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Top/Left: Jonathan Collin, Sam Collin, Jeff Wellington
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From the Publisher

Dr. Gervasio Lamas on the Trial to Assess Chelation Therapy (TACT)

There was a time not too long ago when the practice of chelation was considered to be quackery. It was a line in the sand – physicians either practiced acceptable or unacceptable medicine – and because chelation did not dramatically and immediately reverse atherosclerotic disease, it was considered unacceptable. Those physicians who did practice chelation faced censure, hassle with the insurance companies, big-time harassment with Medicare, and investigation by county medical societies and state medical boards. Quackbusters like Victor Herbert, MD, denigrated and vilified chelationists; talking about one's chelation practice at a social gathering or medical meeting was met with stares of disbelief and repugnance. Yet it was in this alienated milieu of "us" versus "them" that chelating physicians persisted in treating patients. Of course, not a few chelating physicians embraced other approaches that were even more controversial – the most contentious and criticized were unconventional cancer diets and protocols. The *Townsend Letter* was founded in 1983 to provide a forum for practitioners to discuss treatments when journals and news media were unwilling to provide such a platform.

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Letter from the Publisher

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Dr. Gervasio Lamas, MD, chairman of medicine at Miami's Mount Sinai Medical Center as well as professor of medicine at Columbia University School of Medicine, was the first investigator willing to do a large scale, double-blinded study of EDTA chelation for atherosclerotic coronary artery disease. Lamas is a graduate of Harvard Medical School and spent 15 years at the Brigham and Women's Hospital in Boston as a cardiology attending, professor, and researcher. He was willing to put chelation to the test using the resources requisite for an NIH-funded study, inviting the best in the chelation community to contribute to designing the trial. After 10 years TACT was completed and the positive outcome was celebrated by Lamas and the chelation community. Despite naysayers' efforts to downplay the study and its outcome, the American Heart Association categorized chelation with an evidence-based grade of B. This was a total about-face from the nasty anti-chelation opinion that was promulgated through the 1970s-2000s. Lamas writes in this issue that he has now received an NIH grant of $30 million for TACT2. And in the future, he is considering a TACT3 for which he would like our participation.

Cover Article: Ketamine for Depression

Integrative and naturopathic physicians strive to prescribe less drugs, using food as medicine. As Dr. Jacob Schor extols in this issue, we should ask our patients to turn off the TV, get off the couch, and amble through the woods. The old-time naturopaths treated patients with hydrotherapy – good old cold water, as a shower or a bath – and had many a remarkable cure. Even conventional medicine now recognizes the value of tuning "out" the noise through meditation and engaging movement in the healing process through yoga or t'ai chi or dance. But for some patients who suffer with mental illness, the natural prescription may not be enough. Too often the very depressed are extremely fatigued, spending their days couch-bound, dispiritedly brooding over what could help and who they should see. Despite the acclaimed help that SSRIs have offered during the past three decades, many depressed individuals remain listless, unmotivated, caught up in poor sleep and dark emotional pits. Newer pharmaceuticals have been touted to overcome Prozac and Zoloft's shortcomings, but frequently their adverse effects are severe with minimal benefit. Moreover, depression leads to suicidal thinking and suicide itself – the suicide rate in the young and middle-aged has been dramatically increasing. What else is there?

Could depression be addressed with a repurposed drug? A drug is patented and receives FDA approval for a specific

continued on page 6 ➤

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Letter from the Publisher

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medical condition; a repurposed drug is one that is utilized for an unrelated condition. One of the earliest repurposed drugs was thalidomide, originally developed and approved as a sedative; it led to a horror show when it was prescribed to pregnant women who gave birth to infants having deformed upper limbs. However, in the 1960s thalidomide was discovered to be quite effective in the treatment of leprosy, a disease that had limited treatment options. Since that time repurposing has been an ambitious affair with a wide variety of drugs being used in the treatment of parasitic disorders, cancer, and autoimmune disorders. Repositioning medicines is slightly different; it seeks to "reposition" an agent which previously failed to successfully treat a disorder. Ketamine is an anesthetic drug and is widely used in many surgical operations. Notably, ketamine has a well-established profile of altering a person's mental state. Could repurposing ketamine be the next answer for depression?

Our cover story, written by family physician Erica Zelfand, ND, makes just that argument. She cites the story of a male soccer player who tore his ACL and required arthroscopic surgery necessitating anesthesia using ketamine. After he awoke from his surgery, he was amazed to discover that his life-long depression had entirely lifted. He enjoyed ten days of blissful normalcy and then sank back into the darkness of depression. Ketamine appears to impact depression when other therapies have failed, claiming a success rate of 60-70%.

What is the mechanism of how ketamine works? It does not work with serotonin, norepinephrine, or dopamine. Instead, Zelfand reports ketamine directly antagonizes the N-methyl-D-aspartate receptor (NMDAR) leading to an increased level of glutamate. Ketamine has been established to reduce pain and opioid tolerance. Its activity on the NMDAR receptor is thought to be responsible for its "dissociative, anesthetic, amnesic, and hallucinatory properties."

One woman who consulted with Dr. Google learned about ketamine's supposed anti-depressant and anti-anxiety activity. Seeking medical help, she was discouraged that her community physicians were not experienced with using ketamine for depression. She acquired a supply of ketamine and snorted it at home while being observed by a friend. She explained to Dr. Zelfand that she "fell into a 'K-hole.'" K-hole is "slang for the detached feelings and loss of motor control that accompany a moderate to high dose of ketamine." She had "mystical visions while under the influence of the drug." Two weeks later she described to Zelfand how she was able to put her life together in a way that was totally beyond her capability weeks and months earlier. She was able to discontinue without difficulty the Ativan she had been using daily for anxiety.

continued on page 8 ➤

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➤ *continued from page 6*

Furthermore, the patient was looking forward to making dramatic life changes that would have been unthinkable before the ketamine. Note: Zelfand definitely is not in favor of self-administration of ketamine. If this appears to have similarity to the hallucinatory aspects of LSD, mescaline, and other drugs, yes, there is that resemblance. However, while an LSD trip is often prolonged, 24 hours for example, ketamine "visions" are more typically present for one-to-two hours. Of course, ketamine administration requires careful in-office observation and monitoring. But not all protocols lead to mystical visions; the most common approach involves a lower dose administered intravenously over 40-60 minutes, typically without manifesting any mystical visioning.

Is this the road we should begin to travel in the treatment of depression and anxiety? Zelfand would say, yes, but she also incorporates nutrition, naturopathic support, orthomolecular medicine, and natural healing supports. Ketamine is best not used alone. Ketamine treatment may work better if it is administered at the same time the patient is being given psychotherapy counselling. Given the likelihood that some patients will experience mystical visions, physicians intending to administer ketamine need to be well versed in its application and safety measures. Despite claims that ketamine use is a fad, it deserves consideration in all patients who have had protracted, unsuccessfully managed mental illness.

Point and Counterpoint: Urinary Mycotoxin Infection vs Chronic Inflammatory Response Syndrome (CIRS) in Patients Exposed to Water-Damaged Buildings (WDB)

Starting in July 2019, we published a five-part article by Ritchie Shoemaker, MD, et al. on the illness patients face who have been exposed to water-damaged buildings. Shoemaker makes the case that patients exposed to a water-damaged building experience extensive inflammation caused not only by fungus but by a variety of other organisms and chemicals. Inflammation brought about through immune system activation and signaling is directed by epigenetic changes of the RNA. Such inflammatory activity is measurable through appropriate biomarker testing; concurrently RNA modification can be monitored using proteomics and transcriptomics evaluation. Treatment from Shoemaker's vantage point should not be predicated on anti-fungal therapies. Instead, treatment requires well-established protocols seeking to mitigate the epigenetic, RNA-driven sources of inflammation and restoration of normal functioning in affected systems using therapies with documented efficacy. The five-part series (July, August/September, October, November, and December, 2019) is now available on our newly launched website, www.townsendletter.com.

continued on page 10 ➤

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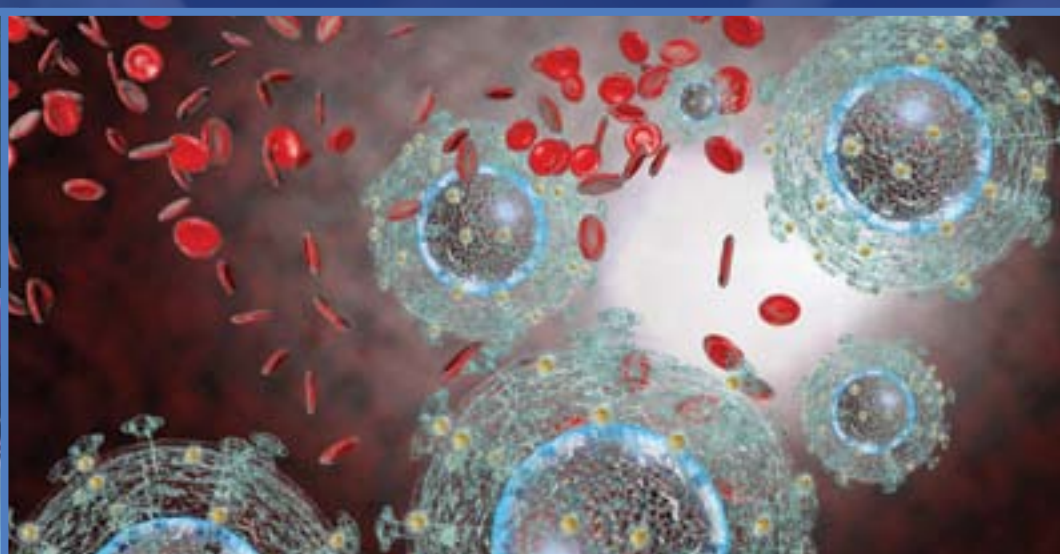

Letter from the Publisher

➤ *continued from page 8*

Matthew Pratt-Hyatt, PhD, and William Shaw, PhD, clinical directors of the Great Plains Laboratory, critique Shoemaker et al.'s article in this issue. They disagree with the assertion by Shoemaker that fungus plays no role in patients made ill by water-damaged buildings. While Shoemaker et al. assert that mycotoxins are not the cause of the symptoms in these patients, Pratt-Hyatt and Shaw argue that the data supporting mycotoxin causation for the illness is well supported diagnostically and therapeutically. Whereas Shoemaker et al. call for testing biomarkers, proteomics, and transcriptomics (genomic testing), Pratt-Hyatt and Shaw call for examining organic acid metabolites and mycotoxins.

Concurrently, we are publishing Shoemaker and David Lark's paper online entitled: "Urinary Mycotoxins: A Review of Contaminated Buildings and Food in Search of a Biomarker Separating Sick Patients from Controls." In the first half they examine the dietary source of mycotoxins; in the second part, they review urinary mycotoxin analyses in patients versus controls. The Shoemaker and Lark article was previously published in *Internal Medicine Review*. To access their article please look on the *Townsend Letter* website www.townsendletter.com and look for it in the January 2020 table of contents.

Please read the Pratt-Hyatt and Shaw critique in this issue and then access the website for the urinary mycotoxin article by Shoemaker and Lark. We would appreciate your feedback on the controversy!

Hyperaldosteronism: A Missing Link for Difficult to Treat Hypertension by Andrea Gruszecki, ND

When I was in medical school, primary hyperaldosteronism was considered a rare disorder. The algorithm I used back then gave limited importance to rare conditions. (Dermatology and ophthalmology are replete with dozens of rare conditions, mostly named after their late 18th and 19th century physician discoverers.) I pretty much gave short shrift to hyperaldosteronism when I would do medical rounds although that would have been a big mistake on course examinations. One of the things about rare pathologies is that they often have dramatic presentations making for very exciting slide presentations at grand rounds. Still when it came to working up a patient with hypertension, primary hyperaldosteronism was not on the top of my list and rarely on the bottom either.

Andrea Gruszecki, ND, who has focused on laboratory assessment and diagnostics, would argue that ignoring mineralcorticoid screening of a hypertensive patient would be a mistake. For one thing, the incidence of primary hyperaldosteronism that once was thought to be less than 1% of the population is now estimated to affect 5-20% of individuals. That really changes the algorithm – considering that the majority of hypertensive patients never get any diagnosis beyond "essential" hypertension. While the workup of hyperaldosteronism focuses on the assessment of serum aldosterone and renin, Gruszecki examines the role of urinary measurement of mineralcorticoids in this issue. We don't think twice about assessment of urinary cortisol – why not equally employ screening of urinary mineralcorticoids? Gruszecki offers natural approaches we may advise for those hypertensive patients with elevated aldosterone.

Jonathan Collin, MD

Shorts

briefed by Jule Klotter
jule@townsendletter.com

Questions from a Real-World Vaccination Program

In a 2019 TEDx talk, Christine S. Benn, MD, discusses "How vaccines train the immune system in ways no one expected." It appears that vaccines have non-specific effects. Live vaccines [oral polio, measles, smallpox (vaccinia), tuberculosis (BCG)] seem to train the immune system to respond to infections that are unrelated to the antigen in the vaccine. In contrast, non-live vaccines appear to increase susceptibility to unrelated infections. Benn and colleagues report in a 2018 study, "...the first studies are now showing that non-live and live vaccines have differential NSEs (non-specific effects) on hospital admissions for infectious diseases in high-income countries." In low-income countries with limited medical resources, these infections can easily lead to death when treatment is unavailable. Using natural experiments with real-world data and randomized trials, Benn and Peter Aaby have documented decreases in mortality when the oral polio vaccine is given with non-live vaccines.

Benn and colleagues conducted studies on the non-live DPT (whole-cell diphtheria, tetanus, pertussis) vaccine, using data from the Bandim Health Project in the capital of the African nation Guinea-Bissau. This health project began conducting and recording tri-monthly weighing sessions for all children in the urban area to identify malnourished children in January 1980. Beginning in June 1981, vaccinations were offered during these weighing sessions. Four health workers encouraged pregnant women in their assigned city sectors to attend an antenatal clinic and maintained records of children's growth patterns and vaccination dates. Children who were sick or weak at a visit were not vaccinated by agreement of the nurse and mother.

In a 2017 Bandim study, led by S. W. Morgensen, all-cause mortality outcomes were compared in babies who received a DPT vaccine between 3-5 months of age to those who were the same age but had not yet received the vaccine: "Children who were just over 3 months old at the time of the tri-monthly weighing session were vaccinated at that age; those who were just below 3 months old would only be vaccinated for the first time at almost 6 months of age." Some of the vaccinated babies also received oral polio vaccine (OPV) drops. While the DPT vaccine did, indeed, reduce incidence of these three diseases, the authors were disturbed to find that all-cause mortality was much higher in the babies who were vaccinated earlier. Children who received DTP (with or without OPV) at three-to-five months of age had an all-cause mortality hazard ratio (HR) of 5.00 (95% CI 1.53-16.3) compared to the control group. The authors state, "The negative effect was particularly strong for children who had received DTP-only and no OPV [HR = 10.0 (2.61-38.6)]. All-cause infant mortality after 3 months of age increased after the introduction of these vaccines [HR = 2.12 (1.07-4.19)]."

In a 2018 study, the researchers used Bandim data to look at children who were older (6-35 months) when given their first DPT vaccine during a "catch-up" program for the children under 3 years who attended the weighing sessions. DTP-vaccinated children had an all-cause mortality risk of 2.14 (1.42-3.23) compared to DTP-unvaccinated children. The negative effect was statistically significant for girls, but not boys: girls (HR = 2.60 (1.57-4.32) and boys (HR = 1.71 (0.99-2.93). The authors say, "The pattern of worse effects for females than for males have turned out to be systematic for several non-live vaccines, including DTP, inactivated polio vaccine, hepatitis B vaccine, pentavalent vaccine, and TRS,S malaria vaccine." The 2018 study, by the way, was supported by a grant from DANIDA (humanitarian aid program from the Danish Ministry of Foreign Affairs) and the Novo Nordisk Foundation.

As Peter C. Gøtzsche, DrMedSci, MSc, former head of Nordic Cochrane, discusses in "Expert Report: Effect of DTP Vaccines on Mortality in Children in Low-Income Countries," the 2017 and 2018 studies from Guinea Bissau are just the latest to show increased mortality in young children who receive the DPT vaccine. Gøtzsche criticized a 2014 WHO systematic review on DTP for downplaying the evidence that this vaccine may be causing more harm than good. DTP is the most commonly used vaccine in low-income countries. The World Health Organization (WHO) recommends three doses of the vaccine and sees such coverage as "the main performance indicator for vaccination programs." Peter Aaby et al say it is

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"illogical" to assess the success of a vaccination program on a vaccine that increases female mortality.

Aaby et al say, "...there is a need for further research to assess the overall mortality effect of DTP and how the negative effects of DTP can be removed or modified." They suggest performing randomized trials to test vaccine schedules to find a protocol that best uses a live-virus vaccine to reduce all-cause mortality from the DPT. In her TEDx talk, Benn suggests that there also may be a need to develop different vaccines for boys and girls. She is concerned that WHO intends to replace the live oral polio vaccine with the non-live vaccine; WHO is reportedly making the change out of concerns that live vaccines shed and can cause the disease to spread.

The current CDC vaccine schedule keeps adding vaccines for individual infections. Using this paradigm and given the number of infectious agents on Planet Earth, that schedule could be endless—with all kinds of non-specific effects. Dr. Benn's observations make me wonder: What if instead of having a vaccine for every infectious illness, we have a few carefully chosen live vaccines, given at the right age, to "train" the immune system to resist many different infections?

Aaby P, et al. Evidence of Increases in Mortality After the Introduction of Diphtheria-Tetanus-Pertussis Vaccine to Children Aged 6-35 Months in Guinea-Bissau: A Time for Reflection? *Frontiers in Public Health.* March 2018;6:79.

Benn CS. How vaccines train the immune system in ways no one expected. TEDxAarhus. January 8, 2019.

Gøtzsche PC. Expert Report: Effect of DTP Vaccines on Mortality in Children in Low-Income Countries. June 19, 2019.

Mogensen SW, et al. The Introduction of Diphtheria-Tetanus-Pertussis and Oral Polio Vaccine Among Young Infants in an Urban African Community: A Natural Experiment. *EBioMedicine.* 2017.

Aspects of Bioenergy Healing

William Bengston, a professor of sociology at St. Joseph's College (Patchogue, New York), has researched bioenergy healing therapies, such as Therapeutic Touch, Reiki, and external qigong, for many years. He helped develop a rapid imaging healing technique (cycling through a series of images that represent end goals while experiencing any emotion) used in combination with a sensation of energy flowing from the hands. When used by volunteers with no belief in hands-on healing, this technique resulted in cancer remission in multiple animal experiments. The technique is based on diverse traditions that claim a person "can free up his or her energy and generate 'power' by witnessing/observing his/her emotions and bodily feelings without attachment."

In a 2010 study, Bengston and Margaret Moga reported that magnetic field oscillations occurred during both hands-on and distant (several hundred miles away) healing sessions at cages holding mice with tumors: "The magnetic field oscillations began as 20-30 Hz oscillations, slowing to 8-9 Hz, and then to less than 1 Hz, at which point the oscillations reverse and increased in frequency, with an over-all symmetrical appearance resembling a 'chirp wave.' The waves ranged from 1-8 milliGauss peak-to-peak in strength and 60-120 seconds in duration." Other researchers have also detected electromagnetic signatures in this type of healing.

In a March 2018 article, Bengston hypothesizes that conscious connection between healer and healee may be unnecessary. Rather, he thinks that healing may be an autonomic response linked to need and has more to do with information than with energy alone. He conducted 16 mice experiments and numerous in vitro cell culture studies with volunteers who were taught his rapid imaging healing technique. These volunteers had no experience or belief in alternative healing. Immune-deficient mice were injected with enough cancer cells to cause death within a few weeks (known from previous research); all formed tumors. Tumors gradually disappeared in the treated mice, which then lived a full lifespan and were immune to re-infection. The more mice in the experiment, the quicker the recovery. Oddly, cells taken from cancer-infected mice that had responded to the healing technique appeared to cure similarly infected mice that were not treated by the volunteer healers. Did the transplanted cells "communicate" how to heal? Bengston says that treating water with healing intent/energy also produced cancer cures in mice.

Research at the University of Connecticut and Thomas Jefferson Medical Schools, using functional MRIs, showed that the brains (primarily towards the back of the frontal lobes) of volunteer healers 'turned on' when they intended to heal; and the same activity occurred in the healee. In another experiment, volunteer healers, while lying in an enclosed fMRI, were given a sealed opaque envelope that contained a picture and hair samples from an animal with cancer or an envelope with a blank index card. "Results clearly indicate that the brains of the volunteer healers 'turned on' only when the envelopes had 'need' expressed in them (pictures and hair samples of cancerous animals)."

Bengston says that the healing process was non-linear and did not conform to the volunteers' conscious desire to prevent tumor growth altogether. He thinks "there is merit to thinking of healing as a non-directed outcome similar to that proposed by Jahn and Dunne." In 2001, R. Jahn and B. Dunne proposed "A Modular Model of Mind/Matter Manifestations" (*J Sci Exploration.* 15(3): 299-329), in which the "conscious mind might connect to the tangible physical world not directly, but by way of a circuitous route involving unconscious processes and intangible physical mechanisms."

Bengston W. Questioning the Importance of Conscious Awareness in Alternative Healing. *Edgescience.* March 2018.

Bengston W. Commentary: A Method Used to Train Skeptical Volunteers to Heal in an Experimental Setting. *J Altern Comple Med.* 2007;13(3):329-331.

Moga MM, Bengston WF. Anomalous Magnetic Field Activity During a Bioenergy Healing Experiment. *J Sci Exploration.* 2010;24(3):397-410.

Heat and Detoxification

"The fundamental principle that governs detoxification is that heat liberates toxins from fats, which then gets flushed out by the sweat and carried off by the blood to the liver, kidney, and GI tract," says Jessica Bonovich, RN, BSN. Gulf War veterans and 9/11 emergency workers, who were exposed to a heavy toxic chemical load, have significantly benefited from the detailed Hubbard protocol for sauna detoxification, according to research; but Bonovich provides a modified sauna

protocol that she feels may be more suitable for most patients.

Before starting a sauna program, patients need to have daily bowel movements and be taking supplements that support liver detoxification and maintain necessary nutrients that can be lost while sweating. Without good elimination, toxic compounds will simply be re-absorbed by the body. Although the pros and cons of various types of saunas have been widely debated, Bonovich points out that any heat source, even heat generated during exercise, can mobilize toxins that are stored primarily in subcutaneous tissue. Some years ago, I made an inexpensive, red-lamp sauna that effectively induces sweating, using Dr. Lawrence Wilson's detailed do-it-yourself plan (found online). It is important to wipe off sweat frequently so that toxins are not re-absorbed through the skin.

In addition to chemicals and heavy metals excreted in sweat, toxins also enter the circulation, moving to the liver, GI tract, and kidneys for eventual elimination. Bonovich recommends that patients take liposomal glutathione (about 400 mg twice a day) with a dose before sauna treatment and one after. Glutathione is an antioxidant and is also used by the liver to breakdown toxic compounds. She also recommends taking vitamins C, E, A, D, and K and monitoring electrolytes (potassium, sodium, calcium, and magnesium) that may be excreted or used up during the process.

To prevent re-absorption of the fat-loving chemicals from the GI tract, Bonovich recommends using bile acid sequesterants (eg, cholestyramine) and binders (eg, bentonite clay, activated charcoal). Christopher Shade, PhD, and Carrie Decker, ND, wrote a comprehensive article, "A Push-Catch System That Enables Effective Detoxification," that discusses the use of bile acids, binders, and more for the *Townsend Letter* (February/March 2018) that is well-worth reading.

Bonovich is cautious about using niacin, which is part of the Hubbard protocol, to induce a greater release of fatty acids (and chemicals bound to them) via a rebound effect. She says high-dose niacin can cause increases in uric acid, prothrombin time, and insulin resistance. Consequently, it may not be appropriate for people with diabetes, a history of gout, or on blood thinners. High-dose niacin also may stress the methylation pathway; "...there are documented cases of hyperhomocysteinemia occurring in patients taking 1000 mg of niacin per day, which is the standard dose for a flush."

"The more time exposed to heat," Bonovich writes, "the more toxins will be liberated, but the body can only do and handle so much of this at once. For this reason, I recommend that when patients are in crisis, they start sauna therapy very slowly and work their way up in time spent per session and how often they do sessions, as they become more tolerant."

Bonovich J. How to Maximize the Benefits of Sauna for Detoxification. December 12, 2016.

Shorts

Glyphosate and Glycine

Over the past year, glyphosate, the active ingredient in the herbicide Round-Up, has attracted much attention as a cause of non-Hodgkin's lymphoma; Monsanto, now owned by Bayer, is facing thousands of lawsuits. But the carcinogenic properties of this chemical, widely used in agriculture, may be just the tip of its adverse health effects. The compound is also a strong chelator, binding to key nutrients and making them unusable by the body; and it is a patented antibiotic that can have negative effects on beneficial bacteria in the GI tract.

In a 2016 paper, Anthony Samsel and Stephanie Seneff report that glyphosate is also a glycine analogue: "Glycine, the smallest amino acid, has unique properties that support flexibility and the ability to anchor to the plasma membrane or the cytoskeleton." Glycine is a major structural component of cells and accounts for 25% of the amino acids in collagen, the most abundant protein in the body. Samsel and Seneff hypothesize that glyphosate may take the place of glycine during protein synthesis, thereby disrupting normal function of associated peptides and proteins. In their paper, the authors report on several protein classes that depend on glycine for proper function and on illnesses related to these proteins.

In a 2016 PowerPoint presentation, Samsel reports that the highest bioaccumulation of glyphosate in animals occurs in bone and bone marrow, the source of gelatin. Gelatin is a rich source of glycine. Every gelatin-containing product that Samsel tested was contaminated with glyphosate. Gelatin is used to make foods (Jell-O, yogurts, ice creams, pastries, gummy candies), gel caps, pharmaceuticals and vaccines. Glyphosate residues are present in virtually all corn, soy, and wheat products and on many other grains and legumes that are sprayed shortly before harvest to facilitate harvest. Choosing organic foods greatly decreases glyphosate consumption.

Samsel A. Glyphosate Herbicide Pathways to Modern Diseases Synthetic Amino Acid, and Analogue of Glycine Misinformation into Diverse Proteins (PowerPoint) 2016.

Samsel A, Seneff S. Glyphosate pathways to modern diseases V: Amino acid analogue of glycine in diverse proteins. *J Biological Physics and Chemistry.* 2016:16:9-46.

◆

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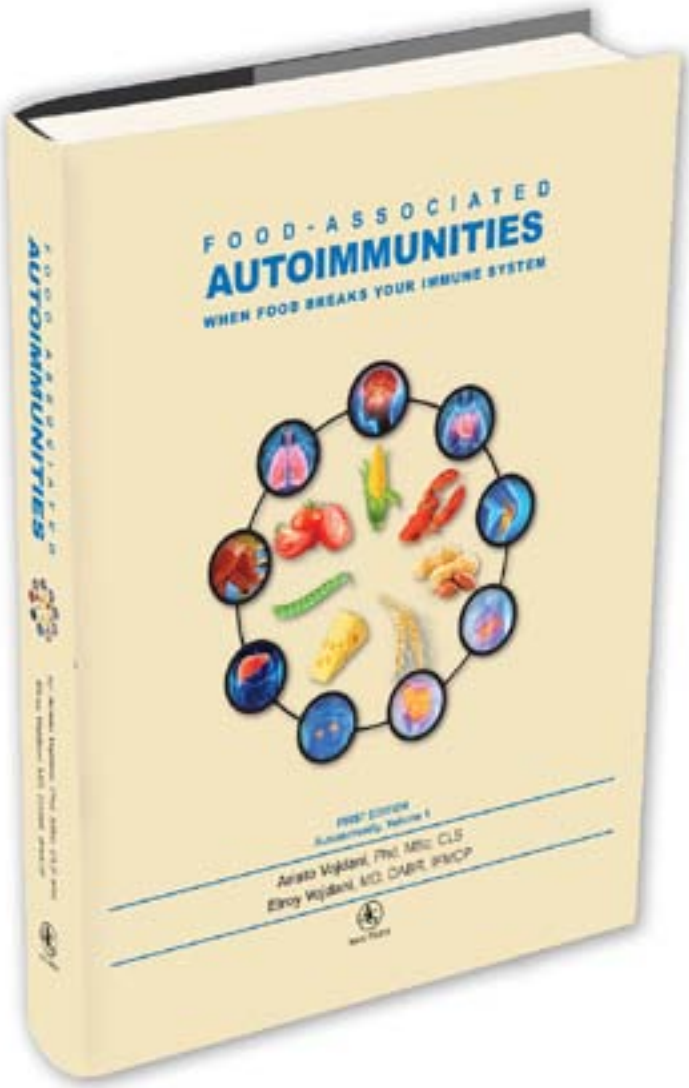

The original inventor of food IgG testing breaks decades of silence regarding the prevalence of innacurate food testing and reporting in many laboratories.

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

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

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

What Clinicians Should Know About Lab Testing: How to Test the Lab and the Test

by Aristo Vojdani, PhD, MSc, CLS

Immunosciences Lab, Inc.

Abstract: Accurate laboratory testing is a vital tool in the field of medicine. Great advancements have been made in lab testing methodology, but sometimes laboratories still get unreliable test results. This article looks at the advantages and disadvantages of the different methods of lab testing: radioimmunoassay, ELISA, Western Blot, Multi-Peptide ELISA, dot blot, and microarray. In comparing these methodologies, we conclude that although each different method has its advantages, all in all ELISA is still the gold standard, as radioimmunoassay uses hazardous materials, the dot blot assay cannot distinguish between equivocals and positives and negatives, and the microarray method, although a reliable technique for the detection of DNA or tumor markers, may suffer from limitations in the detection of antigens or antibodies. This is why for the detection of Lyme disease and many other disorders we prefer ELISA over many other immunological assays. Furthermore, we emphasize that in many cases it is not just the method (be it ELISA or microarray), but also what is used in the method, how it is used, and what sort of standards are followed. The goal of this article is to make the practitioner familiar with the four core principles of antigen-antibody assays: purity, optimization, validation, and replication. Familiarization with these principles will help the practitioners to differentiate between good versus bad lab practices. Otherwise, they will just fall for the next method that is touted as being new and improved, fast and convenient, no matter how grandiose and ridiculous the claims, such as a new hair test for food intolerance, which, for all my 50 years of work and experience, is beyond my comprehension as to how such a thing could actually be offered to people.

