area, the authors and colleagues reported a prevalence rate of hyperinsulinism in 75.1%.[1] A subgroup of twelve participants was designated 'exceptional insulin homeostasis' for two reasons: (1) they showed an extremely low fasting insulin value of <2 uIU/mL (mean peak 14.3 uIU/mL) and peak insulin concentrations <20 uIU/mL accompanied by unimpaired glucose tolerance, and (2) ten of the twelve had no family history of diabetes (parents, siblings, grandparents, children, uncles or aunts), while the mother of the eleventh subject developed T2D in the closing months of her life at age 74 and both parents of the twelfth subject in old age had prediabetes. This subgroup appears to reflect ideal metabolic efficiency of insulin in the larger evolutionary context.

Hyperinsulinism As Pancreatic Response to Cellular Injury

In the author's oxygen-insulin view of insulin dysregulation-to-diabetes continuum, hyperinsulinism results from the response of the pancreas to meet increased energy needs of stressed and injured cells anywhere in the body during the repair processes. This perspective does not challenge the established knowledge of dynamics of hyperglycemia and hyperinsulinism, nor does it abandon any of the regulatory roles of pro-insulin and anti-insulin hormones like glucagon, glucagon-like peptides, and others. The explanatory power of the model, however, reaches far beyond the prevailing understanding of insulin functions and their clinical significance.

The inferences drawn from the author's large personal database and presented here form the scientific basis and rationale for his view that incremental hyperinsulinism develops as a result of growing pancreatic-bioenergetic response for meeting increasing cellular demands for energy, except in cases of ectopic insulin production in hormone-producing neoplasms.[2-5] Additional evidence for this view is drawn from an extensive body of clinical observations concerning improved clinical results of treatment of diverse disorders when hyperinsulinism accompanying them was detected and duly addressed with integrative hyperinsulinism modification plans. It is anticipated that readers, who diligently study the diverse case studies presented here and critically examine the included insulin and glucose data will find them compelling and convincing.

Hyperinsulism Begets Hyperinsulinism

As put forth here, hyperinsulinism developing as pancreatic insulin response to increased tissue demands for energy comes at a cost: a "hyper-insulin" state – so to speak – which results from metabolic and non-metabolic insulin overdrive. This insulin state is fattening, fermenting, inflaming, and self-perpetuating.[2,4,6,7] Simply stated, excess insulin begets excess insulin. From these aspects of pathophysiology of insulin dysfunction and overdrive, abundantly documented by case studies included here and published previously,[2,3,8] hyperinsulinism is expected to play the central role in the pathogenesis and progression of most, if not all chronic metabolic, developmental, inflammatory, infectious, autoimmune, degenerative, and malignant diseases. This, indeed, is observed when insulin homeostasis is assessed in individual patients with appropriate carbohydrate challenges. This is what the author and his colleagues observed in a large survey of hyperinsulinism in a general population in metropolitan New York area.[1] Insulin dysfunction with varying levels of hyperinsulinism was found and documented in all chronic diseases so investigated – acne to dermatitis, psoriasis to sarcoidosis, autism to Alzheimer's disease, liver steatosis to heart amyloidosis, bronchiectasis to pulmonary fibrosis, lupus to scleroderma, rheumatoid arthritis to Lyme polyarthralgia, interstitial cystitis to recurrent prostatitis, and malignant tumors.[4-12]

Tables 1 and 2 present insulin and glucose profiles of survey subjects which meet the numerical criteria of optimal insulin homeostasis. Specifically, the peak blood insulin concentration accompanied by unimpaired glucose tolerance in a female adult is below 20 uIU/mL and a male subject is below 25 uIU/mL.

The insulin and glucose profiles presented in Table 2 provide a rare insight into the dynamics of insulin homeostasis. The patient, a 58-year-old, 5' 11" man weighing 218 Lbs. presented in December 2012 with neuropathy involving legs and an A1c value of 5.3%. The insulin profile of this patient meets the numerical criteria of optimal insulin homeostasis; specifically, the peak blood insulin concentration accompanied by unimpaired glucose tolerance is below 25 uIU/mL. Two years earlier, this patient weighed 300 lbs. when he underwent radical prostatectomy for prostate cancer. Postoperatively he lost 82 Lbs. in weight (which would be expected to be associated with lower insulin levels) and experienced persistent and incremental family stresses (which would be expected to raise insulin levels). The insulin and glucose profiles of the case, then, reveal the sum total of these diverse influences. The blood insulin concentrations in all four post-glucose challenge samples were raised, with a near-fourfold rise in the 1-hr post glucose challenge blood sample (22 rising to 86 uIU/mL). The matter of hyperinsulinism associated with prostate and breast cancer breast has been discussed in the author's two reports.[10,11]

The Oxygen-Insulin Matrix Model of Health and Disease

Human life span is put in jeopardy by disruptions of molecular biology of oxygen and insulin homeostasis; life expectancy of an individual is shortened by diminished signaling of the former[1-7] as well as by excessive signaling of the latter.[2-4,8,9] Oxygen is the organizing principle of human biology and orchestrates all aging processes. In service of oxygen, insulin governs the energy economy of the body. Injured cells need more energy for repairing themselves. Glucose is the primary readily useable fuel

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Table 3. Insulin Homeostasis Categories in 506 Study Subjects Without Type 2 Diabetes.[1]

Insulin Category*		Percentage of Subgroup	Mean Peak Glucose mg/dL (mmol/mL)		Mean Peak Insulin (uIU/mL)
Exceptional Insulin Homeostasis	N = 12**	1.7%	110.2	(6.12)	14.3
Optimal Insulin Homeostasis	N = 126	24.9 %	121.2	(6.73)	26.7
Hyperinsulinism, Mild	N = 197	38.9 %	136.5	(7.58)	58.5
Hyperinsulinism, Moderate	N = 134	26.5 %	147.0	(8.16)	109.1
Hyperinsulinism, Severe	N = 49	9.7 %	150.0	(8.33)	231.0

Correlation coefficient, r value, for means of peak glucose and insulin levels in the five insulin categories is 0.84.

*Criteria for classification: (1) Exceptional insulin homeostasis, a subgroup of optimal insulin homeostasis with fasting insulin concentration of <2 uIU/mL and mean peak insulin concentration of <20; (2) optimal insulin homeostasis, peak insulin <40 accompanied by unimpaired glucose tolerance; (3) mild hyperinsulinism, peak insulin between 40 and <80; (4) moderate hyperinsulinism, peak insulin between 80 and <160; and (5) severe hyperinsulinism, peak insulin 160 and over.

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for ATP energy generation. Insulin activates glucose transporters, drives glucose into the cells, initiates pathways of ATP energy generation, as well as energy utilization for life functions, and regulates energy transformations, producing proteins for cellular structural needs and fats for energy storage.[8] It can be rightfully designated as the "master energy hormone" for the life span.

Oxygen signaling and insulin signaling are so inextricably intertwined throughout the kaleidoscopic bioenergetics mosaic of human biology that these two primary signaling systems of the body cannot be considered as discrete entities. In integrative medicine, clinical imperatives are commonly compelling and the scientific basis for the use of time-tested indigenous therapies with empirical benefits are not forthcoming. Under these conditions, the unifying oxygen-insulin signaling matrix model of health/dis-ease/disease continuum provides valuable and reassuring scientific rationale for integrating indigenous therapies with others, for which clear "scientific basis" has not been established.

Some readers may be interested in the author's prior clinical and research work that led to the conceptualization of oxygen-insulin signaling matrix, disrupted oxygen-insulin matrix model of health/dis-ease/disease continuum, and insulin as the life-span hormone. The author points out his core clinical and research work in chronic disease ranged widely and was the subject of his *Townsend Letter* columns on oxygen homeostasis (from 2004 to 2015) and columns on insulin homeostasis from 2016 to the present. The web site of *Townsend Letter* offers full details of specific subjects covered in addition to the work cited among citations in this column.

Four Dimensions of Insulin Dysregulation

The author recognizes four dimensions of insulin dysregulation: (1) the first dimension of rising blood insulin concentrations (hyperinsulinism) without raised glucose levels (hyperglycemia) that meet criteria of pre-diabetes or diabetic criteria (Table 4); (2) the second dimension of hyperinsulinism with sharp glucose and/or insulin shifts but without meeting the criteria for pre-diabetes or diabetes (Table 5); (3) the third dimension of hyperinsulinism associated with hyperglycemia that meets the criteria of Type 2 diabetes (Table 6); and (4) the fourth dimension of insulin-depletion Type 2 diabetes (T2D Subtype B)[4] is shown in Table 7.

Table 4. Insulin and Glucose Profiles of a 67-Year-Old 5'3" Woman Weighing 215 Lbs. She presented with polymyalgia, osteoarthritis of right knee, allergy, sinusitis, and chronic fatigue.

6.15.2017	Fasting	½ Hr	1 Hr	2 hr	3 Hr
Insulin uIU/mL	12	83.8	64.3	35.3	4.6
Glucose mg/ mL	105	173	144	93	56

Table 5. Insulin and Glucose Profiles of a 50-Year-Old 5'2" Woman Weighing 141 Lbs. She presented with mold allergy, sinusitis, headache, and a history of multiple antibiotic courses.

Insulin uIU/mL	3.5	55.7	68.5	71.5	26.5
Glucose mg/ mL	87	137	136	86	73

Table 6. Insulin and Glucose Profiles of a 61-Year-Old Man Weighing 173 Lbs. He presented with type 2 diabetes of six years duration, hypertension, and osteoarthritis.

6.15.2017	Fasting	½ Hr	1 Hr	2 Hr	3 Hr
Insulin uIU/mL	8.4	52.6	94.9	117.7	46.9
Glucose mg/ mL	82	147	215	201	157

Table 7. Insulin and Glucose Profiles of a 55-Year-Old 5'3" Woman Weighing 145 Lbs. She presented with type 2 diabetes associated insulin-depletion (T2D, subtype B),[4] Hashimoto's disease, polyarthralgia, and inhalant allergy.

Insulin uIU/mL	<2	–	11	7	6
Glucose mg/ mL	221	–	448	399	287

Insulin Dysregulation Neglected in Unwell Individuals

Unwellness is epidemic now in the United States and generally spreading worldwide. It is not attributed to insulin dysregulation, and assessment of insulin homeostasis is not included in the prevailing standards of care. A recent survey of prevalence of hyperinsulinism, as established by the survey criteria, in the general population of New York metropolitan area conducted by the author and his colleagues was 75.1%.[1] This rate was not surprising since they used insulin criteria by contrast to the Chinese who employed blood glucose-based diagnostic criteria and reported a prevalence rate of 50.1% for prediabetes and diabetes among the Chinese adults.[13]

Tables 8 and 9 present two case studies of hyperinsulinism associated with chronic symptom-complexes of unwellness, such as lack of interest and vigor, anxiety, fatigue, mood disorders, cognitive difficulties, brain fog, allergy, abdominal bloating, and digestive symptoms. These symptom-complexes were not relieved by commonly prescribed symptom-suppressive pharmacologic agents. Note the sharp drop of one-hour insulin level from 183.5 to 57.4 uIU/mL. in Table 8, which was accompanied by good clinical response.

Table 8. Insulin and Glucose Profiles of a 41-Yr-Old 6' Man Weighing 260 Lbs. He presented with fatigue, light-headedness, anxiety, facial numbness, and abdominal bloating. He responded well to eight weeks of successful hyperinsulinism modification ("Insulin Detox"), described at www.alidiabetes.org. Note a sharp drop of one-hour insulin level from 183.5 to 57.4 uIU/mL.

9.15.2016	Fasting	½ Hr	1 Hr	2 Hr	3 Hr
Insulin uIU/mL	10.9	148.84	183.5	25.55	9.1
Glucose mg/ mL	83	141	159	91	60
11.17.2016					
Insulin uIU/mL	5.9	38.9	57.4	28.8	6.6
Glucose mg/ mL	76	124	178	136	82

Table 9. A 60-Yr-Old 5'8" Woman Weighing 180 Lbs. Presented with Concern About A1c value of 6%. Her past history included a prior weight of 190 lbs., episodes of anxiety, bronchospastic disorder, and facial rashes. Weight gain with three pregnancies were 40 lbs, 35 lbs, and 50 lbs. respectively.

	Fasting	½ Hr	1 Hr	2 Hr	3 Hr
Insulin uIU/mL	5.1	93.1	58.8	45.8	3.4
Glucose mg/ mL	92	128	111	88	53

Insulin Dysregulation Associated with Unrelenting Stress, Mood Disorders, and Weight Gain

Hyperinsulinism in patients with anxiety-depression complex, unrelenting stress, and weight gain often goes unrecognized even though hyperinsulinism is widely recognized as fattening and inflaming. Tables 10 and 11 present two such patients.

The case study presented in Table 10 reveals the weight gain aspect of insulin toxicity (rising insulin levels) well. The patient, a 46-year-old, 5 ft. 2 in. woman weighing 160 lbs. presented in 2011 with diagnoses of fibromyalgia, cognitive disorder, severe family stress, sleep disorder, constipation, cold sensitivity, and depression treated by a psycho-pharmacologist. In one 2014 office visit, she said, "Everybody at home is sick. I'm so angry, in such rage that I think I'm destroying my two daughters."

Table 10. Insulin and Glucose Profiles of a 46-Year-Old 5'2" Woman Weighing 160 Lbs. She presented in 2011 with diagnoses of fibromyalgia, cognitive disorder, severe family stress, sleep disorder, constipation, cold sensitivity, and depression treated by a psycho-pharmacologist.

11.22.2011	Fasting	½ Hr	1 Hr	2 Hr	3 Hr
Insulin uIU/mL	2.2	37.7	44.2	28	29
Glucose mg/ mL	87	131	150	91	97
7.23.2014 Weight 150 Lbs "Everybody at home is sick. I'm so angry, in such rage that I think I'm destroying my two daughters."					
Insulin uIU/mL	6.3	30.8	61	25	10.9
Glucose mg/ mL	65	114	105	75	68
3.28.2016. Weight 145 Lbs					
Insulin uIU/mL	9.3	39.5	47.0	35.4	7.0
Glucose mg/ mL	86	115	114	73	52
6.23.2017 Weight 190 Lbs.					
Insulin uIU/mL	10.5	37.9	77.0	99.4	17.8
Glucose mg/ mL	83	127	155	115	66

Table 11. Severe Hyperinsulinism Caused by Severe Stress. Insulin and glucose profiles of an 81-year-old 5'3" female weighing 172 lbs. with depression-anxiety complex, hypertension, fibromylagia, mold and food allergy and dizziness. Her 1-hr and 2-hr insulin levels more than doubled (from 105.6 to 213.5 and 92.9 to 243.9 respectively) from 2014 to 2016 with severe emotional stress of family betrayal.

Insulin uIU/mL	11.3	152.6	105.6	92.9	10.3
Glucose mg/ mL	81	152	76	116	56
27 Months Later with Severe Emotional Stress of Family Betrayal					
Insulin uIU/mL	16.7	201.7	213.5	243.9	30.7
Glucose mg/ mL	95	156	180	116	56

Hyperinsulinism Modification with Insulin Detox

Insulin in excess is potently pro-inflammatory. Chronic inflammation causes incremental hyperinsulinism, which usually responds well to robust integrative management plans. The case studies presented in Table 12 and 13 illustrates these points well. The full description of author's hyperinsulinism modification with insulin detox is offered as a part of his free access Diabetes Course at www.alidiabetes.org. "Insulin Detox" are the search words for entry in the search box.

Table 12. Insulin and Glucose Profile of A 59-Year-Old 5' Female Weighing 135 Lbs. She presented with elevated liver enzymes, paresthesia, polyarthralgia, myalgia, and chronic diverticulitis. Insulin reduction was accompanied with marked reduction of paresthesia.

8.27.2015	Fasting	2 HR	1 HR	2 HRS	3 HRS
Insulin uIU/mL	11.5	263.5	356.7	202.1	14.0
Glucose mg/mL	85	109	79	64	–
1.13.2016					
Insulin uIU/mL	9.6	124.8	224.7	112.7	32.6
Glucose mg/mL	85	103	98	78	48

Polycystic Ovarian Syndrome (PCOS) Is Rooted in Insulin Dysregulation

The rising prevalence of polycystic ovarian syndrome (PCOS) among young women in the US (up to 20% in some studies) is disconcerting.[14] Elevated blood concentrations of insulin and testosterone are two primary hormonal abnormalities of the syndrome. These disruptions with clinical symptom-complexes of PCOS generally respond to integrative treatment plans with a focus on the bowel-liver-blood ecosystem. Table 13 presents the changes in insulin and glucose profiles which accompanied a successful pregnancy.

Table 13. Insulin and Glucose Profiles of 33-Year-Old 5'7" Female Weighing 122 Lbs. She presented with polycystic ovarian syndrome (PCOS), IBS, GERD, recurrent vaginitis, mold allergy, and testosterone 49 mg/nL. She delivered a baby on 8.9.2017.*

12.15.2016	Fasting	½ Hr	1 Hr	2 Hr	3 Hr
Insulin uIU/mL	5.2	80.4	69.6	83.9	22.6
Glucose mg/mL	72	152	128	90	54
7.17.2017					
Insulin uIU/mL	<2	44.9	60.9	66.5	10.5
Glucose mg/mL	75	153	132	86	31

*Note the lower blood insulin concentration in the 2017 profile in spite of third-trimester pregnancy status.

Insulin-Monitored Plans for Long-Term Hyperinsulinism Modification and Reversal of Type 2 Diabetes

Two insulin-based diet plans have been employed by the author for his patients with insulin dysregulation: (1) Insulin Diet Plan One for hyperinsulinism modification; and (2) Insulin Diet Plan Two for Reversal of Type 2 Diabetes. The full details of these Insulin Diet Plans are posted at www.alidiabetes.org. For free ready access to these diet plans, readers are invited to enter the following search words in the search box of the website: Insulin Diet Plans Majid Ali.

Table 14 presents a pattern of hyperinsulinism modification and reversal of Type 2 diabetes achieved with an insulin reduction diet plan.[15]

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Table 14. Control of Hyperinsulinism with Reversal of Type 2 Diabetes in A 75-Yr-Old 5'2" Female Weighing 162 Lbs. with Hypertension and Chronic Sinusitis.*

4.30.2013	Fasting	½ Hr	1 Hr	2 Hr	3 Hr
Insulin uIU/mL	16	37	59	113	152
Glucose mg/mL (mmol/L)	112	158	214	241	155
10.17.2014	**A1c, 6.3%**				
Insulin uIU/mL	23.8	19.3	36.9	114.7	75.2
Glucose mg/mL (mmol/L)	116	167	253	297	172
4.14.2015	**A1c, 5.9%**				
Insulin uIU/mL	6.2	22.1	42.9	51.2	39.7
Glucose mg/mL	96	130	193	112	105

Insulin Profiling – Testing and Interpretation

In a previous publication, the author recognized two subtypes of T2D: (1) T2D subtype A (insulin excess diabetes) and T2D subtype (insulin-depletion diabetes), and underscored the clinical imperatives for doing so.[28] In companion publications, he explained why he now reads 3-hour insulin and glucose profiles of individual patients the same way he used to read diagnostic biopsy slides in his hospital based surgical pathology work, pattern recognitions fully mindful of the clinical context.[29] The results of insulin tests performed on randomly drawn blood samples in his opinion, should not be interpreted.