Introduction

I have spent half a century working in research and clinical laboratories. For 35 of those years, I have been the owner of my own clinical lab specializing in the field of immunology. I have personally developed more than 300 immunological assays and handled many thousands of blood samples for immunological assessments. In doing all the above I have been fortunate enough to become known as the father of functional immunology. I have been both gratified and honored many times when practitioners have called me to share the results of tests that they had done by other labs. Sometimes I'm surprised to find that the methodologies used for their tests were actually banned decades ago but have been recycled and brought back under deceptive new names.[1] Some practitioners have also asked me why two labs using the same method can get two different results for the same patient, and I have to explain that labs may be using different testing materials, steps, preparations, procedures, parameters and so on, so that comparing test results from different labs could be like comparing apples and sausages, not even apples and oranges. Very recently I found out that there are so-called labs out there purporting to be able to test for food allergies or sensitivities to more than 700 foods using four or five strands of the patient's hair through the wonders of biomagnetic resonance. Apparently, an MRI-like machine reads your hair and is able to tell you if you are allergic to 700-plus foods because your hair can carry 700-plus biomagnetic signatures! Do I have to tell you what this sounds like? Hair doesn't even contain IgE or other antibodies. The goal of this article is to make practitioners familiar with the most reliable method for measuring antibodies in different specimens. The example given in this article is testing for Lyme disease, but the methodology could be applied to any disease.

Methods for Detecting Antigen-Antibody Reactions

The following different methodologies are used for the detection of antibodies: 1) Radioimmunoassay; 2) ELISA; 3) Western Blot; 4) Multi-Peptide ELISA; (MPE) 5) Dot Blot; 6) Microarray. Each of these methods has its advantages and disadvantages. Although Lyme disease is being used as an example here, these methodologies could also be applied to testing for allergies or autoimmunities.

Radioimmunoassay.

This is an in vitro process whereby a radioisotope-labeled antibody is usually added to antigen-coated tubes, microwells, or beads. If the antibody binds to the antigen, a complex is formed, and the radioactivity of the antibody is measured. The measured level of radioactivity is converted to the amount of antibody in the tested specimens. The radioimmunoassay is highly sensitive and specific. This method is also not restricted to merely serum or plasma; any biological material can theoretically be used in a radioimmunoassay. **Obviously, due to the use of radiolabeled reagents, there are potential radiation hazards with this technique**. This often means only specially trained individuals can handle this assay. Laboratories usually need extra licensure to handle this radioactive material as well as special protocols for storing and disposing of this material. Because of the possible exposure to radioactive materials,

continued on page 18 ➤

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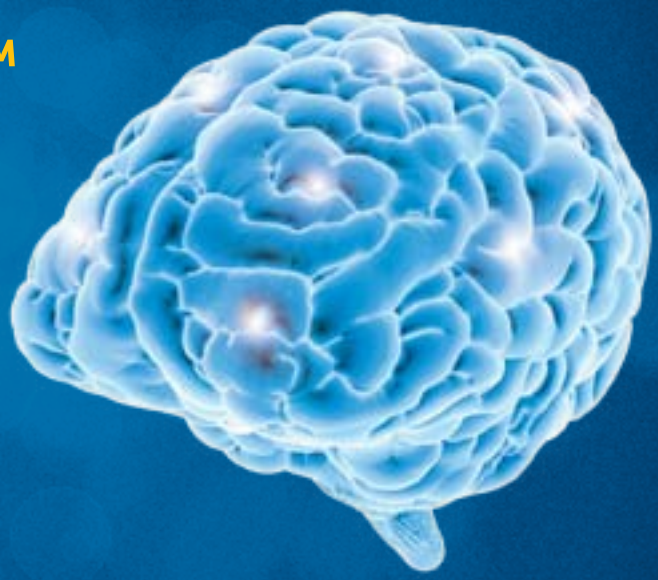

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In this Issue

January 2020 | #438

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➤ *continued from page 15*

no matter how sensitive or specific this method is, many labs have stopped using this type of assay.[2,3]

Enzyme-Linked Immunosorbent Assay (ELISA)

In the ELISA method, enzymes are used instead of radioactive materials. ELISA is a colorimetric assay for accurate measurement of antibodies or antigens in blood and other clinical specimens. ELISA is an analytic biochemistry assay that uses liquid reagents during the "analysis" that will generate a signal that can be easily quantified and interpreted as a measure of the amount of analyte in the sample.[4,5]

Because of its simplicity, reproducibility and reliability, the ELISA method is the internationally recognized gold standard for antibody or antigen testing in the blood or other clinical specimens. It has been the standard for nearly 40 years and has helped form the clinical perspectives of healthcare professionals around the world.

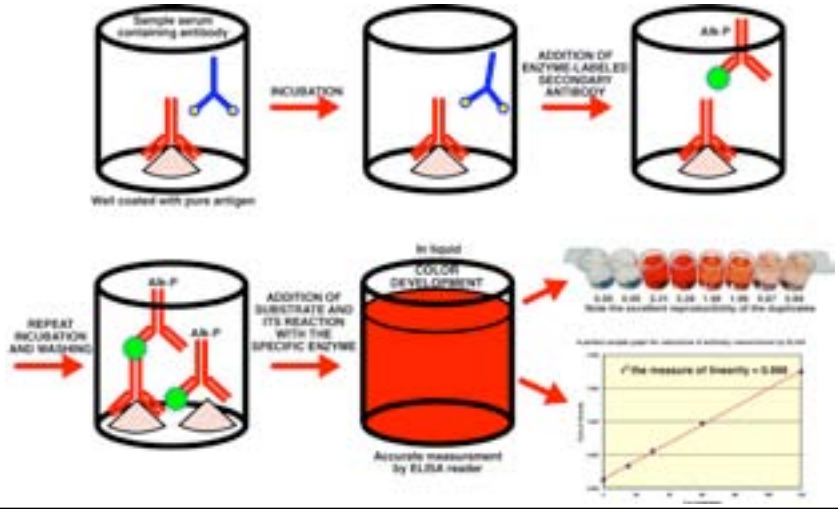
There isn't a modern clinical laboratory today that doesn't use the ELISA or one of its descendants. In the ELISA assay, antigens are attached to the surface of a microtiter plate. Then, the patient's serum is applied over the surface; if an antibody to the antigen is present, it will bind to the antigen-coated well. Then, a secondary antibody that is linked to an enzyme is added. In the final step, a substance containing the substrate to the enzyme is added. The subsequent reaction produces a detectable color that is measured with great accuracy by an ELISA reader. The ELISA technique was conceptualized and developed by Swedish scientists Peter Perlmann and Eva Engvall at Stockholm University in 1971. They were honored for their invention when they received the German scientific award of the "Biochemische Analytik" in 1976.[4] Since then, many improvements have been done to increase the analytical sensitivity and specificity of the ELISA assay. Figure 1 shows the different steps involved in this reliable method.

Measurement of antibody against the agent of Lyme disease by ELISA: a classic example. Prompt diagnosis and treatment of Lyme disease (LD) is the key to avoiding chronic Lyme borreliosis and its serious effects on the human system. Diagnosis can be difficult because symptoms of LD share commonalities with amyotrophic lateral sclerosis (ALS), Alzheimer's, autism, chronic fatigue, fibromyalgia, lupus, Parkinson's, and RA. Therefore, it is crucial to combine clinical symptomatology with the most sensitive technique available to diagnose Lyme disease. Otherwise, if left undetected, Lyme disease may become chronic, and patients may develop Lyme arthritis and neuroborreliosis.

For the detection of Lyme disease, *B. burgdorferi* antigens are usually prepared from spirochetes grown in culture. After centrifugation and washing, the spirochetes undergo sonification to release their major antigens, such as outer surface protein A (OspA), immunodominant protein (C6), leukocyte function associated antigen (LFA), and outer surface protein C (OspC). In this ELISA, pure antigens without any chemical modifications are bound to the surface of a microtiter plate. Then, the patient serum is diluted with a special diluent and added to *B. burgdorferi* antigens bound to the ELISA plate wells. If antibodies to the microbe are present, they bind to the antigen in the coated wells and do not rinse off in the washing process. Subsequently, when enzyme-labeled anti-human IgG/IgM is added, it in turn binds to the immobilized antibodies that have bound with the antigens. After the washing and addition of a chromogenic substrate and stopping solution, samples containing IgG/IgM antibodies to *B. burgdorferi* produce a color endpoint reaction that will be read with an ELISA plate reader, and the results are read quantitatively.[6]

Because antigens prepared from *B. burgdorferi* grown in culture contain many impurities or cross-reactive antigens or peptides, it is possible for false positivity to result with some specimens. Thus, the issue is impurity of the antigen, not the ELISA methodology itself. This is why both the American CDC and European guidelines strongly recommend the two-tier approach. These two steps consist of a sensitive ELISA IgG, IgM, followed by Western Blotting of the samples that were found to be indeterminate (borderline positive) or positive in the first step. However, for patients infected in Europe, the testing should be performed with at least three pathogenic species, such as *B. b. sensu stricto, B. b. garinii,* and *B. b. afzelii,* all of which are part of the Multi-Peptide ELISA (MPE) performed by Immunosciences Lab.[7,8]

Figure 1.
Steps involved in an ELISA assay that generates highly reproducible duplicate test results



Lyme Western Blot Assay

The Western Blot (WB) assay has been widely used to detect the presence of antibodies in human serum and plasma to various infectious disease agents. In this procedure, component proteins of purified, inactivated bacteria or virus are electrophoretically separated by SDS-polyacrylamide electrophoresis followed by electrotransfer to nitrocellulose sheets. Each strip serves as the solid-phase antigen for an ELISA test. Specific antibodies present in human serum/plasma will bind to several of the separated polypeptides upon incubation with the strip. These antibodies are then treated with an enzyme-antibody conjugate that binds to the human antibody, if present. The final

product is visualized upon incubation with a chromogenic enzyme substrate. This will result in a blue-colored "band" at the polypeptide location on the membrane strip if the specific human antibody is present. This assay, which detects *Borrelia*-specific peptide antibodies in human serum, was refined by different investigators who developed the criteria for a better diagnosis of Lyme disease.[7,9]

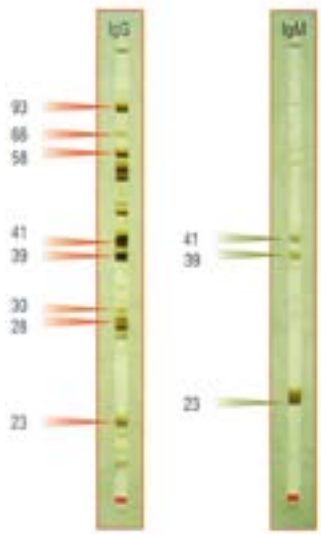
Interpretation of Results. According to the CDC/ASTPHLD working group, an IgG blot is considered positive (reactive) if five of the following ten peptide bands are present: p18, p23, p28, p30, p39, p41, p45, p58, p66, p93. An IgM blot is considered positive (reactive) if two of the following three peptide bands are present: p23, p39, p41. If the IgG or IgM antibodies against the above peptides are negative, the patient is considered non-reactive (see Figure 2).

The advantage of the Western Blot assay is that cross-reactive antibodies are excluded, and antigen-specific antibodies are observed against proteins of different molecular sizes.

The disadvantage is that the antibody reaction with each pure antigen can only be observed qualitatively, or simply a positive or negative, yes or no result.

Another disadvantage of WB is the nature of the antigens used in the assay, which are prepared from *Borrelia* grown in culture. Because antigens prepared from cultured *Borrelia* are not actually representative of the spirochete antigens expressed in the human body, this test may miss the detection of IgG and IgM antibodies against antigens such as variable major protein. Western Blot also does not measure antibodies against the decorin binding protein of *B. burgdorferi sensu stricto, B. garinii, B. afzelii*, and *B.* miyamotoi, and thus is not capable of detecting Lyme arthritis and neuroborreliosis.

Figure 2.
IgG and IgM antibody patterns with different peptides of *Borrelia burgdorferi* in patient confirmed with Lyme disease



In August of 2019 the CDC issued an updated recommendation for the two-tiered testing approach for Lyme disease.[9] Whereas, as stated earlier in this article, the CDC's previous recommendation was that an initial sensitive EIA or immunofluorescence test be followed by a supplemental Western immunoblot assay if the first test were equivocal, the new recommendation is that a second serologic assay using EIA rather than Western immunoblot assay is an acceptable alternative. The CDC made this update upon the approval of the FDA of four previously cleared Lyme disease tests, one of which tests for Variable Major Protein-like sequence E (VlsE), which is only one of the 12 antigens and peptides included in the patented Immunosciences Multi-Peptide ELISA panel.

Multi-Peptide ELISA (MPE)

Multi-Peptide ELISA (MPE) is the most sensitive method for the detection of Lyme disease and other tick-borne diseases (*Babesia, Ehrlichia, Bartonella*). MPE (US Patent 7,390,626 B2) measures antibodies to antigens of *Borrelia* grown in culture (the traditional method), as well as antibodies against antigens expressed *in vivo,* which *Borrelia* uses to invade the immune system during the process of human infection.

The antigenic diversity of *Borrelia burgdorferi* in the host suggests that antigenic variation plays an important role in immune invasion. Multi-Peptide ELISA or MPE uses not only antigens from Borrelia grown in culture but also a technique called *in vivo* induced antigen technology that detects this antigenic variation. This technique identifies pathogen antigens that are immunogenic and expressed *in vivo* during human infection. Utilization of this technique increases the accuracy of the diagnostic process and abridges the time of treatment, resulting in improved quality of care.[10,11]

The MPE uses particular peptides from various components of Borrelia during different cycles, including peptides from outer surface proteins A, C and E, leukocyte function associated (LFA) antigens, immunodominant antigens, variable major proteins, and peptides from decorin-binding proteins of Borrelial subspecies (*B. sensu stricto, B. afzelii, B. garinii, B. miyamotoi*), and co-infections such as *Babesia, Ehrlichia* and *Bartonella.* This test is not only capable of detecting Lyme disease reliably but can also assist in the detection of Lyme arthritis and neuroborreliosis, which are two major manifestations of chronic Lyme disease.

Dot Blot Assays

The immunoblot assay or dot blot is a qualitative variation of the ELISA test that uses impure or a mixture of antigens. Instead of binding antigen to microplate wells, antigen is covalently bound directly to a nitrocellulose or nylon membrane (see Figure 3) and is detected with labeled primary antibody, or indirectly with labeled secondary antibody. The result can only be a positive or negative (yes or no) reaction. **This means this method cannot distinguish between positive, negative, and equivocal, borderline, or weakly positive results.**[12,13] Note that while the dot blot assay can easily distinguish between negative (0 ng) and positive (10 ng), it has more difficulty in distinguishing between 1 ng and 10 ng of antigens that were bound to the matrix.

Microarray Assays

The need to quantify the qualitative results of the dot blot test led to the development of the microarray method, which converts the dot blot signal to a number. A microarray is a high-throughput miniaturized ELISA-based platform for efficient detection of nucleic acids and protein expressions in various types of clinical specimens. It is a 2D array on a solid substrate (usually a glass

➤

Figure 3. Different amounts of antigen give different results.
Note that while the dot blot assay can easily distinguish between negative (0 ng) and positive (10 ng), it has more difficulty in distinguishing between 1 ng and 10 ng of antigens that were bound to the matrix.

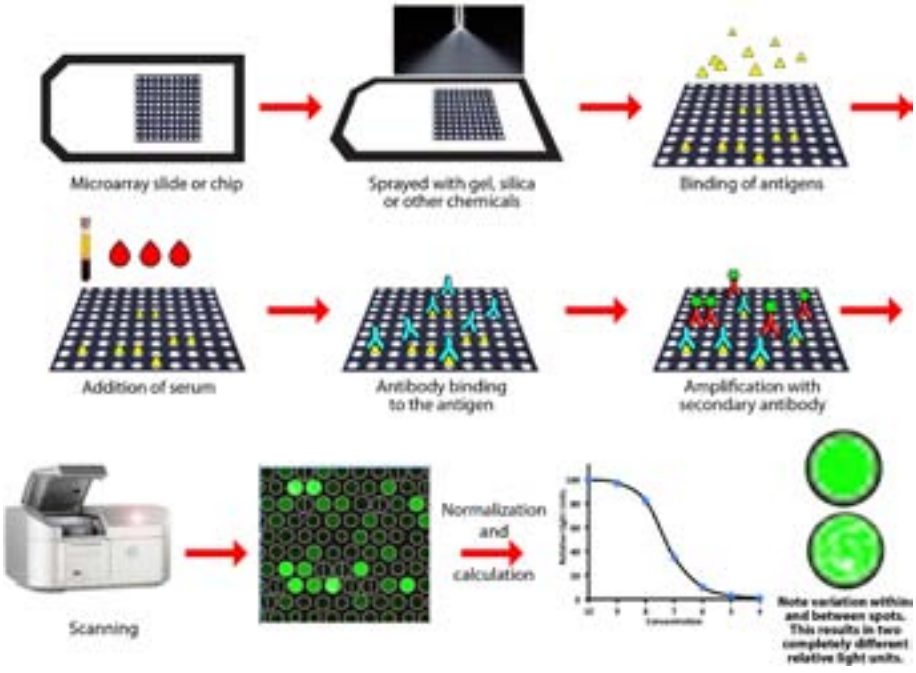
➤

slide or silicon thin-film cell) that assays large numbers of biological materials. Using this technology, a tiny amount of biochemical, (protein, antibody, *etc*.) is spotted and fixed on a solid surface such as a microchip (silicon thin-film cell), glass, or plastic and the interaction between the biochemical, and its target protein (antigen), is detected via a light reader.

As I mentioned above, the basic principle of microarray is the dot blot assay. However, in the microarray method, instead of binding the antigens to a membrane or paper strip, hundreds of antigens can be bound to microscope-size slides, which requires very special chemistry. This chemistry may not be suited for every single protein or peptide. Many harsh chemicals are used to bind the antigens to the glass. The harsh process affects the tertiary structure of proteins and may result in either lack of binding (false negative), or excessive binding of the antibodies in the blood to the chemically modified antigens on the chip. In contrast, with the ELISA assay the antigen is bound to the microplate surface without any chemical treatment. Furthermore, the dot blot is miniaturized in order to save reagents. For example, if five micrograms of antigen worth ten dollars are used in a normal ELISA test, in a microarray the amount of antigen used would be about 100-fold less, say about 50 nanograms of antigen worth ten cents. At the end of the assay procedure, the microarray attempts to improve on the dot blot methodology by taking the qualitative yes or no results and converting them to quantitative results; this requires the use of additional equipment and mathematical formulation and calculation, opening the possibility of conversion error. For these reasons, microarray technology is currently considered experimental and is recommended for the detection of very small quantities of DNA or tumor markers in the blood, not for the determination of high levels of antibodies that are present in the blood in milligram amounts. **Additionally, the miniaturization of the sample means that there is a small area for antigen binding. When a mixture of proteins is added to this minuscule space, some antigens may not bind to the slide, and the test may thus end with false negative results.**

The concept and methodology of microarrays was first introduced and illustrated in antibody microarrays (also referred to as antibody matrix) by Tse Wen Chang in 1983 in a scientific publication and a series of patents.[14] The "gene chip" industry started to grow significantly after the 1995 Science Paper by the Ron Davis and Pat Brown labs at Stanford University.[15]

Figure 4. Steps involved in a microarray assay that generates irreproducible results



However, in the December 2018 issue of *CAP Today*, the monthly news magazine of the College of American Pathologists (CAP), one of the main regulatory and certification bodies for laboratories, an article said: "In allergy testing, microarray technology offers speed and the benefit of smaller sample volumes, but it has a lower sensitivity and is unable to detect IgE antibodies of all specificities in a given extract unless all allergens are on the chip. For routine use, singleplex assays are here to stay." Thus, the same article concluded that "Microarray technology will remain a wonderful research tool but will probably not emerge into the clinical world in a serious way for a variety of reasons," among them a lack of FDA approval, said Robert G. Hamilton, PhD, D.ABMLI, director of the Dermatology, Allergy, and Clinical Immunology Reference Laboratory at Johns Hopkins University School of Medicine.[16]

It should be noted that after more than three decades the microarray system is still regarded only as promising technology. For now, the process involved in microarray testing shows a comparatively greater chance of irreproducible results, as shown in Figures 4 and 5. For these exact reasons, we recommend the gold standard ELISA method, not microarray, for the detection of Lyme disease and other infectious agents.

Even if, in the future, microarray technology should achieve the standard set by ELISA, the reliable reporting of laboratory test results will still depend not just on the nature of the assay but also on what you put into the test or how meticulously the test is performed. This is why I spent years developing and perfecting the **4 Core Principles**[17] for the reliable reporting of laboratory test results (Figure 6).

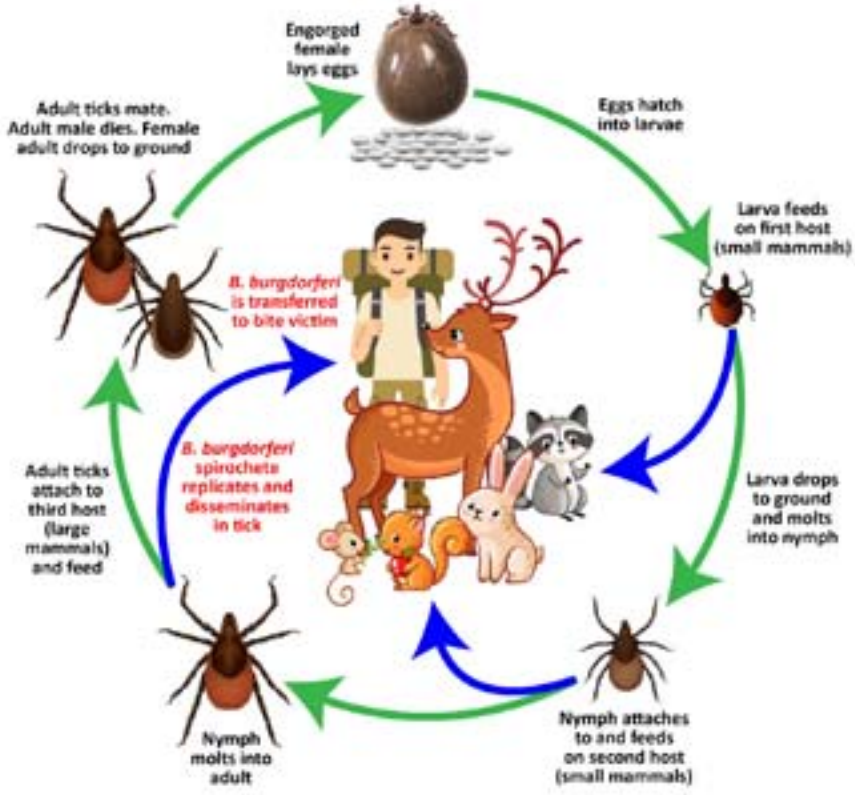
1. *Purity of the antigen* – The ELISA test or any other method for testing antigen-antibody reaction depends on the purity of the antigen. The quality and reliability of a test's results are only as good as the purity of the antigen used in the assay.
2. *Optimized antigen concentration* – Some labs blindly use the same volumes but not the same concentrations for the different antigens used for antibody measurements, assuming that apple and peanut both contain the exact same amount of protein. The problem with this is that indiscriminately using the same volume for all antigens runs the risks of

continued on page 22 ➤

Multi-Peptide ELISA is the most comprehensive method for the detection of Lyme disease and other tick-borne diseases.

(US Patent 7,390,626 B2)

Inaccurate testing for Lyme can result in unneccesary treatment with antibiotics, leading to gut-to-brain abnormalities.



Untreated Lyme disease can turn into chronic Lyme disease, which in turn can lead to Lyme arthritis and neuroborreliosis.

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➤ *continued from page 20*

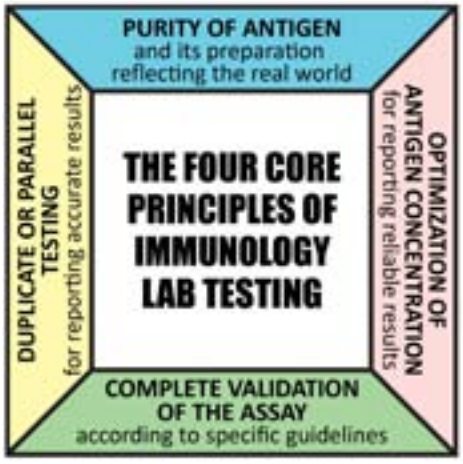
Figure 5. Comparison between the heterogeneity of microarray spots (green) and the homogeneity of ELISA wells (red).

Due to the heterogeneity of the color, if the microarray signal is measured from Spot A, the test result could be negative. A measurement from Spot B, which is relatively more homogenous, may, however, have a positive result. In the ELISA test, since the intensity of the color is measured in the liquid phase, the color is 100% homogenous, resulting in a highly reproducible outcome from well to well, meaning positive will be reported as positive and negative will be reported as negative.

false positivity and false negativity, even if two different foods did contain the same amount of protein, unless conditions were optimized for each antigen during assay development. If not, this may increase the risk of obtaining erroneous results.

3. *Individual antigen-antibody validation* – Many labs do not validate their tests or validate them improperly. This goes against the Federal Clinical Laboratory Improvement Amendments (CLIA) regulations, which state that each method must have validated performance specifications for "accuracy, precision, analytical sensitivity and specificity; the reportable range of patient test results; the reference ranges; and any other applicable performance characteristic." All of these performance specifications should be applied to each and every individual antigen or protein. Unfortunately, some labs validate up to hundreds of proteins together by generating standards from one particular protein and then comparing the others to this one protein. It would be like using wheat protein to generate a standard curve, then using that curve for 99 other proteins, which puts those 99 at a disadvantage. Each antigen has to be validated against its own standard, wheat to wheat, Epstein-Barr to Epstein-Barr, and so on, in order to accurately report the results.
4. *Duplicate or parallel testing* – Each test should be run side-by-side or run twice. Many steps are involved in testing, and a potential for error exists with each step. One way to guard against these errors is to run duplicates from the same patient's sample in side-by-side wells on the same plate. If the results from the 2 determinations correlate, they can be reported. If not, the problem should be investigated and corrected before reporting results. This is particularly important for microarray. Due to the irreproducibility of microarray from dot to dot, many researchers perform this test in quadruplicate so as to reduce the probability of error in their calculation of the results. This dot-to-dot irreproducibility can reach such a degree that it can take as much as ten repeats of microarray testing to come up with an acceptable result, as one group did when testing for allergy.[18] How many replicates do you think commercial clinical labs are using in their microarray assays?

Figure 6. The Four Core Principles for reliable reporting of laboratory test results



Finally, we labs cannot hide behind blanket claims that we are approved by this and that institution. Our own lab does take pride in the fact that it is inspected and approved by the College of American Pathologists, and rightly so. That being said, there are legitimate limits to the oversight provided by state regulations and requirements. We have put forth these four core principles of immunology lab testing and have given solid reasons as to why they MUST be observed by a lab in order to produce reliable, accurate, reproducible results. It is the responsibility of a truly professional lab to go beyond mere compliance of any regulatory body and to always strive for excellence so as to provide the maximum quality of service for its clients. Only by following the four core principles of antigen-antibody assays can labs provide dependable results that practitioners can use for the betterment of their patients.

Comparative Analysis of Methods

In sum, then, the ELISA method still stands as the industry's gold standard because of its reliability, reproducibility, accuracy, and ability to produce quantitative results. The Western Blot method offers the advantages of specific antibody reaction to antigens based on molecular size but can only offer qualitative results, and its inability to distinguish between weak and strong reactions may generate false positives and negatives by an individual who reads the test results incorrectly. The microarray system has the advantage of speed and multiple antigens but has been notably cited for low rate of reproducibility due to variation from dot-to-dot because of the chemistry involved and the minute quantities of antigens contained on the sample chips. *In contrast, the Multi-Peptide ELISA offers the advantages of the ELISA method's reliability, reproducibility and accuracy, which produces quantitative results for antibodies that are generated against different highly pure antigens and peptides derived from B. burgdorferi, its subspecies and co-infections simultaneously.*

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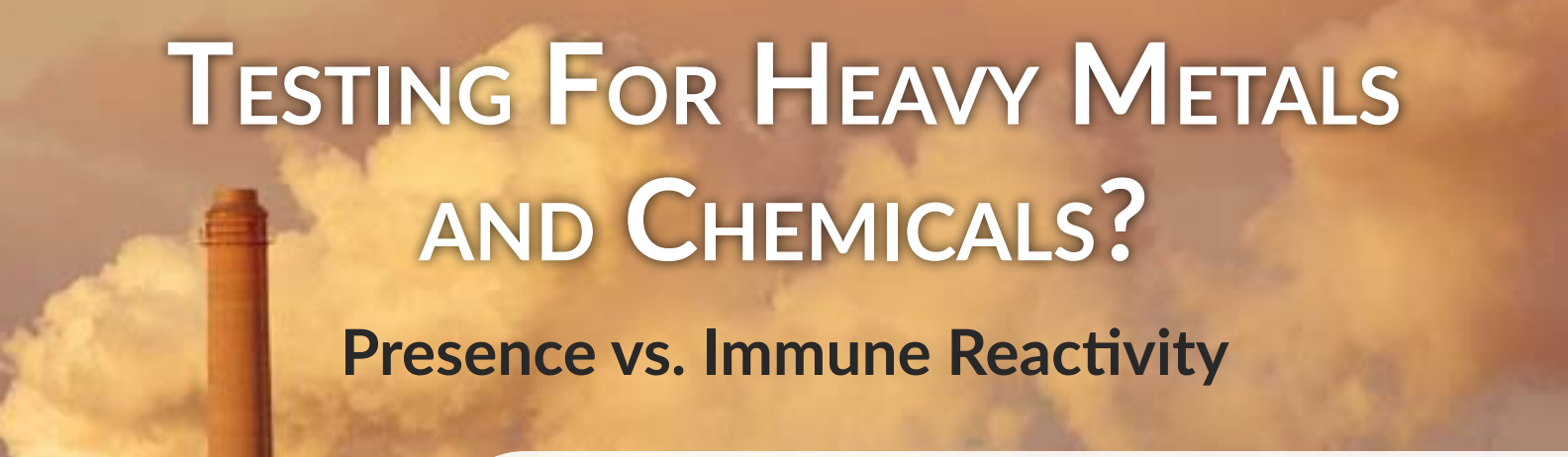

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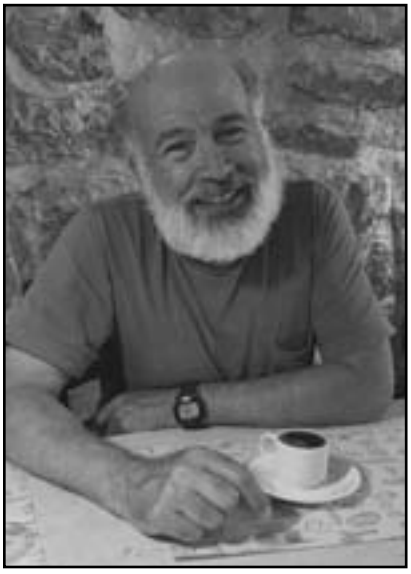

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
drjacobschor1@msn.com

Raking the Forest Floor

Kurt Beil, ND, braved the Maine back roads and an ominous weather forecast and came up to visit me at our log cabin at the end of the road, in what I'm beginning to think of as my forest hermitage.