Recently, the author and his colleagues reported hyperinsulinism prevalence of 75.1% in 684 patients from a general population in New York metropolitan area.[1] The insulin database of this study permitted us to explore the following aspects of insulin homeostasis and insulin dysregulation: (1) pathogenesis of insulin resistance; (2) stratification of hyperinsulinism for optimal clinical use; (3) study of responses to carbohydrates and non-carbohydrate challenges in insulin-based care of hyperinsulinism and T2D[3]; (4) hyperinsulinism-to-T2D progression; (5) proinflammatory and immune-dysregulating roles of insulin dysregulation; (6) the central role of mitochondrial dysfunction in insulin dysregulation; (7) hyperinsulinism as an energetic response to chronic cellular injury; and (8) the profound therapeutic significance of insulin serving as the "minister of metabolism and energy" to "King Oxygen" of the human body.[2,3,23]

The most disappointing aspect of the matter of insulin homeostasis in clinical practice is that, with very uncommon exceptions, hyperinsulinism is not detected with direct insulin testing. Insulin toxicity is allowed to inflict widespread cellular damage for years, sometimes for decades, until glycemic criteria for the diagnosis of Type 2 diabetes are met. This has been amply documented in this and past communications on the subject. Below are some specific issues concerning improper insulin testing:

1. Insulin tests are performed on randomly drawn blood tests (Results of such tests cannot be interpreted with confidence);
2. Laboratories employ utterly unusable references ranges for blood insulin concentrations;
3. Tests for glycemic status (fasting blood glucose, two-hour postprandial glucose level, A1c levels) are performed as substitute indicators of the insulin status;
4. Cut-off points for post-glucose challenge blood insulin concentrations reported in laboratory reports are not based on actual post-glucose-challenge testing data;[17]
5. Gestational diabetes is a hyperinsulinism disorder before it becomes gestational diabetes by glycemic criteria;
6. Pregnant women are unscientifically and improperly assured of their metabolic health simply because their glucose tolerance tests are considered negative for gestational diabetes;
7. Insulin is the primary pro-weight gain and pro-obesity hormone, and yet insulin tests are not done in weight loss and obesity programs.
8. Failure to assess insulin homeostasis with direct post-glucose challenge tests leaves patients and clinicians in the dark concerning the central roles of hyperinsulinism in the pathobiology of chronic inflammatory, infectious, autoimmune, metabolic, neoplastic, and degenerative disorders.

Three important concerns in this context are (1) responses to carbohydrates and non-carbohydrate challenges in insulin-based care of hyperinsulinism and related metabolic disorders[8]; (2) importance of subtyping diabetes type 2 into diabetes type 2A and diabetes type 2B[9]; and (3) hyperinsulinism modification with insulin detox (See Table 12).

It is lamentable that in the dominant medical thought, crucial health and healing aspects of chronically sluggish oxygen signaling and incrementally exaggerated insulin signaling are consistently neglected. How often is the centrality of dysoxygenosis (dysfunctional oxygen signaling) in chronic diseases recognized and effectively addressed in doctors' offices and clinics? How often are the fattening, fermenting, and inflaming effects of simmering hyperinsulinism detected and controlled by restoring optimal insulin metabolism? Mention of mitochondrial malfunctions evokes tired yawns; the word insulin triggers Pavlovian mumbling about diabetes.

Discussion

Oxygen signaling and insulin signaling are so inextricably intertwined throughout the kaleidoscopic bioenergetics mosaic of human biology that, in the author's view, they cannot be considered as discrete entities. He recognized this first as an integrative clinician (finding sharp therapeutic focus on oxygen and insulin equally necessary for reversing and/or controlling chronic diseases) and as a researcher in basic bioenergetics of human biology.

The author was fortunate to have undertaken clinical, bioenergetic, and histopathogical studies of a broad range of chronic allergic, infectious, immune-inflammatory, gastrointestinal, reproductive, neurodevelopmental, degenerative, and neoplastic diseases. This work paved the way for his work in molecular biology of oxygen[2-7] and aging,[13] and then to insulin homeostasis and insulin dysregulation,[1-4,6,15,22-24] including the study of insulin dysregulation in metabolic syndromes, obesity, fatty liver disease, steatonecrosis, Type 2

diabetes, gestational diabetes, Type 1 diabetes, and the range of diabetic complications.

Insulin signaling has widespread established metabolic, developmental, and differentiative roles in human biology.[16-19,25,26] When seen within the broader evolutionary energetic perspective, the core tenet of the insulin being the life span hormone of human biology is logical, rational and completely consistent with the established aspects of the kaleidoscopic hormonal mosaic of human biology.

The author's work in insulin homeostasis cited in this report led him to the development of a completely integrated view of molecular biology of oxygen and insulin signaling, which culminated in conceptualization of a clinico-pathologic "oxygen-insulin signaling matrix model." This model has a strong explanatory power for diverse clinical and bioenergetics phenomena of the health/dis-ease/disease continuum, the primary strength being unrelenting focus on harnessing therapeutic benefits of all relevant oxygen-based and insulin-driven therapies in the treatment of all chronic diseases. From a didactic standpoint, this model helps in reducing many clinical complexities of human biology into workable simplicities, and facilitates presentation of a synthesis of clinical, microscopic, and bioenergetic findings concerning the essential roles of oxygen signaling and insulin homeostasis in the pathobiology of chronic diseases.

For patient education and robust patient compliance, the oxygen-insulin signaling matrix model markedly enhances understanding of the scientific underpinnings of diverse disease processes related to various patterns of impaired oxygen signaling (dysoxygenosis), insulin dysregulation, and treatment options. Specifically, this model calls for deliberating and addressing all relevant oxygen and insulin issues for individual patients.

Closing Comments

Treatment of chronic diseases that is confined to pharmacologic agents can be considered neither scientific nor ethical. Readers are invited to closely examine case studies presented in this column. They are drawn from the author's personal insulin database of over 1100 post-glucose challenge insulin profiles. They can then determine if there is merit to his case for diligence in assessing insulin homeostasis with such laboratory tests. The matters of keeping oxygen homeostasis at the therapeutic center stage for every patient with chronic disease with documentation of clinical outcomes have been covered at length in Darwin and Dysox Triology, the 10th, 11th, and 12th volumes of *The Principles and Practice of Integrative Medicine*.[27-29]

Here, the author sees a glaring clinical deficit: a near-complete neglect of relevant oxygen and insulin issues in patient care in doctor offices and clinics in the prevailing medical model in the US. To assess the scope of this issue, he conducted an informal survey of his patients who had seen two or more physicians (primary physician, internists, endocrinologists, diabetologists, and others) during the year prior to visiting his office. None of them recalled any visit in which relevant issues of insulin homeostasis or oxygen signaling were discussed and appropriate tests were performed. Nearly all of them complied with the request to review their prior medical records. He did not find 3-hour post-glucose challenge insulin studies in *any* patients.

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Legislation Put Forth in Maryland: Senate Bill 950 and House Bill 1266

Lyme Disease is at the forefront today. While such therapies as chelation therapy, IV nutrient therapy, sublingual and provocative allergy testing have long come under attack along with other functional/integrative therapies that combine the tools and approaches that best fit the needs of the individual, these approaches continue to be targeted by insurance companies, Big Pharma, FDA, CDC, and other agencies seeking to suppress what is the patient's right to choose with complete and informed consent. *One would think that the individual would be protected by such a right.*

A Retrospective Look

Compare a physician under attack from 1976-1994 versus today – 2018. I was recently honored to come before the Maryland Assembly to highlight the "extensive scrutiny, sanctions, cost, investigation, and discrimination" that continues to plague physicians utilizing functional medicine testing and treatments. The opinion and judgment of integrative practitioners is questioned and challenged even though integrative modalities often prove to be more efficacious, present fewer risks as well as reduced cost for patients and insurance companies, and for many patients a return to optimal wellness.

We know 80% of chronic illness can be reversed!

Many of you reading this may not know of or have ever heard of my husband, Warren M. Levin, MD. Dr. Levin opened the first integrative and alternative medicine practice in New York City in 1974 as an MD. By 1976, he was under scrutiny and ultimately brought up on 141 charges, which were not dismissed until 1994 when he received a resounding victory by the New York State Board of Regents.

Briefly, his case represents the longest hearing ever heard before the NY State Office of Professional Misconduct (OPMC). The Board of Regents harshly criticized the OPMC for not following legal procedure, abrogating Dr. Levin's rights; and most importantly their decision in this case centered on the opinion(s) of the panel members(s) that *"NO INDIVIDUAL CAN DETERMINE THE STANDARD OF PRACTICE…. before the engines of the State are started up against an individual, there must be some threshold showing of justification for such an intrusion."* To highlight the arrogance and chutzpah of this board, *one* of the witnesses for Dr. Levin was Linus Pauling, PhD, two-time Nobel Prize winner in science and peace and the holder of 49 PhDs. Dr. Pauling was not considered a credible witness over the opinions of the panel members, as he was not an MD.

Science Is Not Decided by Majority Vote!

The result of this case was the passage of an amendment to the New York State Medical Practice Act in the summer of 1994, supported by the work of FAIM (Foundation For the Advancement of Innovative Medicine), which recognized the role of adjunctive/functional/immune supportive therapies. It amended Education Law 6527 by adding paragraph (e) to subdivision (4) allowing physicians to utilize "whatever medical care, conventional or adjunctive therapies *which effectively treats* human disease, pain, or injury, and required placement of two (2) non-conventional physicians on the state professional medical board." Following a similar tact, the Maryland bills require that at least one of the peer reviewers have training in the approach under review.

Today: Just as this law still exists so have 15 other states amended their laws providing physicians with the right to *responsibly deliver integrative diagnostic techniques along with such therapies as IV ozone, UV light therapy, hyperbaric oxygen as well as nutrition, diet, lifestyle coaching, and a variety of other therapies that support the healing of the body.*

Maryland's Proposed Senate Bill 950 / House Bill 1266

The bills being put forth seek to provide physicians specifically treating Lyme and other tick-borne diseases with these same rights. This bill will allow practitioners to consider and employ, in their best judgment, testing and treatment that will serve the best interests of their patients as long as they give informed consent which "(1) fully disclose[s] to the patient that the diagnostic test or treatment is, in fact, integrative or non-conventional and (2) the treatment poses no greater risk than conventional medicine that is not outweighed by the potential benefits of the evaluation or treatment."

Medical Boards Continue to Fight to Maintain the Status Quo

Alan Dumoff, Esq., one of the main authors of the bill, states, "The National Center for Complementary and Alternative Medicine (NCCAM) and the National Institutes of Health (NIH) support a significant number of integrative medical centers at major academic institutions around the country." In addition, there is a plethora of published research available around the world exploring and validating the use of functional and integrative medicine. *However, there is still a bias by practitioners that use solely conventional methods against integrative practitioners.*

Further, when the State Board cannot demonstrate poor judgment, they turn to poor record keeping, billing or other administrative issues they can use to sanction such physicians. The Maryland bill disallows the use of these "proxy" issues as a substitute means of discipline over professional differences of opinion.

The state of Maryland is ranked the fourteenth in the country for reporting of people with Lyme and tick-borne diseases. As such, it is crucial that physicians/providers have in their arsenal every means necessary to treat their patients in a safe and efficacious manner.

Lyme is at epidemic proportions throughout the US, and the time is now when this legislation must be passed, and the voice of the patient must be heard! The voice of the brave constituents who testified at the hearing on March 7, 2018, represents a mere few of the patients, advocates, and physicians seeking to have their voices heard and choices implemented without undue scrutiny. Their voices and the voices of those throughout the country can no longer be denied. "The Standard of Care" has failed millions of people suffering today. The traditional model is broken!

As of this submission, we are still awaiting a decision.

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Ather Ali... Our Friend

by Jacob Schor, ND, FABNO

We were grieved to read in October of this past year that our beloved colleague Ather Ali, ND, MPH, had passed away from metastatic esophageal cancer. It is hard to know how to describe the magnitude of loss his passing means to us and to the world of integrative medicine.

Dr. Ali graduated from Bastyr University in 2003 with a degree in naturopathic medicine. He was one of a select few naturopathic physicians to pursue careers in academic medical centers. He rose to a national leadership position in integrative medicine. He was an assistant professor of pediatrics and medicine at Yale and was at the time of his death the medical director of integrative medicine at Smilow Cancer Hospital. He was a Robert Wood Johnson Foundation Clinical Scholar, a NCCIH F32 postdoctoral fellow, and recipient of a K23 Career Development Award. He consulted to the Turkish Ministry of Health on traditional medicine practices and was a visiting fellow in the Australian Research Centre in complementary and integrative medicine. He was a national and international leader in integrative medicine and health. He completed innovative research on irritable bowel syndrome, Lyme disease, nutritional interventions, diagnostic testing, fibromyalgia, and the microbiome.

Ali was deeply involved in the Academic Consortium for Integrative Medicine and Health, referred to as the Consortium. The group currently includes over 70 highly academic medical centers and affiliate institutions. The Consortium was formed in July 1999, in Kalmazoo, Michigan, by representatives of eight academic institutions, all conventional academic medical centers, all with significant experience in integrative medicine and all with support from the leadership of their institutions. We should underline the word conventional; Bastyr University applied for membership but was turned down as they do not have a hospital.

The Consortium's mission is to advance the principles and practices of integrative healthcare within academic institutions. The Consortium provides its institutional membership with a community of support for its academic missions and a collective voice for influencing change (http://www.imconsortium.org/).

Dr. Ali was the first naturopathic physician to sit on the Consortium's steering committee. He was also chair of the Consortium's research working group, an at-large board member, lead on the group's website redesign, and a member of the conference planning committee.

The Consortium has established a scholarship fund to honor Dr. Ali, a $2500 scholarship earmarked for a naturopathic physician to attend the Consortium's Congress every other year. As of this writing we are waiting to hear who this year's recipient will be.

Two other funds have been established in Ather Ali's memory. Yale University has established a fund to honor Dr. Ali's memory and to provide support to those continuing his work: https://secure.yale.imodules.com/s/1667/giving/17/form.aspx?sid=1667&gid=52&pgid=1801&dids=427&bledit=1. Dr Ali's friends and family have also established a fund that will provide support to charitable causes in his name: https://www.launchgood.com/project/in_honor_of_dr_ather_ali#!/.

Being a naturopathic physician in a conservative, MD-dominant Yale medical culture was no easy task. Nor was being Muslim these days in a country that has become unfriendly to outsiders. John Weeks of the IntegratorBlog.com wrote, "No naturopathic physician in the United States has penetrated so deeply into positions of leadership in a conventional academic health center."

David Katz, MD, MPH, first selected Ather into a Yale residency 15 years ago.

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The first and only naturopathic physician on the staff of Yale New Haven Hospital, and the faculty at the Yale School of Medicine, Ather was quite literally in a class all its own. I am proud beyond words to have played a small part in nurturing his career and privileged to have had an intimate view of the extraordinary trail he blazed. I mourn him, and I miss him – but mostly, my mind keeps turning to the celebration of him, and the need to preserve and replicate what he built.

… Ather was at first my student and protégé, and then my partner and colleague, and most recently – an inspiration, and source of pride. He was the first naturopathic physician ever to join the faculty of the Yale School of Medicine. At the time of his death, he was Medical Director for the program in Integrative Medicine at the renowned Smilow Cancer Hospital. Ironically, and seemingly in the blink of an eye, he became a patient in the very program he helped establish and directed.

Ather epitomized the possibilities in the still rarefied space where care is scientifically careful, intellectually robust, and profoundly humane. He was an unapologetic advocate for holism and patient-centered medicine, and just as unwaveringly committed to embracing the tenets of evidence-based medicine. Along the course he charted, Ather earned two master's degrees from Yale, one in chronic disease epidemiology, the other in patient-oriented research.

Ather is gone from us appallingly too soon, a victim of a rampaging esophageal cancer at the age of 42. He leaves behind his wife, Sumiya, and their two children, Rayhan and Yasin. Those children were privileged to have such a father – but deserved to have him here to see them grow up.[1]

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The other, general message in this tale of both triumph and disaster has to do with the probabilities of prevention, and the potential primacy of outrageous fortune.

I routinely write about the incredible power of lifestyle over our medical destinies, the potential to add years to our lives and life to our years. I write about our capacity to use what we know to prevent some 80% of all chronic disease and premature death, to slash our personal risk of the same. ….

But that power is not absolute. Dr. Ali and I were friends. I know that he never smoked and did not drink. He ate a wholesome diet. He exercised routinely. He was quite expert at stress reduction methods, and natively peaceful. He gave sleep the respect it warrants, and had a large, strong, diverse network of friends and a loving family – his beautiful wife and two children. He did everything right and got the wrong outcome anyway. This is a reminder and a reality check for us all. Prevention is powerful, but imperfectly so. Health outcomes are not merit-based. We are reminded not to blame the victims of calamity, not to think people get what they "deserve." We are reminded to be humble, to respect our ineluctable fragility. Prevention, and lifestyle as medicine, are ultimately arbiters of probability, not certainty. We should not forsake their power, for most of us will be beneficiaries of it. But no one of us will ever get a guarantee…

All I know for sure right now is that too soon, too young, a bright light has been extinguished from the world. The rest of us must strive for the light of meaning in it, to defend against the darkness.[2]

When President Bill Clinton eulogized Yitzhak Rabin at Mt. Herzl cemetery in 1995, he ended his speech with the words, "Shalom chaver, (goodbye my friend). These words so resonated with Israelis that for years afterwards bumper stickers printed with those words adorned their cars. Whether consciously or not, Dr. David Katz echoed the same phrase in the title of the piece he wrote about Ather for the *Huffington Post* and which I have quoted from, shortly after Dr. Ali's death, "Goodbye, my friend."

Whether Dr. Katz knowingly chose to use this phrase or not, it was deeply appropriate as in its own way it transcends the distinctions often made about religion in our country at this time. Intellectual respect, friendship and love have a way of crossing over those boundaries of nationality, religion and even schools of medicine that sometimes separate us.

"I wish Ather were here. In his absence, we have that empty space of loss and legacy, purpose and possibility – to fill together." David Katz MD

Part 2: Research Review

The page designated for Ather Ali on the Yale Medical School website has been updated, and the verbs associated with Dr. Ali have been suitably converted into the past tense.

Dr. Ali **was** Assistant Professor of Pediatrics (General Pediatrics) and of Medicine (General Medicine) at the Yale School of Medicine and Director of the Yale Adult and Pediatric Integrative Medicine Clinic, and Medical Director of Integrative Medicine at Smilow Cancer Hospital. His clinical practice **focused** on the prevention and treatment of chronic disease, including non-pharmacologic approaches to pain and functional somatic syndromes....

The Yale website provides links to about two dozen of Dr. Ali's past publications.[3] The NCBI lists 35 publications.[4] At the time of his death, Ali was recruiting participants for four new studies: two studies related to the microbiome (one to examine the microbiome in patients with fibromyalgia and irritable bowel syndrome, and another study examining the microbiome in obese individuals). Another study was to look at the effects of drinking a fermented soy beverage daily for a month and a fourth study that would look at how blood sugar responds to varying types of sweetener.

This wide range of research interests appears typical in light of Ali's past publications. A portion of his past work examined interventions naturopathic physicians have believed might be helpful for treating specific health conditions and asked, "Does this really work?"

Fibromyalgia

In a 2009 paper, Ali tested whether Myer's cocktails helped patients with fibromyalgia. Thirty-four patients with fibromyalgia were randomized to receive either Myer's cocktail or lactated Ringer's solution weekly for two months. The answer was sort of yes; the Myer's worked and the Ringer's placebo may have worked as well.[5] Fibromyalgia was clearly of special interest to Ali. A 2015 study examined the 'mindfulness characteristics' of nearly 5,000 fibromyalgia patients.[6] A 2014 review that he co-authored provides an excellent summary on complementary and alternative treatments for treating these patients, in particular children with fibromyalgia.[7] In a 2007 article published in *Medical Hypothesis*, Ali advanced the theory that fibromyalgia was secondary to hypofusion of muscle tissue, a theory that might justify a range of potential interventions.[8]

Massage and Osteoarthritis

Ali developed a massage protocol for treating osteoarthritis of the knee[9] and then tested this method in a clinical trial of 125 patients, demonstrating that weekly massages provided significant benefit to sufferers.[10] Not convinced that it was massage that made all the difference, he interviewed study participants trying to understand what triggered the improvements they experienced.[11] Ali understood that improvements in health are often caused by complex interactions. He did not assume that it was the massage alone that 'fixed the osteoarthritis' but that it may have been a combination of relaxation, and other psycho-emotional factors including interactions with the massage therapists themselves and their beliefs about massage benefits.[12]

Chromium

Dr. Ali conducted several in depth trials on chromium supplementation. These trials failed to support the long-held belief that taking chromium helps patients lose weight, prevents or treats diabetes by increasing insulin sensitivity and controls metabolic syndrome. Chromium was not significantly associated with any of these benefits, either in 500 or 1000 ucg/day doses.[13-15]

> In this randomized prospective study involving adult patients at risk for diabetes, chromium supplementation, at two dosing levels, had no substantive effect on any direct measure of glucose metabolism or indirect measures of insulin action. Chromium therefore appeared ineffective on markers thought to be related to the development of T2D [type-3 diabetes] in these high-risk subjects. No differences were seen after six months of active treatment vs. placebo, nor after a six-month post-intervention assessment.[14]

While some of Ali's studies were of a pragmatic nature, many of his papers were deeply academic, examining the complex intersection of naturopathic, complementary, integrative and preventive medicines. He wrote about his experience developing an integrative medicine curriculum in a residency program devoted to preventive medicine.[16]

When reporting in 2010 on the Yale Research Symposium on Complementary and Integrative Medicine he wrote:

> Integrative medicine offers, at least in theory, the opportunity to combine the best of both conventional medicine and CAM to generate better patient outcomes. These outcomes are measured in terms of symptom relief, functional status, patient satisfaction, and cost-effectiveness. The rationale behind implementing integrative medicine depends largely on the rationales for CAM therapies, particularly because the unconventionality of CAM is often a limiting factor in efforts to advance integrative care.[17]

In 2008 Ali was part of a team that reported dark chocolate and cocoa ingestion improved endothelial function and decreased blood pressure in obese individuals.[18] In 2011 they tested a popular multi-level-marketed (MLM) product made of encapsulated fruit and vegetable concentrates to see if it would have a similar effect. The product did not. In fact, the product caused no significant effects compared to the placebo.[19]

In a decade at Yale, Ather Ali contributed more to naturopathic medicine than most of us will in our full life times. We have lost a great deal in his passing.

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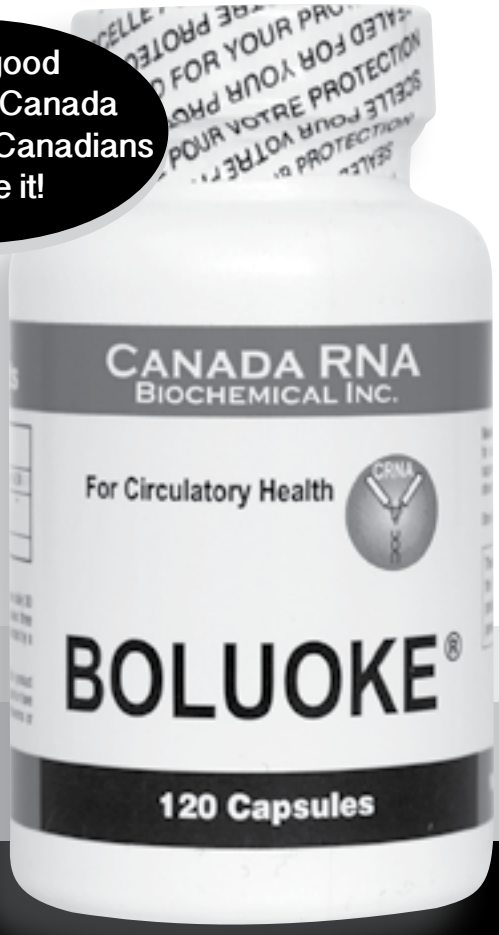

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"Liquid Biopsy" – What Is It and How Can It Be Applied?

by Stephen E. Fry, MD

With the advent of Next Generation DNA Sequencing (NGS), we now have an improved capability to detect and characterize DNA from tumors or circulating tumor cells and DNA that are in the bloodstream of afflicted patients. Liquid Biopsy is currently being used to evaluate therapeutic efficacy and is in the early adoption phase as a screening technology for a variety of cancers. The technology is also known as fluid biopsy, fluid phase biopsy, cfDNA (cell free DNA), ctDNA (circulating tumor DNA) or 'naked DNA'. This general term is also applied to heart attack assays using circulating endothelial cells and from prenatal cell free DNA from amniotic fluid. Fluid biopsy technology alleviates the need for drastic surgeries or procedures as it requires only a simple blood or urine sample. A PubMed publication search on this topic reveals over 130 articles published in 2017, suggesting it has become a very innovative and growing field in laboratory medicine.

Cancer.gov defines *liquid biopsy* as:

> A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment or to find out how well treatment is working or if cancer has come back. Being able to take multiple samples of blood over time may also help doctors understand what kind of molecular changes are taking place in a tumor.[1]

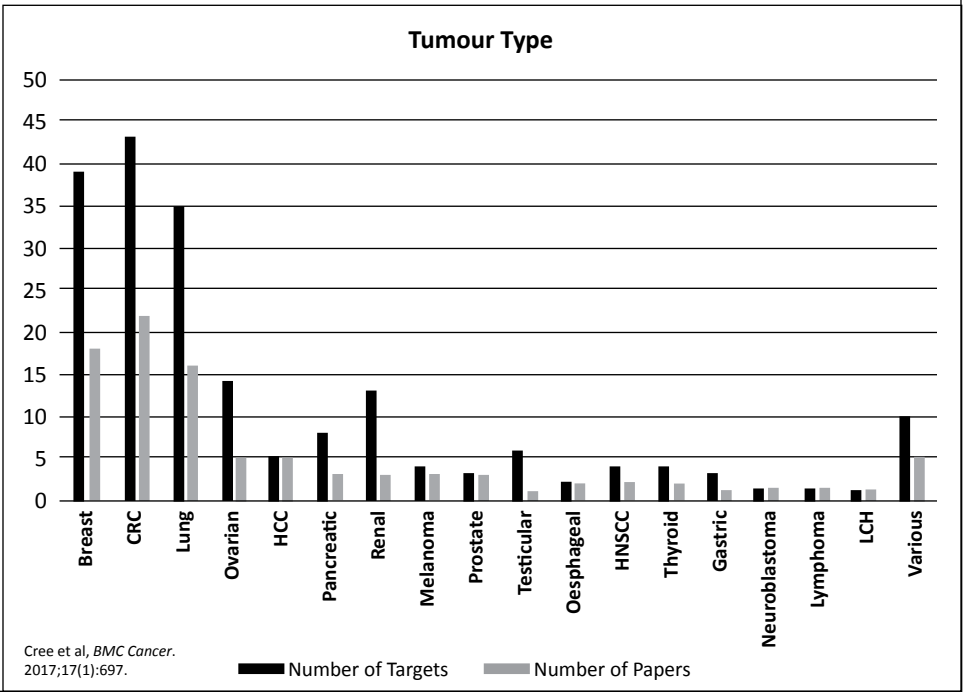
How It Works

Research has demonstrated that cancer cells and tumor DNA circulate in the blood of patients and not just present at the site of the disease. These DNA molecules are detected by a variety of molecular techniques including PCR and DNA sequencing; it is now possible to detect these DNA fragments and tumor cells even in low quantities. It is divided into cell-free DNA (cfDNA) or circulating tumor DNA (ctDNA). The cfDNA is DNA that may not necessarily be associated with tumor and is found in normal healthy individuals but is elevated when patients have tumors. It also is seen in increasing amounts with aging.[2] In ctDNA, small fragments of tumor cells are shed by the tumor into the bloodstream and in mouse studies the DNA fragments are found to have an average size of 166 base pairs.[3]

There are two major applications using technologies to detect these tumor markers. The first application is the early diagnosis of cancer, while the second application is the monitoring of a drug treatment or therapeutic intervention.

Tumor/Cancer Detection

One potential application of cf and ctDNA-based liquid biopsies is for detecting cancer at an early stage when treatment may be most successful. An excellent review article appears this ➤



Cree et al, *BMC Cancer*. 2017;17(1):697.

year in *Precision Oncology*, cf and ctDNA monitoring hold the potential for earlier disease detection in the blood samples collected from patient's months before they were diagnosed with cancer by traditional methods, such as imaging tests.[4]

There is a spectrum of assays available commercially available now for testing, ranging from looking for 1-10 SNP's for a singular type of tumor to searching for a multitude of markers by Next Generation DNA Sequencing (NGS) or multiplexed qPCR. There are at least 10 major companies offering now or developing these technologies: Grail, Guardant Health, Biodesix, Pathway Genomics, Exosome Diagnostics, Frenome, Cynveno, Biosystems, Inivator, Personal Genome Diagnostics, and Cell Max Life.

The first commercial laboratory to offer full NGS for a comprehensive mapping is 'Guardant 360' out of Redwood City, California. Their tumor genomic test evaluates 68 relevant genes, which if abnormal are known to be associated with cancer. This is a more comprehensive test and uses NGS to map portions of these genetic regions with more accuracy. This is similar to the comprehensive capability of our system RIDI™ for mapping and detecting microbes.[5]

A wide variety of studies in recent years have documented and correlated ct/cf DNA in a constellation of tumor types. This indicates the promise of liquid biopsy in many cancer types for both screening and therapeutic monitoring. The following chart displays the number of studies in each tumor type that have been completed and, as can be seen, it appears that liquid biopsy may have broad application.[6]

Therapeutic Monitoring

There is also hope that cf, ctDNA-based liquid biopsies may guide precision medicine treatment by identifying unique molecular characteristics of an individual's cancer. Studies using liquid biopsies have pinpointed cf, ctDNA mutations that could potentially be used to determine the optimal treatment.[6-8]

In 2016, the FDA approved a liquid biopsy test, called the Cobas® EGFR Mutation Test for the detection of EGFR gene mutations in cfDNA of patients with lung cancer. The purpose of the test is to identify patients who may be candidates for treatment with erlotinib (Tarceva®) and osimeritinib (Tagrisso®)—targeted therapies that attack cancer cells with *EGFR* mutations. Because the test may produce a false-negative test result, the FDA recommends a tissue biopsy if the liquid biopsy is negative (meaning it does not detect an *EGFR* mutation.[7] A *New England Journal of Medicine* study published shows that in women with metastatic breast cancer, "circulating tumor DNA is an informative, inherently specific, and highly sensitive biomarker of metastatic breast cancer." In this study, 30 women were tested, and 29/30 somatic mutations were identified. This is in comparison to CA-15-3 where tumor DNA was more sensitive and specific and provided the earliest measure of therapeutic response in 10 of 19 women.[8]

Summary

With the advent of molecular diagnostics and the capabilities of NGS technologies, liquid biopsy is now a reality. The ability to detect cancer early has been demonstrated in various tumor types. This holds the hope of earlier less aggressive interventions and could simplify diagnostics in the future. In addition, cf ,ctDNA monitoring by liquid biopsy allows for improved therapeutic monitoring and can assist in determining therapeutic efficacy.

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Declarations: Dr. Fry is the owner of Fry Laboratories, LLC, a clinical research and development laboratory which provides NGS services to clinics and hospitals worldwide.

Sodium Selenite and Zinc Gluconate – A Cure for Basal Cell Carcinoma?

by Alfred Zamm, MD

Selenium and zinc are both essential minerals; they are innocuous and well tolerated in maintenance or therapeutic dosages. Conveniently, they are inexpensive and available without a medical prescription. Separately, each of these minerals has been reported to enhance resistance to the development of cancer.

This report concerns a single clinical-case observation, an anecdote, describing the rapid disappearance of a cancer, a basal cell carcinoma, shortly after the simultaneous administration of selenium as sodium selenite and zinc as zinc gluconate. No other therapeutic measures were instituted, and no other changes occurred in the patient's geographic location, occupation, or lifestyle. To the best of my knowledge, this is the first report of a basal cell carcinoma being rapidly cured secondary to the simultaneous administration of selenium (as sodium selenite) and zinc (as zinc gluconate).
The following is the narrative of the events that led to this therapeutic outcome.

While riding in a taxicab, I noticed that the driver had a large (approximately 1 cm) textbook example of a basal cell carcinoma on the right side of his nose. (I can tell what a textbook example of a basal cell carcinoma looks like, having looked at "basal cells" for over 50 years in my capacity as a board-certified dermatologist.)

I suggested to the driver that he have the condition treated with Mohs surgery. For those unfamiliar with the term, Mohs surgery is a subspecialty of the specialty of dermatology in which the Mohs surgeon uses a unique, complex, and very effective method of removing a malignancy from the skin with a minimal removal or destruction of healthy tissue.

In order for the driver to prepare for the forthcoming medical visit, I advised him to take selenium (as sodium selenite) 80 mcg per day. Sodium selenite solution is available in a concentration of 40 micrograms per milliliter (note: micrograms – not milligrams) and is obtainable without a prescription in vitamin stores or on line. He was to take two ml (total of 80 mcg) each morning on arising and on an empty stomach, then wait 10 minutes for absorption to take place before swallowing anything else. This is a very small amount of sodium selenite, and it could easily be inactivated or the absorption process could be impeded by material in the stomach or intestine. The two milliliters of sodium selenite solution should be added to two ounces of tap water before swallowing; the increased volume aids in the absorption process. He was to measure the two ml of sodium selenite solution using a dropper calibrated in milliliters, which is obtainable from a pharmacy. In addition to the sodium selenite, I advised him to take zinc (as zinc gluconate) 60 mg bid with food for two weeks then 30 mg bid.

One month later he telephoned me and asked if he should still keep his upcoming appointment with the Mohs surgeon, which was to take place one month hence. Surprised, I asked him why would he consider cancelling his appointment? He replied, "Because I think the basal cell carcinoma may be getting smaller." I then advised him to put off his appointment for an additional month, continue the regimen, and observe what occurs. A happy ending: after four months of only the herein-described treatment, the basal cell carcinoma had disappeared. (Postscript: Two years later, he has remained cancer-free; he still takes sodium selenite and zinc gluconate as herein described.)

As I wish to be as scientific and forthcoming as possible, I acknowledge that there are adverse portions of this report as follows:

1. This presentation is a single-case anecdote (no statistical analysis);
2. No biopsy was done (no objective proof of the diagnosis);
3. The diagnosis of a basal cell carcinoma was based solely on a visual examination (a subjective opinion);
4. No photographs were taken (no objective proof).

Given these unfavorable parameters, why submit this article for publication? Two reasons: This anecdotal report is being presented with the hope that (1) this single finding, such as it is, should not be lost; and (2) this report might serve as a nidus of encouragement for other clinicians to either verify or disprove that the simultaneous administration of sodium selenite and zinc gluconate may be useful in treating basal cell carcinomas (and conjecturally,

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Cure for Basal Cell Carcinoma?

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by extension, perhaps prevent or treat other types of malignancies).

The following information may explain why this reported incident occurred. Selenium is an essential nutritional element. In addition, it has a non-nutritive quality derived from its atomic structure that allows it to firmly bind to and chemically inactivate mercury, a poison.[1] Thus it is able to mitigate mercury's poisoning ability. (Similarly, it binds to and chemically inactivates arsenic, cadmium, and some other heavy metal poisons found in the environment.) In regard to mercury, selenium protects, to some extent, against poisoning from mercury that emanates, as a vapor, or is leached from the normal usage from mercury-containing dental fillings.[1-4] These fillings are deceptively and obfuscatively called "silver" or "amalgam" fillings – terms that obscure the fact that they are 50% mercury. Dental mercury depresses T-cell number[5]; selenium protects against T-cells being poisoned by inactivating mercury. This patient had three mercury-containing "amalgam" fillings.

Selenium protects by other mechanisms against a variety of deleterious environmental xenobiotics. It enhances resistance to the development of cancer[6-19]and enhances the efficacy of treatment against an existing cancer.[20]

Zinc is an essential element that enhances the process of healing[21,22] and enhances white blood cell function. On a weight/weight basis, the white blood cells have a large amount of zinc compared with other cells in the body.[23] The white blood cells are zinc-dependent and adding zinc enhances their function.[23] Zinc also enhances immunocompetence[24] and resistance to the development of cancer.[25,26] It may also enhance efficacy of treatment of existing cancer.

My explanation of why this patient was cured of his basal cell carcinoma:

1. Selenium bound the circulating mercury derived from the patient's dental fillings and therefore mitigated the poisoning effect of mercury on his T cells; the mercury was depressing his T-cell population and interfered with his T-cell function. Certain individuals are more sensitive to mercury than others due to a spectrum of genetic polymorphisms. This patient was apparently in the "more sensitive," i.e., more vulnerable, part of a frequency distribution curve that is concerned with genetic polymorphic sensitivity to mercury.
2. Selenium has an anti-cancer property per se, in addition to its anti-mercury benefit.
3. Zinc enhances white blood cell function. This patient ingested zinc at a therapeutic level, allowing his white blood cells to function at a higher level, i.e., at a therapeutic level, against the foreign invader, the cancer. This benefit would not have been possible if the patient had relied solely on a "normal" "recommended daily allowance" (RDA) level of dietary zinc.

In this modern biochemically hostile world, daily we are unavoidably exposed to toxic heavy metals and toxic xenobiotics; this environment should be considered "a disease state." I believe that if one were to take sodium selenite and zinc gluconate at the innocuous therapeutic level herein described, this protocol would provide at least some defense against the unavoidable assault.

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Dr. Alfred Zamm is a board-certified dermatologist who practiced in Kingston, New York, until he retired to devote his time to research. In his medical practice, Dr. Zamm focused on conducting etiological investigations into his patients' myriad diseases as opposed to prescribing symptom-masking allopathic medications. He received his medical degree from the Chicago Medical School. Postgraduate studies included the Department of Internal Medicine at New York University Medical School, Bellevue Hospital of New York, University Hospital of New York, New York Skin and Cancer Clinic, and New York University Postgraduate Medical School. He is a Fellow of the American Academy of Dermatology, a Fellow of the American College of Allergy, Asthma and Immunology, and a Fellow of the American Academy of Environmental Medicine. He has published numerous medical articles, some of which have been referenced and excerpted in a variety of medical textbooks, and wrote the book *Why Your House May Endanger Your Health*. He was an invited lecturer at the Food and Drug Administration in Washington, DC.

Manual Muscle Testing for Tension-Type and Cervicogenic Headaches

by Scott Cuthbert, DC

Changes in Muscle Strength: A Critical Element in Tension-Type and Cervicogenic Headaches

A high percentage of headaches can be corrected with treatment determined by manual muscle testing (MMT) examination. Thorough knowledge of the mechanism(s) causing the cervicogenic or tension-type headache is important because there often are limited objective findings, especially during the pain-free period.[1] It should be recognized however that muscle imbalance has clearly been measured as a fundamental characteristic of musculoskeletal pain syndromes involving the head and neck.[2-6] The manipulative treatment of muscle imbalance physiology was first elaborated by Dr. George J. Goodheart, Jr.[6] Muscles predictably respond with weakness to pain, inflammation, and/or injury. (Figure 1)

With a lifetime prevalence of 93% in men and 99% in women, headaches are undeniably an extremely common problem.[7] Women consistently reported neck pain 83% more than men in a review of 25 studies by Dennison & Leal.[8] With a prevalence of over 47% reported in some populations, episodic tension-type headache is the most common of all headache types; chronic tension-type headache is found in 1% to 3% of the general population.[9] However, its prevalence may be as high at 15 to 20% in those with chronic headaches.[10]

Given the co-variance of muscle inhibition found in patients with headaches and the cost of headaches to both individuals and society at large, it cannot be stressed enough that MMT should become part of every clinician's assessment of patients with headache.