Regular readers of the *Townsend Letter,* and even more so the *Natural Medicine Journal*, should recognize Dr. Beil's name as he is a regular contributor to both publications. He writes on one topic only, which is, not to be cliché, 'the healing power of nature.' That's a phrase that is overused these days. Nowhere more so than in Colorado, Maine, and other states where recreational marijuana is now legal; *Vis medicatrix* has become an advertising slogan for pot dispensaries.

What Dr. Beil has been fascinated with and has made efforts to share with us over the years is the foundational phenomenon that underlies all of naturopathic medicine, that exposure to nature triggers a healing action in humans. In recent years this phenomenon has become well recognized and accepted in scientific and medical circles. Dr. Beil has been reviewing current studies in the *Natural Medicine Journal* for several years now and has promised to provide regular contributions to the *Townsend Letter* as well.

While "nature as medicine" as an idea has become recognized by modern medicine, it has been oddly slow to permeate naturopathic clinical practice. It is as if we talk so much about the '*Vis Medicatrix Naturae'* as a philosophical concept that we forget that it is also a primary intervention our patients will benefit from. As far as Dr. Beil could tell me, not one of the naturopathic schools currently offer course work in nature as medicine. How many of us start out a treatment plan by telling a patient to spend a prescribed amount of time each day in a specific location experiencing nature?

So, what does one do with Dr. Beil, our profession's prime proponent of forest bathing, when he shows up at your door as a cabin guest? My quiet life morphed into Dr. Schor's summer-camp for burnt-out doctors. What do you do with someone who won't stop talking about how curative nature is? Someone who, for all his talk, still seems like he's from New York City and comes across as too loud, too brash, too rushed, too self-absorbed, too in a rush to update his social media accounts at every turn of the trail, too in love with his girlfriend to not be in constant communication, too much a poster child of modern techno life? It was simple.

Early to bed, early to rise, a two-hour kayak paddle and then some serious forest bathing. Forest bathing as a term doesn't quite do justice to what I put that unsuspecting innocent through. I felt a little like Tom Sawyer doing his fence painting thing. For us to call it forest bathing would be like calling a daylong soak in a hot tub a sponge bath. Forest pressure immersion therapy might be a better term. I've had a bug in my head these past few months that I would like to be able to stroll the perimeter of our forty acres of forest each morning, as a form of morning meditation. In theory it could be an hour walk. The thing is we are surrounded by dense second growth Maine forest. Right now, though not quite a mile, it is a half day's trek. There is no such thing as strolling; thrashing is more like it. Kurt became my trail building assistant. Following a compass bearing as best we could, we cut our way down the line, then tagged the line with surveyor's tape, broke, cut and tossed dead fall off of what we imagined would be a trail, and then went back over it again with lopping and pruning shears. By the time Dr Beil headed home to New York, sections of the line are starting to feel walkable, vaguely reminiscent of a trail. The two of us can see where the path wends its way along, though some people might find it easy to miss.

Those few days entertaining my guest provided plenty of opportunities to chat, as I rested on various logs and boulders along our 'trail.' These chats allowed me to ask the more practical questions. Let me reconstruct some of those conversations.

Jacob Schor (JS): Imagine I'm sitting down with a patient and want to write a prescription for nature exposure. Where do I begin?

Kurt Beil (KB): The most important thing is to assess the patient's needs as well as their abilities, access and interest. What are you trying to accomplish with them, and what are they willing to do? Not everyone is going to be comfortable going on a walkabout in the backcountry, and not everyone even has access to convenient transportation to get to a park. Everyone is an individual (as we know from everything we do). If you are talking about your specific population of patients in suburban Denver, that is probably different than someone that lives in Brooklyn (where I currently am writing from a coffee shop).

continued on page 26 ➤

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Curmudgeon's Corner

➤ *continued from page 24*

That said, if you are interested in the typical "average" person in a urban/suburban area that wants to have a "Park Prescription" there is now a great non-profit called Park Rx America, started by Dr. Robert Zarr (MD pediatrician in Washington, DC) that makes it all very simple. Practitioners can sign up, then put in their patient's info including home zip code and it will generate a list of parks closest to them. It gives you fields to fill out an official 'prescription form' that will print for the patient and will send the patient reminders to their phone or email and keep track of how often they go. They are still building out their listings of parks, so until that is complete, the website is not that useful for many regions outside of their DC home area, but it will be a game changer once the website gets fully populated with enough parks listed to make it useful all over the country… https://parkrxamerica.org/. Check it out.

JS: How should I think about dosing? Are there considerations as to 'wildness'? Is a city park a lower dose exposure than a dense forest?

KB: One of the nice things about dosing is that there is no risk of overdose! We are still discovering what exactly makes a good "dose," but some recent studies have shown us important info in this area. One recent study from Exeter in the UK showed that the optimal amount of time in nature needed before diminishing returns start occurring is 120 minutes per week. That really isn't that much time at all (less than 20 minutes per day, on average).

Kurt Beil, ND

As far as urban vs. forest, that absolutely matters. One of the main criteria for having a "restorative" nature experience in terms of the physical and mental health benefits is the sensation of what is called "Being Away" or feeling that you are removed from the busy-ness and experiences of the modern world. So being in an urban park can be helpful, but if you can still hear traffic or see a lot of other people walking by, it is not as beneficial as going somewhere more remote to calm the mind and the nervous system.

JS: Does what I would call biotic density matter? For example, does a dense lush forest with more weight of organic matter have more impact than a dry desert where "life" is sparse?

KB: Again, we are just learning about these things. I'm not aware of any studies that have compared different biomes (e.g. forest vs. desert) and suspect part of that may be individual preference. But there have been a few studies out of the University of Illinois showing that visual density of vegetation in an urban/suburban location does have direct impact on health benefits. It seems the ideal amount of vegetation occupies about 25-45% of the visual field, which is enough to feel "green" but not so much that it obscures the view of other objects.

JS: I've read that Olmstead's Central Park design of grassy meadows and clumps of trees, which mimics the African Savannah where humans evolved, is the most familiar and most soothing natural environment. Any truth to that?

KB: Yes! One of the early papers in this area of environmental psychology established exactly this, that one of the landscapes that is most universally preferred both globally and in the US is this kind of open area with scattered vegetation for protection and refuge that our proto-human ancestors likely lived in for tens or hundreds of thousands of years in Africa. This "Savannah Hypothesis" has been tested and verified; it is one of the foundational ideas in this area of study. I don't think Olmsted himself was consciously aware of this effect (he pre-dated the formal hypothesis by 100 years…) and was likely just working with his own intuition and what he liked and didn't like about other public spaces he had visited around the world.

JS: Don't we have to worry about lions?

KB: Ha-ha. It depends on where you are! But yes, "nature" is not all calming trees and relaxing babbling brooks. There is certainly the "red in tooth and claw" aspect of nature that needs to be considered, as well as weather effects, dangerous terrain (and inadequate gear), multiple insect vectors that may carry disease, etc.… For the average person though, going on a walk in their local park, none of these concerns are really relevant but it is always worthwhile to consider what an outdoor experience may involve. As they taught us in Boy Scouts, 'Be prepared.'

JS: Dosing, is there an optimum time or amount of nature per week. Is one full day better than two half-days or even 30 minutes several times a week? Do we worry about overdosing? Concerns about building up tolerance. Is there such a thing as too much of a good thing?

KB: As mentioned above, one study showed that 120 minutes per week seems to be the minimum optimal dose. Considering that our prehistoric ancestors evolved in direct connection with nature such that their outdoor time was 100% of the time, it is extremely unlikely that there is a maximum dose, or risk of overdose. As far as tolerance, some studies have shown there may be a leveling off effect such that further exposure past a certain amount of time doesn't confer continual added benefits, but it isn't like that extra time is detrimental. It just doesn't seem to continue to get better and better until a person achieves total consciousness just by sitting under a tree (it takes additional internal work to do that, I'm told). By the way, that leveling off time seems to be three-to-four days of complete "away" nature time.

JS: Side effects, contraindications? Can you mix nature with a cellphone without adverse reactions? Are there synergistic things to add to nature that will enhance effect? (Dancing naked in moonlight say?)

continued on page 28 ➤

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Curmudgeon's Corner

➤ *continued from page 26*

KB: There are not any studies that I am aware of that have looked at these questions. This is some of the most interesting research yet to be done, in my opinion. One of the unique aspects of this area of research is that we are looking at the environment as if it were a health intervention, but the environment is a context, it is the field (sometimes literally) in which other things can happen that also may have an impact, either positively or negatively. In this way, it takes a true holistic perspective to understand all of the interacting stimuli, inputs, behaviors, etc. that might affect health.

Specifically, in terms of synergy, there are currently studies underway to look at the effect of various natural psychotropic plants on human consciousness, well-being and mental health. Some of these are now legal for medical and even recreational purposes. Traditionally these plants have been used in the natural settings in which they originated, and there is much anecdotal evidence that being out in nature may be the optimal environment for their use. It is going to be interesting to see how research scientists address and investigate the use of these medicines in their traditional natural contexts, rather than the typical "controlled" setting of a research lab. I would speculate that the synergistic effects would be positively cumulative.

Drs. Kurt Beil and Jacob Schor wondering if they are lost

J: If you are broaching this idea with patients for the first time and they are 'nature naïve' and totally unfamiliar with the concept that it offers health benefit, where do you start?

KB: Because "nature" is primarily about environmental context, I start by asking them where they live. That can tell you a lot about their familiarity and openness to natural experiences, as well as give you an idea about their potential opportunities and access. I also ask them about their current level of nature or "green time" exposure, to gauge what they are doing right now. (As an aside, I always contrast this by also asking about their digital "screen time" exposures, since this is the flip side of the same coin). From there, I get a sense if recommending going to a park two-to-three times a week is something that they might be willing to do, or if just sitting in their backyard with their bare feet on the ground might be more their speed. For some people with social anxiety or who have mobility issues, I might even start with some indoor nature: buying some houseplants or a good quality nature poster or wall calendar and have them spend time with that. There are lots of options, and there is no one right thing for everyone. As always, we work with the individual where they are.

JS: Is there a trick to making this work?

KB: Finding what is going to work for them. If the various hypotheses and theories in this area are correct, we all have an inherent affinity for the natural world that is the result of millions of years of evolutionary adaptation. It is something that is a part of each of us because we are all living beings that evolved on planet Earth. It may take some work to find how an individual person best resonates with nature, but we all have it in us somewhere. As with many things in medicine, some of it is trial and error but once we find "it" the person instantly knows it is something that works for them. People will often say they've found a missing piece of themselves they didn't even know was missing. When that happens, it can be a beautiful thing.

A Zen Sort of Thing

Fir trees are uncommon in this region, but my father got a deal on a box of seedlings forty years ago and my mother planted them. There are now fir trees leaning over three sides of the cabin. I go out each morning and sweep the needles off our back deck. If this isn't done almost daily, they get tracked into the cabin. Seeing the overstory of needles above me with their endless capacity to drop onto the deck made me laugh. My desire to keep them out of the cabin is a lost cause, I'll never keep up. Yet I went back to sweeping because that's what I do.

What's even funnier is that I've started walking the property perimeter with a rake so I can make our fledgling trail appear more distinct by moving the leaves about. That's a kind of ridiculous idea, especially in October when this year's deciduous leaves are on the verge of dropping. What's the Greek myth, the one about the fellow trapped rolling a boulder uphill, Sisyphus? Kind of like that, pointless. Yet I'm trapped in doing so. Wanting to keep our floors and carpets clean indoors is one thing, funny enough on its own. Sweeping a path through a deciduous forest is past ridiculous. I laugh at myself for a few minutes, the absurdity of such a task, and then conclude, "It would be a Zen kind of thing." Though admittedly I couldn't explain to you what that means if you were to ask.

Still, the routine would be good for me. A good time to think. It's good exercise; there's nothing like raking wet leaves while walking uphill to build up that core strength thing everyone's talking about.

Many of the things we do lose their point if one looks at them from too long or too wide a perspective. This is no different.

We spend our workdays trying to extend the lives of our patients, to preserve their health. Yet from another perspective, the one thing the world is not deficient in, is people. There is little rationale to think the world will be improved by increasing our human population further. Yet caring for people and preserving life is what we do.

I have to get my work boots on, find those work gloves to protect those hands accustomed to keyboards and pack a snack. I've got some intentional raking to do before this year's leaves start to drop. There is some forest bathing waiting to be had.

continued on page 87 ➤

Colostrum and the Gut-Brain Axis

Scientific hypotheses, medical beliefs, and accepted treatment methods come and go over the decades, and now, a "new" idea has emerged on the origins of brain health (see box). Over the past several years, scientists have been accumulating vast amounts of research on the gut microbiome and are increasingly accepting of the idea that gut bacteria have a major impact on one's mental health as well as physical health. This connection (the gut-brain axis) does not function in just one direction, but is bi-directional. The brain influences gastrointestinal and immune functions that control the populations of good and bad bacteria in the gut and these same good and bad bacteria influence the creation and regulation of neurotransmitters and metabolites that act upon the brain.

To date, the majority of research in this field has been done in germ-free mice; altering or disrupting their microbiome has been demonstrated to mimic human depression, anxiety, and autism. Germ-free mice lack social skills and are unable to recognize other mice with whom they would normally interact, but when specific strains of good bacteria were re-introduced into the mice's guts, their social behavior returned to normal. When researchers introduced intestinal bacteria from a different type of mouse, the germ-free mice would exhibit behavior similar to the donor's personality. And when the germ-free mice received intestinal bacteria from people suffering with irritable bowel syndrome (IBS), the mice not only developed symptoms similar to IBS but symptoms of anxiety. This helps explain why people with IBS and other intestinal illnesses often have mental health issues such as depression and anxiety which are not attributable to the emotional impact of having a chronic disease.

Although in its infancy, gut-brain axis research is significant because it may eventually provide a window of understanding into how and why some individuals develop mental health problems. It will also provide hope for the future of treating mental illness, including Alzheimer's disease, with a more nutritionally-based solution than a pharmacologic solution. In the meantime, powdered bovine colostrum, with its plethora of immune and growth factors, is the one sure way to maintain integrity of the gut lining while maintaining a healthy ratio of beneficial to pathogenic gut bacteria.

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100-Year-Old Theory "Re-Discovered"

The notion that the state of our gut governs our state of mind dates back more than 100 years. Many 19th- and early 20th-century scientists believed that accumulating wastes in the colon triggered a state of "auto-intoxication," whereby poisons from the gut produced infections that were then linked with depression, anxiety and psychosis. Patients were treated with colonic purges and even bowel surgeries until dismissed as quackery. *Charles Schmidt, 2015*

Literature Review & Commentary

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

ALCAT 5 Test: Is It Reliable for Identifying Non-Celiac Gluten Sensitivity?

Twenty-five patients (mean age, 32 years) with severe functional abdominal pain and bloating, who considered gluten to be the main causative factor, went on a gluten-free diet for two weeks followed by double-blind challenges with gluten and placebo. All patients had previously been tested for gluten sensitivity with the ALCAT 5 test while they were on a gluten-containing diet. The study investigators were blind to the results of the ALCAT 5 test. The gluten challenge was considered positive if symptom severity was 30% greater after gluten than after placebo. After gluten challenge, 13 of 25 patients (52%) had an increase in abdominal pain and 11 of 25 (44%) had an increase in abdominal bloating relative to placebo. Sixty-four percent of the patients had an increase in one or both of these symptoms after gluten challenge relative to placebo. The ALCAT 5 test was positive in 20 patients and negative in 5. The ALCAT 5 test result agreed with the double-blind challenge in 64% of cases and disagreed in 36%. The sensitivity of the ALCAT 5 test was 81%, the specificity was 22%, the positive predictive value was 65%, and the negative predictive value was 40%.

Comment: ALCAT 5 is an automated *in vitro* test that evaluates the toxic effect of gluten on neutrophils by the exposure of these cells to a gluten-containing extract of gluten-containing cereals. The authors of this report concluded that ALCAT 5 could be used to support the clinical suspicion of non-celiac gluten sensitivity (NCGS) and to help identify which patients should undergo a blinded gluten challenge. However, my reading of the data suggests that this test is too unreliable to be of much clinical value. The reported results for positive and negative predictive value indicate that 35% of patients who had a positive ALCAT 5 test actually did not have NCGS and 60% of those who had a negative ALCAT 5 test actually did have NCGS. Therefore, among patients in whom NCGS is suspected, neither a positive nor a negative test result would obviate the need for an elimination diet followed by a gluten-challenge test.

Di Stefano M, et al. Non-celiac gluten sensitivity in patients with severe abdominal pain and bloating: The accuracy of ALCAT 5. *Clin Nutr ESPEN*. 2018;28:127-131.

Blood Test for 25-Hydroxyvitamin D: Result Depends on the Time of Day

Serum 25-hydroxyvitamin D (25[OH]D) levels were measured at three different times of the day on each of four days in a healthy woman in her mid-forties who had been taking 5,000 IU per day of vitamin D for more than a year. The 25(OH)D level at mid-day was approximately 20% higher than the level in the morning and approximately 13% higher than the measurement in the evening. The 25(OH)D level did not vary according to whether the daily vitamin D dose was taken before or one hour after the measurement. The level fell by about 25% at all three time points on the day immediately before the onset of a cold.

Comment: I have previously argued that serum 25(OH)D is an unreliable indicator of vitamin D status, except in people with vitamin D toxicity or severe vitamin D deficiency.[1] One problem with measuring 25(OH)D is that commercially available lab tests cannot distinguish true 25(OH)D from an endogenous 25(OH)D isomer or from other endogenous compounds that have the same molecular weight as 25(OH)D (such as a specific bile acid precursor). Another issue is

continued on page 32 ➤

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➤ *continued from page 30*

that 25(OH)D levels decline in response to inflammation. In people with chronic inflammation, a low 25(OH)D level may not indicate a deficiency. A third factor that may decrease the clinical value of the test is that the proportion of 25(OH)D that is biologically active depends on the serum concentration of vitamin D-binding protein, which can vary substantially from one person to another. The results of the present n-of-1 study suggest that another factor to take into account when measuring 25(OH)D is the time of day the blood was drawn.

French CB, et al. 25-Hydroxyvitamin D variability within-person due to diurnal rhythm and illness: a case report. *J Med Case Rep*. 2019;13:29.

Does Fish Oil Increase the Risk of Perioperative Bleeding?

Some 1,516 patients (mean age, 63 years) who were undergoing cardiac surgery at one of 28 centers in the United States, Italy, or Argentina, who were not using fish oil supplements regularly were randomly assigned to receive, in double-blind fashion, fish oil or placebo (olive oil) in the perioperative period. Each 1-g fish oil capsule (Lovaza) contained at least 840 mg of omega-3 fatty acids (465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid) as ethyl esters. The preoperative dosage was 10 g over three to five days or 8 g over two days. The postoperative dosage was 2 g per day until hospital discharge or postoperative day 10, whichever came first.

The incidence of major perioperative bleeding (as defined by the Bleeding Academic Research Consortium) was 6.1% in the group as a whole and was non-significantly lower in the fish oil group than in the placebo group (odds ratio = 0.81; 95% confidence interval, 0.53-1.24). The mean number of units of blood transfused was significantly lower by 16% in the fish oil group than in the placebo group (1.61 vs. 1.92; $p < 0.001$).

Comment: Because fish oil inhibits platelet aggregation, concerns have been raised that taking fish oil could increase the risk of bleeding during and after surgery. For that reason, many surgeons recommend that patients avoid fish oil before surgery. In previous case-control studies, however, patients who took fish oil supplements until an average of two to five days before surgery did not have higher perioperative blood loss, when compared with patients who did not take fish oil within 14 days of surgery.[2,3] The results of the present randomized controlled trial demonstrate that taking fish oil around the time of surgery does not increase perioperative bleeding. In fact, it might have the opposite effect, as indicated by a significant decrease in the need for blood transfusions. The authors of this study suggested that current recommendations to stop fish oil supplements before cardiac surgery should be reconsidered.

Akintoye E, et al. Fish oil and perioperative bleeding. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004584.

Does Skipping Breakfast Increase the Risk of Developing Diabetes?

A meta-analysis was conducted on six prospective cohort studies (including a total of 96,175 participants) that examined the effect of skipping breakfast on the incidence of type 2 diabetes. In the pooled analysis, the risk of type 2 diabetes was 33% higher among those who ever skipped breakfast than among those who never skipped breakfast (relative risk = 1.33; 95% confidence interval [CI], 1.22-1.46). The increased risk was attenuated after adjustment for body mass index but remained statistically significant (relative risk=1.22; 95% CI, 1.12-1.34). The risk of type 2 diabetes increased with every additional day per week of breakfast skipping, but the curve reached a plateau at four to five days per week, showing a relative risk of 1.55 (95% CI, 1.41-1.71).

Comment: In last month's issue of the *Townsend Letter*, I reviewed another observational study in which skipping breakfast was associated with an increased risk of developing cardiovascular disease. In the new study, skipping breakfast was associated with an increased risk of developing type 2 diabetes. This association was partly mediated by higher body mass index among people who skipped breakfast, but other factors appeared to be involved as well. While observational studies cannot prove causation, the findings from this study are consistent with those from a randomized controlled trial. In that study, skipping breakfast was found to increase insulin resistance,[4] which is one of the hallmarks of type 2 diabetes.

Ballon A, et al. Breakfast skipping is associated with increased risk of type 2 diabetes among adults: a systematic review and meta-analysis of prospective cohort studies. *J Nutr*. 2019;149:106-113.

Avoiding Sugar Improves Nonalcoholic Fatty Liver Disease

Forty US boys (aged 11-16 years), mostly Hispanic, with histologically diagnosed nonalcoholic fatty liver disease (NAFLD) and evidence of active disease (hepatic steatosis greater than 10% and alanine aminotransferase level of 45 U/L or higher) were randomly assigned to consume an intervention diet or their usual diet (control) for eight weeks. Those assigned to the intervention diet were given meals for the entire family that were similar to the family's usual diet but which contained less than 3% of daily calories in the form of free sugars (sugars added to foods and beverages or occurring naturally in fruit juices). The mean decrease in hepatic steatosis from baseline to week 8 was significantly greater in the intervention group (25% to 17%) than in the control group (21% to 20%) ($p < 0.001$ for the difference in the change between groups). The mean decrease in alanine aminotransferase level from baseline to eight weeks was also significantly greater in the intervention

group (103 U/L to 61 U/L) than in the control group (82 U/L to 75 U/L) ($p < 0.001$ for the difference in the change between groups).

Comment: This study supports previous research (both epidemiological and experimental) suggesting that excessive consumption of sugars (particularly fructose and sucrose) plays an important role in the pathogenesis of NAFLD. Excessive sugar consumption can lead to obesity, which is a risk factor for NAFLD. However, fructose (either in its free form as a component of sucrose) also appears to have an adverse effect on the liver that is independent of changes in body weight.[5]

Schwimmer JB, et al. Effect of a low free sugar diet vs usual diet on nonalcoholic fatty liver disease in adolescent boys: a randomized clinical trial. *JAMA*. 2019;321:256-265.

Vitamin C Improves Outcomes After Surgery for Ankle Fractures

Sixty healthy patients (mean age, 39 years) who had undergone surgery for a closed ankle fracture were randomly assigned to receive, in double-blind fashion, 500 mg of vitamin C twice a day or placebo, beginning on postoperative day 1 and continuing for six weeks. Functional outcome was measured at three months using the American Academy of Orthopedic Surgeons foot and ankle outcome instrument (FAI), which is a 100-point scale, with higher numbers indicating better outcomes. The mean FAI score was significantly higher in the vitamin C group than in the placebo group (71.9 vs. 61.9; $p < 0.001$). The mean visual analogue scale score for pain was significantly lower (indicating less pain) at two and six weeks in the vitamin C group than in the placebo group.

Comment: In this study, vitamin C supplementation decreased pain and resulted in better functional outcomes in patients undergoing surgery for an ankle fracture. Vitamin C may work in part by enhancing the healing of bone and soft tissue. It has also been hypothesized that vitamin C decreases microvascular leakage of fluid and proteins following trauma, an effect that could improve the healing process.[6]

Jain SK, et al. Role of anti-oxidant (vitamin-C) in post-operative pain relief in foot and ankle trauma surgery: A prospective randomized trial. *Foot Ankle Surg*. 2019;25:542-545.

Adverse Effect of Excessive Potassium Consumption

The authors of this study reviewed 44 case reports from the medical literature in which patients developed hyperkalemia. Seventeen of the patients had normal renal function and were not dehydrated, and only two of those 17 patients were on medications that can inhibit renal potassium excretion. The most common cause of hyperkalemia was high oral potassium intake from fruits and vegetables or their respective juices, or from the use of salt substitutes or supplements. The main symptoms were muscle weakness, vomiting, and dyspnea. When electrocardiograms were performed (n = 30), abnormalities were present in 87% of cases. Treatment involved administration of insulin, sodium/calcium polystyrene sulfonate, and/or calcium gluconate. Most patients recovered, but three (all with normal renal function) died.

Comment: Severe hyperkalemia can lead to cardiac arrest and death. The most common cause of hyperkalemia is decreased renal excretion of potassium (resulting from renal failure or from the use of drugs that inhibit potassium excretion). Dehydration can also increase the risk of developing hyperkalemia. The present report makes it clear that excessive oral potassium intake can cause hyperkalemia, even in people with normal renal function who are not taking drugs that inhibit potassium excretion.

Most Western diets provide suboptimal amounts of potassium; and increasing potassium intake may be useful for preventing and treating hypertension and possibly for preventing cardiovascular disease. However, as this report emphasizes, it is important not to overdo it.

Te Dorsthorst RP, et al. Review of case reports on hyperkalemia induced by dietary intake: not restricted to chronic kidney disease patients. *Eur J Clin Nutr*. 2019;73:38-45.

Ultraviolet Light More Effective Than Vitamin D for Preventing Eczema

One hundred ninety-five newborn infants in Australia were randomly assigned to receive, in double-blind fashion, 400 IU per day of vitamin D or placebo until 6 months of age. Eighty-six of these infants also wore ultraviolet (UV) dosimeters to measure cumulative exposure to UV light from the sun. The prevalence of eczema at three and six months of age did not differ significantly between the vitamin D and placebo groups. Median cumulative UV exposure was significantly lower by 44% in infants with eczema than in those without eczema ($p = 0.02$). At six months of age, cumulative UV exposure was significantly and inversely associated with levels of immune factors related to allergic inflammation.

Comment: Some studies have found that vitamin D supplementation can decrease the severity of eczema in both adults and children, although the research is conflicting. The present study investigated whether vitamin D supplementation or UV exposure from sunlight can prevent eczema in infants. Vitamin D was not more effective than placebo, whereas UV appeared to be protective. UV exposure has a number of effects unrelated to vitamin D synthesis, including influencing immune function and the hypothalamic-pituitary axis. If sunlight exposure prevents the development of eczema, the mechanism might be related to some of these non-vitamin D effects.

Rueter K, et al. Direct infant UV light exposure is associated with eczema and immune development. *J Allergy Clin Immunol*. 2019;143:1012-1020.e2.

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Irritable Bowel Syndrome: Microbiome Profiling and Fecal Microbiota Transplantation

by David Quig, PhD

Vice President of Scientific Support, Doctor's Data, Inc.

Irritable bowel syndrome (IBS) affects up to 20% of adults and is associated with life-disruptive symptomatology. The multifactorial pathogenesis of IBS includes gastrointestinal dysbiosis, altered microbial metabolism, intestinal barrier dysfunction, and dietary intolerance – especially to soluble fiber. Intervention with a traditional IBS diet or a low FODMAP diet may not be sufficient for amelioration of immoderately disrupted gut microbiota and metabolism, and recent efforts indicate that fecal microbial transplantation may provide an effective option.

Microbial-host crosstalk between key gut bacteria and the mucosa is essential for intestinal barrier functions, inclusive of surveillance, protection and selection of the microbial ecosystem. Disruption of a healthy microbiome, and/or insufficient consumption of soluble fiber (SF), blunts desirable production of short chain fatty acids (SCFA) and stymies communication with specialized cells in the mucosa.[1] Propionate contributes to immune defense via binding to the G protein coupled receptor GPR-43 that is expressed on lymphocytes.[2] Propionate and butyrate stimulate release of glucagon-like peptide-1 (GLP-1) by enteroendocrine L cells; GLP-1 facilitates regulation of mucosal barrier function and glucose metabolism.[3] Butyrate and acetate stimulate colonic cells to "breath" via activation of peroxisome activated receptor-γ (PPAR-γ); PPAR-γ mediates increased fatty acid uptake, β-oxidation and oxygen consumption.[4] Removal of oxygen from the microenvironment directly adjacent to the mucosa limits colonization of anaerobic pathogens such as *Escherichia* and *Salmonella*.[5] Butyrate and acetate stimulate the release by goblet cells of vast quantities of mucins that constitute the essential, and too often underappreciated, mucus barrier.[6] Diminished regulation of mucosal metabolism subsequently perpetuates dysbiosis and causes low-grade mucosal inflammation and breaches of the barrier system. Low levels of fecal SCFA are common for IBS patients.

Extensive research has culminated in a novel PCR-based microbiome profiling approach that targets the most clinically relevant bacteria to differentiate normobiosis from dysbiosis in IBS patients (classified by Rome III criteria).[7] From that model a dysbiosis index (DI) was algorithmically derived; DI>2 (maximum 5) indicates the extent to which a microbiota profile deviates from that of a healthy reference population (n=500). Dysbiosis was evident across subtypes in 73% of IBS patients (n=297) with a significant percentage of DI values >4 (severe dysbiosis). Predominant bacteria contributing to the IBS-associated dysbiosis were *Proteobacteria* (*Shigella/Escherichia*), *Bacilli*, *Acintobacteria,* and *Ruminococcus gnarvus.*

Formal studies indicate that the "traditional" and low FODMAPs diets variably alleviate symptoms for some IBS patients, but in many cases the gut dysbiosis appears to be irreparable with reasonable dietary intervention. Long-term adherence to a strict low FODMAPs diet has adverse effects on gut microbiota and intestinal barrier integrity; the clinical ramifications are under deliberation. A four-week study of IBS patients consuming a low FODMAP diet indicated higher than baseline DI despite some symptom improvement; many patients did not respond favorably at all.[8]

Fecal microbiota transplantation (FMT) may be an effective alternative option for long-standing immoderate dysbiosis. FMT is widely accepted as the treatment of choice for *C. difficile* enterocolitis. The efficacy and kinetics of FMT was studied in IBS patients and healthy donors (n=16).[9] The aforementioned targeted PCR-based microbiota profiling method was used to follow both donor and FMT recipients before and at intervals up to 28 weeks after a single FMT. At baseline IBS patients had significantly higher DI than donors (4±0.5 and 2.6±0.2, respectively). Patient DI decreased steadily over 12 weeks (2.9±0.20, mild) but trended up after seven months. At that time the microbiota profiles for patients and donors were very similar (abundance and diversity). The most significant changes in bacteria were *Bifiodobacteria* (increase), and *Proteobacteria* and *Shigella*/*Escherichia* (decrease). Symptoms improved rapidly and markedly.