In patients with cervicogenic or tension-type headaches, there are specific and measurable motor control losses that can be assessed, identified and become the focus of therapeutic interventions. Applied Kinesiology is a system that suggests that muscle dysfunctions arising from, or part of the etiology of cervicogenic headaches, should be recognized and corrected as part of the over-all treatment strategy.

Substantial research has shown how general functional ability can be measured with simple, reliable, inexpensive, time-efficient tests…tests that have obvious "face-validity."[11] MMT qualifies on each of these counts. If a test has good 'responsiveness', then the test results should improve as a person's health status improves. MMT has shown excellent responsiveness because it accurately shows change when it has occurred in the patient.[12] Like a light dimmer switch, muscle strength is thought to be turned down by the central nervous system in order to unload and protect the sensitive or damaged tissues.[13] Manipulative treatment to these damaged or sensitive tissues corrects the motor control problems found in these patients.[12, 14-15]

Alterations in Cervical Motor Control

Briefly, the following data emerges from the current literature concerning the muscular inhibitions co-present in patients with tension-type or cervicogenic headaches and neck pain:

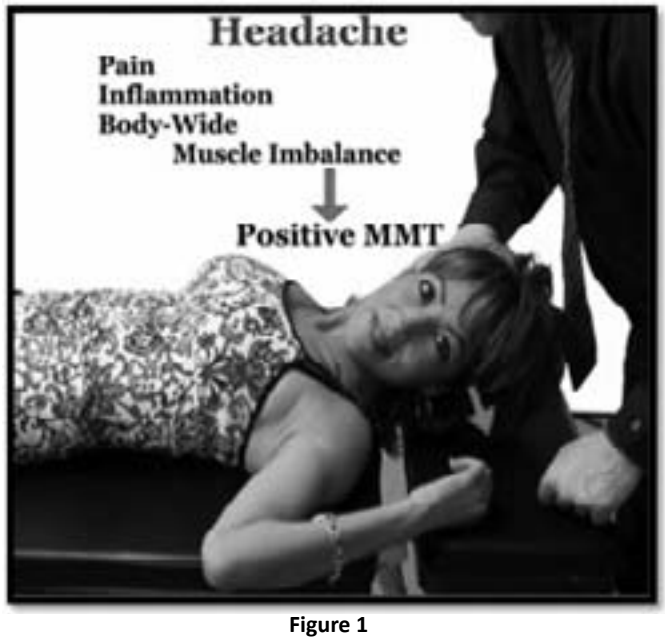

Figure 1
MMT makes it possible to diagnose this fundamental component of tension-type or cervicogenic headaches

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- Reduced force of contraction: In agreement with observations in people with neck pain, cervicogenic headache sufferers demonstrate deficits in the strength of the muscles producing cervical flexion and extension or cervical flexor muscles, the longus colli and longus capitis.[16-23]
- Reduced range of motion: Reduced range of motion, usually due to muscle inhibition, is well documented in these patients; and current classification criteria for cervicogenic headache include restricted range of motion of the cervical spine.[16-17, 24] Individuals with high pain-related fear also have smaller excursions of cervical spine.
- Decreased proprioceptive acuity with neck and headache pain.[25-26]
- Decreased endurance of muscles: Increased fatigability of craniomandibular and axioscapular muscles in patients with cervicogenic headache and neck pain.[22, 27-28]
- Alterations in timing of muscular contraction and impaired coordination control of muscles as well as cervical joint coordination are each altered in headache patients.[29-30]
- Impaired balance and decreased postural stability: Changes in postural control in migraine and neck pain patients.[31-32] Impaired postural control of the axioscapular muscles is associated with delayed muscle response times in neck pain patients.[33] Cervical muscle pain changes feed-forward postural responses of the muscles throughout the body.[34-35]
- Impaired reaction time: Compared to healthy controls, persons with cervicogenic headache exhibit a reduced ability to adapt spinal muscle coordination and activity and show a slower reaction time.[36]

Similar lists are available of contemporary research showing the muscle inhibitions accompanying most of the other physical disorders experienced by patients who visit physicians around the world.[12, 28, 37-41]

The author recently showed that in a symptomatic group of patients with mechanical neck pain (148 patients) demonstrated significantly increased MMT findings in the form of reduced strength levels compared to a control group (100 patients).[16] Weaknesses were broadly and to a large extent equally distributed (32.4%-43.2%) across the four muscle groups tested. (Table 1)

This evidence suggests that MMT is potentially a sensitive and specific test for evaluating cervical spine muscular impairments in patients with mechanical neck pain. Using a 95% confidence interval, we estimated that between 88.8% and 97.2% of all patients with mechanical neck pain have positive MMT findings in one or more of the four muscle pairs tested.

Table 1. Number and Percentages of Patients with Positive MMT findings, by Muscle Group

	Control Group (100 patients)	**Mechanical Neck Pain Group** (148 Patients)
Sternocleidomastoid	18 (18%)	61 (41.2%)
Anterior scalene	13 (13%)	49 (33.1%)
Upper trapezius	4 (4%)	64 (43.2%)
Cervical extensors	2 (2%)	48 (32.4%)

In a second paper the author again investigated the prevalence of positive MMT findings for 52 patients with headache according to the International Classification of Headache Disorders.[42] Muscle dysfunctions (inhibition) were found to be associated with headache (HA) in these patients as follows:

Table 2. Number and Percentages of Patients with Positive MMT findings, by Muscle Group with Headache (52 Patients)

Sternocleidomastoid	42 (81%)
Anterior scalene	24 (46%)
Upper trapezius	24 (46%)
Deep neck flexors	33 (63%)

In this group of 52 patients with HA, 49 patients had cranial dysfunctions that when treated with applied kinesiology improved all or a portion of the muscle inhibitions, while the initial Numeric Pain Scale of Neck and Associated Head Pain simultaneously fell from an average of 6.75 to an average of 0.49. Odds ratios were calculated to be >1, meaning there was a positive correlation between positive MMT of these muscles (as well as upper cervical and cranial dysfunctions), and headaches in this cohort. The evidence of this study suggests that MMT is a potentially useful diagnostic tool for evaluating peri-cranial muscular impairments in patients with both cranial dysfunctions and headache.

Tension-type or cervicogenic headache being associated with muscle inhibition and motor impairments is not a new concept. However, in recent years there has been an increase in the investigation of cervical motor impairment associated with headache. It is now known that cervicogenic headache sufferers present with an array of neuromuscular changes that are not unexpectedly different from those observed in people with neck pain.[6, 16-17]

In 1920 Cyriax first described the relationship between muscle weakness (detected with MMT) and headaches.[21] In 2008 an important literature review on neck muscle strength by Dvir confirmed that "overall studies indicate that, compared to normal subjects, patients suffering from neck-related disorders present with significant reductions in cervical muscle strength."[16-28]

In 1991 Lund et al.[28] described the pain adaptation model, reviewing the muscular changes in five chronic musculoskeletal pain conditions (muscle tension headache, TMJ dysfunction, fibromyalgia, chronic lower back pain, and post-exercise muscle soreness). Lund determined that these types of musculoskeletal pain disorders are not due to the older model of pain-spasm-pain cycle; instead, these conditions are mediated by the CNS as inhibition of the agonists and hypertonicity of the antagonists. Deficits in strength, endurance, and increased fatigability have been consistently demonstrated in the muscles that attach to the cranium in patients with whiplash-associated disorders, neck pain; and headache, using many different muscular assessment techniques.

It has been hypothesized that the powerful muscles attaching directly to the head and the cranial bones (which

move rhythmically and in complex patterns) are capable of being specifically tested and treated.[2-3, 12, 43]

Manual Assessments in Tension-Type and Cervicogenic Headaches

Visual images of the manual muscle tests for headache and neck dysfunctions are presented below.

Falla has reported that both the sternocleidomastoid and anterior scalene muscles' strength were significantly reduced in patients with neck pain at 25% of maximum voluntary contraction ($p<0.05$).[44]

Recent studies by Nederhand et al have confirmed that cervical muscle dysfunction appears to be a general sign in diverse chronic neck pain syndromes, especially related to whiplash injuries.[45-46] These studies suggest that the performance of the upper trapezius muscle is an invaluable diagnostic measurement in the evaluation of patients with chronic neck pain and chronic whiplash-associated disorders.

Cervicogenic headaches involve not only altered biomechanics, psychosocial anxieties, as well as significant costs to society, but also measurable motor control errors and local as well as remote muscular dysfunction that are part of the nervous system's response to pain and dysfunction.

If we are not capable of diagnosing this fundamental problem in patients with cervicogenic headaches, we are missing a fundamental component of their dysfunction making the treatment of complex neuromusculoskeletal disorders that much more difficult.

Manual Muscle Testing Management of Cervicogenic and Tension-Type Headache

During the past 3,000 years many diagnostic methods have been developed to discover the causes of human pain. In l972, a significant step forward in the evaluation of neurological disturbances related to functional-structural impairments was made by Goodheart.[48] The system consists of the examiner manually pressing on the vertebra in various ➤

Figure 2. Sternocleidomastoid MMT and muscle

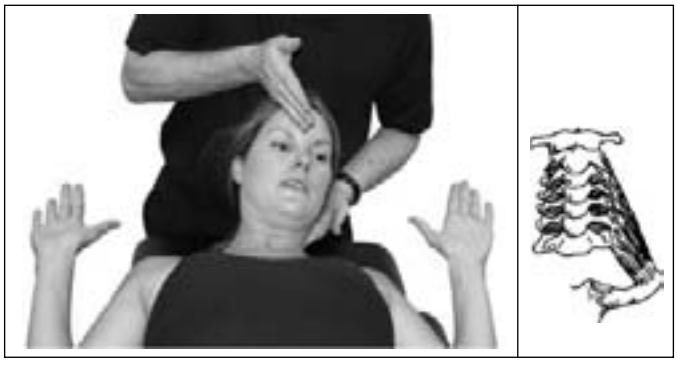

Figure 3. Anterior scalene MMT and muscle

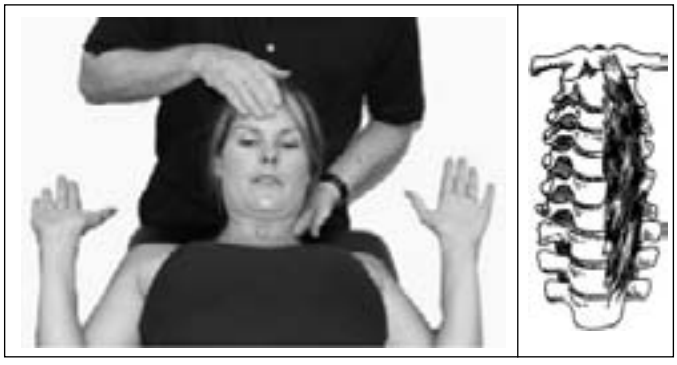

Figure 4. Deep neck flexor MMT

Figure 5. Upper trapezius MMT and muscle

Figure 6. Cervical extensor (unilateral) MMT and muscle

Figure 7. Cervical extensor (bilateral) MMT and muscle

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directions and locations, and immediately testing a muscle to determine change of strength. Goodheart named this procedure the "vertebral challenge." It has been widely used by doctors practicing applied kinesiology, and by thousands of other clinicians and therapists around the world who practice some portion of the applied kinesiology methodology, with significant success. It provides the opportunity for evaluating chiropractic subluxations, joint dysfunctions, osteopathic lesions, and body-wide articular dysfunctions in an effective, efficient manner.

The challenge method is the one used in applied kinesiology to determine the precise vector of any manipulative treatment. When the challenge is applied to an abnormally functioning vertebra, a skeletal muscle associated with the dysfunction will become temporarily very strong, as observed on manual muscle testing, for a period of many seconds to minutes.

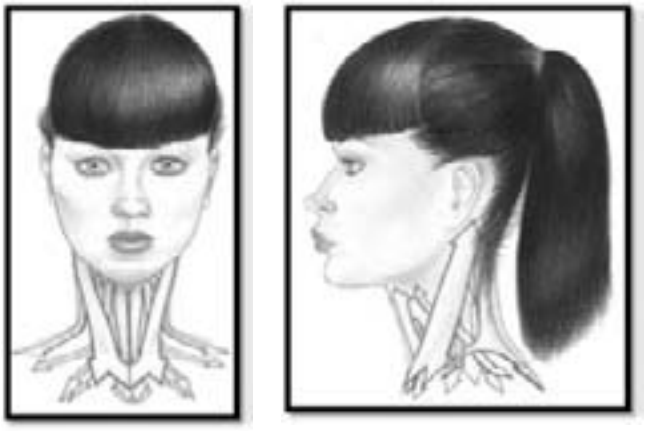

Figure 8.
Manual muscle tests are designed to replicate the primary vector of motion of a muscle while minimizing the contribution of secondary mover muscles. There is an ideal starting position and vector of testing force that places the cervical muscle being tested as the prime mover and the synergists at a disadvantage during the test. Accurate MMT must be done with a high level of anatomical and physiological knowledge.[47]

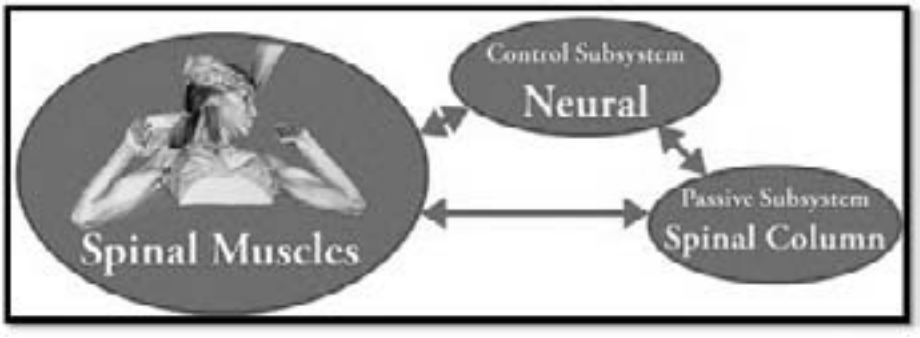

Figure 9.
Head and neck muscular dysfunction, recognized as critical in patients with head and neck pain, involves the disruption of what Dr. Panjabi terms the stability system of the spine. Improper stabilization responses may serve as a perpetuating factor in patients.[3]

Because MMT identifies neuromuscular dysfunction in the muscle, the directional preference of a local or remote joint dysfunction can be identified by applied kinesiology challenge.[12] If the sternocleidomastoid muscle on the right is inhibited (and related to a suspected cervical joint dysfunction and headache), a challenge of the C6 vertebra from lateral to medial may immediately strengthen the sternocleidomastoid. This is the subluxation responsible, and the direction necessary for correction, of the sternocleidomastoid muscle impairment.

The most common reason for muscle inhibition (an inability to generate adequate force for the optimal execution of movement) is direct physiological and pathological changes to the muscle's innervation. In recent years, both chiropractic and manual medical research and theory have highlighted the role of muscles, joints, and nerves in the function of the neuro-musculoskeletal system. This system has been described as the Primary Machinery of Life[49] as it is how we, and all tissues within us, move and communicate. If we are not capable of diagnosing this fundamental problem in the muscles of the head and neck, we are missing a fundamental component of headache dysfunction, thereby making the treatment of this complex neuromusculoskeletal pain disorder that much more difficult.

Conclusions

Several hundred studies have shown that cervicogenic or tension-type headache pain is associated with muscle inhibition, the detection of which makes MMT for cervicogenic headache and neck dysfunctions invaluable in clinical practice. Functional pathology of the muscle system is the most common clinical finding in tension-type and cervicogenic headache pain patients presenting to chiropractors, osteopaths, neurologists, rheumatologists, orthopedists, massage and physical therapists.[16] Yet this disorder of the muscle system is routinely ignored in the diagnosis and treatment of these patients.

In the triad of health model of health care (namely holistic and integrative health care), many factors that disturb and influence muscle function in the head and neck may be "challenged" or "therapy localized," including joint dysfunctions, reflex points, lymphatic and vascular receptors, meridian points, cranial dysfunctions, the origin and insertion of the muscles, proprioceptors within the muscle, myofascial kinematic interconnections with the lower body, foot and gait disturbances, and many more. Each of these elements in the patient's adaptation to injury or pain must be addressed if an integrated, holistic and interdisciplinary method to manage the complexities of headache pain is to be realized.

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Figure 10.
Sensorimotor "challenge" is a diagnostic procedure unique to Applied Kinesiology manual muscle testing that is used to determine the body's ability to cope with external stimuli, which can be physical, chemical, or emotional. After an external stimulus is applied, muscle-testing procedures are done to determine a change in the muscle strength as a result of the stimulus.

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Insights from the International Center for Cannabis Therapy, Part 2:

Evidence for the Clinical Use of Cannabinoid-Rich Hemp Oil in the Management of Pain, Inflammation, and Stress

by Chris D. Meletis, ND, and Kimberly Wilkes

In last month's *Townsend Letter,* Dr. Chris Meletis discussed the International Center for Cannabis Therapy (ICCT) cannabinoid certification programs for dietary supplement manufacturers and healthcare practitioners. As the Chief Medical Officer–USA of the ICCT, a Czech Republic-based partnership of qualified doctors and scientists who specialize in the medical application of cannabis, Dr. Meletis is an expert on the clinical applications and research supporting the use of cannabinoid-rich hemp oil and its effects on the endocannabinoid system. In this article, we will talk about the endocannabinoid system, its role in health, and how the endocannabinoid system interacts with the adrenals, sex hormones, and gut. We'll also share pre-clinical and clinical research and Dr. Meletis' observations about the use of cannabinoid-rich hemp oil in clinical practice, with an emphasis on the management of pain and inflammation and how to balance the endocannabinoid system without overwhelming its receptors. The next part of this article in a future issue of *Townsend Letter* will address the use of cannabinoid-rich hemp oil in applications such as epilepsy, stroke, irritable bowel syndrome, depression, anxiety, and psychosis, among other uses.

These articles can only touch the surface of everything there is to know about the endocannabinoid system and hemp oil. Healthcare practitioners who want to delve deeper into the benefits of cannabinoid-rich hemp oil, understand the legal ramifications of prescribing it, and become certified as a respected hemp oil expert who understands proper dosing and other nuances of hemp oil use, can sign up for the ICCT online medical certification program at www.icctcertification.com.

The endocannabinoid system is a fascinating regulator of many aspects of our health. Endogenous endocannabinoids that are produced within the body, including anandamide (arachi-donylethanolamide) and 2-arachidonylglycerol (2-AG), are able to activate receptors in this system. Phytocannabinoids such as Δ^9-tetrahydrocannabinol (THC), the psychoactive component of *Cannabis sativa*, and cannabidiol (CBD), a non-psychoactive component, are also able to activate endocannabinoid receptors. Additionally, synthetic cannabinoids have been synthesized and have an effect on endocannabinoid system pathways.

Two of the main receptors in the endocannabinoid system are CB_1 and CB_2. CB_1 is the primary receptor in the nervous system. It is also found in the adrenal gland, adipose tissue, heart, liver, lungs, prostate, uterus, ovary, testis, bone marrow, thymus, and tonsils.[1] Its expression is weak in the areas of the brain stem that regulate respiration, which is why respiratory depression, a potentially fatal adverse effect of opioid drugs, does not occur when using phytocannabinoids as painkillers.[1]

The CB_2 receptor is typically not expressed in neurons, which is why it was originally called the peripheral cannabinoid receptor. The immune system is the primary site of its expression. However, its presence has been detected in dorsal root ganglia, a cluster of cells in spinal nerves.[2] CB_2 receptors can also be expressed in bone, the gastrointestinal tract, and in activated microglia in the central nervous system.[2] Microglia are cells found in the brain and spinal column that defend the central nervous system against immune assaults. Because antibodies are too large to penetrate the blood brain barrier, microglia serve as the last defense against pathogens that enter the brain. Activated microglia, sometimes referred to as reactive microglia, create an inflammatory response linked to diseases of the brain.[3] The presence of CB_2 receptors in activated microglia indicate they may be involved in blocking the effect of painful stimuli in inflammatory processes of the nervous system.[4]

Different phytocannabinoids have different effects on endocannabinoid receptors. THC directly acts on CB_1 receptors of the endocannabinoid system,[5] which are primarily expressed in the brain. CBD indirectly acts on the CB_1 receptors by suppressing the enzymatic breakdown of the

endogenous cannabinoid anandamide, increasing the duration of time it stays in the system.[6] CBD's effects on the CB_1 receptor counteract the psychoactive effects of THC.[7] CBD thus inhibits adverse effects of THC including intoxication, sedation, and tachycardia.[7] CBD also acts on the CB_2 receptor, which is expressed in the periphery and is involved in immunity.[8]

From Fetus to Newborn: The Endocannabinoid System's Important Role

The endocannabinoid system plays an important role in our health long before we are born. The endocannabinoid system has been observed in cell types that play a role in male reproduction.[9] Endocannabinoids and cannabinoid receptors have been detected in testicular tissue, including Sertoli and Leydig cells and spermatozoa.[10] The endocannabinoid system also is involved in the hypothalamus-pituitary-gonadal (HPG) axis.[10] The anandamide-degrading enzyme FAAH regulates key steps in sperm biology pathways, and this action involves the CB1 receptor.[10]

Furthermore, the endocannabinoid system is important and highly expressed during fetal development. Too much cannabinoid resulting in the over expression of anandamide could lead to negative outcomes such as ectopic pregnancy.[11] Therefore, anandamide concentrations in the uterus must be tightly regulated for conception to occur.[12] During vaginal birth, the newborn's exposure to high endocannabinoid levels assists with the transition from fetus to becoming an infant. During birth, the levels of anandamide and an anti-inflammatory fatty acid amide known as palmitoylethanolamide (PEA) are markedly higher in vaginally delivered babies compared with infants delivered by cesarean section,[13] indicating that vaginally born infants would have a naturally higher degree of protection against pain and inflammation.

Another rodent study serving as a good example of the importance of the endocannabinoid system in prenatal and postnatal health involved female rats who were subjected to dietary restriction involving 20% fewer calories than a normal diet during pre-gestation and gestation. At birth, a significant decline in the levels of anandamide, 2-AG, and PEA were detected in the hypothalamus of the offspring of the calorie-restricted rodents. As adults, these offspring were more likely to gain excessive weight and body weight and be overweight as well as have increased anxiety-related responses.[14]

Furthermore, endocannabinoids have been detected in breast milk, and activation of CB_1 receptors was found to be critically important for milk sucking by newborn mice, helping them to develop oral-motor musculature.[15] This means that if a baby is delivered by C-section and then is bottle fed, he or she may be seriously depleted in endocannabinoids and may be at a disadvantage both as infants and later in life both mentally and physically. CB_1 receptors are temporarily present in white matter regions of the pre- and postnatal nervous system.[15] This implies that CB_1 receptors have a part to play in brain development and endocannabinoid deprivation in newborns can therefore be especially concerning.

The importance of the endocannabinoid system to infants is supported by a study showing that anandamide was neuroprotective against lesions induced in perinatal rodents.[16] Another study demonstrated that in rats that receive poor rearing during the neonatal timeframe, the neuroendocrine response to early life stress is reduced. Increasing anandamide levels ameliorates these stress-induced changes in glucocorticoid synthesis in these rats.[17]

Beyond CB_1 and CB_2 Receptors

Research is beginning to look beyond the classical CB_1 and CB_2 receptors as potential mediators of some of the beneficial effects of phytocannabinoids. Other receptors targeted by phytocannabinoids include G-protein coupled receptors (GP- CRs: GPR_{18}, GPR_{55} and GPR_{119}). Both GPR_{18} and GPR_{55} may recognize the phytocannabinoid CBD. Evidence indicates this phytocannabinoid serves as a GPR_{55} antagonist, as well as a weak partial agonist.[1] GPR_{18} is expressed primarily in immune cells while GPR_{55} is expressed in several brain regions as well as in the dorsal root ganglia in neurons with larger diameters, the hippocampus, frontal cortex, cerebellum, striatum, and hypothalamus. GPR_{55} may also be expressed in the immune system as well as in the microglia and bone.[1]

Research suggests that type 1 vanilloid receptors ($TRPV_1$) may regulate some cannabinoid effects. The $TRPV_1$ receptor has been identified in neurons that play a role in pain signaling.[18] Other undiscovered cannabinoid receptors may exist, and these receptors may partly mediate some of the analgesic effects associated with cannabinoids.[19,20]

Interaction of CBD Receptors and Other Physiological Pathways

The role of endocannabinoids and phytocannabinoids in mood enhancement and reduction of pain and inflammation cannot be completely explained by their effects on CB_1 and CB_2 receptors alone as well as the other receptors mentioned above. Cannabinoids influence other pathways and their effects on these pathways may play a role in their myriad health benefits. Peroxisome proliferator-activated receptor gamma (PPAR-gamma) is one of those pathways. PPAR-gamma is a nuclear receptor whose actions include regulation of glucose homeostasis and inflammatory processes and connective tissue health.[21] Mice experiencing a loss of PPAR-gamma function in fibroblasts were more likely to suffer from skin fibrosis.[21] Some endocannabinoids and associated signaling lipids as well as certain natural and synthetic cannabinoids can activate PPAR-gamma including THC and CBD.[22] The anti-inflammatory effects of anandamide and 2-arachidonoylglycerol are mediated by PPAR-gamma.[22]

Moreover, CBD blocks microglial activation in vitro through a mechanism that involves the activation of PPAR-gamma.[23] This effect was mediated by the inhibition of the inflammatory nuclear kappa factor beta (NF-KB)

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pathway.[23] The ability of cannabinoids to target both CB receptors and PPAR-gamma may explain their regulation of a number of processes including neuroprotection, inflammation, immunomodulation, and vascular responses.[24]

Cannabinoids also interact with 5HT1A serotonin receptors. It has been shown that the anxiety-reducing effects of CBD are dependent upon neurotransmission that is mediated by 5HT1A.[23] It is thought that CBD indirectly influences the 5HT1A receptors through interactions with the receptor binding site and/or modulating intracellular pathways.[23] CBD's effects on stress-reduction and anxiety as well as its mood-enhancing abilities are also mediated through the 5HT1A receptor.[23] Furthermore, CBD's ability to reduce brain tissue damage in mice caused by cerebral artery occlusion is blocked when 5HT1A receptors are inactivated.[25] The fact that CBD interacts with multiple receptors was shown in an animal study where CBD's ability to prevent hypoxic-induced brain damage was dependent upon both 5HT1A and CB2 receptors.[26]

CB_2 receptors themselves are able to indirectly stimulate opioid receptors located in primary afferent pathways, and this may be a means by which CBD inhibits pain.[27]

Endocannabinoid System Burdens

A number of factors can interfere with the proper functioning of the endocannabinoid system, throwing the body out of homeostasis. For example, obesity is associated with an over activated endocannabinoid system in adult subjects.[28] Moreover, offspring of female rodents that consumed a high-fat diet during pregnancy were obese with fat cell hypertrophy and buildup of lipids in brown adipose tissue.[29] These effects correlated with alterations in the endocannabinoid system of the rat pups. In male offspring of mothers fed a high-fat diet, CB_1 and CB_2 receptor levels declined in subcutaneous adipose tissue. In female offspring of mothers fed a high-fat diet, visceral CB_1 levels increased while subcutaneous concentrations decreased. CB_1 concentrations increased in brown adipose tissue from both male and female offspring of mothers that consumed the high-fat diet.

Toxins can serve as another disrupter of the endocannabinoid system. For example, the mechanism by which BPA causes fatty liver is thought to involve up-regulation of the endocannabinoid system.[30]

An imbalance of the gut microbiota known as dysbiosis is another threat to the optimal functioning of the endocannabinoid system. A rodent study found that dysbiosis of the gut microbiota led to changes in the endocannabinoid system.[31] In this study, researchers administered antimicrobials to mice for two weeks in order to cause dysbiosis. Afterward, the animals were given 10^9 CFU/day of *Lactobacillus casei* DG or a placebo for up to a week. Antimicrobial administration resulted in dysbiosis of the microbiota. At the same time, there was a general inflammatory state and changes in some aspects of the endocannabinoid system in the gut. These changes were accompanied by behavioral alterations, including increased immobility in the tail suspension test (an indicator of depression), as well as biochemical and functional changes in the brain such as neuronal firing in the hippocampus and rearrangements of non-neuronal cells in brain regions controlling emotional behavior. Probiotic intake eliminated most of these changes.

Sex Hormones and Cannabinoids

The association between the endocannabinoid system and estrogen indicates that declining estrogen levels with menopause may disrupt this system. The endocannabinoid system has an under-recognized role in male and female health. Cannabinoids and sex hormones influence common molecular pathways involved in cell proliferation.[32] Furthermore, estrogen plays an important role in the endocannabinoid system expression in the female reproductive tract.[12] Administering the estrogen estradiol to ovariectomized rats caused a marked increase in CB_1, CB_2, the anandamide-degrading enzyme fatty acid amide hydrolase (FAAH), and COX-2 expression.[12] These effects were estrogen-receptor dependent. Anandamide levels also increased in the plasma after estradiol treatment. According to the study authors, "Thus, estradiol may have a direct regulatory role in the modulation of ECS [the endocannabinoid system] in female reproductive tissues."

These findings may explain anecdotal reports of CBD oil reducing hot flashes and other symptoms of surgically induced menopause in women.

Endocannabinoid Imbalance and Psychological Stress

One characteristic of an imbalanced endocannabinoid system is the inability to cope with stress.[33-35] That's why this system is often dysfunctional in people with post-traumatic stress disorder. Stimulation of the endocannabinoid system inhibits the activation of the hypothalamus-pituitary-adrenal axis that occurs after stress.[33-35] In this way, this system helps us recover from anxious experiences and brings us back to homeostasis. In male rodents, when the CB_1 receptor is blocked, it takes longer for the HPA axis to recover from stress.[36]

Significant concentrations of nitric oxide (NO) are found in the brain and adrenal glands and NO may be involved in the stress response. During stress, anandamide suppresses the activity of the nitric oxide synthase enzyme, indicating that endocannabinoids may reduce stress by inhibiting the generation of NO in the hypothalamus and adrenals.[37]

An impaired endocannabinoid system may also be one of the reasons why stress impacts gastrointestinal function.[38] The endocannabinoid system in the gastrointestinal tract regulates motility, secretion, sensation, emesis, satiety, and inflammation. It also influences visceral sensation.

Beyond stress, there are many other consequences of a dysfunctional endocannabinoid system including pain, cognitive dysfunction, depression, epilepsy, and more. We will discuss some of these in further detail in this article while we will address others in next month's issue of *Townsend Letter*.

Improving Endocannabinoid System Function with Cannabinoid-Rich Hemp Oil

Cannabinoid-rich hemp oil is an ideal choice to optimize the endocannabinoid system. Throughout the remainder of this article and the next part of this article we will discuss the justification for using hemp oil in a variety of clinical applications. The primary cannabinoid in hemp oil is CBD. However, it also contains other phytocannabinoids as well as terpenes, which work with CBD to support endocannabinoid system function and therefore make hemp oil uniquely suited to enhance areas of health regulated by the endocannabinoid system. The entourage effect – sometimes called the "hemptourage effect" – refers to the ability of other more minor components of hemp oil such as the terpenes to support the activity of its main player, CBD. For example, the terpenes limonene, pinene, and linalool can provide a complementary action to CBD's cognitive-enhancing abilities by improving mood.[39] Pinene is also known to enhance mental clarity, thus acting synergistically to CBD.[39] The entourage effect is a fascinating aspect of cannabinoid therapy, and Dr. Chris Meletis explores this effect in more detail in the ICCT medical certification program.

Like so many herbals that are popularly used around the world, hemp has been employed for centuries with many health benefits. The moment we start eliminating certain constituents we may lose certain therapeutic benefits often attributed to the entourage or hemptourage effect. Yet, even with that said, we still don't fully know all the effects of the cannabinoids and terpenes either as standalone substances or in concert.

Cannabinoid-Rich Hemp Oil and Pain Control

As noted earlier, various receptors in the endocannabinoid system are involved in the regulation of pain including CB_1, CB_2, and $TRPV_1$. Pain is a common complaint among patients as evidenced by the fact sales of opioid drugs almost quadrupled from 1999 to 2014.[40] CB^2 indirectly activates opioid receptors, thus blocking painful stimuli.[41] In part through this mechanism, cannabinoids reduce inflammatory and neuropathic pain, which are notoriously difficult to successfully treat.[42] Animal models, human studies, and experience from clinical practice indicate that cannabinoid-rich hemp oil or CBD are useful in various types of pain. In a rodent model of osteoarthritis, CBD administered locally to the area surrounding the joint reduced the initial inflammatory response and thus subsequent pain and inflammation.[43] Furthermore, cannabinoid-rich hemp oil reduced body pain and improved other symptoms in girls who had an adverse reaction to the human papillomavirus (HPV) vaccine.[44] Other evidence indicates the oil of cannabis seeds reduces pain in patients with chronic musculoskeletal inflammation, an effect attributed to the ideal omega-3/omega-6 ratio content.[45]

Treating pain properly involves addressing more than just physical discomfort. Pain is a multidimensional problem that also encompasses impairments in mood, cognition, and function. This is one way where management of pain with opioids goes wrong as opioids can actually worsen all of these components of pain. Phytocannabinoids found in hemp oil, on the other hand, can improve all of these accompanying mental health factors as we will discuss in the next part of this article.

Proper Dosing Is Crucial

Before concluding this article, we want to caution that it is important to keep in mind proper dosing protocols when employing cannabinoid-rich hemp oil. CBD is less potent than THC and much higher doses may be needed for its beneficial effects on pain and inflammation. At the same time, it's crucial not to over activate the endocannabinoid system as scientists at the ICCT have found that overdosing on CBD can worsen certain conditions such as epilepsy. It's best to begin dosing at modest levels and then increase the dose slowly over two weeks.

Diligent education and a conservative approach to dose for each individual patient and the patient pool in general needs to be in the forefront of the prescriber. As Dr. Meletis has shared in the classroom setting as an associate professor of natural pharmacology, if a natural substance is strong enough to nudge a biochemical pathway towards optimized homeostasis, it also holds the potential to disturb homeostasis when not employed judiciously. Keeping up with the rapidly growing and burgeoning research field on hemp is critical. This is one reason why Dr. Meletis applauded the ICCT when they decided to create their certification programs. The medical certification program is a more precise way to establish the proper dose by using established ICCT protocols.

We also recommend that healthcare practitioners seek out hemp-oil manufacturers who are recommending the use of products that have been certified by the ICCT so as to avoid hemp oil products that may have contaminants or overly high concentrations of THC.

Conclusion

From long before birth, our bodies are dependent upon the homeostasis provided by the endocannabinoid system, which casts a wide net over various aspects of health including pain management and control of psychological stress, among many others. The endocannabinoid system functions through the activation of a number of receptors. Endocannabinoids as well as phytocannabinoids such as those found in hemp oil interact with these receptors. Consequently,

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supporting the function of the endocannabinoid system is an under-recognized way to enhance virtually every aspect of health.

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A Naturopath's View of Homeopathy or Psychotherapy with Props

by Dr. Douglas Lobay, BSc, ND

When I was a teenager growing up in a small town in the Pacific Northwest in the 1980s I had a voracious appetite for science books. I was particularly drawn to the style and reasoning of the renowned science fiction writer Isaac Asimov. He wrote in his book *The Roving Mind*:

> I believe in evidence. I believe in observation, measurement, and reasoning, confirmed by independent observers. I'll believe anything, no matter how wild and ridiculous, if there is evidence for it. The wilder and more ridiculous something is, however, the firmer and more solid the evidence will have to be.

I graduated from the University of British Columbia with a Bachelor of Science degree in biology and chemistry in 1987. I started naturopathic medical school at Bastyr College in Seattle in 1987. I loved the science classes and the blending of science with art of medicine and healing. I was amazed at homeopathy classes. I didn't know much about homeopathy, but I learned about its history, provings and treatment remedies.

After I graduated from naturopathic school in 1991, I endeavored to experiment and use all different facets of natural medicine and find out what worked and what didn't. I tried to use all sorts of homeopathic medicines from low potency, single remedies like arnica, to high potency ignatia and Oscillococcinum, to combination remedies like Traumeel and Lymphomyosot.

I was at the Advancing Naturopathic Medicine Conference at the Pan Pacific Hotel in Vancouver, British Columbia, in October of 2016. I went for a walk around the seawall near Stanley Park with a knowledgeable pharmacist friend after a session at the conference. We were chatting about health-related matters and somehow got on the topic of homeopathy. She concluded that homeopathy was nothing more than placebo or in her words "it was psychotherapy with props." I nodded and agreed with her.

As a scientifically trained and practicing naturopathic physician with over 25 years of experience, I still find it hard to believe that homeopathy is nothing more than placebo. I also feel compelled to write about my experience and understanding on the rationale for the use of homeopathy in the practice of modern naturopathic medicine.

I understand that homeopathy is based on the principle of "like cures like." In small doses a homeopathic medicine will treat symptoms that in larger doses it causes. The dilution is an integral part of the mystique about this theory. The more dilute the medicine, the more potent it becomes. Serial dilutions of a mother tincture can be based on 1/10 or "X" dilution or 1/100 or "C" dilution. A 6X dilution is a 1/10 progressive dilution of the original solution six times. A 12C dilution is a 1/100 progressive dilution of the original solution 12 times. Obviously, at low potencies or low dilutions there is a specific quantity of atoms and molecules in the dilution. However, beyond 24X or 12C dilution, there is a low probability that any atoms or molecules remain. Many homeopathic medicines have dilutions beyond these limits. 200C and 1M are common dilutions in classical homeopathy.

Avogadro's number is the number of atoms or molecules in one mole of a substance. By definition, Avogadro's number is 6.02 x 10 exponent 23. According to dilution, the inverse of this number is 6.02 x 10 exponent minus 23. Beyond this dilution, no actual physical atoms or molecules remain. And yet, according to homeopathic medicine, these medicines are active and stronger than lower dilutions. This is at direct odds with the current scientific theories of chemistry and biology. ➤

A Naturopath's View of Homeopathy

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Many homeopathic practitioners argue that there is "water memory" that is left after such high-dilution medicines are mixed or succussed. But according to analysis of such solutions, no memory or imprint remains, other than the random movement of atoms or molecules in solution. Graphic comparisons of such dilutions are analogous to one drop of a substance in the entire Pacific Ocean, one atom in the entire solar system and even one molecule in the entire Milky Way Galaxy. It is hard to explain from a rationale, scientific perspective that such dilutions with little or absolutely no substances can actually do something.

Over the years, I have tried to research homeopathic medicine on reliable scientific sites such as Medline, PubMed, and Cochrane databases. I have come to the conclusion that most scientific research on homeopathic medicines is limited, weak, and flawed. Poor methodology, weak study design, small sample size, and selection bias are frequently confounding factors in homeopathic studies. The gold standard of modern clinical research is the double-blind, placebo-controlled trial. After rigorous evaluation, most homeopathic studies that were double-blind placebo-controlled offer the same or a little more benefit than placebo.