Application of the novel PCR-based targeted microbiota profiling method of analysis, along with symptom improvement, provides evidence that FMT may be an effective means to restore microbial balance for IBS patients with long-standing dysbiosis. Follow up studies should evaluate appropriate "feeding" in addition to microbiota "seeding" towards support of intestinal barrier functions and staying power of FMT.

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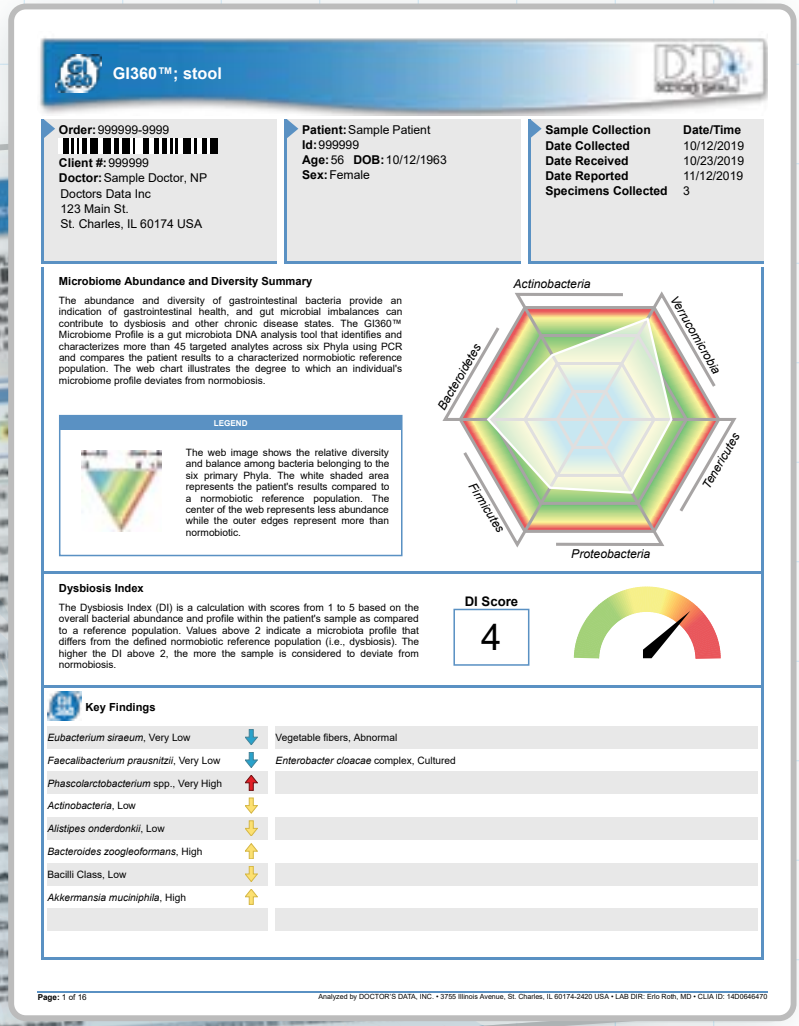

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Functional Gastroenterology Bolus

by Steven Sandberg-Lewis, ND, DHANP

"Slightly" Anemic?

In the *Organon of Medicine* (aphorism 260), Samuel Hahnemann, the founder of homeopathic medicine, discussed "obstacles to cure." Hahnemann's list of impediments included such things as certain foods, perfumes and spices; wearing woolen clothes next to the skin; reading in a horizontal position; keeping late hours; mental and physical overexertion; and sedentary lifestyle.

Homeopathy is a vitalistic, not mechanistic form of medicine. Functional medicine, on the other hand, may include vitalistic components but is essentially mechanistic. There are physiological obstacles to cure that can be investigated through lab diagnosis that aid our work with patients.

When I took Dr. Datis Kharazian's functional blood chemistry analysis training a few decades ago, one of the many pearls that stuck with me was the following: Patients won't get well if they are anemic or their blood sugar is imbalanced. These issues are basic to proper functioning of all human cells, including those of the central nervous system. Even a slightly reduced supply of oxygen or glucose can have major consequences on energy metabolism and overall functioning. Even the slightest levels of anemia may be considered a physiological impediment to cure in functional medicine.

When reviewing complete blood count reports, physicians often see borderline anemia. The red cell count, hematocrit or hemoglobin may be just a fraction of a point below the low end of the normal range.

Consider the following about "slight" anemia: normal RBC values are 4.52-5.90 mm3 (or $x10^{12}$/L) in adult males and 4.10-5.10 mm3 (or $x10^{12}$/L in adult females.[1] Let's take the example of a slightly low red blood cell count for a male, such as 4.42 mm3 (4,420,000 RBCs per mm3). With the decimal point after the first numeral, it may be forgotten that we are talking about *millions* here. A male with 4.42 mm3 RBCs is deficient by 100,000 RBCs in *each* cubic millimeter of blood. It takes about 50 cubic millimeters to make one *drop* of blood. Considering that it takes 1 million cubic millimeters to equal one liter and there is an average of 5.5 liters of blood in the body, this patient is actually deficient by 550 billion RBCs!

A very smart doctor, mother, and my most recent resident told me how she explains the difference between one million and one billion to her children: 1 million seconds is 11.5 days, but 1 billion seconds is 31.7 years.[2] When you consider a deficiency of 550 billion RBCs, there is likely to be a significant negative effect on cellular respiration and energy.

If a patient's "slight anemia" is low by 0.1, they are deficient by 550 billion red blood cells.

RBCs are unique because they have no nucleus or organelles and therefore no mitochondria. In addition to their basic function of carriage and release of oxygen to tissue, they also release nitric oxide into tissues to regulate local circulation.[3] RBCs are involved in regulation of blood pH and viscosity. Anemia may be associated with an increased risk of venous thrombosis and stroke.[4] Red cells are essential for detoxification of free radicals and prevention of lipid peroxidation via erythrocyte superoxide dismutase, glutathione, vitamin A, and vitamin C.

The next time you encounter a patient with a touch of anemia, please keep in mind how significant a deficiency of erythrocytes may be as an impediment to cure. The health of every tissue is at stake.

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Female Physiology, Copper Metabolism, and Oxidative Stress

by Judith Bowman, MD

Cofounder, Mensah Medical, LLC

The treatment of thousands of women during the first 12 years of my over-23-year career in family medicine brought me to realize that there was a subset of females that did not respond well to the addition of exogenous estrogens (estrogen-based birth control, hormone replacement and hormone-based IUDs). More specifically, females with hormonal imbalances, particularly those with estrogen dominance and poor copper excretion, experienced adverse reactions when additional estrogen, in whatever form, was introduced. These reactions call into question estrogen's role in copper metabolism, as well as additional factors that contribute to oxidative stress.

First, let's discuss the relationship of copper and estrogen. As estrogen rises, copper also rises. In response to that, the protein that binds copper (ceruloplasmin) should also rise to capture it, or so we hope. Over a lifetime, the ability to excrete copper may not always be efficient. That is a problem. This process is also necessary for angiogenesis (the production of blood vessels). In high levels, estrogen supports tumor growth in estrogen sensitive tissue. That being said, controlling copper levels is important. I must point out that dysregulation does not apply to all women. Those that manage copper normally, present with the fewest complaints regarding female health issues. To help explain this, the imagery I often use is what happens on an average school day when children are being picked up by the yellow school bus. Let the school bus represent ceruloplasmin (the protein that binds copper). Think of the children as free radical copper units waiting to get picked up and transported to their targeted destination. So, what happens if there are not enough school buses? Most of the kids usually choose some other, non-beneficial activity that may include playing hooky and traumatizing the neighborhood or each other. These little "charged, radical-rascals" roam free, usually getting into trouble. Free radical copper tends to provoke oxidative stress (a fancy term for the accumulation of "human body rust" that produces inflammation). Free radicals are charged particles that cause damage to enzymes, hormones, neurotransmitters, cell membranes, other proteins and DNA. I believe that most pathologists would agree that many conditions and disease processes develop secondary to inflammatory changes produced by oxidative stress.

As copper accumulates, challenges that women may experience may be few or multiple. This subset of estrogen dominant females (whether natural or imposed by birth control or hormone replacement) usually has impaired copper excretion sometimes starting with the first few menstrual cycles. This phenomenon tends to be an inherited pattern seen mostly through the maternal female line. There may be a family history of several disorders: 1) moderate to severe PMS, 2) heavy menstrual cycles, 3) fibroid tumors, 4) endometriosis, 5) fibromyalgia, 6) moderate to severe postpartum depression or psychosis, 7) chronic fatigue, and 8) adrenal fatigue. These disorders often continue through menopause. With each pregnancy, the process usually worsens. Examples of the most extreme presentations of females with copper toxicity seem to occur after the second or third child is born. In those cases, postpartum psychosis is far more intense than what is seen as the typical "baby blues." We hear horrific stories too often on the news of the mother who drowns the children, shoots the husband, or walks off the roof within six months of giving birth. Close family and friends often comment that "she suddenly snapped." However, this process, in actuality, had been smoldering over a significant period of time before the fire raged. If not recognized and treated, it then worsens over time.

Women with a history of painful menstrual cycles, fibroid tumors, and postpartum depression should be checked for high copper levels.

The brain is both electrical as well as chemical in nature. It can, therefore, experience a "short-circuit" in neural-processing. The fact is, copper is a great conductor. It is likely that copper, a charged particle itself, is a major influence on electrical charges and neurotransmitter signaling. ➤

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Additionally, excess copper can affect zinc levels. When copper is elevated, zinc levels fall. When that happens, many different processes utilizing zinc are impaired. There are really too many to list here but some of the basic functions include immune system support, neurotransmitter production, metabolism, signaling transduction, cell growth, general body growth and development, hair, skin and nail health and DNA / protein regulation to name a few.

In one case study, a 50-year-old peri-menopausal female came into our office with a 30-year history of severe depression, anxiety, history of post-partum depression, horrific and painful menstrual cycles, fibroid tumors, and chronic fatigue. She had spent the last twenty years seeking help and was told it was simply hormonal in nature and that medication was the best way to treat her condition. In her twenties, she had been placed on oral contraceptives, which made her feel worse. She related not being able to bond with her children early in their toddler years. This emotional blunting severely impaired her relationship with her first three children. She had six children total and with each successive pregnancy, her postpartum depression worsened. She then discovered the potential relationship between her symptoms, estrogen dominance, and copper toxicity. When tested, she discovered that her copper was severely elevated. Upon treatment by way of regulating copper, not only did her cognitive symptoms improve but her physiologic challenges as well. She expressed that never before had she known such lightheartedness. In fact, she expressed that this was the first time in her life that she was able to feel. She never truly understood the meaning of joy until after her treatment. She stated, "It's as though a cloud has been lifted" and that she could now truly experience joy and life the way it was intended. She was able to re-establish a wonderful and meaningful relationship with her three youngest children. Unfortunately, her relationship with her first three children remains challenging to this day.

A second case history involves a 20-year-old female with severe acne and painful menses. She was advised to use oral contraceptive to improve both her skin and menstrual irregularity.

While her acne improved, her mother called to report the onset of panic and anxiety after two months of use. These symptoms had never been present before. Her mother described a previously stable young lady with no mental health history. This began to have a negative impact on her scholastic efforts and her ability to maintain her grades. Upon testing, it was discovered that she also had elevated copper levels. We advised her that the oral contraceptives needed to be stopped. Because her acne had cleared up, she elected not to stop the oral contraceptive. We agreed to monitor her copper level and symptoms for another six months. Upon retesting, her copper levels had risen severely; her symptoms were so prominent and her anxiety and panic so prevalent that she had to take a temporary leave from school. As we treated her copper toxicity, episodes of panic became less severe and less frequent. Eventually, her symptoms normalized and she was able to continue her academic pursuits.

Cognitive, mental, and sensory processing as well as social engagement and executive function may also be impaired. Neurotransmitter imbalance may decrease our ability to calm ourselves in a timely manner. Interestingly, copper in the presence of dopamine is converted into noradrenaline, which is then converted to adrenaline. Adrenaline raises sympathetic nervous system response which can, and often does, provoke anxiety and panic. For the estrogen-dominant female this compounds the issue.

As mentioned earlier, copper is a source of oxidative stress. It is not the only source, however. There are other compounding factors. There are several environmental sources that include cosmic radiation, chemical exposures, contaminants in our water supply, air pollution, viruses, bacteria, genetics, parasites, seasonal affect, physical trauma, stress, emotional drama, and even medications. Though modern medicine continues to be life-saving in so many ways, we still may encounter side-effect profiles that do not position us with acceptable options or outcomes.

By definition, oxidation refers to a process that causes a substance to undergo a reaction in which electrons are lost to another species or substance. Here's another way to look at oxidative stress. Picture this. It's harvest time at the orchard and you pick the most

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After medical school, Dr. Bowman worked as a staff physician for the Lake County Health Department (Illinois) and as the Midwest site staff physician providing medical services for patients with learning disabilities at The Dore Achievement Center in Schaumburg, Illinois. Her interest and experience with behavioral/learning issues and autism steadily increased when she joined the medical team at Pfeiffer Treatment Center in 2005. During her tenure at Pfeiffer, Dr. Bowman became known for her consistent presence and care at each and every US Outreach Clinic.

Dr. Bowman co-founded Mensah Medical in 2008 with her colleague, Albert Mensah, MD. Dr. Bowman combines traditional medicine with the biochemical approach to treat the symptoms of behavioral and cognitive disorders, autism spectrum disorder, depression (including postpartum depression), anxiety, eating disorders, bipolar disorder, schizophrenia and other biochemical imbalances.

beautiful, delicious apples to take home. Once you get home you can't wait to bite into one of your prize possessions. It has been about an hour since you picked the apple from the tree. The purpose of course is to utilize its nutritional value for your own nutritional support and enjoyment. You slice or take a bite of the apple, but the phone rings before you can finish it and you become distracted for several minutes. When you return, you find that the color of the apple has darkened somewhat. It is much less appealing now as its color has a rusty-brown tinge. You are not sure you want to continue to eat it. What is happening? The apple is undergoing oxidative stress. The environment initiates oxidation after the inner flesh of the apple is exposed. Living things can rust (oxidize). Generally speaking, most of us would rather not eat oxidized food.

Disease or dysfunction may result if there is diminished capacity to replenish, repair or restore. This includes repair of our DNA. So, let's get back to this discussion of the apple. Of course, we benefit from the anti-oxidant support that the apple provides assuming that we have consumed it in a timely manner. What If we were able to decrease or delay the oxidative stress imposed upon the apple? Most chefs would advise that squeezing a little lemon juice on the apple should help it to look and stay fresher much longer. Why would that be so? By pouring lemon juice on the apple we are offering a source of anti-oxidation in the form of vitamin C. There are micronutrients (like vitamin C) that directly and indirectly lower copper levels while providing powerful antioxidant support.

Clearly, many systems can become dysregulated with copper toxicity. They range from absolute aberrant physiology to emotional instability. Many women have suffered for decades, not realizing that those two groups of challenges may not only be related but can be fairly simply treated. The first key is awareness. The next step is a simple blood test. The third is appropriate guidance from a knowledgeable physician to help regulate the copper challenge.

Once again, not all women fall into the category of estrogen dominance or have challenged copper metabolism and excretion. However, for anyone who seeks a different perspective and for those who are having a difficult time "connecting the dots," I am hopeful to have imparted some understanding as to what may be happening regarding how the environment, estrogen, copper, mood, and demeanor relate.

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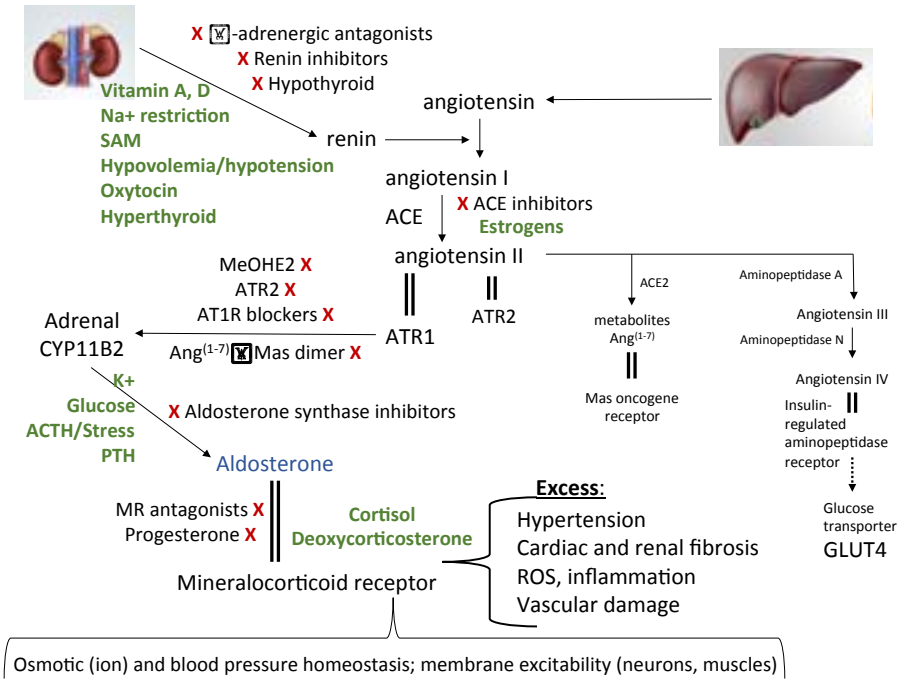
The Clinical Importance of Mineralocorticoid Screening in Hypertension

by Andrea Gruszecki, ND

Introduction

High blood pressure, or hypertension, may be a primary or contributing cause, worldwide, to approximately 7.5 million deaths per year.[1,2] Dysregulation of the renin-angiotensin-aldosterone system (RAAS) has a significant effect on blood pressure dynamics and other aspects of health (Figure 1). Hyperaldosteronism may occur for a variety of reasons, and recent evidence indicates that primary aldosteronism, once considered a rare disorder, may be present in a significant number of normotensive and hypertensive individuals.[3] These human studies also indicate that there is a wide variety of clinical presentations. Early in the course of the disorder, circulating potassium levels may be within normal limits, and up to 85% of normotensive individuals may only develop hypertension over time as "classical" primary aldosteronism may actually be a later stage of the disease process.[4,5] Based on these studies, routine screening of aldosterone levels may be considered an essential aspect of health care.

Figure 1. The Renin-Angiotensin-Aldosterone System



Primary Aldosteronism

Primary aldosteronism is defined as aldosterone secretion independent of typical regulators such as renin, angiotensin II, or sodium status.[3,5] Primary aldosteronism is the most common cause of secondary hypertension. Symptoms of primary aldosteronism may include muscle weakness or cramps, skin sensations (tingling, burning, numbness), low blood potassium (hypokalemia), high blood sodium, high urinary potassium (hyperkaluria), alkalosis, and hypertension independent of elevated cortisol (Cushing's syndrome). These symptoms occur with significantly elevated urinary aldosterone and urinary sodium excretion. The chronic exposure to high aldosterone levels significantly increases the risk of atrial fibrillation, stroke, and myocardial infarction. Previous human studies agree that higher levels of aldosterone can only induce hypertension and urinary excretion of potassium when renin levels are low.[6] This fact allows clinicians to perform a very simple screen, prior to pursuing more complicated confirmatory testing. The presence of a high aldosterone level, high urinary sodium, and suppressed (low) plasma renin should raise suspicion for RAAS dysregulation and possible primary aldosteronism, regardless of the individual's current blood pressure status, and particularly if there is potassium dysregulation.[3,5]

Routine screening is most important in populations with increased risk, such as those with hypertension, African-Americans, and aging populations.[6,7]

When stimulated by adreno-corticotropic hormone (ACTH), both cortisol and aldosterone will rise; and during adrenal insufficiency, both cortisol and aldosterone are low.[8] Human studies indicate that during ACTH stimulation, plasma aldosterone concentrations are significantly higher in primary hyperaldosteronism when compared with hypertension due to other causes.[9] While aldosterone secretion is also controlled by circulating potassium and RAAS angiotensin II levels, ACTH is independent of the usual aldosterone RAAS/potassium feedback loops. Although studies are needed for confirmation, it is possible that stress-induced endogenous ACTH stimulation plays a role in some types of sporadic primary aldosteronism, as aldosterone may respond to lower levels of stress-induced ACTH stimulation than cortisol does.[10,11]

The comparison of mineralocorti-coids (aldosterone) with glucocorticoids (cortisol) may improve diagnosis and treatment, as high levels of aldosterone mimic the effects of high levels of cortisol. Simply checking cortisol levels may not disclose the true cause of symptoms or disease. While not common, it is possible for cortisol/cortisone levels to be low or normal, while aldosterone levels are elevated; it is also possible for the reverse to be true (see Figure 2).[12] Each hormone system requires specialized treatments; it is essential, therefore, for both systems to be evaluated if either system is suspect.[13-15]

Fortunately, the assessment of urinary aldosterone, mineralocorticoid metabolites and urinary potassium may be performed simultaneously with a 24-hour urine hormone assessment (see Figure 2.). Simultaneous assessment of sex hormones and estrogen metabolites, in addition to adrenal hormones, may have additional advantages for clinical interpretation. Two of the estrogen metabolites measured can provide further information about the overall risk of RAAS dysregulation (see Figure 3).[16,17]

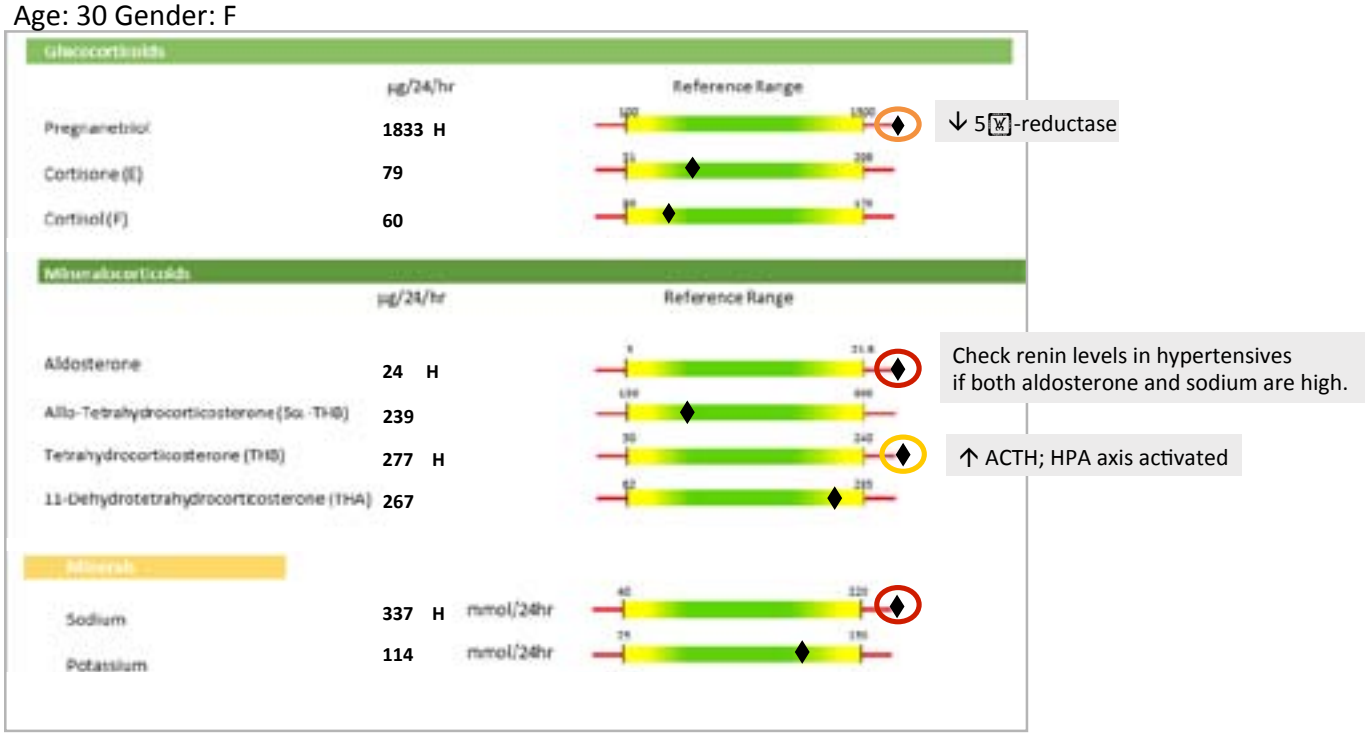
Sex Hormone Effects

The primary sex hormones, such as estrogens and androgens affect vascular angiotensin II sensitivity and regulate different aspects of the RAAS.[18] Estrogens have been shown to increase angiotensin and the expression of angiotensin-converting enzyme 2, angiotensin receptor 2, and endothelial nitric oxide synthase. ➤

Lifestyle Interventions for Aldosteronism

- Normalize weight
- Supplement with vitamin D3 (>800 IU daily)
- Herbal hypertension support: Aged garlic, berberine, hawthorne, saffron, roselle, black cumin seed, ginger
- Taurine (>3 grams daily)
- Stress management
- Bioidentical hormone replacement (if indicated)
- Manage detoxification pathways
  - CYP1B1: 10 grams ground flaxseed; Plant compounds (resveratrol, curcumin, flavanols)
  - COMT: Magnesium (350 milligrams daily); SAMe (600-1,200 milligrams daily) (if indicated)

Figure 2. Urine Gluco and Mineralocorticoid Results



Estrogens decrease renin production, oxidative stress, and the expression of angiotensin-converting enzyme 1 and angiotensin receptor 1 (see Figure 1). The combination of estrogen-related effects favors the vasodilator function of the RAAS, and the effect is mimicked by transdermal bio-identical hormone replacement, which tends to lower blood pressure. Of note, oral conjugated equine estrogen replacements *increase* angiotensin levels and the risk of hypertension in human studies.[19,20] The evaluation of estrogen metabolites may provide additional information regarding the RAAS (see Figure 3). The status of the phase I detoxification estrogen metabolite 4-hydroxyestrone (4OHE1) depends upon the activity of cytochrome P450 1B1 (CYB1B1); this enzyme is associated with hypertension and kidney dysfunction in animal studies.[21] The phase II metabolite 2-methoxyestradiol has been shown to decrease RAAS-induced hypertension and kidney dysfunction in animal studies.[22] Both metabolite pathways can be managed with nutritional supports.

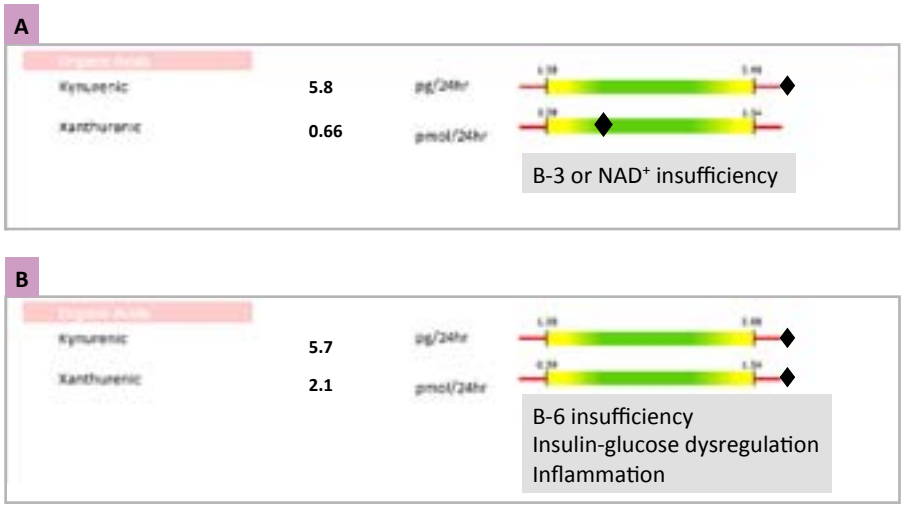
Testosterone, compared to estrogens, has the opposite effect, and favors the vasoconstriction function of the RAAS, increases blood pressure.[18] Progesterone, important for both genders, is a precursor molecule for aldosterone and competes directly with aldosterone for mineralocorticoid receptors.[23] Along with estrogens, progesterone also influences signaling pathways to inhibit ACTH-induced aldosterone secretion.[24]

In addition to sex hormone status, blood glucose regulation is equally important, as high glucose levels can induce the expression of aldosterone synthase, the last enzyme in the aldosterone synthesis pathway.[25] In what may become a vicious circle, the high aldosterone levels then inhibit insulin production in pancreatic ß-cells. High aldosterone levels also impair insulin signaling in peripheral tissues and exacerbate glucose intolerance and diabetes.[26] Two other biomarkers indicative of metabolic status may be evaluated with urine hormones, glucocorticoids and mineralocorticoids: xanthurenic acid and kynurenic acid (Figure 4). Elevated levels of xanthurenic acid are associated with type II diabetes in human studies and indicate an increased need for vitamin B-6.[27] If only kynurenic acid is elevated it is associated with a need for vitamin B-3, the precursor to nicotinamide adenine dinucleotide (NAD^+), an essential cellular cofactor.