A 2010 Cochrane review of homeopathy concluded that the most reliable evidence failed to demonstrate that homeopathic medicines have any effect beyond placebo.[1] A 2009 submission to the British House of Commons on homeopathy concluded that there was no compelling evidence of effect other than placebo.[2] A 2012 Swiss systematic review and meta-analysis of homeopathy showed most studies were flawed and biased.[3] In 2015, the Australian National Health and Medical Research Council concluded that there were no health conditions for which there was reliable evidence that homeopathy was effective. Additionally, there was no good quality, well designed studies with enough participants for meaningful results.[4] In 2005, the *Lancet* reported on a review of 110 placebo-controlled homeopathic trials. They concluded that the clinical effect of homeopathy was nothing more than placebo.[5] A 2009 and 2017 systematic review and meta-analysis from the most reliable studies did not support the evidence that non-individualized homeopathy was effective.[6,7] In 1987, French immunologist Jacques Benveniste reported in the *Nature* journal that basophils released histamine when exposed to anti-immunoglobulin IgE from a homeopathic medicine. A 1988 re-evaluation of this research concluded that there was lack of evidence for this conclusion.[8]

Some may argue that there are scientific studies on Medline and Pubmed that show statistically significant benefits of homeopathic medicines. There are, as Dana Ullman points out in his blog for the *Huffington Post*.[9] Some positive studies include the use of homeopathic medicines in treating COPD, hayfever, fibromyalgia, fibrositis, childhood diarrhea, ADD, and ADHD.[10-15] Of course it is important to realize that one study by itself does not provide conclusive evidence of scientific effectiveness. This can be true for any drug or therapy being tested. There are often questions about study design, objective measurements and how the conclusions are reached. And of course, the reproducibility of the study achieving the same results can be questionable. Homeopathy continues to be at diametrical odds to the current theories of physics and chemistry. Most mainstream scientists from universities that I have spoken to think that homeopathy is nothing more than placebo. Most reviews and meta-analyses conclude that although the study may be positive, more research is warranted to prove the effectiveness of this unproven medicine. Homeopathy remains controversial, inconclusive and unconfirmed in the face of a few equivocal studies. More rigourous research with better study design, methodology, and sample size is warranted. Homeopathy must prove itself.

Placebos are an integral part of medicine. By definition, a placebo has no active ingredient. Placebos have been shown to have clinical effects on health and healing. Personal expectation is important for a positive result. Pain relief, immune enhancement, anxiety, depression, fatigue, and fibromyalgia are just a few of the conditions that have benefitted from treatment with placebo. This underscores the importance of the brain's role in physical health. Larger pills seem to work better than smaller pills, capsules seem to be better than tablets, colored medicine appears to be better than white, and injections seem to work slightly better than pills. Some research indicates that placebos activate serotonin-dopamine pathways and/or the endocannabinoid system in the brain. Some individuals, whether

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genetically based or not, are more susceptible to the action of placebos than others. The doctor-patient relationship and belief in the medicine and the result is also important in its effectiveness.

Psychotherapy with props implies that counseling and listening to the patient is the actual therapy that imparts healing, and the prop would be the inert, diluted homeopathic medicine without any actual ingredient. Homeopathic practitioners are renowned for having long, extended visits with the patient and asking a myriad of questions including likes and dislikes, aversions and unusual quirks. Spending an inordinate amount of time with the patient, listening intently, and asking questions show caring, kindness, and concern on the part of the physician. Based on this extensive office interview, the homeopath would then decide on an appropriate medicine for the patient. Healing is believed to occur because of the medicine but would in fact be due to the extended interaction between the patient and doctor. The homeopathic medicine would be a prop that helps facilitates healing.

As a practicing naturopathic physician, I will continue to use some homeopathic medicines in my clinical practice. I believe that low-dose homeopathic medicine, from mother tincture dilutions upwards, to the limit of Avogadro's number, have atoms and molecules that can have direct physiological effects on health and healing. Beyond this number, I believe, that the effects of homeopathic medicines are comparable as placebos. One thing I have learned through naturopathic medical school is to keep an open mind in the realm of possibilities.

Several years after I graduated from naturopathic school in 1991, somebody gave me a copy of the book called *The Demon-Haunted World: Science as a Candle in the Dark* by the astrophysicist Carl Sagan. He directly and succinctly explains that rationale of the scientific method in evaluating phenomena around us. One quote of his made a lasting impact on me:

> And, after all, some illnesses are psychogenic. Many can be at least ameliorated by a positive cast of mind. Placebos are dummy drugs, often sugar pills. Drug companies routinely compare the effectiveness of their drugs against placebos given to patients with the same disease who had no way to tell the difference between the drug and the placebo. Placebos can be astonishingly effective, especially for colds, anxiety, depression, pain, and symptoms that are plausibly generated by the mind. Conceivably, endorphins – the small brain proteins with morphine-like effects – can be elicited by belief. A placebo works only if the patient believes it's an effective medicine. Within strict limits, hope, it seems, can be transformed into biochemistry.

This is just what I believe and have learned about homeopathy as practicing naturopathic physician and is not meant to disparage or demean anybody else who has a different opinion other than mine.

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Upcoming July Issue on Lyme Disease

Scott Forsgren, a Lyme disease writer and patient, explores the "Broad Net to Maximize Lyme Disease Recovery."

Jill Carnahan, ND, examines the critical role "Mold-Related Illness and Mycotoxins" play in chronic illness.

Carrie Decker, ND, reviews non-pharmaceutical antimicrobial therapies to implement in treating Lyme disease.

Functional Gastroenterology Bolus

by Steven Sandberg-Lewis, ND, DHANP

Understanding Chronic Nausea and Gastroparesis

Chronic nausea with or without vomiting is an often poorly understood problem. I have seen many patients who have suffered for years, sometimes with no clear diagnosis or poorly managed on symptomatic treatment measures. Typical medications include Zofran (ondansetron), which blocks 5-HT3 receptors.

The vomiting reflex has three phases:

1. The first is nausea. Nausea involves inhibition of gastric tone, reverse peristalsis beginning in the jejunum, and reflux of duodenal contents into stomach. This is what is occurring in the patient who has nausea alone.
2. The second phase is retching. This includes orad (toward the mouth) compression of the stomach by the diaphragm and external abdominal muscles, but the lower and upper esophageal sphincters are closed.
3. The third and final phase is vomiting. This causes orad propulsion of the contents of the upper GI tract through the open pyloric and esophageal sphincters.

The three phases are controlled by the brain's vomiting center, which is located just inferior to the fourth ventricle. Nausea/vomiting is triggered when sensory neurons convey distention or irritation of gastrointestinal organs (e.g., appendicitis, bowel obstruction, biliary tract obstruction), but also by cerebral events such as emotion, pain, and vestibular rotation.[1]

Certain extra-gastrointestinal stimuli alter body chemistry and may activate the chemoreceptor trigger zone in the brainstem. These include irritation of the diaphragm from lung infections or inferior wall myocardial infarctions, uremia (in acute or chronic kidney disease), toxins, and certain drugs (e.g., ipecac, digitalis).

The key additional underlying issues I have found in chronic nausea include gastroparesis, chronic liver issues, yeast overgrowth, small intestine bacterial overgrowth, hypochlorhydria, and gluten intolerance.

Gastroparesis is a delay in gastric emptying that can lead to prolonged distention and nausea with or without vomiting. Causes of gastroparesis include diabetes (up to 40% of DM1 patients; 10-20% of DM2 patients). Glycosylated hemoglobin levels may correlate with the presence of gastroparesis.[2,3] The mechanism is generally considered to be autonomic neuropathy. If a diabetic has any other form of neuropathy (e.g., decreased deep tendon reflexes, peripheral neuropathy), they will likely also experience altered gastrointestinal motility.

Other causes of gastroparesis include hypothyroidism, traumatic brain injury, systemic lupus erythematosus, progressive systemic sclerosis (scleroderma), Parkinson's disease, and stroke. Drugs that often lead to delayed gastric emptying include tobacco, calcium channel blockers, L-dopa, hyoscyamine, anticholinergics, and opiates. Other symptoms of gastroparesis include heartburn, regurgitation, belching, early satiety, and epigastric cramping.

Testing for gastroparesis may include the upper GI barium series ("barium swallow"), which reveals evidence of emptying by the findings of gastric dilatation, delayed emptying of barium, retained gastric debris (bezoars) or retained gastric fluid.[4] Electrogastrogram (EGG) or R-R interval testing with the electrocardiogram (EKG) measure the basic electrical rhythm alterations in gastroparesis.[1]

Most commonly employed is the gastric emptying study (gastric scintigraphy).[2] An isotope-labeled solid test meal is eaten by the patient, and four hourly x-ray images are used to calculate the gastric emptying time. The test meal contains technetium-99 sulphur-colloid bound to egg. This is in the form of a sandwich or added to scrambled eggs or a mashed potato. Additionally, for gluten- or egg-sensitive patients, gluten-free oats may be used.[5] Following ingestion of the test meal, scintigraphy should be performed for at least two hours; and by extending the test out to four hours the most accurate results are seen. If there is greater than 10% residual gastric content of the test meal at the fourth hour, gastroparesis is diagnosed. A smartpill or capsule endoscopy may also give evidence for delayed gastric emptying.[6]

Treatments for gastroparesis include diabetes management (if this is the cause), mindfulness at mealtimes, diet, replacement of acid and/or enzymes, therapeutic exercises, and botanical or prescription prokinetics.

Diet

Diet modifications may include smaller meals, reduced dietary fiber and fat, avoidance of red meat, reduced portions of protein and fat at evening meals and smaller evening meals in general. Other important considerations may include adequate hydration, reduced alcohol consumption, reduction or avoidance of cruciferous vegetables and gluten-free or grain-free diets.[7] Meticulous attention to detail with respect to a prescribed low carbohydrate diet has been found to reverse glycation of the vagus nerve, thereby gradually normalizing gastric emptying in diabetics.[8]

Botanical Medicine

Aloe vera juice may be used in doses from 0.5 - 8 ounces 15-30 minutes before meals.[8] If SIBO is a current co-condition, lower polysaccharide liquid preparations may be preferred. Papain or bromelain extracts may be very useful before meals.

Prokinetic herbs may improve gastric emptying and significantly relieve nausea. *Zingiber officinalis* (ginger) is a standby for relief of nausea and 500-1000 mg. may be used at bedtime or before or with meals. The mechanism behind ginger's prokinetic action is in part due to 5-HT3 receptor inhibition.[9] Amy Rothenberg, ND, has found excellent nausea relief for her patients undergoing chemotherapy by using a candy called "Gin-Gins double strength."[10] Iberogast is a German liquid prokinetic herbal formula. It has been studied for the treatment of functional dyspepsia and found to be more effective than metoclopramide. Using guinea pig tissue in vitro, it was found to have a relaxing effect on the muscles of the gastric fundus and a prokinetic effect in the antrum.[11] Adults may take 20 drops before meals and at bedtime, or occasionally the full dose of 60 drops at bedtime is even more effective.

Prescription Prokinetics

Prescription prokinetics may also be employed. The one I have used most commonly is low-dose erythromycin (sub-antibiotic dosage), which is a motilin receptor agonist. Motilin activates gastric emptying and the migrating motor complex of the upper GI tract. Erythromycin can be compounded as a 50 mg capsule for adults, given as a pediatric suspension, or the commercial 250 mg tablet can be divided into fourths (with a pill cutter) providing a dose in the 50-65 mg range.[12] Some patients with a history of "allergy" to erythromycin may have experienced the cramp-like effects of standard dosage erythromycin and are not in fact allergic to it. If there is no history of rash or true allergic response to the drug, they may have a very effective prokinetic response to the lower dose discussed above. If the patient has a history of QT interval prolongation – or is currently taking other medications that can cause QT interval prolongation – any dosage of erythromycin should be used with caution. (See www.crediblemeds.org for a list of drugs with QT interval effects.) Other prescriptions used are dopamine receptor modulators such as Reglan (metoclopramide) and domperidone (available through compounding pharmacies or Canadian pharmacies). I have never prescribed either of these. The chemoreceptor trigger zone in the brainstem employs dopamine D2 and serotonin (5HT3) receptors to control the vomiting reflex, therefore drugs that modulate these receptors affect nausea and vomiting. Metoclopramide, a dopamine and serotonin receptor modulator, is reported to cause side-effects including CNS side-effects in up to 40% of patients. Domperidone is said to have fewer side effects perhaps because it is a peripherally acting selective dopamine modulator. All these prescriptions should be checked for QT interval interactions with other medications. A screening EKG is recommended prior to starting these.[13]

Carmello Scarpignato, MD, notes that some highly constipated patients may have abdominal pain or other poor responses to prescription prokinetics.[14] He suggests using a standard colonoscopy bowel prep protocol to clear retained colonic material prior to initiating a prokinetic for these patients. I have found that colonic hydrotherapy is also useful for many of these cases.

For stimulation of digestive juices, vinegar or bitters may be used before meals. Betaine HCL may also be an effective treatment when taken with meals. Its necessity and dosage may be determined by Heidelberg radio-telemetry capsule testing or - if this is not available – a cautious clinical titration. Plant pancreatic enzymes before meals or porcine-based enzymes after meals may also prove helpful. Stool elastase or chymotrypsin testing may be used to assess the need for the latter.

Understanding the underlying causes of chronic nausea allows for targeted, specific treatment for this troubling problem.

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Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Our Debt to Richard Nixon: Low Birth Weight and Air Pollution

We owe a debt to Richard Nixon. Few people remember him in a favorable light. We remember him for sabotaging the Vietnam peace talks, the whole Watergate thing, and of course the business about being a crook or not. We forget that he established the EPA.

It was Richard Nixon who signed the executive order that created the Environmental Protection Agency (EPA) back in 1970. The first legislation put forward by the EPA was the Clean Air Act, which passed into law in 1972. What we now call the clean water act began as the Federal Water Pollution Act first of 1948 but was rewritten in 1972 as the Federal Water Pollution Control Act during Nixon's tenure. We can't give him credit for its passage. He vetoed the bill on October 17, 1972, but the House and the Senate overrode this veto the very next day and the Clean Water Act became law without his aid.

Thus, one should probably give Nixon credit for passing at least some of the legislation that has had the most lasting impact on environmental quality in US history. It's weird to think about, I know.

Airborne particulates and or air pollution are blamed for a long list of health problems. Nitrous oxide levels are linked with suicide rates.[1] Fine particulates appear to increase anxiety levels in women[2] and worsen diabetes.[3,4] Urban air pollution increases mortality rates; what we should call the bottom line in health.[5]

Given the EPA's current lack of enforcement of existing regulations, outdoor air quality may deteriorate in the near future. We can still influence our indoor air quality to a great extent by simply using air filters. Even short-term utilization of a HEPA air filter has significant impact on biomarkers of illness, for example, lowering c-reactive protein levels significantly in days.[6]

The current theory to explain why these tiny particles have such a profound impact on health suggests that once inhaled they actually translocate across the membranes of the lungs, enter the circulation and deposit at various sites in the body; in particular they accumulate where there is preexisting inflammation, triggering further inflammatory reaction.[7] They make bad things worse.

Over the past few months there have been a number of papers published that link air pollution, particularly superfine particulates, to risk of low birth weight infants.

In early December the *British Medical Journal* published an article that examined the impact of air and noise pollution on birth weights of infants in London.[8] Rachel Smith and colleagues conducted a retrospective population-based cohort study to examine the relation between exposure to air and noise pollution from road traffic and whether there was an effect on birth weight. Their study included all live births in the greater London area occurring between 2006 and 2010. They used official birth registries and identified 671,509 births. Some of these births were excluded because the moms lived too close to the area boundary, had premature births at less than 24 weeks, the infants had implausible birth weights, or missing gestational ages. In the end, the researchers still had 540,365 births for analysis.

Modern software allowed the researchers to pinpoint the location of homes where the moms lived to almost inches. Pollution and noise levels were calculated to 20-meter grids across the city. Low birth weight (LBW) was defined as less than 2500 grams (~88 ounces) and a gestational age of 37 weeks.

Air pollution from road traffic in London was clearly not good for babies. The authors estimated that 3% of the low birth weight births in London are directly caused by exposure during pregnancy to fine particulate matter (PM2.5) levels greater than 13.8 $\mu g/ m^3$.

The study did find a link between traffic noise and birth weight. For each interquartile increase in air pollution exposure however there was a 2-6% increase in the odds of a LBW delivery.

We want very much to prevent babies coming out small. That is because underweight babies are more likely to have bad things happen; they are born too early, suffer from worse fetal distress, are delivered by C-section more often, have lower Apgar scores, end up with hypoglycemia, are in the hospital more often, and are more likely to die.[9] Low birth weight girls are more likely to end up with preeclampsia themselves when they become pregnant years later.[10] Very low birth weight is associated with brain structure abnormalities and cognitive impairment.[11] Preterm birth leads to hyper-reactive cognitive control processing and poor white matter organization in adulthood.[12]

Low birth weight is also a predictor of person's future health.[13,14] A low birth weight is associated with high low-density lipoprotein and total cholesterol levels in men, and hypertension and diabetes mellitus in women as they age.[15]

This study on its own should make us worry about the health risks of air pollution. Yet there is more to it; this paper by Smith et al is just one of a series of recent studies that came to similar conclusions. As I write this during the second week of December 2017, Smith et al is one of four significant studies already published this month.

Also published in December is a study by Kingsley et al that examined ambient air pollution and preterm births in Rhode Island. The air is relatively clean in Rhode Island, yet Kingsley's group reported that increased PM2.5 exposure was still associated with a 12-16 grams lower birth weight (n=61,640). Kingsley's group estimated that for every 2.5 $\mu g/m^3$ increase in PM2.5 exposure during pregnancy, risk of preterm birth increased 4%.[16]

Liu et al examined maternal exposures to particular matter in Shanghai, China, and reported, also in December, more dramatic effects than the Rhode Island researchers, probably because pollution in Shanghai is far worse. In Shanghai where the annual average PM2.5 concentration was 56.19$\mu g/m^3$, the study estimated that 33% of preterm births and 23% of low birth weight births were directly caused by pollution.[17]

In yet another December publication, Ng et al report analysis of data on births in California (N=1,050,330). Interquartile increases in exposure to total PM2.5 were associated with a 7.7% increased risk of LBW births.[18]

As mentioned these studies were published in just the first two weeks of December. My haphazard search going back through last summer finds similar reports from across the world including Jinan, China,[19] Scotland,[20] Connecticut,[21] and Cape Cod, Massachusetts.[22] These research results are consistent enough for us to pay attention. Air pollution exposure during pregnancy is very likely to increase risk of a LBW birth. This is a problem.

This brings to mind an article Walter Crinnion, ND, wrote on air pollution back in 2015. Dr. Crinnion is well known for teaching courses on environmental medicine through a group called SpiritMed.

> Much more focus needs to be placed on recognizing the important role that common air pollutants hold in health, with commensurate actions being taken to reduce the levels of common air pollutants in the home—the one environment most people are in control of. It is quite possible that one of the most effective preventive medicine modalities would be the installation of a high-quality air purifier in the home.[23]

This conclusion is even truer today; it is doubly true for women during pregnancy. Using an air filter may be the most effective single thing a person can do to improve their health. Based on these recent studies I guess we should amend this to read, "Using an air filter may be the most effective single thing a person can do to improve their health and that of their babies."

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Healing with Homeopathy

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

Surviving Travel Stress with Homeopathy and Good Humor

What Kind of Traveler Are You?