Figure 3. Urine Hormone Results

Age: 29 Gender: F

Figure 4. Xanthurenic and Kynurenic Acid



Interventions

There are several types of inherited (familial) hyperaldosteronism, one of which responds to glucocorticoid therapy.[5] There are several other gain-of-function genetic changes also associated with primary aldosteronism; these changes are found either in tumors or in aldosterone-producing cell clusters (APCC) within the adrenal

tissues. If a tumor is identified, then surgical removal of the overactive tissues is often curative. Control of APCCs is more difficult and may require pharmaceutical interventions if sodium restriction < 65 mmol (preferably < 50 mmol) daily does not control the primary aldosteronism and increase renin levels. If the cause is unilateral adrenal hyperplasia, then surgery may again be considered; if the adrenal hyperplasia is bilateral, then medication is the preferred treatment.[28] Current evidence indicates that mineralocorticoid receptor blockers may be the preferred first-line medication.[10]

While human studies have not yet been performed, it is possible that early interventions and management of nutritional and lifestyle factors may either prevent or slow the progression of primary hyperaldosteronism. In addition to sodium restriction, interventions that might be considered include the following:

- Normalize body weight if body mass index (BMI) > 25 for women or 27 for men.[29]
- Vitamin D3
  - Vitamin D3 (> 800 IU daily) reduced both systolic and diastolic blood pressure in hypertensive individuals of normal weight. However, vitamin D with calcium, or vitamin D in overweight or obese individuals, may increase blood pressure.[30]
- Consider anti-hypertensive herbs for high-normal blood pressure or mild hypertension.[31] NOTE: Anti-hypertensive herbs may not be appropriate during pregnancy or nursing.
  - Aged garlic extract (960 mg QD) may lower systolic pressure by < 10 mmHg.
  - Berberine (< 1.5 mg QD) may decrease systolic pressure < 5 mmHg and diastolic pressure 2 mmHg.
  - *Crataegus* (hawthorn species) (500 mg QD) or water-alcohol extracts may decrease systolic pressure < 13 mmHg and diastolic pressure by < 8 mmHg.
  - *Crocus sativus* (saffron) (400 mg QD) may decrease systolic pressure < 11 mHg and diastolic pressure < 5 mmHg.
  - *Hibiscus sabdariffa* (roselle) dried calyx extract (250 mg) or dried calyx (10 gm), has reduced systolic pressure by <15 mmHg and diastolic pressure by <11 mmHg.
  - *Nigella sativa* (black cumin seed) 2.5 mL *N. sativa* oil BID may decrease systolic pressure <10 mmHg and diastolic pressure < 9 mmHg.
  - *Zingiber officinale* (ginger) constituent (6)-gingerol may antagonize the angiotensin type II receptor and inhibit angiotensin-converting enzyme I activity. A mean dose of 105 mg/kg body weight was required to decrease blood pressure.
- Taurine
  - Taurine has antioxidant properties, promotes vascular relaxation and improves vascular inflammation.[32] Taurine supplementation decreases hypertension and RAAS activity in animal models.[33]
  - Human studies demonstrate that taurine (six grams/day) reduced systolic, diastolic and mean arterial blood pressure in six weeks in salt-restricted hypertensives; another human study saw results within seven days, compared to placebo.[32] Doses as low as three grams have been found effective in other human hypertension studies. ➤

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- Stress management, specifically interventions that promote "rest and digest" signaling from the vagus nerve and increased heart rate variability, may decrease mineralocorticoid levels via reduced ACTH "fight or flight" signaling.[11,34,35]
- Consider bio-identical hormone replacement in post-menopausal women and, possibly, men with testosterone insufficiency to normalize estrogen levels.[36,37]
  - Confirm low hormone levels with laboratory testing and monitor to ensure that supplementation brings levels only into the physiological range.[38,39,40]
  - In post-menopausal women, human studies indicate that hormone replacement therapy significantly reduces blood pressure in both normotensive and hypertensive women.[41] Transdermal estradiol was superior to oral conjugated equine estrogens in reducing blood pressure.
  - Caution is indicated in men with testosterone insufficiency: use hormone evaluations pre- and post-supplementation both androgens and estrogens to ensure that conversion into vaso-dilating estrogens occurs via the aromatase enzyme. Use supplementation to achieve physiological levels of androgens; high levels of testosterone exacerbate hypertension.[42]
- Quercetin, 1,500-3,000 mg daily, in conjunction with other dietary flavonoids such as genistein, may induce aromatase activity in individuals with inherited low-activity forms of the enzyme.[43-45]
  - Modify cytochrome 1B1 activity through diet to decrease hypertension risk.
- Human studies indicate that 10 grams of ground flaxseed can modify CYP1B1 activity in women; studies on men are required.[46]
- Plant compounds such as stilbenes (resveratrol), coumarins (curcumin) flavonoids and flavanols (tea, fruits, vegetables, cocoa), have all been shown to inhibit CYP1B1 *in vitro*.[47,48]
  - 2-methoxyestradiol production may be improved by providing the nutritional co-factors of catechol-O-methyltransferase with magnesium (350 milligrams) and s-adenosylmethionine (600-1,200 mg daily).[49-51]

Conclusion

The prevalence of hypertension in adults was estimated to exceed 1.3 billion in 2016. The increased cardiovascular risk that accompanies high blood pressure can be managed most effectively if the cause, rather than the symptom, of hypertension is treated. Routine screening for aldosterone, renin and sodium in adult patients, particularly in those with a family history of hypertension or cardiovascular disease, is the best way to determine if primary aldosteronism is the cause.

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Testing for IgG, IgG4, and IgA-Mediated Reactions: Beneficial Implications for GI Health, Mood Disorders, Respiratory Health, and More

by Chris D. Meletis, ND

Exposure to food antigens can result in the production of different classes of antibodies, including immunoglobulin G (IgG), IgA, and IgE. IgE-mediated reactions are true allergies that can lead to hives and anaphylactic type reactions. These IgE-mediated reactions are obvious and occur soon after eating a particular food. In contrast, IgG reactions are delayed-type hypersensitivity reactions. The symptoms can occur hours or even days after consuming the problematic food and therefore can masquerade behind other apparent causes. IgE has a half-life of only two to three days, whereas IgG has a much longer half-life of 23 days.[1] Typically, these types of IgG reactions have been associated with gastrointestinal symptoms such as diarrhea, constipation, and abdominal bloating. However, newer research shows that IgG-mediated hypersensitivity reactions may be to blame for a more expansive number of health concerns, including nasal congestion, chronic sinus infections, joint pain, and headaches.[2]

IgG testing has long been used to pinpoint these delayed hypersensitivity reactions. However, there is a relative newcomer in the testing arena that can paint a more detailed picture of a patient's health: IgA testing. This article will address the newest research on IgG testing, explain the benefits of testing specifically for IgG4, and discuss the importance of IgA testing and which groups of patients can benefit the most from it. These testing options can be used together to yield clinically meaningful results.

New Research on IgG Testing's Role in Health

One of the most abundant proteins in circulation, IgG comprises approximately 10% to 20% of the plasma protein.[3] IgG testing is an important means of identifying delayed hypersensitivity reactions to food and other environmental irritants. IgG1-IgG3 trigger complement, leading to an inflammatory response associated with a number of health concerns. For example, IgG-mediated reactions are associated with the following:

Depression. In 184 adolescent patients with depressive disorder, markedly higher serum food antigen-specific IgG positive rates were detected compared to healthy controls.[4] Food antigens can enter the systemic circulation and create an immune complex with food antigen-specific IgG. Macrophages can remove the larger complexes, but the smaller ones can escape into the central nervous system (CNS), leading to neuroinflammation, or are deposited in blood vessels, joints, glomeruli, and other tissues, resulting in tissue damage, inflammation, and metabolic problems.[4] In the study of adolescents, the depressive disorder patients also had higher levels of histamine. A higher level of histamine indicates hypersensitivity mediated by food antigen-specific IgG, which suggests that the resulting blood brain barrier leakage may play a potential role in the pathogenesis of adolescent depression.[4]

Ankylosing spondylitis (AS). AS is a chronic autoimmune disease characterized by arthritis and inflammation at the sites where tendons and ligaments connect with the bone. Compared to healthy controls, people with AS have markedly higher serum concentrations of beef-, crab-, and pork-specific IgG.[5] In one study, serum concentrations of pork-specific IgG were significantly and positively associated with the inflammatory marker C-reactive protein (CRP).[5] This suggests that food

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intolerances induce inflammation, and this inflammation can in turn disrupt the gut microbiome.[5] According to the researchers, "These results suggest that α-Gal, the predominant natural antigen in mammalian red meat, might play a potential role in the pathogenesis of AS, and therefore, AS patients should exclude such allergenic foods, including beef, crab and pork, from their daily diet."

Migraines. In 30 patients with migraines, IgG antibodies against 266 food antigens were measured by ELISA.[6] The patients were randomized to a group participating in a six-week diet that either excluded or included specific foods that were shown to raise IgG antibodies. After the first diet period, the patients underwent two weeks of no dieting and then were put on the opposite diet for six weeks. When the participants were consuming an elimination diet (excluding foods to which they tested IgG positive), they experienced significantly reduced number of headache days and number of migraine attacks.

Asthma. In a case report of two patients, a diet that eliminated foods that demonstrated reactivity to IgG in serum testing such as wheat, dairy, and eggs led to less asthma symptoms, decreased dependence on medications, and improved quality of life.[7]

Table 1: Reliability and Reproducibility of US BioTek ELISA IgG Testing.[2]

Consistency of Testing During a Week	US BioTek ELISA Methodology (Number of foods out of 96 tested)
Identical Results	82% (79)
1 Reactivity Level Difference	17% (16)
2 Reactivity Level Difference	1% (1)
3 Reactivity Level Difference	0%
Coefficient of Variance	0.05
Intraclass Correlation Coefficient	0.99

Sleep. In a randomized controlled trial of overweight and obese adults, participants were randomly divided to either a group eating an elimination diet based on IgG test results for three months or a waitlist group.[8] The people eating the elimination diet were told to eliminate up to 10 foods for which they had high IgG levels. Health coaches also provided nutritional counseling to this group. The waitlist group were not informed of their IgG test results and did not receive health coaching. The group eating the elimination diet experienced an improvement in sleep during the study.

Irritable bowel syndrome (IBS). A number of studies have shown that IgG is associated with ulcerative colitis and Crohn's disease.[9] In a double-blind, randomized, controlled parallel study, patients with IBS had a significant decline in severity of symptoms and improved quality of life after they were put on an IgG-testing-based elimination diet compared to a sham diet. In an open label pilot study, IBS patients who had failed standard medical treatments demonstrated improvement in pain, stool frequency, and quality of life after they began eating a food elimination and rotation diet based on the results of IgG testing.[10]

Effectiveness of IgG Testing

Research indicates that when measuring IgG levels, ELISA testing is a highly effective means.[2] Hodsdon and Zwickey sent blood samples to US BioTek lab to measure IgG concentrations to various foods.[2] The researchers then determined results according to test repeatability on a split sample and test variability during a week. In the samples undergoing US BioTek ELISA IgG testing, of 96 foods tested, 91 foods (95%) were identical between split samples. The reported results were consistent on both a split sample over one day and during a week. The researchers found that ELISA IgG testing is a reliable and reproducible way to detect delayed hypersensitivity reactions. The study authors stated, "While the sample size was small, these tests are completed for individual patients in a clinical setting and thus, variability must be minimal for the test to be clinically valid."

The Clinical Usefulness of Testing for IgG4

In addition to IgG testing, patients can be tested specifically for IgG4. This IgG subclass does not bind to complement and therefore does not trigger inflammation.[11] IgG4 blocks more serious IgE-mediated allergic reactions through competing with IgE for the binding of an allergen to the same epitopes.[11,12] Thus, it can suppress the activation of mast cells and basophils.[12] It also blocks IgE-mediated antigen presentation to T cells.[11] IgG4 antibodies are produced after long-term exposure to an antigen. Consequently, IgG4 serves as an indicator of the extent of allergen exposure.[12] Furthermore, IgG4 antibodies are able to influence the immune response to an allergen.[11,12] IgG4 testing is useful in a number of applications. For example, it can be used to monitor the effectiveness of Allergen Specific Immunotherapy. As immunotherapy progresses, the IgG4/IgE ratio increases.[12] Immunotherapy regulates IgG4's blocking ability of IgE-mediated allergic responses.[12] Additionally, there is a relationship between increased IgG4 blocking activity and successful immunotherapy.[12]

IgG4 and Autism

Autism spectrum disorders (ASD) are associated with higher IgG4 levels, probably on account of the altered immune response that occurs in this disorder.[13] Researchers determined circulating plasma levels of IgG1, IgG3,

continued on page 48 ➤

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Testing for IgG, IgG4, and IgA-Mediated Reactions

➤ *continued from page 46*

and IgG4 in 241 children participating in the Childhood Autism Risks from Genetics and the Environment (CHARGE) trial.[13] The study included 114 children with ASD, 31 children with developmental delays, and 96 normally developing controls. Compared with developmental delay children and with healthy controls, significantly higher concentrations of IgG4 were detected in children with ASD. The study authors concluded, "These results may suggest an underlying immunological abnormality in AU [autism disorder] subjects resulting in elevated IgG4 production." Some studies have also indicated there is a relationship between high IgG4 levels in children with autism and behavioral symptoms.[14]

IgG4 and Irritable Bowel Syndrome

IBS patients have high IgG4 reactivity to certain foods. Compared to 43 controls, in 108 IBS patients, IgG4 antibodies to wheat, beef, pork, and lamb were higher.[15] Another study showed that IgG4 antibodies to milk, eggs, wheat, beef, pork, and lamb were often higher in 25 people with IBS.[16] After an elimination diet, pronounced improvement was noted at three months in pain severity, pain frequency, bloating severity, satisfaction with bowel habits, and effect of IBS on quality of life. The improvements continued at six months. Furthermore, other researchers have found that compared to controls, IgG4 antibodies to wheat, leek, and taro were significantly higher in patients with IBS.[17] Serum IgG4 antibodies to ginger, cocoa, walnut, white radish, onion, and lettuce tended to be higher in IBS patients than controls.[17] In a subgroup of IBS patients with diarrhea, IgG4 antibodies to wheat, gluten and gliadin tended to be higher compared with controls.[17]

IgG4 and Allergic Rhinitis

In 46 children with allergic rhinitis, IgG4 testing revealed 89.1% of participants had a strong reaction to egg white IgG4.[18] More than half the patients were significantly reactive to egg yolk, milk, peanuts, almonds, wheat, and soybeans. In examining the association between specific IgE and specific IgG4, the study authors found that egg whites, milk, peanuts, and almonds had significant correlations. Cod, shrimp, and crab yielded very significant correlations. The researchers concluded, "Food allergy generates highly concentrated IgG4 and may play a role in children with allergic rhinitis."

The Significance of IgA Testing

IgA is the second most abundant primary immunoglobulin antibody in circulation after IgG.[19] It is a seromucosa antibody and protects the mucous membranes such as the eyes, nose, throat, lungs, GI tract, and female urogenital tract from pathogens in the outside world. [19] It triggers an immune response to viruses and bacteria and other pathogens.[19,20]

Unlike IgG1-3, IgA does not activate complement, which would trigger inflammation.[20] This prevents the mucous membranes from remaining in a constant inflammatory state due to daily exposure to foreign substances.[20] IgA reactions to foods may result from inflammatory damage to the intestinal mucous membranes and the resulting intestinal permeability (leaky gut). Stress, alcohol, a diet filled with sugar and processed food, or even certain medications such as non-steroidal anti-inflammatory drugs (NSAIDS), oral contraceptives, and proton pump inhibitors are all implicated in this damage.[21-26]

Elevated IgA to specific foods indicates mucosal membrane damage. Measurement of this antibody is useful in patients with Crohn's disease, ulcerative colitis, or celiac disease as well as to verify the presence of leaky gut. In the presence of overt symptoms of mucous membrane impairment, measuring IgA-related responses is essential.

Conclusion

Testing for IgG, IgG4, and IgA antibodies against specific foods can be used effectively to develop a regimen for patients with gastrointestinal issues, mood disorders, allergic rhinitis, and asthma, among other conditions. IgA testing is especially meaningful in patients who have irritable bowel syndrome, celiac disease, or symptoms of leaky gut. US BioTek is currently the only lab that offers all three tests.

Dr. Chris D. Meletis is an educator, international author, and lecturer. His personal mission is "Changing World's Health, One Person at a Time." He believes that when people become educated about their bodies is the moment when positive change begins.

He is widely recognized as a world-renowned expert on the science of CBDs and has authored 16 books and over 200 national scientific articles in such journals and magazines as *Natural Health*, *Alternative and Complementary Therapies*, *Townsend Letter*, *Life Extension*, and *The Journal of Restorative Medicine*.

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Evaluation of Abnormal Liver Enzymes

by Keivan Jinnah, ND, MSOM, LAc

A new patient comes in to see you with recent lab results (CBC and CMP) in hand. Everything is within reference range except for a mild elevation of the ALT and AST (59 and 43 IU/l respectively). Her previous doctor told her not to worry about it, but she wasn't comfortable with that advice. She is coming to see you to figure out why her liver enzymes are high. She feels fine but is worried by her high enzymes. What is the thought process you go through to evaluate what is going on?

The most common cause of asymptomatic high enzymes is fatty liver disease.

This hypothetical (but very common) situation may present in many ways. My goal in this article is to walk through the thought process, differential, and lab testing involved in thoroughly evaluating an asymptomatic patient with abnormal liver chemistries.

First, a little bit about laboratory reference ranges or "normal" values. Reference ranges are not based on optimal ranges, or even necessarily healthy ranges. Each laboratory establishes its ranges based on a bell curve of all the people tested in that lab company. The reference range is set at 2 standard deviations from the mean, which, by definition, includes 95% of all people tested. This is why some labs will have upper normal limits of AST and ALT in the 40s IU/l, while others will be up to the 50s or 60s IU/l. I can't help but think about all of the occult chronic hepatitis C infection, endemic fatty liver disease, and polypharmacy usage in the population driving up the mean level of liver enzymes. We know how important healthy liver function is for maintaining homeodynamic balance and health in the body. I want my patients' liver enzymes to be optimal, not just within a range of mostly ill people, and if the enzymes are higher than that, I want to know why.

What are optimal liver enzyme levels? Fortunately, there have been a few good studies looking at this question and how the optimal ranges differ for women and men. One large study published in 2004 looked at 94,533 men and 47,522 women in Korea aged 35-59 years old.[1] They looked at the connection between a normal range of serum aminotransferase concentration and mortality from liver disease according to death certificate. What they found is that there was a positive association between the aminotransferase concentration, even within normal range (35-40 IU/l), and increased mortality from liver disease. Compared with <20 IU/l, the relative risks of dying from liver disease for an AST concentration of 20-29 IU/l and 30-39 IU/l were 2.5 and 8.0 in men and 3.3 and 18.2 in women, respectively. The corresponding risks for ALT were 2.9 and 9.5 in men and 3.8 and 6.6 in women, respectively. The study concluded that the best cut-off values for the prediction of liver disease in men were 31 IU/l for AST and 30 IU/l for ALT. The study was not able to calculate best cut-off values for women due to insufficient data; but it is clear, and concluded by the researchers, that the optimal values for women would be lower than for men, especially for AST.

In 2017 the American College of Gastroenterology (ACG) published its assessment for optimal liver chemistry ranges.[2] The ACG stated that multiple studies have demonstrated that an elevated ALT has been associated with increased liver-related mortality and that a true healthy normal ALT level ranges from 29 to 33 IU/l for males, 19 to 25 IU/l for females. The ACG recommended evaluation of any patient with liver chemistries above those optimal values.

Both ALT (formerly SGPT) and AST (formerly SGOT) exist in highest quantity in the hepatocytes of the liver. ALT is found almost exclusively in the hepatocytes whereas AST is also found in significant quantities in other cells of the body. AST outside of the liver, in descending order of quantity, is found in cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes. For this reason, an elevated AST may be the result of breakdown of one of these extra-hepatic tissues whereas ALT is much more specific to damage in the liver.

An isolated elevation of AST is worrisome for muscle breakdown (consider injury, extreme exercise, polymyositis), or cardiac muscle deterioration (high isolated AST has been used historically as a marker for possible myocardial infarction), acute hemolytic anemia, acute pancreatitis, and acute renal disease. The healthy upper limit of AST for males is higher than that for females because, as a population average, males have higher muscle mass which will contribute to higher normal AST levels. This would be true of any larger person, regardless of gender. Said in a different way, a

high normal or mildly elevated AST in a woman, or smaller person, is more clinically significant and in need of investigation.

If both AST and ALT are elevated, then liver inflammation is almost certainly the source. Alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and bilirubin should be looked at for concomitant elevations as markers of inflammation and stasis in the biliary tree system. Elevations of GGT in addition to elevated ALP will help identify the ALP as coming from the liver as opposed to bone. A higher ALP elevation in relation to liver enzyme elevation will indicate primarily a biliary tree inflammation, and conditions involving cholestasis should be investigated, including primary biliary cholangitis (PBC – previously called primary biliary cirrhosis), primary sclerosing cholangitis (PSC), cholelithiasis, stricture, and cancer. Higher liver enzyme elevation relative to ALP will indicate a primarily hepatocyte injury. In hepatocyte injury, ALT will typically be elevated higher than AST (because of greater ALT in the liver cells), but important exceptions are alcoholic hepatitis, Wilson's disease, and potentially liver cirrhosis and liver cancer. Alcoholic liver disease has a classic reversed ratio of AST>ALT, often ≥ 2:1. This is due to alcohol's depletion of pyridoxal-5-phosphate that is a necessary cofactor in the production of ALT.

The classic differential for mild transaminase elevation, defined as <5x above normal limit, (which we know now is really any liver enzyme between 30-150 IU/l) is

- Fatty liver,
- Alcoholic liver disease,
- Chronic viral hepatitis B or C ,
- Pharmaceutical, OTC, street drug, or herbal supplement reaction,
- Hemochromatosis (autosomal recessive, homozygous 1/400, heterozygous 1/12),[3]
- Neoplasm,
- Autoimmune liver disease,
- Biliary cholangitis,
- Wilson's disease, and
- Alpha-1 antitrypsin deficiency.

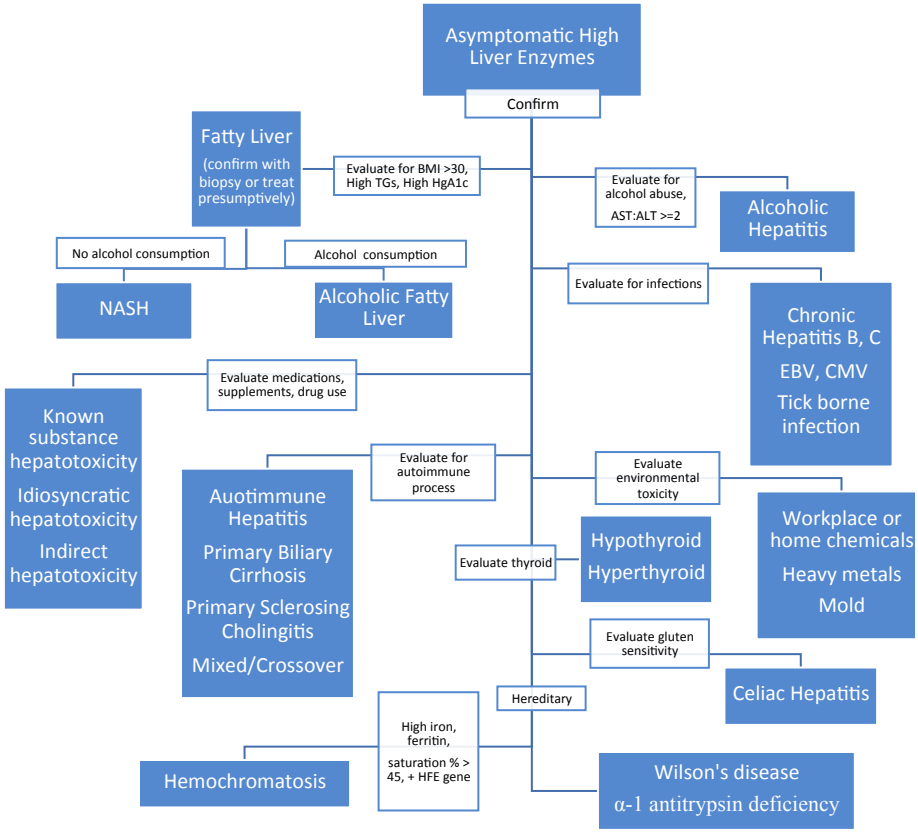
Other causes of mildly elevated liver enzymes that are often overlooked in the classical differential include the following:

- Acute or chronic infection with EBV and other herpes strain viruses such as cytomegalovirus,
- Environmental or heavy metal hepatotoxicity,
- A highly processed or fast food diet,
- Gluten sensitivity,
- Thyroid disease (hypo or hyper), and
- Tick-borne disease.

Any and all these things may result in increased hepatocyte membrane injury, leading to an increase of transaminase enzymes being dumped into the blood stream. The short way of saying this is that they all create liver inflammation. The reality, of course, is that many patients have more than one thing inflaming their liver. A good history and some follow-up lab work should help focus in on the singular, or multiple, causes of the liver inflammation and help determine whether a liver biopsy is necessary for definitive diagnosis or evaluation of the extent of the liver damage.

In terms of prevalence, (in order to keep our eyes on the horses before we go chasing the zebras), the most common cause of asymptomatic high enzymes is fatty liver disease (FLD), followed by chronic viral hepatitis (CVH), then alcohol-related liver disease (ALD). A 1996 review of four studies found asymptomatic elevation of liver enzymes was due in 42% of cases to FLD, in 24% of cases to CVH, in 14% to ALD, in 11% to rare liver disease or no cause found, and in 7% to liver cirrhosis.[4] The rare liver diseases included drug reactions, hemochromatosis, alpha-1 antitrypsin disease, biliary cirrhosis, Wilson's disease, sclerosing cholangitis, granulomatous colitis, sarcoidosis, and extrahepatic obstruction. Other studies have found that the prevalence of the cause of elevations of enzymes depends greatly on the population studied.[5] With those top three conditions responsible for roughly 80% of cases, they need to be ruled out first. One of the difficulties posed is that the definitive diagnosis of FLD requires a liver biopsy, and it is debatable if that intervention is warranted. There are many less invasive clues that will indicate the likelihood of fatty liver disease and may inform the need for that intervention. Thorough work up and exclusion of other ➤

Figure 1: Flow Chart for Differential of Asymptomatic Hypertransaminasemia



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conditions is still necessary to clarify all contributing causes and to prioritize action.

Back to our hypothetical patient: Is an ALT of 59 and an AST of 43 IU/l something to investigate? Absolutely.

The steps of how I would evaluate any patient presenting with a mild (30-150 IU/L) to moderate (150-450 IU/L) elevation of their ALT and AST would look like the following (See Figure 1):

1. Confirm high liver enzymes with follow up test. Not necessary if patient has had repeated history of high enzymes.
2. To save on time and blood draws, include the second level of tests at this time, including lipid panel (looking for elevated fasting triglycerides), HgA1c, fasting glucose and fasting insulin (helpful in evaluating the likelihood of FLD); hepatitis C Ab, hepatitis B sAg, sAb, cAb (CVH); tTg IgA and IgG, DGP IgA and IgG, total SIgA (celiac disease/gluten sensitivity); serum iron, TIBC, transferrin saturation %, and ferritin levels (hemochromatosis); ANA and F-actin antibody (autoimmune hepatitis), serum ceruloplasmin (Wilson's disease), and full thyroid panel. Consider serum protein electrophoresis (marked decrease in alpha-globulin bands suggests alpha1-antitrypsin deficiency).

Depending on history, I may also consider hormone evaluation, especially looking for low testosterone in middle-aged men as a risk factor for FLD.[6]

3. Evaluate patient's diet, BMI, and blood sugar control as risk factors for FLD as well as inflammation due to nutrient-poor, highly processed food diet. Indications of FLD include elevated fasting triglycerides, high HgA1c,[7] higher waist circumference, elevated fasting insulin, and elevated body mass index.[8] We know that FLD is strongly associated with insulin resistance, diabetes, and obesity.[9,10] Consumption of alcohol may contribute to the development of FLD, but it is not a necessary component. Non-alcoholic steatohepatitis (NASH) is strongly linked to obesity, blood sugar dysregulation and insulin resistance, independent of alcohol.[11] Further workup to establish the presence of insulin resistance and diabetes should be done.
4. If the AST:ALT ratio is ≥2:1, then strongly consider the likelihood of ALD. Greater than 90% of patients with >2:1 ratio of AST:ALT were found to have ALD.[12] This potential cause of high enzymes will need to be evaluated with a good history and discussion with the patient. Alcohol consumption is notoriously underreported by patients. (One rule of thumb is to take what a patient tells you and multiply by 5.) One lab marker that may indicate chronic alcohol abuse is an elevated GGT. This enzyme is very sensitive to alcohol but is not specific. GGT is also raised in pancreatic disease, myocardial infarction, renal failure, COPD, diabetes, and certain medications, including phenytoin and barbiturates.[13] If the patient is a heavy alcohol user, or alcoholic, then that would be the primary issue to address to reduce liver inflammation even if other things are going on. Naltrexone may be helpful to reduce the patient's alcohol cravings.
5. If testing is positive for either chronic hepatitis B or C, then evaluation for conventional antiviral therapy is warranted. A positive HBVsAg indicates current hepatitis B infection. A positive HBVsAb indicates past cleared infection or past immunization to hepatitis B. A positive HBVcAb indicates a past infection.
6. Medications, supplements, and street drugs need to be evaluated for contributing to, or causing, liver inflammation in our patients. The National Institutes of Health website LiverTox (http://livertox.nih.gov) lists over 1200 agents, including prescription and over-the-counter medications, herbal products, nutritional supplements, metals, and toxins, and describes their potential to cause liver injury; 447 prescription drugs have been implicated in at least one published case of liver injury.[14] There are three types of drug or herbal induced liver injury: direct, idiosyncratic, and indirect.[15]

Table 1: Liver Toxicity of Botanicals[17,21]

Potentially Liver Toxic Herbs	Proposed Mechanism
Pyrrolizidine Alkaloid containing herbs: *Petasites hybridus* Senecio Symphytum (Comfrey) Borage Eupatorium Lithosperma Tussilago (colt's foot)	Direct hepatotoxicity. Pyrrolizidine alkaloids which are metabolized by the cytochrome P450 enzymes into highly toxic pyrrole metabolites can damage hepatic endothelial cells and can cause sinusoidal obstruction. The toxicity is dose dependent and can be increased by P450 enzyme inducers such as phenobarbital.
Germander	Direct hepatotoxicity, dose dependent. Well established.
Cascara Green tea extract/catechin Senna Usnic acid/kombucha tea	Direct hepatotoxicity possible in very high doses, perhaps in the context of some degree of host susceptibility.
Aloe vera Black cohosh Chaparral Ephedra (ma huang) Jin Bu Huan - Chinese herbal Kava Kava Red Rice Yeast Scutellaria (Skullcap) Sho Saiko To/ Xiao Chai Hu Tang – Japanese/Chinese herbal Turmeric	Idiosyncratic toxicity. No direct toxicity found. Rare cases have been reported. It is possible that contamination of the herbal products is responsible for the hepatotoxicity as cases are very few and these herbs are widely used.

Direct hepatotoxicity is caused by medications and other substances that have an intrinsically toxic effect to the liver. This toxicity is dose dependent, predictable, and reproducible in animal models.[15] The drugs most associated with this direct hepatotoxicity are high doses of acetaminophen, aspirin, niacin, amiodarone, and many antineoplastic agents, as well as intravenous buprenorphine, methylprednisolone and tetracycline.[14]

Special attention needs to be paid to acetaminophen-containing products as they are available over-the-counter in many forms and are responsible for more than 56,000 emergency room visits, 2,600 hospitalizations, and an

estimated 458 deaths due to acute liver failure each year in the US as of information published in 2004.[16] The US Acute Liver Failure Study Group registry of more than 700 patients with acute liver failure across the United States implicates acetaminophen poisoning in nearly 50% of all acute liver failure in this country.[16] The hepatotoxic potential of acetaminophen is magnified greatly if it is used in conjunction with alcohol, or by someone who is a chronic user of alcohol, due to the depletion of glutathione that is needed for acetaminophen detoxification. As William Lee asked in his article in *Hepatology* in 2004 in regards to the incredible human toll and hepatotoxicity of acetaminophen: "Is this amount of injury and death really acceptable for an over-the-counter pain reliever?"[16]

The number of cases of liver toxicity as a result of herbal or supplement ingestion is very small in comparison to that of acetaminophen, but they seem to receive an outsized amount of attention and reaction. Table 1 shows the botanical medicines most associated with hepatotoxicity.

Idiosyncratic hepatotoxicity involves substances that have little or no intrinsic liver toxicity but can cause liver toxicity in rare cases. (1 in 2000 to 1 in 100,000 patient exposures).[15] These injuries are not dose-dependent, not predictable and not reproducible in animal models. The prescription drugs that are most likely to cause idiosyncratic hepatotoxicity, in descending order of reported cases, are amoxicillin-clavulanate, isoniazid, nitrofurantoin, TMP-SMZ, minocycline, cefazolin, azithromycin, ciprofloxacin, levofloxacin, diclofenac, phenytoin, methyldopa, and azathioprine.[15] It is important to note that nine of the top ten drugs reported are antimicrobial agents, mostly antibiotics. The cholesterol lowering statin class of medications appears to have both mild direct as well as idiosyncratic liver toxicity.[17]

The third, and more recently recognized, category is indirect drug-induced liver injury.[15] These medications result in an induction or exacerbation of a liver disease rather than injuring the liver directly. Examples include risperidone, lomitapide, and glucocorticoids worsening fatty liver disease because of their effect on weight gain, or triglycerides, or insulin sensitivity. Another example is anticancer chemotherapeutic agents or corticosteroids reactivating a hepatitis B infection resulting in acute hepatitis. A third example is immunomodulating agents, such as monoclonal antibodies or interferon, creating immune-mediated liver injury.[15]

Liver Enzymes

In a patient with unexplained liver enzyme elevations, I recommend discontinuing any medications, supplements, and drugs, that are not absolutely necessary with extra attention to those more recently added to the patient's regimen.

The next steps of how I would evaluate any patient presenting with a ➤

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mild (30-150 IU/L) to moderate (150-450 IU/L) elevation of their ALT and AST include the following:

7. Exposure to environmental toxicity, including workplace and home chemicals, heavy metals, and mold should also be assessed. History is very important here. The different lab assessments available for such toxicity is a topic much discussed in the *Townsend Letter,* and I will not enter the discussion here other than to bring attention to the hepato-inflammatory potential of these toxins.
8. Don't forget the possibility of dietary gluten as a cause of your patient's liver inflammation. Celiac disease was found to be present in about 9% of patients with chronic unexplained liver enzyme elevation.[18] In another study, it was found that isolated transaminitis with nonspecific histological changes in a liver biopsy is the most common hepatic presentation of celiac disease.[19] Gluten reactivity also frequently co-exists with autoimmune liver disease.[19] In the studies that I reviewed that looked at different causes of asymptomatic liver enzyme elevations, there is always a percentage that are found to be of unknown cause, typically in the high single digits. Rarely in these studies is gluten sensitivity or celiac disease tested as a potential cause. I think it is very possible that gluten sensitivity, and the resultant hepatic inflammation, may account for at least part, if not all, of the "unknown cause" found in these studies.

I believe that gluten sensitivity exists on a continuum, with celiac disease in its most extreme form on one end and mild non-celiac gluten sensitivity (NCGS) on the other end. There are many shades of intensities as we move from one end of the spectrum to the other. It makes complete sense to me that the hepatic inflammatory potential of gluten can exist anywhere on this continuum and is not reserved for only the most extreme gluten sensitivity (ie. celiac disease). Based on this, laboratory testing for gluten sensitivity, in the context of liver inflammation, is challenging. Standard screening tests for celiac disease include tissue Transglutaminase (tTG) and deaminated gliadin peptide (DGP) antibodies in the serum. These antibodies should be tested with the patient eating gluten in their diet for at least four weeks prior to testing. A definitive diagnosis of full-blown celiac requires a small intestinal biopsy with visualized villous atrophy. My concern here is that many people are not at the far end of the spectrum and that these tests will not capture the patient who has NCGS and reactive enough to gluten that its consumption is resulting in liver inflammation.

We know that eating a gluten-free diet normalizes liver enzymes and histological changes in celiac patients.[19] I will often recommend that patients adopt a gluten-free, whole foods diet while we are determining the cause of their high enzymes.

9. After two-to-three months of gluten-free whole foods diet and elimination of potentially hepato-inflammatory medications and supplements, retest patient's liver enzymes.
10. If the patient has been compliant and enzymes are still elevated and the first level of lab testing did not uncover an explanation, then consider the next level of testing. This would include Epstein Barr virus comprehensive panel, including early antigen as an indication of reactivation of the virus, Cytomegalovirus, and possibly other herpes strains. Mild liver disease can be produced by all the human herpesviruses in the course of systemic illness.[20]
11. If other causes have been excluded and/or history warrants, then tick-borne infections should also be considered as a cause of liver inflammation. Again, testing is imperfect and, in these infections, expensive. I would want a stronger clinical case than just mildly elevated liver enzymes to justify pursuing this path.

Through the process of differentiating, we may employ imaging or liver biopsy. A liver ultrasound is minimally invasive and will help with the diagnosis of fatty liver disease as well as liver tumor and cholelithiasis. A liver biopsy is sometimes needed for definitive diagnosis (fatty liver disease, cancer, alcoholic liver disease) and is often employed both to confirm diagnosis and to assess the degree of fibrosis and inflammation in the liver from the disease process. Utilization of these procedures will depend on the uncertainty of the diagnosis and the chronicity of the liver enzyme elevation.

As wholistic practitioners we know how vital the liver is (the only organ with the word "live" in it) in keeping us healthy. Any elevation of liver enzymes in your patient should be investigated.

Keivan Jinnah, ND, MSOM, LAc, is a naturopathic physician, licensed acupuncturist, and a board-certified Chinese herbalist. He completed a four-year doctorate of naturopathic medicine and a three-year masters of science in Oriental medicine at the Natural College of Naturopathic Medicine (NCNM) in Portland, Oregon. His thesis work investigated both naturopathic and Chinese medicine treatments for hepatitis C and chronic liver disease.

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Dr. Jinnah is in private practice at Clinton Street Health Care in Portland, Oregon, where he continues to lecture and synthesize Eastern and Western natural treatments for hepatitis C

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On the cover

Ketamine for Depression and Mood Disorders

by Erica Zelfand, ND

"I did something crazy. Don't get mad," says May, a 30-year-old woman with a longstanding history of severe anxiety. I look at her and raise my eyebrows.

May explains that after reading some articles on the use of the anesthesia drug ketamine in the treatment of mood disorders, she became eager to try it for herself. She consulted a few doctors locally, all of whom were unfamiliar with the treatment, before finally finding a ketamine provider in another state – whom she couldn't afford to see. May then did something I would never recommend doing: she procured a small pouch of the stuff, called her best friend over to "chaperone," and snorted a line.

I can barely see May as she tells me her story, as I've reflexively covered my face with my hands. Realizing that I am probably *not* creating a supportive atmosphere with this body language, I peel my palms away from my face, place them on my knees, take a deep breath, and ask, "Okay, so then what happened?"

"I fell into a K-hole," she says, and my hands are back on my cheeks. "K-hole" is slang for the detached feelings and loss of motor control that accompany a moderate to high dose of ketamine.

"…but I knew that might happen," she continues cautiously, "so I didn't freak out. I just kept breathing." May does her best to describe the mystical visions she saw while under the drug's acute influence. "I viewed my life from totally new angles, like my consciousness was this golden cake batter being mixed and folded over and over. And then I could really see what my life might look like if I made some intimidating but totally doable changes."

The above conversation happened about two weeks after May's ketamine experience. In that short period of time, May had ended a toxic three-year relationship and applied to graduate school. She also denied having had *any* panic attacks in that time and was happy to report that she hadn't popped a single Ativan, the benzodiazepine medication she used to take almost daily for anxiety.

I had heard of ketamine's off-label use in the care of treatment-resistant depression and other mood disorders before but hadn't thought much of the matter until this conversation with May. Since then, my understanding of and appreciation for ketamine's role in the treatment of a variety of stubborn mental health conditions has deepened greatly.

Ketamine's Antidepressant and Mood-Stabilizing Effects

Ketamine is readily available, is inexpensive to manufacture, and has a relatively good safety profile. It is likely for these reasons that it is the most popular anesthesia drug worldwide, used to induce temporary anesthesia, amnesia, and paralysis.[1] Its low risk for causing respiratory suppression and other complications make ketamine the anesthetic of choice in various surgical and procedural settings, including those in adults, children, and animals.[2-4]

When used at sub-anesthesia doses, ketamine causes dissociation, or feelings of detachment from one's own body. At a slightly higher dose – somewhere between dissociation and loss of consciousness – ketamine can also induce a mystical journey, in which the user experiences transcendental visualizations and potentially gleans new insights about their life. Ketamine is sometimes used recreationally, a context in which the drug is referred to as "Special K."

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Ketamine

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Although it is by no means a new substance, ketamine is now being viewed from an entirely new angle. The recent explosion of interest in ketamine in the treatment of mood disorders has yielded several clinical trials demonstrating the drug's great potential as a treatment for severe, chronic, and/or treatment-resistant depression and suicidality.[5-10]

Ketamine treatment is well-suited for patients who are "stuck" in chronic depression.

The drug is further being investigated as a potential treatment for anxiety,[11,12] alcohol and substance use disorders (addictions),[13] depression associated with acute alcohol withdrawal,[14] bipolar depression (manic depression),[15,16] obsessive-compulsive disorder (OCD),[17] post-traumatic stress disorder (PTSD),[18,19] various chronic pain disorders,[20,21] and personality disorders.[22]

Megan Oxley, MD, an emergency room doctor turned ketamine specialist and one of the founding members of American Society of Ketamine Physicians (ASKP), explains that ketamine treatment is well suited for patients who are "stuck." "There is a specific pattern happening in the brain that will not stop firing in certain conditions," she explains, "and the goal is to 'unstick' people so they can move forward."

Post-treatment, Dr. Oxley often hears her patients say things like, "I feel like a layer of dust has been cleared off of my brain," and "I feel like my brain went through the carwash." Or, as one patient put it, "I have a presence of mind now that I knew was there but that I could not reach before. It's just calm now."

Do We Really Need Another Antidepressant Drug?

Depression is the most common mental illness and the leading cause of disability worldwide.[23] It afflicts women more often than men.[24] Anxiety too is a common ailment – so common that it is often mislabeled as stress, insomnia, or just a natural consequence of living in a fast-paced society. According to a 2017 survey conducted by the National Institute of Mental Health (NIMH), over 18% of American adults live with mental illness – that's almost one in five people, or an estimated 46.6 million individuals.[25]

Despite the liberal prescription of pharmaceutical antidepressant medications, depression and anxiety rates have unfortunately continued to steadily climb.[26] In recent years it has become clear that antidepressant and anxiolytic drugs don't work nearly as well as they used to or as we once thought they did,[27] and the theory that depression is caused by serotonin deficiency or a shortage of other monoamine neurotransmitters has yet to be substantiated.[28] Patients, providers, researchers, and even journalists are questioning the efficacy of antidepressant drugs with such intensity that somehow the field of psychiatry itself has come under serious scrutiny.[29] With a paucity of new drugs going to market, there has been a growing interest in considering new applications of already-existing drugs, ketamine being among the most promising.

Ketamine has been shown to yield robust, rapid improvements in mood and behavior, significantly alleviating depressive symptoms and suicidal ideation within a matter of mere hours or days.[30-32] It has been demonstrated to affect brain chemistry more quickly and effectively than conventional antidepressant drugs,[33] which typically require daily dosing for a matter of weeks before yielding inconsistent results.[34] Ketamine further appears to be less likely than SSRI drugs to trigger mania in those with bipolar disorder.[35,36]

How Does It Work?

Discovered in 1962 and approved by the FDA in 1970, ketamine (2-O-chlorophenyl-2-methylamino cyclo-hexanone) is by no means a new drug.[37] Most of our understanding of its chemical mechanisms, however, is appreciated through the lens of anesthesiology. Specifically, the drug is an uncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDAR) and subsequently influences glutamate concentrations.[38-41]

NMDAR antagonism helps mitigate pain by dampening central hypersensitivity and reducing opioid tolerance,[42] and is also likely responsible for ketamine's dissociative, anesthetic, amnesic, and hallucinatory properties.[43]

It's not entirely clear how NMDAR antagonism yields positive outcomes for mental health, however.[44] One hypothesis is that ketamine causes a persistent increase in glutamate release in certain regions of the brain, which in turn engenders and sustains antidepressant effects.[45-48] Another hypothesis suggests that ketamine's inhibitory effect on NMDARs influences a cascade of cellular signaling in such a manner as to augment synaptic plasticity.[49] To this point, ketamine's antidepressant effects are not only rapid in onset, but are also quite durable, outlasting the drug's physical presence in the body post administration.[50]

NMDAR antagonism is likely not the full story on how the drug alleviates depressive symptoms, however.[51]

Ketamine has been shown to influence opioid receptor sites and affect dopamine turnover, which may further explain not only its calming, antidepressant, and pain-relieving benefits, but also its potential for abuse.[52,53]

Ketamine has further been demonstrated to stimulate the production of brain-derived neurotrophic factor (BDNF), a protein that supports adult neurogenesis.[54,55] Ketamine has also been shown to augment synaptogenesis, thereby enhancing synaptic function and plasticity far greater than the SSRIs and other common antidepressants.[56] When administered to rats, ketamine led to increased growth and improved function in the dendritic spine synapses of the prefrontal cortex. It has been hypothesized that ketamine rapidly enhances neural connectivity by creating new

connections between already-existing neurons – a process that yields benefits much more rapidly than waiting for new nerve cells to grow. This improved connectivity between neurons may very well alleviate mood imbalances.[57]

Models for Ketamine Treatment

A quickly growing base of practitioners are eagerly treating their patients with ketamine, employing a variety of administration routes and dosing regimens. There is no one set protocol for using ketamine in the treatment of mental health ailments, however; and practitioners disagree on how to best use the drug in these off-label contexts. The lack of one clear gold standard of use reflects not only the novelty of ketamine as a mental health drug, but also its versatility. "The beautiful thing about ketamine is there are so many ways to use it," explains Dr. Oxley.

Most of the approaches to using ketamine in patients with depression and other mood disorders fall into one of four categories: (1a) stand-alone intravenous infusion [upon which is modeled the (1b) FDA-approved use of S-ketamine nasal spray]; (2) very low-dose nasal spray or troche as daily or semi-weekly maintenance; (3) ketamine-assisted psychotherapy; and (4) ketamine-induced mystical journey followed by integration counseling.

Stand-Alone Intravenous Infusions

In this approach, also known as the Diamond & McShane protocol, a patient receives ketamine through a chemotherapy-based model entailing an intravenous (IV) infusion of the drug at a dose of 0.5 mg/kg delivered over 40 to 60 minutes. A typical course of treatment consists of an initial burst of six such treatments clustered within a two-week period to "reset" the NMDARs followed by ongoing maintenance treatments every four to six weeks or as needed.

Curiously, the 40-to-60-minute appointment length of the Diamond & McShane protocol was likely inspired by the business model of chemotherapy and applied to ketamine treatment for scheduling convenience. Likewise, the choice of six infusions over two weeks is likely borrowed from the world of electroconvulsive therapy (ECT).

Nevertheless, this method of ketamine administration has been endorsed by the National Institute of Mental Health (NIMH) and the American Psychiatric Association (APA).[58,59] Serial IV infusion is perhaps the most common (above-board) method of ketamine administration in America today, and for good reason: a series of six ketamine infusions was shown in one (small) study to send 66% of depressed patients into remission,[60] and a whopping response rate of 71% was observed in another trial.[61]

Although this approach typically yields robust antidepressant effects for most patients,[62,63] that relief is typically nondurable, with benefits lasting anywhere from a few days to a few weeks post infusion and thus necessitating ongoing treatment. This model also reflects a staunchly Western emphasis on biochemical properties, pulling the locus of healing away from the patient and nature, instead projecting it onto a synthetic chemical delivered in a rather "medicalized" milieu. Patients receiving this method of treatment have an IV catheter in their arm for around an hour, which is neither the most comfortable (nor comforting) experience for most people.

But Raquel Bennett, PsyD, ketamine treatment specialist and the founder of the KRIYA Ketamine Research Institute, patiently points out the merits of this protocol, explaining that it's a fantastic treatment option for those who are too depressed to engage in the psychotherapeutic counseling process, those who have already tried therapy or feel "talked out," those who are acutely suicidal, and/or those with genetically-influenced glutamate processing issues.

Eli, a 53-year-old with chronic depression and a strong family history of depression and death by suicide, is one such patient who benefitted from IV ketamine. After tearing his ACL playing soccer, Eli underwent arthroscopic surgery and woke in the recovery room with his depression nowhere to be found. Much to his surprise, the following ten days were some of the best of his adult life, mood-wise, after which time the dark clouds of depression slowly crept back.

Convinced his temporary improvement in mood had something to do with the surgery, Eli procured his medical records and "Googled" every drug listed in the procedure notes. This led Eli to articles about ketamine's off-label use in the treatment of depression, which motivated him to find a ketamine provider and begin a course of treatment. Twenty-four hours after his first ketamine infusion, Eli's PHQ-9 depression scale score dropped from 19 to 6. He now receives ketamine infusions every six weeks or so, incorporating the drug into his ongoing maintenance plan of counseling, healthy eating, and exercise. He says this is the best he's consistently felt in his entire adult life.

FDA-Approved Nasal Spray

The FDA has recently approved an S-ketamine (esketamine) nasal spray for the treatment of depression.[64]

Ketamine is a chiral molecule, meaning it exists in both "left hand" and "right hand" forms, known as S- and R-enantiomers, respectively. The FDA has not approved both enantiomers in the treatment of depression, however, just the "left-handed" S- form.

Manufactured by Johnson & Johnson and sold under the brand name Spravato, S-ketamine is administered under medical supervision at approved treatment facilities using a model quite similar to the IV infusion approach described above.[65,66] Spravato comes with a price tag of $590 per 56 mg and $885 per 84 mg, which means that bi-weekly treatments during the first month of care run anywhere from $4,720 to $6,785 – and that's just for the drug itself, before administration and observation costs.[67] It's likely no coincidence that the patentable (read: profitable) form

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of the drug was used in the studies funded by J&J that ultimately led to the FDA's approval of S-ketamine – and not generic ketamine – for the treatment of depression.

Regular, racemic ketamine – a fraction of the cost at $0.50 to $3.75 for 100 mL – yields great results, however, making doctors question if the "fancy" S-form is truly any better. Nevertheless, the FDA's approval of S-ketamine has paved the way for insurance coverage of ketamine therapy, which may be a win for patients who could not otherwise afford the treatment.

Daily or Semi-Weekly Ketamine Maintenance

Another approach to ketamine treatment entails taking the drug at low doses daily or semi-weekly, typically in the form of nasal spray or troche prepared by a compounding pharmacy and dispensed directly to the patient.

With the nasal spray, a patient takes anywhere from 60 to 100 mg of ketamine spray daily. A dosage commonly seen at one compounding pharmacy I consulted is one spray per nostril three to five times daily, with each pump delivering 10 mg of ketamine. As an alternative option, the drug can also be administered in sublingual or buccal troche format, at a dose ranging anywhere from 20 to 600 mg. Many individuals experience poor absorption of ketamine in troche form; hence the higher dosage use and the broad range of dosages available. The most common side effect of these formulations is feeling "disconnected," which is perhaps unsurprising, considering that ketamine is a dissociative drug. Reducing the dose typically resolves this symptom.

Low-dose ketamine therapy can be used as an ongoing standalone therapy or in conjunction with the Diamond & McShane protocol to prolong the intervals between infusions. In fact, Dr. Oxley estimates that ketamine troches taken two to three times weekly allow her patients to double the length of time they can wait between intravenous treatments.

Ketamine-Assisted Psychotherapy

In another application of ketamine in the treatment of mood disorders, the drug is administered within the context of an individual or group therapy session overseen by a medical provider and a trained counselor. In this setting, the drug can be taken via intramuscular or subcutaneous injection in the dose range of 0.3 to 0.8 mg/kg. The drug can also be taken as a troche or drank as a "cocktail" of the injectable liquid mixed with juice. Lasting anywhere from 90 minutes to three hours, these ketamine-supported sessions leverage the dissociative effects of the drug to improve the "mileage" of psychotherapy, allowing patients to take a more active role in the healing process.

"The goal is typically to get the patient to focus on something they want to address but that's otherwise been difficult to access emotionally," explains psychologist and qualitative researcher Will Barone, PsyD. The dissociative effects of the drug at this dosage help to ease hypervigilance and relax defense mechanisms, thus allowing patients to explore subject matter that might otherwise be too painful to approach in therapy.

Ketamine's influence on synaptic function and plasticity may further serve as an adjuvant to psychotherapeutic counseling and may help patients make new connections – both literally and metaphorically. Considering the transient nature of ketamine's pharmacological effects, pairing the drug's acute actions with psychotherapy is highly likely to enhance the durability of its therapeutic outcomes.[68]

The approach of ketamine-assisted therapy is not dissimilar to the model of using MDMA during therapy sessions in the treatment of treatment-resistant PTSD – a breakthrough therapy currently in Phase 3 clinical trials that's showing great promise.[69,70]

One ketamine-assisted therapy success story is that of Moe, a 26-year-old graduate student who had struggled with depression since adolescence. After trying numerous medications, from antidepressants to testosterone injections, Moe decided to try ketamine-assisted psychotherapy. Moe relaxed as the dissociative effects of the drug took hold. Sensing a great distance between himself and his woes, Moe was able to fully admit to himself that he was gay and that there wasn't anything he could do to change that. Unveiling and acknowledging this piece of his identity allowed Moe to make sense of his lifelong struggles: raised in a religious household, Moe's staunchly conservative father had often beaten up on Moe, pushing him to be more "masculine." Moe always knew his father was ashamed of him, and he unknowingly took on that shame in childhood, hating himself for being "a sissy boy." Since uncovering and reprocessing this piece of his history, Moe has focused subsequent (non-medicated) therapy sessions on fostering self-acceptance and creating healthy boundaries.

When we consider the situational undertones of depression and anxiety, as seen in the case of Moe, it's clear that ketamine synergizes beautifully with psychotherapy.

Ketamine As Psychedelic Medicine

In another model of using ketamine to treat severe, chronic, and treatment-resistant mental ailments, a ketamine-induced mystical journey is followed by integration psychotherapeutic counseling.

In a carefully selected pool of patients well prepared for mystical journeying, ketamine is administered by a medical professional at a typical dose of 1.0 to 2.0 mg/kg, usually through intramuscular or subcutaneous injection but sometimes intravenously. Within a few minutes of receiving the drug, the patient enters a state of altered consciousness, during which dream-like visions appear and motor function is impaired.[71] These visions are often accompanied by other experiences typically associated with mystical journeys, such as new insight into the nature of one's existence,

feelings of unity, and a sensed presence of God/Gaia/Spirit. The dissociative properties of the drug, furthermore, allow patients the unique experience of softening into a disembodied state and letting go.

The journey, which lasts anywhere from one to two hours, is a largely internal process, during which the patient typically lays silently with their eyes closed while listening to music. The primary role of the provider on "trip day" is to ensure the patient's physical safety. The day after the session (or sometimes later that same day), the provider meets with the patient to explore the themes of the journey, reflect upon their relevance, and explore ways to integrate them into the patient's life moving forward.

In her recent article on the subject, Dr. Bennett explains: "When clinicians choose to work in this way, they are working in a psychedelic and shamanic paradigm, in which the mystical visions are valued."[72]

As we've seen with the new wave of research concerning other psychotropic substances, psychotherapeutic counseling can make all the difference within the context of psychedelic therapy. In fact, both new and old models of psychedelic medicine regard mystical experiences as powerful adjuvants to psychotherapy.[73-75]

Dr. Barone explains: "The medicine induces a new awareness for a reason; it opens up the therapeutic process and gets [the patient] thinking about different themes in new ways." In this light, patients are often able to reach new breakthroughs in therapy that they might otherwise spend weeks, months, or even years skirting around.

May's story, shared at the beginning of this article, is one such example (albeit an offbeat one) of how a ketamine-fueled mystical experience can yield profound healing benefit.

Although little research has been done comparing ketamine-induced psychedelic journeys to those of other entheogenic substances, one clear benefit to ketamine is its lack of negative interactions with other medications, mainly because it does not significantly affect serotonin levels.

Whereas patients must taper off of psychiatric medications before taking MDMA, ayahuasca, and some other psychedelic medicines that affect the 5HT2A serotonin receptors,[76-78] this is not a prerequisite for healing with ketamine.[79,80] Another difference between ketamine and many other psychedelics is the relatively short duration of the associated trip. Whereas a journey with LSD can last up to 14 hours, a ketamine-associated trip lasts an average of 75 minutes.[81]

As beautiful as mystical experiences can be, they can also be potentially terrifying to those who are not ready or willing to explore different states of consciousness or to those who have not been adequately prepared for the experience. For this reason, patients must be carefully selected and supported prior to receiving ketamine at psychedelic doses. Likewise, clinicians using ketamine in this way should be skilled themselves in mystical journeying, trip sitting, and entheogenic integration.

Ketamine

Is "Special K" the Special Cure?

Given the paucity of effective and rapid-acting treatments for depression and other mood disorders, providers and consumers have understandably been quick to pounce on the promise of ketamine. But have they been hasty?

According to the data Dr. Bennett encountered at the 2018 International Conference on Ketamine in Psychiatry,

Ketamine is a powerful adjuvant to psychotherapy.

the reported efficacy of ketamine in the treatment of depression in the general psychiatric population has dropped from 66% to now 30% to 40%.

This drop-in efficacy could be because ketamine is now being used to treat non-clinically indicated conditions in patients who might be better served by a different therapy. "What stood out to me about these data sets is that the statistical efficacy appeared to go down as the researchers loosened the criteria for inclusion in the studies," explains Dr. Bennett. "That made it clear to me that ketamine is not equally useful for all of the different kinds of psychiatric or psychological distress."

She elaborates that grief, stress, physical illness, sleep deprivation, and unexpressed anger can all present as depression, but do not warrant treatment with ketamine.

In a quick-fix culture in constant search of miracle drugs that *act now*, however, overzealous consumers may be demanding the wrong remedy for their ailments – and overzealous providers may be obliging them.

To meet the sudden and growing demand for the drug, a number of anesthesiologists have begun offering intravenous infusions of ketamine to those with depression and other mood disorders. Dr. Bennett points out that while anesthesiologists are undoubtedly familiar with the administration of ketamine and the management of its side effects, they are not always trained in psychological assessment and thus may be at risk of over-prescribing the therapy. The best practice would therefore likely be to have a mental health provider (such as a psychiatrist) recommend a treatment regimen that would then be administered by an anesthesiologist (or another licensed provider).

The protocols for using ketamine in surgical, procedural, and pain-management settings, furthermore, may not be entirely fitting within the field of mental health. For example, in settings not related to depression, the benzodiazepine drug midazolam (Versed) is often administered concurrently to help soothe the anxiety and dysphoria that patients may experience while under the acute effects of ketamine. While midazolam does in fact help dampen some of ketamine's unpleasant side effects, it has also been observed to reduce the antidepressant actions of ketamine, thus undermining

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the point of treatment.[82] For this reason, patients are likely to be better served by abstaining from all benzodiazepine medications in the days before, during, and after ketamine treatments.

Ketamine treatment is not without its risks, furthermore, which include bladder problems, kidney disease, and memory deficits.[83,84] As with all medical interventions, it is important to mindfully select patient candidates and to deliver the lowest cumulative amount of the drug to yield the maximum therapeutic benefit.

Like all psychiatric drugs, ketamine is likely to work best when used as a part of a comprehensive treatment plan and not as a standalone therapy. Sleep, healthy eating, mindfulness meditation practices, exercise, psychotherapy, time in nature, and meaningful social connections are all cornerstones in both the prevention and treatment of mood disorders. Some patients also require nutritional supplements, herbal therapies, and/or pharmaceutical psychiatric drugs – not in lieu of the above practices and ketamine treatment, but in addition to them.

Integrative practitioners are endowed with an impressive toolkit of therapies relevant to mental health. These include but are by no means limited to neurofeedback, hypnosis, craniosacral therapy, life coaching, and shamanic healing – all of which can occasion powerful shifts on the spiritual and physical planes. Energetic therapies like Reiki, acupuncture, homeopathy, and bio-therapeutic drainage may be helpful as well. Breathing techniques such as pranayama, holotropic breathwork, and biodynamic breathing may further help with emotional recovery. Assessment of a patient's endocrine, nervous, and digestive systems is also imperative in the comprehensive workup and treatment of mood disorders and is best done by a naturopathic physician (or another well-trained integrative provider). Considering that the pathophysiology of depression includes inflammatory processes,[85] assessing and addressing a patient's inflammatory response is likely an important step in treatment. Screening for food intolerances, environmental exposures, and stealth infections is further indicated in some cases. Nutritional deficiencies have been implicated in numerous mood disorders and are surprisingly common,[86-88] as are high intestinal permeability (aka "leaky gut"), celiac disease, non-celiac gluten sensitivity, and other digestive conditions that predispose patients to nutritional malabsorption and neuroinflammation[89,90] – all of which can be both diagnosed and treated by naturopathic physicians.

Summary

Ketamine is an affordable, widely available drug that rapidly engenders robust antidepressant effects. Unlike most antidepressant drugs, which affect the monoaminergic neurotransmitters and/or their receptor sites, ketamine acts strongly on NMDARs, affects glutamate concentrations, moderately stimulates opioid receptors, and promotes synaptogenesis. These properties may explain ketamine's rapid onset of action and the durability of its effects, as well as its relative paucity of negative side effects and its lower risk of triggering mania in those with bipolar disorder as compared to other antidepressant drugs. Unlike SSRIs, which can take weeks to yield improvements, ketamine acts within mere hours or days.