If you are like most folks, you either find traveling appealing, exhilarating, even addicting, or just too expensive and a hassle. We happen to be in the first group. We thrive on the change in climate, environment, and interactions of the northern and southern hemispheres. Not to mention east and west! Every time we travel, we get ideas from fellow travelers of other magical destinations. However, we certainly have our challenging moments, especially involving air travel with our golden retrievers. For moments we want nothing more than to retreat to the comfort and security of our own beds for good. But, mostly, we love not knowing what is around the next bend in the road. We relish the continual surprises, ever-changing vistas, and the excitement of making new friends from the far corners of the earth. And conversing in Spanish and French whenever the opportunity arises.

What they say about six degrees of separation is true: how many of you have found yourselves in the most unlikely places and ended up, to your mutual delight, meeting a long-lost friend, or at least a friend of a friend? We persisted in finding an off-the-beaten track vegetarian restaurant, Lehka hlava, for lunch in Prague last September. We were greeted, upon arrival, and asked whether we had a reservation, which we did not. No problem, we were assured, as the hostess led us to a small waiting area while a table became available. Ten minutes later another couple arrived, also awaiting a table. Noticing that they were speaking English, we inquired as to where they were from: Vancouver, Washington. Hmmm. We commented that we were from Whidbey Island, Washington, to which they responded that they had just visited Langley a few weeks earlier. On the beach of Whidbey Island. We live in Langley, on the beach, a five-minute walk from where they stayed. Small world. "Oh," Bob asked the gentleman, "Is that where you were born?" The gentleman revealed his birthplace: Collegeville, Pennsylvania. Now, would you believe that Bob attended college in that very town, which must have had a population of 5,000 max at the time? Hearing a hint of an accent in the woman's voice, we wondered aloud where she was from originally. "Chile." Now that rang a chord, since we live half-time in Chile. At that point the hostess returned to inform us that our table was ready. We suggested that, given the synchronicity, we share lunch.

As the menus arrived, Judyth asked the Chilean woman where she had grown up. "Santiago." Santiago is quite a metropolis, but a surprisingly small one. Then for some odd reason her intuition led Judyth to press forward, "You don't, by any chance, know a musician friend of ours, Andres Cóndon, do you?" Broadly smiling, the woman, quickly becoming a friend, told us, "We went to high school together at St. George's." "Because," Judyth continued, "we are on our way to visit him and his wife in Germany. And they stayed with us last year on a music tour of the Northwest." "No way," was the next reply. "They performed a concert at *our* home just before they visited you!" And that is not the first time something like that has happened to us on our travels. Had we not befriended the couple in the first place, we never would have discovered the remarkable synchronicities.

Which leads us to our first universal stress-relieving tip, even before homeopathy!

Be Friendly!

Whether or not you speak the same language or have anything else in common, smiles are universal. And knowing a few basic words in a number of languages comes in handy in a pinch. *Bonjour* brings out the pearly whites of many a Haitian visitor here in Chile (apparently 125,000 have immigrated over the past year to work). *A salaam aleikhum* brightens the countenance of Muslims worldwide, and you can always count on *Buenos días* to open doors! Petting the local Fidos (*mon p'tit bon bon* or whatever the local *nom de preférence*) will make you quite popular and admiring a baby anywhere can almost make you part of the family! Whether you are enjoying a day on the beach or stuck in a crowded subway or interminable airport line, it's always more pleasant to make connections. This is the polar opposite of the, unfortunately true, tale of the rude, impatient businessman, annoyed to no end that he had to wait in line along with many other, far less entitled, travelers after their plane was canceled. Butting in line, he bellowed to the flight attendant, flaunting his self-perceived importance: "Do you know who I am?" The quick-

witted, courageous, likely exhausted attendant announced over the intercom: "We have a gentleman here who doesn't remember who he is. Can someone help him?" Outraged, he responded with a different F word…. the opposite of "friendly!"

Be Flexible!

Staying home, although it may bring its ups and downs, is nothing like the unpredictability of travel! The more you try to calculate, pigeon hole, plan ahead, nail down, and get your ducks in a row, the more you will be thrown a curve! We're not surfers, but travel must be like riding the next wave. The fun, if we can remind ourselves in those trying moments, is in not knowing, letting go, being surprised. The bathroom may be a hole in the ground that smells terrible (love that Chilean word, *hediondo* which means malodorous), the food a gourmet delight or a tough piece of shoe leather, the mattress and pillow hard as a rock. But it all depends on how you look at it.

One of our most dicey travel moments turned out quite nicely. One of the heartiest adventures of our lives (2010), in the Brazilian Amazon, was "supposed to" end with a return flight from Rio de Janeiro to Santiago, Chile, where we had left a box of our belongings in *custodia*, ending with a few days in the Maipo Valley with expat friends, then home to Seattle. We were greeted, unnervingly, by the LAN Airlines (now LATAM) gate attendant with, no joke, the Spanish equivalent of "There has just been a massive earthquake in Chile and the world is ending." Chilean travelers were in chaos, no phone calls to Chile were going through, and LAN was particularly unhelpful. Alaska Airlines came to our rescue, probably the opposite of LAN, assuring us that they would happily reroute our mileage plan tickets and get us back to Seattle the next day via American Airlines, one of their partners (the box stuck in the Santiago airport was another expensive and much delayed story). With a day to spare in Rio, we turned lemons into lemonade by spending a night at a charming hostel in the delightful, artistic Santa Teresa district and enjoyed a guided tour of *Rocinha*, the largest *favela* (slum) in Rio, which, at the time had a population of 69,000 and more weapons than a small country. We were warned (seriously) not to take photos of anyone with a cell phone (they were the drug lords and didn't play around). That three-hour experience was one of the most fascinating anywhere anytime. If we had just freaked out and stayed at the airport, we would have truly missed out.

Be Curious!

For those whose plans and ideas are not set in stone, travel is a wonderful way to learn totally new ways of thinking, eating, being, doing, and leading your life. It was Judyth's first trip to South America in 1970 that completely diverted her plans to pursue a PhD in Spanish literature at Stanford, which ended instead with her working as a Vista volunteer with *chicanos* in El Paso. What if your next trip were to totally change the course of your life? What if you were to meet someone unforgettable who would have a profound impact on you? What if a destination that you least expected ended up being a home for you? When we

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set off on a mother-ship kayaking journey in Patagonia thirteen years ago, we never would have dreamed of stewarding a piece of land in Chile, then turning it into a paradise! An unending sense of wonder, awe, and even bewilderment can be just the medicine you need to shake you out of your previous "reality."

Stay Healthy!

Speaking of medicine, you may be wondering how we plan to interweave homeopathy into this discussion. Wait no longer. Our latest book, *The Savvy Traveler's Guide to Homeopathy and Natural Medicine: Tips to Stay Healthy Wherever You Go* is full of indispensable advice from how to prevent being ripped off, sun-damaged, mosquito-ridden, water- and food-poisoned. We give user-friendly tips on how to prevent, heal, and survive 68 common travel health problems from altitude sickness to deep vein thrombosis, fear of flying to head lice, hepatitis, and parasites, and lots more. the book and kit weigh only a little over a pound, even lighter if you choose the app *Natural Travel Doctor.* Apple version https://tinyurl.com/song8; Android: https://tinyurl.com/m7cnexh

Travel Anxiety and Panic

It can be a frightening ride for travelers these days, especially for immigrants or racial minorities. Plane seats are more cramped than ever, amenities greatly reduced; and whether it be a proud, feisty peacock or a disgruntled human in the seat next to you, there's simply a much higher level of unpredictability and edginess. There are many places in the world where tension is prevalent, and a mood of chaos seems to be on the rise. You may worry about finding yourself in a situation of danger, though you are probably more likely to encounter problems close to home.

First, remember our suggestions above: be friendly, flexible, and curious! If you are in an uncomfortable, difficult, or dangerous situation, plain and simple, take *Aconite*. *Aconitum napellus* (Monkshood) is the first remedy to consider for sheer anxiety or panic. Whether you are dreading planes and crowds, fearful of riots and unexpected natural disasters, *Aconite* is likely to help. If you find yourself in an airplane with terrifying turbulence, on a dark street in questionable company, or in a stadium or theater where confusion and panic arise, this is the remedy of choice.

Our friends and colleagues, Roger Morrison, MD, and Nancy Herrick, PA, traveled to Bali in October 2005, just as we headed to Costa Rica for a yoga retreat. Rather than enjoy the R and R that they expected, they found themselves on a working vacation administering homeopathic and emergency assistance to the traumatized, mostly-Australian bombing victims. You never know!

After taking Aconite, there should be a change in the shock, restlessness, panic, heart palpitations, rapid heartbeat, and fear of impending death to a relative feeling of calm, sometimes within minutes. If you don't have access to *Aconite*, in a pinch take some Rescue Remedy.

Travel Discomfort Plain and Simple

Unless you have the great fortune to travel first or business class, you are likely to be crammed, cramped, and crowded. Each year that we travel, we seem to encounter some new affront or insult to our comfort, even on the same airlines and flights that we have known for years. The bulkhead is either not available or you may be pushed out (the euphemism is "asked to be reseated") by a passenger with disabilities. (Anyone with disabilities should surely be given the most comfortable seats, but it can be discouraging to choose seats far ahead then be moved to a highly undesirable seat.) Or you are required to pay for your seat of choice. Then there is the added inconvenience, indignity, and anxiety of not being able to reserve a seat at all if you have been lucky enough to score a cut-rate budget fare. We used to enjoy our often-successful strategy of getting to sleep two or even three seats across on international flights, but that is extremely rare now. (Sorry, but we're keeping a few road warrior secrets to ourselves.)

*Rhus toxicodendron (*poison ivy*)* is by far the most common remedy for travel muscle and joint stiffness and cramps. For the tension, tightness, and contraction that results from feeling like a sardine in a can. Getting up to stretch, using rubber resistance bands, practicing plane yoga, walking loops up and down the plane aisles and around the back are not always possible these days. Nor is sticking your feet out into aisle (those bulkhead passengers are the lucky ducks). *Rhus tox.* is a lifesaver when all you want to do is wiggle, stretch, move… anything to offset the feeling of being stuck, contracted, stiff, and tight.

Gotta Get There Yesterday

There are a couple of remedies that the testy traveler at the ticket counter whom we talked about earlier could have used. They are *Nux vomica* (poison nut) and *Argentum nitricum* (silver nitrate). *Nux vomica* is the answer for downright Type-A impatience, irritability, and rudeness. The individual is pushy, highly competitive, may suffer from heartburn, and tends to drink too much. If this sounds like you, best to pass on the free airplane booze. *Argentum nitricum* is a better fit if you are constantly eyeing your watch to make sure you're not late or haven't missed a meeting. It's also another good airplane anxiety remedy for folks who get anxious in tight spaces (like planes or elevators) or on bridges.

Breathe In, Breathe Out

No matter where you are, where you've been, or where you're going, you can count on one thing: you need to breathe to live. That's the bottom line regardless of whatever thoughts float in and out of your brain. So, if you forget everything else we've mentioned in this article, just BREATHE! News flash: Just as we were about to submit this article, concluding with our advice about breathing, we happened upon this *Huffington Post* news feed: "Farting Passenger Forces Plane to Make Emergency Landing." We still stand by our advice to breathe heartily. (In yoga, they say that the lifespan is counted in breaths rather than years – the slower you breathe, the longer you will live.) But, if you find yourself on a plane in a situation like this, maybe it's a good time to pull out your gas mask!

Judyth Reichenberg-Ullman and Robert Ullman are licensed naturopathic physicians, board certified in homeopathy. We have written eight books on homeopathy as well as *Mystics, Masters, Saints and Sages – Stories of Enlightenment*. We also have an app: Natural Travel Doctor: Apple version: https://tinyurl.com/l7song8 and Android: https://tinyurl.com/m7cnexh**.** We are more passionate than ever about homeopathy, and we never seem to tire of traveling.

We practice in Edmonds, Washington, and by Skype. The Edmonds office address has changed, as you will see on our website. We live on Whidbey Island, Washington, and in Pucón, Chile. Visit our website www.healthyhomeopathy.com. Please friend us on Facebook at Healthy Homeopathy. Call us at 425-774-5599 or email us at drreichenberg@gmail.com or drbobullman@gmail.com.

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Clues for Clinical Treatment Plans Through Understanding Methylation

by Debby Hamilton, MD, MPH

As an integrative practitioner, my patients typically present with complex medical issues. Even in pediatrics, this is becoming the norm. Any tools we can use as practitioners to guide treatment can be beneficial. Understanding the nutritional biochemistry in methylation can aid treatment plans by creating a protocol more likely to benefit the patient. Complex illness often needs step-by-step treatment, but knowing which treatment to start first can play a significant role in recovery time and lessen potential adverse reactions.

Methylation influences multiple mechanisms in the body by adding and subtracting methyl groups. This transfer of methyl groups functions as an on/off switch in the body to control cell activity. The control of gene expression is through the message relayed by the addition or subtraction of a methyl group. Neurotransmitters influencing our mood, sleep patterns, and mental functioning are balanced by methylation. Hormones, which also influence mood and regulate our physiologic homeostasis, rely on proper methylation. Our detoxification system is dependent on this process and its connection with the sulfur pathway, producing one of our main antioxidants – glutathione.

Even our cellular energy produced by our mitochondria depends on proper functioning of our methylation cycle. Critical to mitochondrial function is an intact mitochondrial membrane. Phosphatidylcholine is a key component of this membrane. The PEMT enzyme uses the compound SAMe formed through the methylation cycle to form phosphatidylcholine. Therefore, if methylation is not functioning well this can lead to problems forming proper cell membranes, negatively impacting cell and mitochondrial function.

Many practitioners think methylation means a person needs methylfolate. Yet if this is done as a first step, many people will have a worsening of their symptoms. Parents are not happy if their hyperactive child has an increase in their hyperactivity from a supplement you have given them. Understanding that methylation is more than just MTHFR and methylfolate allows a practitioner to identify multiple different genetic SNPs that contribute to how someone will react to a supplement.

Too many methyl groups in someone who is overmethylated may lead to increased reactions to stress, hyperactivity, anxiety, sleep disorders, food and chemical sensitivities. Their neurotransmitters such as serotonin, norepinephrine and epinephrine tend to be high. On the other extreme are people who are undermethylated and have low serotonin levels. Lower serotonin levels are associated with depression and obsessive-compulsive symptoms. A high percentage of people who have too few methyl groups may also have decreased levels of calcium, magnesium, methionine, and Vitamin B-6.

In addition to the genetic SNP's we inherit, our environment through epigenetics plays a role in the expression of our methylation genes. Everything from our diet to infections and toxins can impact genetic stability and alter gene expression. Understanding the interplay of a patient's methylation genes in addition to genes involving detox pathways and neurotransmitters can help provide a pathway towards treatment in complex illness. For those practitioners looking for a guidebook, methylation can often provide some insight.

We invite you to learn all this and more at the two-day Methylation 2018 Summit in Chicago, Illinois, July 13-15, 2018. For more information on this CME-based conference, please go to www.Methylation2018Summit.com or contact the Healthy Medicine Academy at eveco247@gmail.com (1 303 990 7958).

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Calendar

Please submit an announcement of your event 90 days in advance.
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MAY 24-26: AUTISM ONE 2018 CONFERENCE in Chicago, Illinois. CMEs available. CONTACT: http://www.autismone.org/CUTTING-EDGE-AUTISM-CME-PROGRAM

MAY 31- JUNE 2: INSTITUTE FOR FUNCTIONAL MEDICINE ANNUAL INTERNATIONAL CONFERENCE – Solving the Puzzle of Autoimmunity: The Interplay of Gut, Genes, and Environment in Hollywood, Florida. CONTACT: 800-228-0622; https://www.ifm.org/

JUNE 1-3: ADVANCED APPLICATIONS IN MEDICAL PRACTICE SPRING EVENT in Scottsdale, Arizona. CONTACT: 954-540-1896; https://aampconferences.com/

JUNE 1-4: MEDICINES FROM THE EARTH HERB SYMPOSIUM in Black Mountain, North Carolina. CE credits available. CONTACT: 541-482-3016; http://www.botanicalmedicine.org

JUNE 9-10: 5th ANNUAL SIBO SYMPOSIUM at National University of Natural Medicine in Portland, Oregon. Contact: nunm.edu/ce

JUNE 14-16: HOMEOPATHY RESEARCH INSTITUTE CONFERENCE in London, United Kingdom. CONTACT: https://www.hri-research.org/

JUNE 16-23: CLINICAL & COMPARATIVE MATERIA MEDICA with Dr. Subrata K. Banerjea at Allen College of Homeopathy in Chelmsford, Essex, United Kingdom. CONTACT: http://www.homeopathy-course.com/index.php/training-courses

JUNE 20-23: SOCIETY OF PROGRESSIVE MEDICAL EDUCATION (SOPMed) INTEGRATIVE THERAPY TRAINING AND ANNUAL CONVENTION in Colorado Springs, Colorado. Includes pre-conference events. CONTACT: 517-242-5813; https://sopmed.org/

JULY 6-8: 5th INTERNATIONAL CONGRESS ON NATUROPATHIC MEDICINE – Promoting Excellence in Natural Medicine in London, United Kingdom. CONTACT: + 44 (0)1745 828 400 Email: secretariat@icnmnaturopathy.eu; http://icnmnaturopathy.eu/en/

JULY 7: LDN 2018 CONFERENCE in Glascow, Scotland, UK. CONTACT: https://www.ldnresearchtrust.org/conference-2018/

JULY 12-14: INSTITUTE FOR FUNCTIONAL MEDICINE – HORMONE APM in Portland, Oregon. CONTACT: 800-228-0622; https://www.ifm.org/

JULY 12-14: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS (AANP) ANNUAL CONVENTION AND EXPOSITION in San Diego, California. CONTACT: http://www.naturopathic.org/aanp2018

JULY 13-15: METHYLATION 2018 SUMMIT – Integrating Methylation into Clinical Treatment Plans in Chicago, Illinois. CONTACT: 800-755-3402; https://www.methylation2018summit.com

JULY 15-17: INSTITUTE FOR FUNCTIONAL MEDICINE – ENERGY APM in Portland, Oregon. CONTACT: 800-228-0622; https://www.ifm.org/

JULY 21: GENETICS IN CLINICAL PRACTICE WORKSHOP in Portland, Oregon. CONTACT: https://kashilab.com/core-training/

JULY 23-24: INTERNATIONAL MEETING ON TRADITIONAL AND ALTERNATIVE MEDICINE in Osaka, Japan. CONTACT: https://www.meetingsint.com/conferences/traditional-medicine

AUGUST 4-5: THE GREAT PLAINS LABORATORY, INC. presents GPL ACADEMY PRACTITIONER WORKSHOPS in Denver, Colorado. This workshop will review organic acids testing, toxic chemical testing, and mycotoxin testing. CONTACT: http://www.GPLWorkshops.com

AUGUST 10-12: INTERNATIONAL HYPERBARIC MEDICINE CONFERENCE & EXPO – ADVANCING HYPERBARIC MEDICINE GLOBALLY in Denver, Colorado. CONTACT: https://www.hyperbaricmedicalassociation.org/conference-agenda

AUGUST 24-26: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING For Doctors, Dentists & Health Professionals: Detecting Chronic Diseases & Causes with Simon Yu, MD, in St. Louis, Missouri. CONTACT: http://www.preventionandhealing.com/

AUGUST 27-29: 3rd INTERNATIONAL CONGRESS ON RESTORATIVE AND ALTERNATIVE MEDICINE – Ancient Herbal Wisdom for Modern Day Healing in Paris, France. CONTACT: https://restorativecongress.conferenceseries.com/

SEPTEMBER 1-3: 46th ANNUAL CANCER CONVENTION in Glendale, California. CONTACT: 323-663-7801; http://cancercontrolsociety.org/