Time will tell if the expensive S-ketamine formulation patented by Johnson & Johnson and approved by the FDA for the treatment of depression works any better than the generic racemic ketamine currently used off-label.

Ketamine therapy is highly customizable to the unique needs of the patient and can be delivered via a number of different routes of administration and in a variety of settings, from the staunchly Western to the shamanic. It is likely most effective when paired with psychotherapy and is in fact a powerful adjuvant to counseling.

When used in mystical contexts, ketamine engenders transcendental experiences accompanied by vivid images seen in the mind's eye. Unlike the "classic" psychedelics, ketamine is legal, is widely available, delivers a relatively short journey, and can be safely combined with most antidepressant drugs (although ideally not with benzodiazepines, which seem to attenuate its antidepressant effects).

Ketamine is a not a miraculous one-size-fits-all cure but rather a considerably powerful synergist to other dietary, lifestyle, and therapeutic practices in a mindfully selected pool of patients. Within the context of a comprehensive healing plan, ketamine offers patients a highly effective, novel approach to managing and treating depression, suicidal ideation, and other mood disorders. Indeed, it seems that ketamine has fairly earned its moniker "Special K."

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Clinical Due Diligence: Drug Interactions with Cannabis and Cautions for Practitioners

A Clinician's Perspective

by David G. Knox, MD

With spreading legalization of *Cannabis sativa* and the increasing popularity of cannabidiol (CBD) especially, there is increasing concern about the concomitant use of cannabis with prescription medications. Cannabis is a poly-pharmaceutical botanical comprised of well over 400 pharmacologically active compounds, many with potential for drug interactions.

Cannabis Pharmacokinetics

In order to understand drug interactions with cannabis, we need a basic working understanding of cannabis pharmacokinetics, which is the study of the absorption, distribution, metabolism, and excretion of cannabinoids in the human body. While simple in theory, cannabis pharmacokinetics are complicated by the plant itself. Hundreds of chemically distinct varieties (chemovars) of cannabis currently exist, of which phytocannabinoids and terpenes are hallmark constituents. These varied phytochemical compositions, or chemical profiles, add complexity to pharmacokinetic determination. Each of the constituents follows its own kinetic pathway, but this may be affected by all of the others. Of these 400+ known compounds found in cannabis, we have limited information about the pharmacokinetics of just a few. Much of what we do know is based on the studies done on the pharmacodynamics of the best known phytocannabinoids, CBD and THC.[1]

The rate of cannabis absorption, bioavailability, and duration of activity are dependent on the route of administration, chemical profile, product concentration, and amount consumed. Bioavailability refers to the fraction of an administered dose of a substance that reaches the systemic circulation and is then measurable as serum concentration. The data shown in Figure 1 are based on the pharmacodynamic study of THC and show the variability across the different routes of administration. The bioavailability of CBD, other cannabinoids, and terpenes have not been studied as well as THC; and there are some differences between the different cannabinoids. A number of other factors also play a role, which results in this broad range of bioavailability, as shown in Figure 1.

The overall bioavailability of an administered dose of cannabis has a broad range and is relatively low regardless of the method used, but the duration of action is quite variable between methods.

Distribution in the body is also somewhat dependent on the route of administration; but once cannabinoids enter the serum, there is rapid redistribution, primarily into highly vascularized tissues, including the brain, liver, and kidneys. As the cannabinoids are strongly lipophilic, overall redistribution is predominantly into fat. A smaller proportion of cannabinoids and their metabolites bind to serum protein.

Excretion is relatively slow, due to the high volume of distribution, with 80-90% being eliminated within five days. Most excretion is through feces (>65%) and through urine (20%).[2-4]

The majority of our understanding about drug interactions comes from studies on the metabolism of cannabinoids in the body. Cannabinoid metabolism occurs to a small degree in multiple tissues and organs, but predominantly occurs in the liver.

Figure 1. Absorption of Cannabis as a Function of Route of Administration

	Pulmonary	GI	Transmucosal (Nasal/Oral)	Suppository (Rectal/Vaginal)	Topical/ Transdermal
Onset	3-10 min	90-100 min	15-45 min	10-15 min	30 min-2 hrs
Duration of Action	2-4 hrs	6-8 hrs	45 min-6 hrs	2-8 hrs	1-8 hrs Patch: up to 48 hrs
Bioavailability	25-30% CBD ~ 13%	<6-20% (dependent on GI health & contents)	20-30%	*THC-hemisuccinate BA 13% up to 40% (double GI)	Permeability of CBD & CBN 10x THC

Microsomal hydroxylation and subsequent oxidation are catalyzed by cytochrome P450 enzymes, which are also responsible for the metabolism of most chemicals and hundreds of pharmaceutical drugs that enter into systemic and hepatic circulation. Chemicals and drugs may be neutral substrates, inhibitors, or inducers of CYP450 enzymes. Neutral substrates are simply metabolized by the enzyme, while inhibitors reduce enzymatic activity, preventing or decreasing the metabolism of its substrates and thus increasing the concentration of the substrate and duration of its effect. Inducers increase the activity of the enzyme, enhancing the metabolism of its substrates and thus decreasing the substrates' concentration and duration of effect. Note that THC and CBD are non-neutral substrates.[5]

THC:CYP450 Interaction

THC is metabolized by isoenzymes CYP3A4 and CYP2C9. THC is first hydroxylated to 11-OH-THC, then oxidized to water soluble THC-COOH (11-nor-9-carboxy-THC) and other inactive metabolites. This is an area where route of administration matters. Noting the rapid redistribution of cannabinoids into fat and other tissues, only about 10-20% of inhaled THC is converted to 11-OH-THC. When ingested, however, THC first enters the portal circulation and, as a result, nearly 100% may be metabolized to 11-OH-THC. This active metabolite binds more strongly to CB1 receptors than THC does and can enhance euphorigenic or intoxicating effects by up to 10-fold.[6] (This also means a higher risk of adverse or toxic effects.)

Inhibitors of CYP3A4 slightly increase serum THC concentration and duration of activity. Inducers of CYP3A4 slightly decrease serum THC concentration and duration of activity. (See Figure 2)

THC itself is a CYP1A2 inducer, hastening metabolism of its substrates and decreasing serum concentrations of many drugs. The degree of induction is dependent on the route and amount of THC consumed. THC and CBN have also been seen to confer a small degree of inhibition on other CYP isoenzymes.[6,7]

Figure 2: CYP and Cannabis Interactions

CYP3A4 Inhibitors	CYP3A4 Inducers
Grapefruit (bergamottin and 6'7'dihroxy-bergamottin)	Phenytoin
Protease inhibitors	St. John's wort
Macrolides	Antiandrogens
Azole antifungals	Rifampin
	Carbamazepine
	Phenobarbital

CBD:CYP450 Interaction

CBD is metabolized by CYP3A4, CYP2C9, and CYP2C19. (See Figure 3) CBD is oxidized to 7-OH-CBD and 6-OH-CBD. CBD is a potent competitive inhibitor of CYP3A4 and CYP2D6, which are responsible for metabolizing another 25% of all pharmaceutical drugs. As a competitive inhibitor, it displaces other substrates at the site of enzymatic activity, slowing the metabolism of many other substrates including THC. The degree of inhibition is dependent on the route and amount of CBD consumed, with high doses more likely to cause significant interactions.[8,9]

This brief review of pharmacology provides many clues as to how certain drugs may interact with the presence of cannabinoids, but how does this translate to clinical practice? Multiple studies have been conducted on patients reviewing potential drug interactions with cannabis use. Some of these studies have shown[3,4,10]:

- THC and CBD increased coumadin levels and INR. A single case of INR >10 with high cannabis use has been reported.
- CBD increases serum levels of seizure medications, including the metabolite des-methyl-clobazam while decreasing clobazam levels.
- Smoked cannabis decreases serum theophylline.
- Cannabis may increase serum levels of blood pressure medications e.g. carvedilol, HCTZ, lisinopril, and valsartan, with a potential for decreased heart rate and hypotension.
- No significant (i.e. only minor) interactions were seen with co-administration of antiretrovirals (indinavir or nelfinavir), or chemotherapeutic agents (docetaxel or irinotecan).

Of note, increases in serum levels of drugs tested were rarely outside of therapeutic windows, with the exception of clobazam, where higher levels of its metabolite bear the potential for increased side effects. The vast majority of patients do not experience side effects when taking cannabis in conjunction with other common medications. There has been little cause for concern over a long period of concomitant use in a significant population of cannabis users. This may be a reflection of dose, as CBD inhibition shown in the lab was primarily a function of higher CBD concentrations than would be seen in typical patient use. Interactions may be more of a concern with high doses of oral CBD (600 mg or more).[7,11]

Many interactions of the cannabinoids with other drugs are not based on their metabolic interactions, but on their activity on similar receptor systems. Additive CNS depressant effects are seen with alcohol, barbiturates, and benzodiazepines, but notably not with opioids. Concomitant use of cannabis with anticholinergics can enhance tachycardia and hypertension. ➤

Figure 3. Examples of Cannabis and CYP450 Interactions

THC induction of CYP1A2 increases metabolism and lowers serum levels; drugs affected:	Caffeine	Melatonin	Imipramine
	Clozapine	Naproxen	Nabumetone
	Olanzapine	Propranolol	Theophylline
	Duloxetine	Cyclobenzaprine	Tizanidine
	Estradiol	Haloperidol	Triamterene
	Lidocaine	Chlorpromazine	Zolmitriptan
CBD inhibition of CYP3A4 decreases metabolism and increases serum levels; drugs affected:	Amiodarone	Beta blockers	Macrolide antibiotics
	Antihistamines	Calcium channel blockers	Opioids
	Antiretrovirals	Many chemotherapeutic agents	Sildenafil
	Anxiolytics (Benzos)	Carbamazepine	Statins
	Azole antifungals	Cyclosporine	SSRIs
	Antipsychotics	Haloperidol	Tricyclics
	Benzodiazepines		Trazodone

A Clinical Case of Drug:Drug Interactions

A 54-year-old female presents to her physician with symptoms of altered mental functioning, including somnolence and difficulty thinking clearly, to the degree that she had not been able to return to work for several weeks. She reports her symptoms began several months earlier but markedly worsened after a recent influenza-like illness. She had been seen in an urgent care setting with acute symptoms of cough, malaise, and body aches and was diagnosed with influenza A. She was prescribed oseltamivir for antiviral treatment, albuterol MDI, and prednisone for her respiratory symptoms, and was advised to use generic guaifenesin/dextromethorphan for cough control. She returned to urgent care five days later as she continued having severe cough with occasional vomiting, and she was prescribed Phenergan with codeine syrup. Her acute influenza symptoms subsided, but she continued to feel confused and sedated even two weeks later.

A review of symptoms also revealed a complaint of numbness on the left side of her face, raising her worry about a possible stroke or brain tumor. She also noted waves of a rapid pounding heart, night sweats, vivid dreams, and hearing voices singing.

The patient's past medical history was most notable for migraine headaches since adolescence, for which she uses sumatriptan prn; six months prior, after a series of recurrent migraines, she was prescribed Topiramate XR, 150 mg daily, as prophylaxis. She has a history of mild asthma, usually associated with respiratory illness as noted above. She has some osteoarthritis complaints. Her history also includes major depression, but she has felt stable on a prescription of fluoxetine, 60 mg daily, for years. Patient denied medication allergies but reports experiencing prolonged oversedation with trazodone she had tried for insomnia.

She denied any use of alcohol or other drugs but does report that she has been taking CBD after a friend advised her of the results she had experienced with CBD for her arthritis. Patient was taking a dropperful of CBD tincture three times a day, although she did not know the exact dose it contained.

Physical exam revealed vital signs of Height 5'4", Weight 163 lbs, Temperature of 36.9°C, Pulse 107, BP 143/86 and O2 saturation of 95%. HEENT showed injected oropharynx, but no sinus pain or tenderness. Heart sounds were rapid but regular without murmur. Lungs showed faint basilar rales and wheezing but good air movement. The abdomen was benign to palpation. The neurologic exam showed slight nystagmus and subjective numbness to the left side of the face, but there was no facial droop and cranial nerves otherwise appeared normal. Some unsteadiness of gait was noted, but motor strength was 5/5 bilaterally. She was fully oriented but exhibited slowness in her responses to questions and commands.

A full evaluation was commenced with lab and imaging studies. EKG showed sinus tachycardia, otherwise a normal tracing. CXR was negative for infiltrates. Unenhanced CT scan of the head was normal. WBC was slightly elevated at 13.7 but no anemia found. BUN was high at 36 mg/dL but the remainder of her CMP was normal. T4 and TSH also were normal. Urine drug screen was negative. Serum level of topiramate was significantly elevated at 73 mcg/ml (Therapeutic range 5-20 mcg/ml).

Discussion: This patient has experienced adverse effects from several possible drug:drug interactions. Topiramate is the most significant of the drugs involved, and it frequently can cause cognitive slowing as a side effect even at therapeutic levels. It was originally prescribed for seizures, but recently it is often used for migraine prophylaxis. Topiramate and trazodone are metabolized in the liver primarily by the CYP3A4 isoenzyme. Patients can exhibit different expressions of the CYP3A4 gene, which can account for differences in drug efficacy or toxicity, and many drugs affect enzymatic function. In general, it takes five full half-lives of a substance to be cleared from the body; Topiramate XR has a 57-hour half-life (compared to 25 hours for immediate release formulations), so normal clearance could take nearly 12 days. Clearance could be much longer with impaired metabolism or dehydration with an acute illness.

CBD has been noted to be an inhibitor of CYP3A4 as discussed in the accompanying article and could play a significant role in prolonging an elevated serum level of topiramate. As noted, it is not uncommon for patients to not know the actual dose of cannabinoids they are taking, due to uncertain source, or lack of testing or labeling. Commercial tinctures may range from 300 to 3000 mg in a 30 ml bottle, so her 1 ml dropperful could range from 10 to 100 mg per dose, with significant inhibition at the high end. Fluoxetine is predominantly an inhibitor of CYP2D6 but is also a modest inhibitor of CYP3A4. This additive inhibitory effect likely resulted in decreased topiramate clearance, with the elevated levels causing the patient's protracted sedation and cognitive dysfunction.

Other potential interactions may be due to dextromethorphan and/or promethazine, both of which are metabolized by the CYP2D6 isoenzyme. Both of these drugs could have elevated levels due to inhibition of this enzyme by fluoxetine. High levels of dextromethorphan can cause neurologic symptoms such as dystonia, fatigue, drowsiness, dizziness and nystagmus, and auditory hallucinations as this patient experienced. Promethazine has significant anticholinergic activity and is frequently sedating and can affect memory and cognition. Codeine is also metabolized by CYP2D6 and can cause drowsiness.

Clinical course: After recognizing these interactions, the patient was advised to discontinue her Topiramate XR and CBD. With subsidence of her flu symptoms, she had quit her cough medications. She also decreased her fluoxetine dose to 30 mg/day. At a one-week follow-up, her topiramate levels remained elevated, consistent with slower than normal metabolism. At one month, the patient had complete resolution of all of her presenting symptoms.

This case scenario reveals the risk of inadequate history taking and consideration of possible drug interactions, as may happen in a busy ER or urgent care setting treating a seemingly simple flu-like illness. This patient's history of oversedation with trazodone gives a hint of possible low metabolism via CYP3A4 and prior unreported use of CBD turns out to be a significant contributor to her presentation. Acute illness and the other drugs prescribed reveal the increased risks with polypharmacy. Early recognition of these issues may have avoided the need for an extensive workup with neuroimaging and other studies to rule out CNS pathology.

Case studies have suggested that combining cannabis with SSRIs can induce hypomania (elevated mood with symptoms e.g. racing thoughts, decreased sleep, grandiose thoughts, talkativeness).[11,12]

Clinical Pearls and Precautions

Understanding dynamic drug-drug interactions is critical to optimizing medical management and safety when co-administering any medication. This is especially true when a co-administered drug has a narrow therapeutic window or major adverse side effect potential. Again, while most pharmaceuticals are made of a single substrate, cannabis does pose challenges as a poly-pharmaceutical botanical substance.

So, what is the clinical approach to co-administration of cannabis and medical management? Clinical pragmatism:

- Rely on the standard of care and biochemistry.
- Know your CYPs and the effects of their strongest substrates.
- Monitor serum markers and other relevant labs more closely; e.g. INR, anti-epileptic or chemotherapeutic drug levels, and LFTs.
- Make dose adjustments as necessary.

Integrate your fundamental knowledge and principles of endo-cannabinology:

- Review the chemical profiles of cannabis products: chemovars should be characterized by analytical chemistry, i.e. which cannabinoids, ratios and concentrations, terpenes, etc. are present.
- Advise your patients to begin with micro-dosing (using a fraction of 1-5 mg /dose) and consider the best route of administration. Doses can then be titrated slowly and weaned back as needed.
- The dose and route of administration influences bioavailability, which in turn influences cannabinoid-CYP engagement.
- Combining methods with topicals may lower the dose needed by ingestion.
- Monitor the subjective and objective effects of cannabis use reported by patients.
- Know the common signs of THC overconsumption (e.g. red eyes, dry mouth, reduced tear flow, cough & bronchitis, dysphoria, anxiety, panic, transient tachycardia, hypotension, hyperemesis).
- Remember the potency of 11-OH-THC with its potential for increasing adverse side effects.
- When using other drugs with cannabis, interactions can be reduced by staggering the timing of administration. Also, other drug doses can be adjusted: e.g. cannabis can reduce opioid dose requirements.
- When in doubt about any potential interaction, look it up or confer with a pharmacist for further guidance.

In summary, clinically significant drug interactions with cannabis are not common, but we should remain informed and vigilant, and counsel our patients anyway – this is our clinical due diligence. Whether using a conventional pharmaceutical or a cannabis-derived product, dosing should start low and be titrated slowly. Match close monitoring with documentation. Always encourage patients to discuss their cannabis use with ALL of their pharmaceutical prescribers. Involved co-management of drug interactions and dosing adjustments are paramount for success in optimizing treatment for our patients.

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A Personal Account of the Trials to Assess Chelation Therapy – The End of the Beginning?

by Gervasio A. Lamas, MD, FACC, FAHA, FESC

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Introduction

To the reader: This is meant to be a scientific article but written in a narrative style for the *Townsend Letter* to improve its readability and decrease boredom. I do digress and share some personal details so the reader may gain a better understanding of the origin of this unique study and the future lines of study it engendered. The materials I discuss have all been peer reviewed and published and presented – most as full-length papers, some as abstracts – and the distinction is clear in the references. To the best of my ability, I always lean towards a conservative interpretation of the data.

Digression

Me. Typical "immigrant makes good" story: I left Cuba at age 8 for Miami. I lucked out by being accepted to Harvard, then NYU medical school. I again lucked out by being accepted to the *best*, bar none, internal medicine and then cardiovascular program in the US – the Brigham and Women's Hospital of Harvard Medical School. I stayed as Harvard faculty for an additional 9 years. Those 15 years at the Brigham imprinted an uncompromising pursuit of excellence, the value of science, and a certainty that if you have clean data, you can save lives. I started working on clinical trials in the 1980s with incredible mentors and never looked back.

While this seems a digression, I want to make sure that the reader understands that I come from a completely conventional, albeit excellent medical education and background.

The Beginning

This takes us to 1999. I was chief of cardiology at Mount Sinai Medical Center in Miami Beach, Florida, having built an academic division within a community hospital. My first trial, on heart pacemakers, funded by the National Heart, Lung, and Blood Institute (NHLBI) was well under way, and all was right in my happy bubble of patient care, teaching, and research.

Then in August of 1999 I saw an unusual consultation for a new patient. He was mildly shabby in the style of Peter Falk's Lt. Columbo character, and he wanted EDTA (ethylenediamine tetra acetic acid) chelation. I told him that chelation was nonsense, quackery, expensive, and probably dangerous. So he left.

Later I realized I had been rude. And while I could not undo rudeness, I figured I would feel less rude if I could prove to myself that what I had said was right – so I hit the books and tortured the hospital librarian. In reality my having to go to the library was proof that I had spoken out of bias and ignorance and should have kept my mouth closed.

Before Planning TACT

I learned that EDTA was an artificial amino acid first synthesized in Germany in 1937, and that medical use started about a decade later. By the 1950s the medical community used infusions to treat high blood calcium levels and even toxicity from the only cardiac drug of the era, digoxin. EDTA, a chelating agent, is like a baseball mitt with a magnet inside, a molecule with a pocket. The baseball that sticks in the center is a small ion with a positive charge, like calcium, lead, cadmium, and many other charged particles. Once it sticks, the kidneys harmlessly excrete the EDTA

and the small particle. Because EDTA has a magnetic charge, it always travels with sodium, calcium, or magnesium.

The 1950s were the Stone Age of cardiology; we really had no drugs, no catheterization, no stents, no bypasses, no statins, no aspirin use to prevent heart attacks. It was the ham and eggs with a cigarette for breakfast era. When patients died of a heart attack and went to autopsy, the coronary arteries, whose job it is to feed the pumping heart muscle, were plugged up and their walls were full of calcium. So on the one hand were calcified arteries and on the other hand a drug that bound calcium. Some smart docs decided that perhaps this might be a match made in heaven and tried disodium EDTA infusions – this is the EDTA that takes out calcium. Much to their surprise, of 20 patients with severe coronary disease, 19 showed improvement. This first paper of EDTA for coronary disease[1] was published in 1956! But EDTA did not get the expected boost, or patients the potential benefit. It is not clear to me why chelation did not spread like wildfire, but it did not. In the 1960s some tiny clinical trials suggested that benefit might be less than expected, and chelation dropped off the scene. By the 1970s it had jumped to the realm of alternative medicine and practiced by what traditional practitioners called quacks. In the 1980s and early 1990s all medical associations, for the most part, either ignored chelation or declared it ineffective nonsense. State medical boards censured chelation practitioners. But the practice of chelation persisted.

Alternative medicine physicians published that there was vascular benefit.[2] These publications were case series in non-mainstream journals, and cardiologists did not read them. Mainstream cardiology journals published additional small, better-designed studies in the 1990s and early 2000s. These studies showed no benefit of chelation for relief of symptoms of atherosclerosis. On the other hand, the studies were not large enough to exclude a small to moderate benefit of chelation on clinical events like heart attacks. And this is where matters stood when my patient walked in to ask for chelation in August of 1999.

I decided that modern clinical trials methodology could address the lingering question of chelation for coronary artery disease, and called a deputy director I knew at the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). Much to my surprise, he said they were interested in seeing a proposal from a clinical trialist. The background here is that, unbeknownst to me, for years leading chelation practitioners had been pleading for a chelation trial. They had the ear and support of powerful congressmen and senators, who had put pressure on NHLBI to study chelation; but there had been no proposals forthcoming from established clinical scientists, until I walked in – better lucky than smart.

TACT

There are four essential elements to an NIH clinical trial: an idea, a team, funding, and obsession. With chelation, there are no pharma companies who stand to make billions. You are chronically underfunded. You push through because of obsession. And I was hooked.

I gathered the "A" team: I provided obsession; my small team at Sinai would coordinate all the moving parts; the Duke Clinical Research Institute would lead data collection and statistics; clinical events would be evaluated at Harvard. The work would be carried out at hospitals and clinics in the US and Canada, including Hopkins and Mayo, as well as many alternative medicine practices. All the parts would be connected by a new computerized data collection and study management system. Three years later, in August of 2002, Mount Sinai Medical Center of Florida, my hospital, received a federal grant of $30 million to carry out the Trial to Assess Chelation Therapy (TACT). Once the study design was finalized, and FDA and NIH gave their okay, we were off and running. The first patient was enrolled in September 2003.

The TACT design is well known.[3] We randomly assigned patients with a prior heart attack who were at least 50 years old and had at least fair kidney function to 40 edetate disodium chelation or placebo infusions – 30 weekly infusions followed by 10 maintenance infusions.

The active infusions contained up to 3 g of edetate disodium, adjusted for kidney function, 2 g of magnesium chloride, 100 mg of procaine HCL, 2500 U of heparin, 7 g of ascorbate, 2 mEq KCl, 840 mg sodium bicarbonate, 250 mg pantothenic acid, 100 mg of thiamine, 100 mg of pyridoxine, and sterile water to complete 500 mL.

Chelation practitioners in the community always give high doses of oral multivitamins and multiminerals in conjunction with chelation, so we developed a high dose vitamin and mineral regimen for patients to take throughout the entire study that was also placebo controlled. Because it was such a rich oral supplement, patients had to take 3 large pills twice daily. As the reader can see, this becomes two studies in one: Active IV chelation vs. Placebo IV chelation, and Active oral high-dose vitamins vs. Placebo oral "vitamins". The most interesting comparison here is that of the patients taking "active-active" vs. "placebo-placebo," shaded in Table 1. But we will get to that.

We had decided to study patients who'd had a prior heart attack, were at least 50 years of age, and had at worse, fair renal function. The primary end-point of the study – what we were trying to prevent – was a laundry list of all the bad things that can occur to cardiac patients: death, stroke, recurrent heart attack, stents or bypass, and hospitalizations for cardiac pains. We also decided to look at patients with diabetes as a separate group.

The study took 10 years to complete, instead of the expected five. We ➤

Table 1. Factorial randomization in TACT: two studies in one

Active infusions + Active oral vitamins	Active infusions + Placebo oral vitamins
Placebo infusions + Active oral vitamins	Placebo infusions + Placebo oral vitamins

➤

enrolled slowly in a tough study with a lot of patient burden, every minute compounded by controversy. Misguided scientists and hostile reporters tried to stop the trial. But, here is where a clean "A" Team study reinforced with obsession counts – we were unstoppable and science triumphed. Eventually we counted 134 enrolling sites in the US and Canada enrolling 1708 patients. We administered 55,222 infusions and spent innumerable hours managing the sites all the while dodging arrows of controversy.

Like all the best NIH clinical trials, TACT employed a double-blind design. So after 10 years, only a select group of statisticians, NIH scientists, and a supervisory board had seen unblinded results. I was not in that group. So picture the unblinding ceremony. We sat at a long table at Duke – blinded clinicians on one side and about 10 statisticians on the other side. We spent about 30 minutes dying through some conversation. Finally, the Duke team distributes the unblinded data books. We speed to the right pages. I address Kerry Lee, PhD, professor of biostatistics, "Kerry, are you telling me this is a positive study?" "Why yes, Tony. It is."

OOPS. The study we conceived 13 years before, which was supposed to show chelation was nonsense, instead showed that it reduced cardiovascular events. I put my head on the table. I knew that one way or another, the "A" Team would have to do it again – unexpected results have to be reproduced.

We wrote up our results and submitted to the leading medical journal. We received a Bronx raspberry by return mail. We then opened negotiations with the next best journal, which was led by more open-minded scientists. It took about half a year of negotiating and rebutting critiques, before we received the coveted acceptance letter to the *Journal of the American Medical Association*.[4] In the meantime, I presented at the American Heart Association. Big meeting – lots of media – I was treated as I imagine a medieval leper might have been…quite disappointing. But who cares, after all. We had stumbled across a new way to treat patients with heart attacks; we were flying high, leaving the critics in the dust.

So, what did we learn?

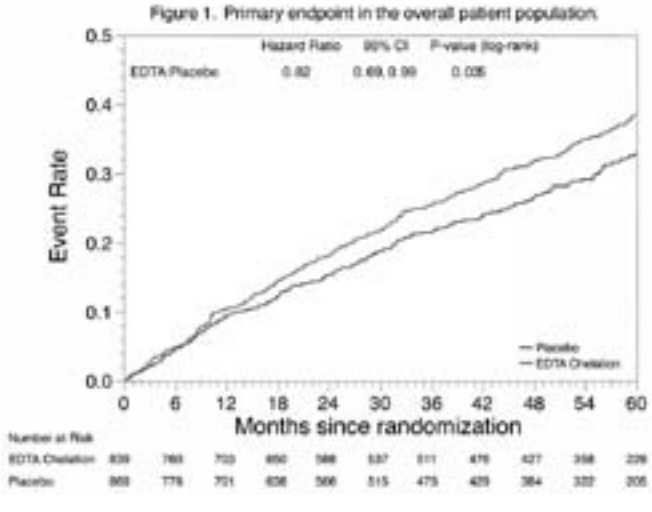
- In patients with a prior heart attack, a course of edetate disodium-based chelation reduces recurrent cardiac events by 18% (Figure 1).[4]
- In patients who are on double active therapy (chelation+oral vitamins), compared with double placebo, events are reduced by 26%.
- In patients that have diabetes as well as a prior heart attack, we reduced the risk of a subsequent cardiac event by 41%; the risk of another heart attack by about 50%, and the risk of death by 43% (Figure 2).[5]

Along the way we also learned that after a TACT infusion, the amount of lead in the urine increases by nearly 4000%, and cadmium nearly 700%.[6] We are all polluted. We also learned that low-level lead exposure may be responsible for hundreds of thousands of deaths annually.[7] So our results made sense.

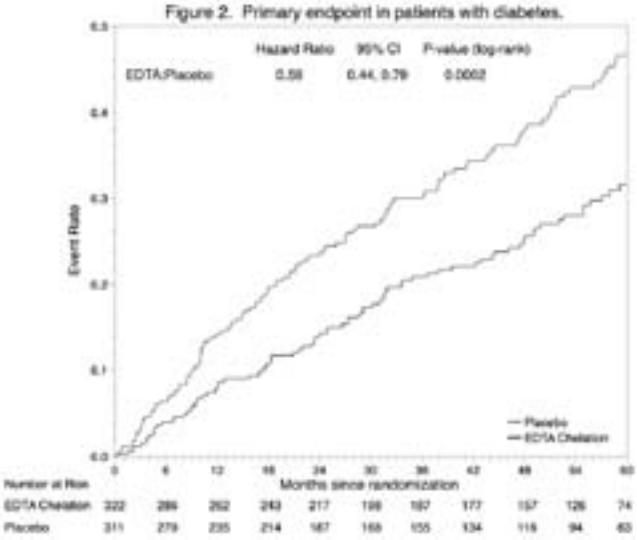
At this point I really found out who were the real scientists. Our NIH supervisors and colleagues had walked the same path for a decade and knew the data were clean; they were excited about a new way to treat atherosclerosis. They came with us to FDA. Predictably, FDA said, "Nice study, do it again." And so, the "A" Team committed to another decade of chelation research.

Enter TACT2

On September 27, 2016, Mount Sinai received an NIH grant for $36 million for TACT2. Same design as TACT1, but



Event curves showing chelation (lower line) and placebo (upper) in patients with a prior heart attack.. There are fewer cardiac events – death, heart attack, stroke, stents, cardiac bypass, or hospitalization for chest pains – in patients receiving chelation.