SEPTEMBER 6-9: 9th INTEGRATIVE MEDICINE FOR MENTAL HEALTH CONFERENCE (IMMH) in Dallas, Texas. Evidence-based diagnostic and treatment options to reduce symptoms of autism, ADHD, depression, anxiety, Alzheimer's, and more. CONTACT: http://www.IMMH2018.com

SEPTEMBER 7-9: INTERNATIONAL CONFERENCE ON CHRONIC PATHOLOGIES in Antwerp, Belgium. CONTACT: https://chronic-pathologies.com/

SEPTEMBER 8-9: BUHNER METHOD OF HEALING LYME AND COINFECTIONS with clinical herbalist Julie McIntyre in Halifax, Nova Scotia. Learn updated protocols from Stephen Buhner's esteemed colleague. CONTACT: eastcoastnaturopathic@gmail.com

SEPTEMBER 14-15: CLINICAL MITOCHONDRIAL AND ENVIRONMENTAL MEDICINE in Heidelberg, Germany. Specialist lectures in English. CONTACT: info@mito-medizin.de; http://www.mito-medizin.de/

SEPTEMBER 14-23: KLINGHARDT ACADEMY LYME & LIGHT MASTERMINDS in Kenmore, Washington. With Neural Therapy-Autonomic Response. CONTACT: 908-899-1650; info@klinghardtacademy.com; http://www.kinghardtacademy.com

OCTOBER 17-22: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE – An Orthomolecular Approach to Cancer in Minneapolis, Minnesota. CONTACT: http://icimed.com/

OCTOBER 19-20: DERMVEDA INTEGRATIVE SKIN CARE SYMPOSIUM in Sacramento, California. CONTACT: http://2018.integrativeskinsymposium.com/

OCTOBER 19-21: AMERICAN INSTITUTE OF HOMEOPATHY ANNUAL CONFERENCE – TACKLING PATIENTS WITH SEVERE PATHOLOGY with Andre Saine, ND, in Cleveland, Ohio. CONTACT: https://homeopathyusa.org/education/2018-conference.html

OCTOBER 25-27: INSTITUTE FOR FUNCTIONAL MEDICINE – GASTROINTESTINAL APM in Nashville, Tennessee. CONTACT: 800-228-0622; https://www.ifm.org/

JANUARY 9-13: 16th ANNUAL NATURAL SUPPLEMENTS: AN EVIDENCE-BASED UPDATE in San Diego, California. CEs available. CONTACT: http://www.scripps.org/naturalsupplements

FEBRUARY 15-17, 2019: 8th ANNUAL OncANP NATUROPATHIC ONCOLOGY CONFERENCE in San Diego, California. CONTACT: https://oncanp.org/

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Classified Advertising

Tenth International Medical Conference
Curing the Incurables

Dental Problems

- Nick Meyer, DDS, *Cavitations, MARCoNS, & Other Microbes: A Clinical Journey*, analyzed infected root canals in collaboration with Dr. Ritchie Shoemaker.
- Doug Cook, DDS, *Dental Energy*, presented cases of serious health problems found by bioenergetic testing, and how they resolved after successful dental treatment.
- Martin McClure, DMD, *Biological Dentistry and Integrative Medicine*, 80 percent of health problems can be traced to the mouth: mercury, focal infections, structural issues.
- Michael Rehme, DDS, *Fundamentals of Biological Dentistry: Fact or Fiction*. The key is to evaluate each patient individually; patients vary in their adaptive capabilities.
- Stewart Moreland, DMD, *Mucosal and Bone Pathology: The Road Less Travelled,* gave a global research tour of reactions to medical and dental materials,
- Michael Gerber, MD, MD(H), *Removing Environmental & Metabolic Toxins,* on using orthomolecular medicine. The hardest sell in show business – taking out teeth.

Fungus and Parasites

- Doug Kaufmann, *The Fungal Etiology of Cancer,* described his Cancer Hypothesis: fungal and human DNA merge to form cancer cells. www.knowthecause.com.
- Christine Salter, MD, DC, *Case Studies*, said IL-12, which plays a key role in activating natural killer cells and inhibiting angiogenesis, is inhibited by mycotoxins.
- Lee Cowden, MD, MD(H), *Chronic Fungal Dis-ease*, reviewed treatments, skull adjustment, and the need to treat both the home and the body.
- John Trowbridge, MD, *Death By Doctor: Can You Blame Those Who Don't Know?* To get better, focus on: Who eats whom? These microbes are parasites.
- Antonio Jimenez, MD, ND, CNC, *The Pathogenic Sphere of Cancer* and microbes with characteristics similar to fungi, cell wall deficient bacteria, pathogens, parasites, viruses.
- Dietrich Klinghardt, MD, *Toxic Metal Contaminated Terrain: Breeding Place for Pathogens & Parasites,* on Lyme and coinfections; his treatment approach.

We cannot solve our problems with the same thinking we used when we created them, and we must work together. I invite you to my next Acupuncture Meridian Assessment (AMA) Training Seminar, August 24-26, 2018, in St. Louis, Missouri.

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Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Curcumin-Boswellia for Osteoarthritis

Osteoarthritis is the most common form of arthritis, and women have much higher rates than men. Women face a quadruple threat for osteoarthritis: hormones, biology, a genetic predisposition and, more recently, obesity.

About 60% of the 27 million individuals in the US that have arthritis are women. Prior to age 55, more men tend to have arthritis but after age 55, women catch up and then surpass the number of men.

Biologically, women's tendons are more elastic causing the joints to have more motion, and the pelvis is wider, putting more stress on the knees. Hormonally, estrogen protects cartilage (the cushion between the joints) from inflammation and then after menopause the estrogen declines naturally, leaving the cartilage more vulnerable to inflammation and thus degeneration. Genetics also play a role in osteoarthritis with the disease running in families and a particular genetic link in women, even at the same locations as their mother. In more recent years, obesity statistics show that more women than men are obese or severely obese. Extra body weight puts more stress on the joints with increasing pressure on the cartilage and faster wear. More abdominal fat puts more pressure on the lower joints.

All this is to say that we need many tools to prevent and treat osteoarthritis. One tool is the use of botanicals and one of the most studied botanicals for osteoarthritis is turmeric. In the study published in early 2018, a curcumin product was compared to curcumin plus boswellia and compared to placebo. A curcumin 500 mg capsule, containing 333 mg curcuminoids was given three times daily for 12 weeks to one group. Another group was given a 500 mg capsule three times daily containing 330 mg curcuminoids and 150 mg boswellic acid, also for 12 weeks. A third group received placebo. Research participants had osteoarthritis of the knees.

Both preparations, whether curcumin alone or the curcumin-boswellia combination were favorable compared to placebo after only three months of continuous use in men and women with osteoarthritis of the knees. The combination produced was significant compared to placebo in both physical performance tests and pain and function scores, including morning stiffness, limited function and disease severity while the curcumin-only product was superior to placebo in physical performance tests only.

Commentary: Curcumin results from many clinical studies, animal studies and in vitro studies demonstrate beneficial effects in treating chronic inflammation. The ability to affect inflammation is through various enzymes, transcription factors, growth factors, cytokines and other genes. Curcumin appears to be the most studied botanical for its anti-inflammatory and disease-modulating effects on osteoarthritis. Rheumatoid arthritis has also been improved by curcumin in at least one clinical trial. The results of the current study showed that after 12 weeks of use of a curcuminoid product or in combination with boswellic acid, improvement in pain-related symptoms, and function can be improved although the combination of the two plants is more effective.

Haroyan A, et al. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. *BMC Complementary and Alternative Medicine*. 2018; 18:7

Premenstrual Syndrome – Comparison of Chamomile to Mefenamic Acid

The purpose of this study was to compare the effects of chamomile extract and mefenamic acid (MA) on the severity of symptoms of premenstrual syndrome (PMS). The participants, initially 118 women, were randomly divided into the two groups with 59 in each. One group received chamomile capsule 100 mg three times a day from day 21 until the onset of the menstrual period, and for two cycles. Group two receive the MA capsules of 250 mg three times a day and again, from day 21 until the first day of the menstrual period, for two cycles. Of the 118 in the study, 11 women for the chamomile group and 8 from the MA group were excluded from the study due

to non-compliance issues in the first stage of treatment. In the second stage of treatment, three from the chamomile group and six from the MA were excluded due to improper use of the capsules (chamomile group) or from GI disorders (MA group). That left 90 women, with 45 in each group, to complete the study and be evaluated.

Women studied were Iranian college students in Iran, single, ages 18-35, of normal body mass index, regular menstrual cycles with a diagnosis of PMS and who did not have chronic mental or physical illnesses. Women also had to not be on medications such as hormones, anti-depressants, aspirin or warfarin, as well as no vitamins and herbs. They also had to have no previous herbal allergies, no sad life event occurrence or operation in the last six months and could not be a professional athlete. Each woman had to have at least five symptoms based on the DSM-IV for PMS diagnosis. Women were excluded if they had any drug allergies, improper use of taking capsules, taking medications during the study, or developing a significant disease during the study.

The mean values of severity of general physical and psychological symptoms in the premenstrual period were similar between the two groups prior to the onset of the treatment. The mean reduction in overall intensity of symptoms after the two courses of treatment was significantly different between the two groups, and the chamomile was modestly more effective, after the treatment of two cycles. Specifically, the reduction of psychological symptoms was more effective with chamomile, and there were similar results in the relief of the physical symptoms between the two groups. The results also indicated that the chamomile was more significantly effective for anger and irritability, and mefenamic acid was more effective for arthralgia, muscular aches, and abdominal and pelvic pains.

Commentary: PMS is one of the most common problems in reproductive-age women with a prevalence of 62.4% to 83.1%. The most frequent physical symptoms of PMS include abdominal bloating, fatigue, breast tenderness, and headache. The common behavioral and psychological symptoms include irritability, anger, depression, increased appetite, and loss of concentration. PMS symptoms start any time after ovulation and then end with the onset of menses or towards the end of menses. In other studies, chamomile has been found to be effective against anxiety and anger.

It is interesting that the treatment cycle was only seven days, which is certainly more economical for individuals. However, for those women with more severe intensity and longer duration of PMS symptoms – from ovulation through the end of the cycle – I would likely give the chamomile all month long, or at least the two-plus weeks.

Sharifi F, et al. Comparison of the effects of Matricaria chamomile (Chamomile) extract and mefenamic acid on the intensity of premenstrual syndrome. *Complementary Therapies in Clinical Practice*. 2014;20:81-88

Women's Health Update

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Chamomile Cream for Episiotomy Pain

This triple-blind clinical trial was done on 114 women admitted to a hospital in Iran. A cream made of chamomile extract was made by crushing 60 gr of crushed chamomile and then extracted with 70% alcohol. The solvent was then removed by rotary evaporation and a 1.3% cream was made of the combination of the chamomile extract with cold cream and placebo cream. After expulsion of the placenta and episiotomy repair, patients were given either the chamomile cream or placebo cream two hours after episiotomy and rubbed 0.5 gm of the cream on the stitches every 12 hours for 10 days. Pain in the perineal area was evaluated immediately before applying the cream, 12 hours after the complete repair of the episiotomy on days 1, 7, 10, and again on day 14 if there was any moderate to severe pain on day 10. Women complete the short form McGill Pain Questionnaire to assess episiotomy pain. The questionnaire consists of three parts: 1) sensory-emotional-verbal descriptions from painless to severe pain 2) Visual Pain Scale 0=10 3) pain intensity from painless to severe pain. The total score of pain is equal to the total score obtained in almost all categories in the different aspects of the pain, which is a range of 0-60 scores.

Primiparous, 18-35 y.o. women were included if they had a vaginal delivery with episiotomy, were living with their husband, had a BMI of 19.8-30.0, were without any disease that affected wound healing, were not using drugs affecting wound healing, had a single pregnancy with a cephalic vaginal delivery, a lack of a vaginal or vulvar infection, no rectocele or cystocele grade 2 or higher, no septum or mass in the vagina, no problematic obstetrical history, no use of sedatives for four hours prior to delivery, and no history of vaginal or perineal reconstructive surgery. In the end, 98 women completed the study.

The questionnaire analysis was conducted on 48 women in the control group and 50 in the chamomile group. Comparing scores of 17 McGill Pain Questionnaire variables, there was no significant difference between the two groups before the intervention, at 12 hours after episiotomy recovery, and the first day after delivery. However, on day 7, 10, and 14 after delivery, episiotomy pain was significantly different between the two groups. Comparison scores revealed that episiotomy pain intensity in women treated with chamomile cream was decreased on the seventh day, tenth day, and fourteenth day after delivery compared to placebo. When considering sensory components of episiotomy pain, the irritant pain was significantly better in the chamomile group on days 7 and 10 after delivery, the heaviness sensation was better on day 7 in chamomile users vs placebo, and the emotional components of pain were significantly better in the chamomile group on day 10 after delivery. The mean pain score on day 7 after delivery for chamomile was 11.36 vs 14.88 in the placebo group. The mean pain score on day 10 after delivery for chamomile was 7.10 vs 9.86 for placebo. In addition, the need for prescription and over-the-counter sedatives/analgesics was decreased in the chamomile group compared to the placebo group.

Commentary: While the results of this study indicate that using chamomile cream did not reduce pain within 12 hours after episiotomy recovery of day 1, it did reduce all measurements by day 7. The authors of the study point out that this study many not have used a potent enough amount, especially important in the first 24 hours after delivery. I would recommend more robust dosing especially within the first 24 hours when the greatest need for pain management occurs. Dosing can be increased by both frequency, (consider four times daily vs only twice), and by a more concentrated product.

Aradmehr M, et al. The effect of chamomile cream on episiotomy pain in primiparous women: A randomized clinical trial. *J Caring Sciences*. 2017;6(1): 19-28.

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➤ *continued from page 96*

To which I responded;

> *Thank you kindly for your reply. I will contact the medical school as you suggested.*
>
> *To answer your question, I have an M.S. in biochemistry (Emory University, 1975) and an M.D. from the University of Maryland (1979). I helped develop the nutritional medicine curriculum for Dr. Andrew Weil's Integrative Medicine fellowship program at the University of Arizona. Also, many physicians use my self-published Nutritional Medicine textbook on a daily basis in their medical practices. However, my nutrition education is primarily self-taught (having reviewed about 75,000 journal articles over the past 40 years and practiced "nutritional medicine" for 19 years). In that respect, I may not have acceptable credentials; kind of a Catch 22 since academia does not teach or officially recognize much of what I would teach. And yet, a large body of published research and a growing number of practitioners are doing this kind of work, and many medical students would like to learn about it.*
>
> *A couple of examples of what I call "nutritional medicine:"*
>
> *In over half of migraine patients, "hidden" food sensitivities (separate from vasoactive amines) are the main cause of migraine recurrences, and identifying offending foods (via an elimination diet followed by individual food challenges) can prevent recurrences. This has been reported in the medical literature about a dozen times in the past 100 years, but conventional medicine does not generally consider hidden food allergy in the evaluation and management of migraine.*
>
> *A patient presenting to my clinic with a 3-week history of viral pneumonia received an intravenous infusion of 50 grams of vitamin C, and became permanently symptom-free within 90 minutes.*
>
> *Perhaps one should not call this type of work "nutrition." However, I believe it should be an integral part of an internal medicine program, so I will pursue that avenue with the medical school.*
>
> *Again, thank you for your kind response.*

To which she replied:

> *No, academia does not teach nor recognize what you call nutrition. I teach strictly Evidence Based Medicine. Sorry, but I'm not sure what journals you read. Probably not published by scientists from Harvard, Cornell, Tufts, or Duke. Best wishes. [redacted] Medical School would probably love you, because they have been all about keeping the medical students happy and "entertained," not about educating them properly. I call your "nutritional medicine" [expletive deleted].*

My next step is to contact the medical school directly. Hopefully, the authorities there will not view their credentials as a license to remain close-minded; and hopefully they will allow me to "entertain" their students.

Alan R. Gaby, MD

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Academia Still Has Eyes Wide Shut

When I first became interested in "alternative medicine" in the early 1970s, the idea that dietary modifications and nutritional supplements could be an effective treatment strategy for many health conditions was considered crazy. Pioneers like Linus Pauling, Abram Hoffer, Roger Williams, and Carlton Fredericks who were advocating this approach were generally either ignored or ridiculed. Since that time, thousands of studies have been published that support the safety and efficacy of nutritional therapies. During the same time, interest in what is variably called "integrative medicine," "orthomolecular medicine," "holistic medicine," or "functional medicine" has increased exponentially. The greater acceptance of this approach to healthcare is evidenced by the growing number of institutions that are offering postdoctoral fellowships in integrative medicine; by the recent recognition of integrative medicine as a medical specialty by the American Board of Medical Specialties; by the proliferation of masters-degree nutrition programs that emphasize the integrative approach; by the growth of the naturopathic profession; and by the growing public interest in alternatives to drugs and surgery.

One of my long-time dreams has been to see nutritional medicine incorporated into mainstream medical education. Considering the large body of scientific evidence and the substantial public interest, I recently concluded that the time was right to try to turn that dream to a reality. I therefore approached one of the medical schools on the east coast to see if they might be interested in my teaching an elective course or presenting a seminar on nutritional medicine. Not knowing whom to contact, I wrote to the physician who is the course director for a basic-nutrition class taught to second-year medical students. My letter was as follows:

Dear Dr. [redacted],

I am a physician who specializes in the use of dietary modifications and nutritional supplements as a primary modality for the treatment of many conditions that are encountered in a family practice setting. This treatment approach has been referred to by various names, including "orthomolecular medicine" and "integrative medicine." While still considered controversial, there is a large body of evidence supporting its use. For example, the textbook I authored (Nutritional Medicine, now in its second edition) cites over 16,000 references.

I am writing to see whether [redacted] Medical School might be interested in my teaching an elective course or presenting a seminar to medical students and others who are interested in this field.

Best regards,
Alan R. Gaby, M.D.

To which the doctor replied:

Hello. If you are interested in teaching an elective course, you should contact the medical school directly. Where did you study nutrition? The medical school may want credentials like a Ph.D. in nutrition or certification as a Nutrition Specialist through the American College of Nutrition before they would let you teach nutrition.

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Our unique scientific process turns elemental mineral forms into easily digested and absorbed nutrients

1 Start with high quality raw materials
We use only the best food grade minerals

2 Select quality organic ligands
Our organic glycine ligands have the ideal molecular structure and size

3 Use patented chelation and bonding technology
Our minerals are fully reacted to form the most bioavailable and stable ring structure

4 Employ proven manufacturing processes
We carefully control reaction conditions to ensure each mineral form is fully chelated

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We use FT-IR spectroscopy to guarantee each batch has our signature chelate ring structure

6 Continue research and development
We dedicate extensive resources to ongoing research and educational efforts

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Clinically Tested & Patent Protected Strains of the Predominant Vaginal Microflora

1. *L. crispatus* LbV 88
2. *L. jensenii* LbV 116
3. *L. gasseri* LbV 150N
4. *L. rhamnosus* LbV 96

Unlike the intestinal flora, the predominant vaginal microbiome are confined to much fewer species. Accordingly, only a few such vaginal specific *Lactobacillus* strains have been clinically tested for their ability to support vaginal health.*

Jarro-Dophilus® Women contains the four predominant *Lactobacillus* strains of the healthy vaginal tract known as the "Astarte" strains. All four Astarte strains were originally isolated from the vaginal tracts of young, healthy women in their third month of pregnancy. The samples were enumerated for the predominant strains and then screened for efficacy. The Astarte strains have been clinically documented to promote vaginal microflora and urinary tract health.*

Clinical Study #1 (1999)

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

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

Clinical Study #2 (2007)

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

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

Clinical Study #3 (2014)

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

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

Clinical Study #4 (2016)

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

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

ASTARTE

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