Event curves showing chelation (lower line) and placebo (upper) for patients with a prior heart attack and diabetes. There are fewer cardiac events – death, heart attack, stroke, stents, cardiac bypass, or hospitalization for chest pains – in patients receiving chelation.

now restricted to patients with a heart attack who also had diabetes. But now we have broad NIH support, and we are also keeping a biorepository to assess changes in toxic metals and more. Long and short of this, we expect to report on 1100 patients in 2023. In the meantime, we are blinded – boring and frustrating, but necessary.

Enter TACT3a

Still, we are not sitting on our hands. Mount Sinai and the James Carter Estate funded a pilot study of patients with diabetes and critical limb ischemia, including gangrene. I have seen gangrene regress and have saved legs.[8] But nothing is real without a placebo control, so the Florida Heart Research Foundation and a generous private donor teamed up to allow us to start TACT3a. This is a small, placebo-controlled, randomized trial of 50 patients with critical limb ischemia.

What Do We Need?

At this point we are on track with the TACT program, but we need patients. We need TACT2 patients (diabetes, prior heart attack), and TACT3a patients (diabetes and critical limb ischemia). **Please visit our website www.tact2.org for all the papers and results referenced here, as well as lectures and more. You can reach me through the website.**

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Psychiatry Redefined: Integrative Medicine for Binge Eating

by James M. Greenblatt, MD

Adapted from *Integrative Medicine for Binge Eating: A Comprehensive Guide to the New Hope Model for the Elimination of Binge Eating and Food Cravings*
by James M. Greenblatt, MD

We live in a world obsessed with food. Food is everywhere at once, and everything at once – a source of energy with which to fuel the human body, a source of pleasure, and a source of potential weight gain that prevailing cultural norms and aesthetic sensibilities frame as something to be, at least, regarded with caution.

In a place where food is entwined with nearly everything we do, the biologic mechanism that once served as a lynchpin of human survival – appetite – can quickly become maladaptive. An appetite gone off the rails permeates all areas of one's life, from social interactions, mood, and emotional connections to the physical health of the immune, cardiovascular, and digestive systems. Food addiction and binge eating disorder are serious medical diagnoses that emerge when appetite, or the intricate biochemical apparatus which regulates appetite, becomes disrupted.

Arising not from a paucity of resolution or self-discipline but rather from the commanding directives of one's own biology, binge eating disorder is pervasive, complex, and impossible to resolve with logic or willpower alone. Any treatment plan that is to be effective will necessarily incorporate advanced medical and psychological approaches specifically tailored for each patient's unique biochemistry and experiences.

Many clinicians who work with disordered eating believe they must be entrenched in one camp or another, i.e. they must treat patients with medications *or* offer psychotherapy *or* recommend nutritional supplements. My approach, refined over thirty years of clinical practice with eating disorder patients and informed by the latest in scientific research, does not suggest that there is ONE answer to binge eating. Instead, mine is a comprehensive approach that evolves from the field of integrative medicine. This, the New Hope model, integrates nutritional therapies along with medications, psychotherapy, and other lifestyle changes as needed. It is dysregulation in the brain that causes the appetite to run wild; accordingly, the New Hope model is designed to restore brain health. A return to brain health invites the realization of mental and emotional freedom as well as physical balance and well-being, ending a frantic and tortured roller-coaster ride for those who suffer from an appetite spun out of control.

Binge eating disorder (BED) is a severe disorder characterized by recurrent episodes of eating large quantities of food within a relatively short period of time (a phenomenon identified as a binge), often to the point of physical discomfort. Binge episodes are associated with distinct emotional manifestations, most often a profound sense of lack of control during the binge and feelings of shame, distress, and/or self-disgust immediately afterwards. While bingeing behaviors are characteristic of both bulimia nervosa and BED, BED is distinct (and classified accordingly in the DSM) in that BED binge eating is *not* accompanied by recurrent compensatory behaviors such as compulsive over-exercise and/or purging.

To the casual observer it may seem that BED, in comparison to other eating disorders, "isn't all that bad." It does not boast the mortality rates of anorexia nervosa and is not generally associated with the acute physical damages conferred by the purging behaviors of bulimia. But it is widely prevalent, with statistics confirming BED to be a stunning *three times more common* than anorexia nervosa and bulimia nervosa *combined*.[1] And – as any BED sufferer can attest and as I have witnessed firsthand in my decades of work with BED patients – BED can be as insidious and damaging as any psychiatric disorder, with consequences that can wreak havoc upon one's ability to live a balanced life. The physiologic sequelae of BED are most commonly associated with obesity and weight cycling; while BED can be diagnosed at any weight, up to two-thirds of sufferers meet clinical criteria for obesity.[2] The emotional and psychological consequences of BED can be severe, with many individuals withdrawing from friends and family, abstaining from normal daily activities, and isolating themselves in order to accommodate binge episodes, effectively damaging

social support networks and cultivating feelings of depression, guilt, and low self-esteem. For the BED sufferer, food is both the source of mental anguish and the focus of an ongoing addiction that cannot feasibly be avoided. Alcoholics can steer clear of bars, and gambling addicts may eschew social contexts that may trigger impulses… No one can *not* eat, however, and BED sufferers must confront the source of their mental and physical anguish every single day.

For the BED sufferer, then, the roller-coaster ride of restricting, bingeing, and self-blame can be endless. He or she may go through periods of perceived progress and effectuate measures of dietary restriction in spite of dysregulated appetite cues, which foster mental obsessions; inevitably, however, cravings become overpowering and inspire new binges, bringing the up/down/better/worse roller coaster cycle right back to the beginning.

While a roller coaster ride may be thrill-inspiring at an amusement park, being stuck on one by forces outside of conscious control is *not* a pleasant way to live. *No one chooses to eat in a manner that damages health, self-esteem, and personal relationships. The question then becomes: how to get off the roller coaster?*

Diet and exercise plans, no matter how expensive or Draconian, do not work in the long-term, a fact emphatically substantiated by research. Even when people follow a diet with the utmost precision, they experience food cravings at a much higher rate that non-dieters – a recipe for disaster for those with BED. Burdening a mind already struggling with food obsessions with mandated calorie counting is not a viable solution and will not unlock the roller coaster door. Nor will the prevailing sentiments of mainstream medical culture. "Just stop!" counsels many a healthcare provider, well-intentioned advice that often makes a BED patient feel worse – not just about his weight but also about his lack of willpower.

As scientific research demonstrates, strict adherence to the latest weight loss program is not an answer. The reason? *Disordered eating arises not from a deficit in willpower but rather from biology,* a tipping of neurochemical scales that regulate hunger and satiety and a dysregulation of the brain's reward pathways.

The connection between what research has revealed about the physical bases of addiction and disordered eating has powerful implications. First, as food addiction arises from brain function and biochemistry, we know with certainty that BED is a disease and *not* a moral failing. Second – and more importantly – the door has been opened to the exploration of biologic mechanisms underlying food addiction, and research has illuminated powerful new avenues to treatment – not temporary fixes that suppress symptoms for a time and then shatter when biology dominates willpower, but rather targeted interventions that address the underlying causes of dysregulated appetite and cut food addiction off at its source.

Food addictions and disordered eating arise from alterations in brain function and biochemistry.

To effectively control appetite, patients need to experience fullness after eating, a physical sense of satiety. And what creates satiety? Amino acids.

Supporting the diet of patients suffering from BED with amino acids is the first step towards achieving a healthy and balanced appetite. In my years of practice, I have found amino acids to be exceptionally beneficial in cases of binge eating, chronic cravings, depression, and anxiety; *in fact, I would go so far as to say that supplemental amino acids are the single most helpful intervention in the treatment of these disorders.*

In this article, we will explore amino acids and the biologic pathways through which they influence hunger and satiety, factors that influence amino acid availability within the body, and scientific evidence supporting the efficacy of amino acid supplementation as an intervention for dysregulated eating. I hope to share with readers invaluable information that has helped thousands of my patients and can for countless more provide an answer to appetite control…and a way off the roller coaster.

The foundation of modern psychiatry is one of neurotransmitter regulation, a paradigm of altering neurologic function by influencing the availability, transport, or degradation of neurotransmitters to effect cognitive and behavioral change. In traditional approaches, this is accomplished through the administration of psychotropic medications. In functional medicine, this is accomplished by providing the body with the raw materials from which complex essential molecules are constructed.

Muscle and soft tissues, enzymes that catalyze essential biochemical reactions, neurotransmitters, hormones, neuropeptides, receptors embedded within cell membranes – all these things, all vital to life, are built from proteins.

Along with carbohydrates and fats, proteins are macronutrients taken into the body that are deconstructed into their constituent components, the amino acids. Amino acid molecules, which contain carbon, hydrogen, oxygen, and nitrogen atoms in specific configurations, are strung together in unique sequences to form peptides, which then combine to form proteins. From basic amino acid "building blocks" – of which there are only twenty – the body manufactures more than fifty thousand different proteins to fulfill needs ranging from soft tissue repair to neurotransmitter synthesis, facilitating the balanced and coordinated dance of energy production, metabolism, and renewal.

Essential and Nonessential Amino Acids

The twenty essential amino acids are designated as "essential" or "nonessential" according to whether the body can synthesize them. Eleven

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of the twenty can be manufactured by the liver, while the remaining nine must be obtained through diet. While universally employed by the scientific, healthcare, and nutrition industries, the terms "essential" vs. "nonessential" are a bit misleading: *all* of the amino acids are essential to health; what varies are the sources from which they can be obtained. Nine amino acids can only be obtained from outside the body, from food or from nutritional supplements. If these nine are supplied in adequate amounts, the body can produce the other eleven.

How the Amino Acids Work

Once consumed, dietary proteins enter the digestive tract, where they are stripped of their amino acids. These amino acids are then absorbed and distributed throughout the body as raw materials that, along with vitamins and minerals, spark the chemical reactions that keep the body functioning. Many of these reactions are related to the generation and regulation of appetite.

Like thoughts and emotions, appetite is influenced and regulated by neurotransmitters and neuropeptides. These amino-acid-based chemical messengers relay information from one nerve cell to another throughout the brain, maintain dialogue between the brain and gut, and keep the various physical components of the digestive system in sync. Any disruption in neurotransmitter or neuropeptide production, such as may be caused by amino acid depletion, can therefore have profound physiologic and psychiatric implications and can lead to symptoms of disordered eating.

Neuropeptides

Small molecules produced and released by neurons that influence the activity of distinct neural substrates, *neuropeptides,* are the focus of some of the most promising scientific research in appetite control, having been identified as the biomolecular triggers of hunger and satiety. Thanks to advances in bioinformatics and gene sequencing technologies, a tremendous amount of progress has been made on this front over the last several years: over one hundred genes coding for neuropeptides have been identified in the human genome, with more likely to be discovered.[3] The neuropeptides involved in satiety and energetic homeostasis are among the most well-researched, and ongoing studies are focusing on molecules like ghrelin, leptin, neuropeptide Y (NPY), peptide YY (PYY), cholecystokinin (CCK), and gamma-aminobutyric acid (GABA) to examine the potential clinical applications of peptides for the treatment of obesity and binge-eating disorder. While a detailed analysis of the functions and biologic mechanisms of these peptides exceeds the scope of this article, there are two things that are critical for readers to note: (1) abnormal neuropeptide activity is a major factor in disordered eating; and (2) ***all* neuropeptides and neurotransmitters are *absolutely* dependent upon the availability of amino acids**.

Why Amino Acid Levels Fall

I regularly test fasting plasma amino acid levels of all essential and nonessential amino acids. For decades I have found that not only are amino acids commonly low in many patients who present with psychiatric illness, but they are also – frequently! – low even in individuals who eat a balanced diet with plenty of protein.

One would expect vegans, vegetarians, eating disorder patients, and other individuals who adhere to restricted diets that either eliminate or minimize consumption of protein to present with amino acid deficiencies, and indeed research has shown that such deficiencies are common in these populations. Yet time and again I have observed patients who eat healthy, organic diets inclusive of meats and fish to have low amino acid levels. What I have learned, and what clinical research corroborates, is that **diet alone is *not* a reliable predictor of amino acid levels**, and that adequate protein intake *can* present concurrently with amino acid deficiency states.

Why?

There are myriad factors that can contribute to amino acid deficiency. Diet is, of course, the go-to suspect, and as we have discussed, individuals who restrict diet and avoid protein, be they anorexic patients or teens subsisting on a diet of pasta-and-only-pasta, are vulnerable to deficiency states.

Another potential contributing factor is **inadequate protein digestion**. If the body cannot effectively strip amino acids from the proteins in food, none will be made available for the subsequent synthesis of peptides, hormones, neurotransmitters, and every other amino-acid-based molecule in our biology that is necessary to sustain health. Protein digestion begins in the stomach, which secretes **hydrochloric acid (HCl).** This powerful acid converts a substance called pepsinogen into pepsin, the enzyme that reduces proteins into smaller polypeptides. In the absence of sufficient HCl, protein digestion is *in*sufficient. HCl also facilitates the absorption of vitamin B12 and certain minerals that, in addition to fulfilling various important biologic functions, contribute to the transmission of satiety signals to the brain. Without adequate vitamin B12, satiety signals may be weakened, contributing to appetite dysregulation and patterns of overeating.

It strikes many of my patients as odd that much of my work as a psychiatrist involves optimizing digestion; and yet, this is something I do regularly, as many individuals that I treat test low for amino acids, a state often related to low HCl levels. This being the case, I also regularly test patients' levels of the mineral zinc. *Every single digestive enzyme in the body – including pepsin – is zinc-dependent,* as is every single protein, fat, and carbohydrate-derived digestive substrate. Beyond impacting a host of neurologic processes related

to cognition, a **deficiency of zinc** can significantly diminish digestive activity and efficacy, the downstream effects of which include metabolic dysregulation as a consequence of amino acid depletion. Without enough zinc, the body cannot properly digest proteins.

A third factor that can contribute to low amino acid levels is **age.** As we age, our production of gastric acid decreases; in fact, HCl levels drop by almost forty percent between adolescence and our thirties, thereafter dropping by nearly half by the time we reach our seventies. Consequently, our ability to digest protein diminishes over time, a phenomenon that is often a factor in functional amino acid deficiencies that I observe in older patients.

Finally, we cannot discount the effects of **medications** that deplete amino acid levels, of which there are many and many of which are common. The most notorious of these are **antacids**. Millions of people who experience stomach discomfort or indigestion as a result of overeating treat themselves with these acid-reducing or blocking medications, a tactic that actually makes an unpleasant situation worse. People attempting to address discomfort with antacids may unwittingly exacerbate problems with protein digestion by reducing already-low HCl levels. As stomach acid facilitates the control of appetite, decreasing levels with antacids can reinforce disordered patterns of eating.

Although eating a diet rich in protein is important, my initial recommendation for patients struggling with disordered eating is to try amino acid supplements. These can be administered as targeted interventions, broad-spectrum interventions, or a combination of both in order to address amino acid deficiencies that may be contributing to neurotransmitter and/or neuropeptide imbalances.

Targeted Interventions

5-Hydroxytryptophan (5-HTP) is an intermediate in the biosynthesis of serotonin, derived in the body from the amino acid tryptophan. Fascinatingly, this molecular intermediate of one of the most important neurotransmitters in mammalian biology is also found in botany; 5-HTP is among the many phytochemical constituents of the plant *Griffonia simplicifolia* and has for decades been isolated for use as a medical dietary supplement.

While it would seem both logical and simple to administer tryptophan to a patient whose serotonin levels are low, there are many reasons why 5-HTP is a superior choice as a serotonin-boosting intervention.

Not only does 5-HTP bypass the initial step in the chemical conversion

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of tryptophan to serotonin (rendering low tryptophan levels, if present, a non-issue), but it is able to cross the blood-brain barrier freely, has no feedback mechanism, and is not incorporated into proteins (meaning the body can and will only use it for serotonin synthesis). I often describe 5-HTP as a 'guided missile' that directly targets and increases brain serotonin, and both *research and clinical data emphatically support the use of 5-HTP as an intervention for a range of psychiatric disorders.*

Clinicians and researchers worldwide have used 5-HTP for decades as a treatment for anxiety and depression, with generally excellent results. Upon the strength of this evidence, *more recent studies have explored the efficacy of 5-HTP for appetite and weight loss, and what data has been amassed to-date is encouraging.* A series of clinical trials conducted in Italy demonstrated that obese subjects who received supplemental 5-HTP lost significantly more weight and consumed fewer carbohydrate-derived calories than did overweight subjects receiving a placebo, regardless of other experimental dietary restrictions.[4-6] Given that these studies were conducted within relatively short spans of time – a mere five to twelve weeks – these results are both striking and promising.

More recently, scientists from the University of Pavia in Italy explored the effects of sublingual 5-HTP on measures of food consumption and satiety in healthy but overweight adult women.[7] Subjects were randomized to use either a sublingual spray containing 5-HTP or a placebo spray five times a day for two months. Post-trial analysis revealed that women using the 5-HTP spray felt a greater sense of fullness than the control group. The 5-HTP group also completed the study with a lower body mass index than did the placebo group.

Current research emphatically supports the theory that supplying the brain with 5-HTP can help increase serotonin levels and facilitate appetite regulation. More research is needed; however, 5-HTP has been useful as an adjunct to treatment, particularly when combined with another essential amino acid, phenylalanine.

Phenylalanine, like tryptophan, is an essential amino acid that cannot be synthesized by the body and must therefore be obtained through diet. It is found not only in animal products but also in many plant-based proteins; meats, milk products, cereals, and legumes are all rich natural sources of phenylalanine.

Supplemental amino acids are the most helpful intervention for binge eating and chronic cravings.

In the body, phenylalanine serves as the molecular precursor to **dopamine**, the primary catecholamine neurotransmitter with a variety of roles including the activation of the brain's reward circuits. Dopamine itself is also the precursor from which two other important neurotransmitters are synthesized: **norepinephrine** (which triggers the neuroendocrine stress response) and **epinephrine** (familiar to most of us as adrenaline, epinephrine furthers the acute stress response by readying the body to "fight or flight"). Individuals who experience high levels of chronic stress are vulnerable to phenylalanine depletion, as sustaining a physiologic stress response will over time exhaust phenylalanine stores. Symptoms of phenylalanine *deficiency* include fatigue, depression, lack of alertness, memory problems, and increased appetite.

There are three distinct mechanisms underlying phenylalanine's influence on appetite and satiety. First, as the direct precursor to dopamine, phenylalanine boosts mood and decreases the urge to binge. Second, phenylalanine stimulates the production of **cholecystokinin (CCK)**, a neuropeptide that inhibits gastric emptying and induces feelings of fullness. The third mechanism through which phenylalanine influences appetite is related to the stimulation of thyroid hormones. Phenylalanine is a precursor to tyrosine, the amino acid from which **thyroxine** is synthesized. As the major form of thyroid hormone in the bloodstream, thyroxine is essential for regulating metabolism and also plays a role in protein synthesis, growth and development, and modulating the body's sensitivity to adrenaline.

Research suggests that phenylalanine, when administered as a dietary supplement, can facilitate appetite regulation and promote feelings of satiety, and is a more potent stimulator of CCK release than other amino acids.[8,9] Phenylalanine has been demonstrated in human studies to elicit a five-fold release of CCK within twenty minutes and reduce food intake by up to thirty percent within one to two hours of consumption.[8,10-12] In one noteworthy study, in which the effects of phenylalanine administration on endogenous CCK release were explored, six fasting, normal-weight subjects were given 10 g of either phenylalanine or placebo before being offered a meal.[10] Before, during, and after the meal, all subjects completed visual analog scales to assess their hunger, desire to eat, and satiety; in addition, blood samples were drawn immediately pre- and post-meal to assay CCK levels. Subjects who received phenylalanine consumed significantly fewer calories than did those who received placebo; this reduction in caloric intake was correlated with a significantly greater sensation of fullness. The authoring investigators concluded that CCK release triggered by phenylalanine administration can reduce food intake, confirming CCK's role as an important satiety hormone and highlighting phenylalanine's therapeutic potential as a treatment for binge-eating disorder.

It should be noted that research studies have examined the effects of both L- and D-phenylalanine, the former being the natural form of the amino acid

and the latter being lab-synthesized. While they are structural isomers, *only L-phenylalanine has been shown to induce CCK release and stimulate feelings of satiety. Phenylalanine supplements administered for purposes of appetite regulation should therefore always contain the L-form, in a combination known as DL-phenylalanine.*

Broad-Spectrum Intervention: Free-Form Amino Acids

While a diet rich in natural proteins is important, I reiterate that my very first recommendation to patients who struggle with disordered eating or who suffer from BED is often to try free-form amino acid supplements. Whereas 5-HTP and phenylalanine are targeted interventions that bolster production of specific protein-based molecules, free-form amino acids are a 'catch all,' a strategy that covers all possible bases insofar as endogenous protein synthesis requirements are concerned. Any existing amino acid depletions or deficiencies are effectively addressed through free-form amino acid supplementation, which provides the body with all the building blocks that it may need to build whatever molecules are required to cultivate health.

Although laboratory tests are not necessary prior to initiating a regimen of free-form amino acids, personalized supplementation based on fasting amino acid testing is always preferable. Clinicians considering the use of amino acids for specific patients should always evaluate potential risks, side-effects, and drug interactions before making any recommendations; monoamine oxidase inhibitors (MAOIs), for example, should not be used with amino acid supplements.

It is best to start with a free-form amino acid blend containing all the essential amino acids. A free-form blend bypasses the digestive process and is easily absorbed by the body to be utilized in protein, neurotransmitter, and neuropeptide synthesis.

Available in both capsule and powder form, amino acid blends are easy to take. Women should take a maximum of 10 grams of amino acid blend three times a day; men can take 15 grams three times a day. To ensure maximum absorption, amino acid supplements should be taken at least thirty minutes prior or two hours after a meal.

A Way Off the Roller Coaster

From simple peptides to complex neurotransmitters and hormones, amino acids serve as the molecular foundations for the vast majority of the biochemistry underlying appetite control. Through the optimization of amino acid levels, patients struggling with binge eating disorder will be able to synthesize both simple and complicated proteins that are required to maintain energetic balance, modulate reward ➤

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pathways, and normalize eating behavior. The most critical steps to take immediately after optimizing digestion are

1. Utilize free-form amino acids that are easily absorbed by the body to provide all the essential amino acids, such as tryptophan, to serve as precursors for important neurotransmitter synthesis; and
2. Try targeted amino acid supplementation that incorporates 5-hydroxytryptophan (5-HTP) and DL-phenylalanine. This combination of single amino acids provides the most dramatic regulation of appetite by optimizing the synthesis of serotonin and peptides involved in appetite control.

The use of amino acids is by no means a medical breakthrough, nor is it some "alternative" tactic supported by dubious science. It is a therapeutic strategy as fundamental, logical, and scientific as any: if a nutritional deficiency causes a problem, then mitigating the deficiency will resolve the problem. If the body is missing amino acids, then supplying the body with supplemental amino acids fills in these gaps…and permits the restoration of normal function.

In over thirty years of clinical practice, which has involved extensive work with complex eating disorder populations, I have found that the most significant intervention for treatment of disordered eating is, very frequently, one of the simplest: providing the body with adequate precursor amino acids. A major element of my New Hope model for restoring healthy appetite is optimizing neurotransmitter and neuropeptide levels with amino acids, which can often be the only intervention needed to reinstate balance, hope, and health…and bring the roller coaster ride to an end.

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Dr. Greenblatt is the chief medical officer and vice president of medical services at Walden Behavioral Care, a nationally recognized leader in the treatment of eating disorders. Originally founded in 2003, Walden Behavioral Care has grown from a single facility in Waltham, Massachusetts, to an integrated network of 15 different locations, each offering a range of eating disorder treatment services including inpatient, residential, intensive outpatient, and outpatient programs.

In addition to his professional roles at Walden Behavioral Care, Dr. Greenblatt serves as a clinical professor of psychiatry at Tufts University and the Dartmouth College Schools of Medicine. He is also the medical director of Psychiatry Redefined, an educational platform dedicated to the advancement of the field of integrative psychiatry offering books, online courses, and professional fellowship opportunities.

For more information on Dr. Greenblatt, Psychiatry Redefined, and Psychiatry Redefined educational opportunities, please visit www.psychiatryredefined.org.

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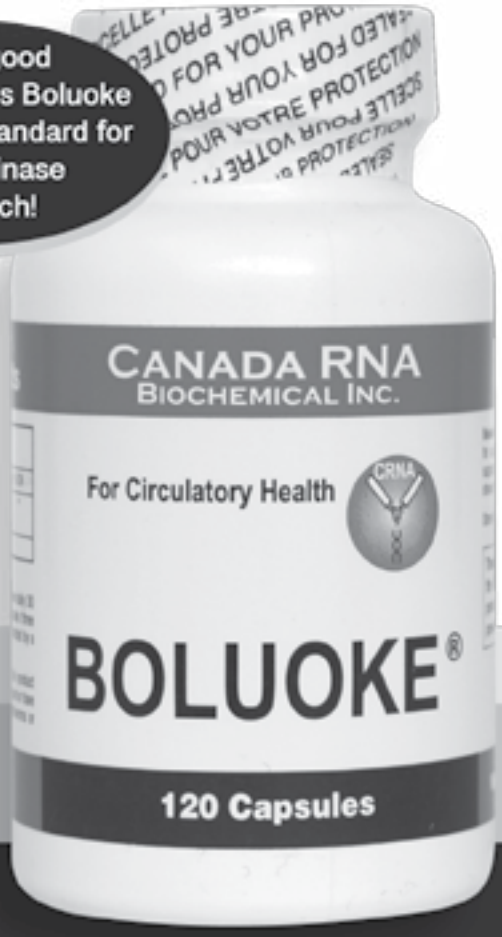

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Letters to the Editor

P-Hacking, Cherry-Picking and Data Dredging

I wholeheartedly agree with Dr. Gaby in his recent editorial "Why I Am Believing More and More Nutrition Research Less and Less" in the July 2019 issue of the *Townsend Letter*. He does some excellent detective work to uncover blatant research fraud. However, I am more inclined to believe that flagrant manipulation of data is less prevalent than unintentional research bias.

"P-Hacking," "cherry-picking," and "data dredging" are synonymous terms that explain the unintentional and sometimes intentional statistical manipulation of data to suit a particular hypothesis. As I understand it, a p value is a probability of an event or outcome that is entirely due to chance. It can also be used to mean the null hypothesis or the opposite effect of what the hypothesis is testing. A p value is important in medical research because it sets the bar at which a particular outcome is due to the desired effect of what is being tested. A lower p-value is desired because it lowers the probability that the outcome is due to chance or the null hypothesis. In medical research, an arbitrary p-value of 5% or 0.05 is often used. A p-value higher than 0.05 is typically not considered statistically significant or reliable in the scientific medical world.[1,2]

When I was in grade 9, I took a basic science course that introduced me to the scientific method. I learned that the hypothesis is a fundamental cornerstone of scientific research. The teacher drummed the lesson that a hypothesis begins with the supposition "if" and ends with purported outcome "then." The hypothesis was rudimentarily based on cause and effect. In its simplest form it was evaluating only one variable and measuring only one effect. As in example of a hypothesis, I studied the effect of temperature on the rate at which crickets chirp. My hypothesis was that *if* the ambient temperature increases, *then* the rate at which crickets chirp also increases. I lived in a small rural town that was near a slough that was full of wildlife. I took my thermometer and stopwatch to the swamp for several weeks and happily timed the chirps and measured the air temperature. I was excited to discover that my hypothesis was correct and indeed the ambient air temperature was directly correlated with the rate at which crickets chirp. I have never forgotten the lesson of basic scientific research and what the definition of a hypothesis is.

In 2010, I took the pharmacy upgrade course for naturopathic doctors in Vancouver. It was a daunting course with a lot of material. As I had been practicing naturopathic medicine and out of school for 19 years, it was a good opportunity to dust off the cobwebs and exercise some grey matter. The instructors were pharmacy doctorates from the University of British Columbia and were the same teachers that instructed at the UBC School of Medicine. Dr. James McCormack was a knowledgeable and entertaining instructor

who introduced the concepts of basic statistics to medical students. He provided a basic understanding of biostatistics as it related to medical research. He defined p-values, relative rate of reduction, absolute rate of reduction and number needed to treat in simplistic terms. He said that this understanding would allow our group of practicing physicians to critically evaluate medical research as it related to drug therapy. In one example, he pointed out that the incidence of myocardial infarction in a particular age group was 8%. He explained that taking a particular statin medicine for a period of time reduced the risk of MI to slightly less than 6%. He further explained that the absolute rate of risk reduction was 8% minus 6% or about 2%. He calculated the relative rate of risk reduction as 8% minus 6% divided by 8% or 0.25 or a 25% reduction in the occurrence of MI. He said that this 25% relative rate of risk reduction was the number that drug companies frequently used in their advertising brochures. I was dumbfounded to learn that a 2% decrease in absolute risk reduction translates to a 25% relative risk reduction rate. Dr. McCormack was also quick to point out that the effects of vitamins and herbs on different health parameters was equally or even less as impressive.

My eldest daughter is doing her master's degree in statistics at the University of British Columbia in Vancouver. Even though I have degrees in biology and naturopathic medicine, I must admit I still have an indelible difficulty understanding biomedical statistics. Her textbooks read like an unintelligible foreign language to me. However, I do know statistics is extremely important in evaluating scientific research. I can appreciate the language of statistics that includes p-values, relative rate of reduction, absolute rate of reduction, number needed to treat, confidence intervals and odds ratio. I can read a medical journal paper and critique it with a basic understanding of statistics. After one of our phone calls in which she was explaining what a p-value really means for the umpteen time, she sent me a YouTube video that introduced me to the concept of p-hacking.[3]

P-Hacking involves the manipulation of data to support the hypothesis while maintaining a reliable p-value. It is done by performing multiple statistical tests on subgroups of the original group of data. As this is done, it increases the probability that a significant result will occur. This purported positive result is then interpreted to be a direct result of the intervention. However, the effect is entirely due to chance alone.[4,5]

In the quest to come up with positive test results, research funding, and getting published in prestigious journals, researcher bias can occur. While often not blatantly intentional, p-hacking is a more common practice in medical research than originally thought. In one review of psychological researchers over 50% of participants admitted to "failing to report all of a study's dependent measures" and "deciding whether to collect more data after looking to see whether the results were significant." The authors concluded that "this indicates that many researchers p-hack but do not appreciate the extent to which this is a form of scientific misconduct."[6]

Some statisticians offer ways to reduce p-hacking, cherry-picking and data dredging that include setting out with an original hypothesis at the beginning of the experiment, providing clear guidelines of what exactly is being tested, paying attention to quality data research and data collection, avoiding sub-group data analysis and inference, adhering to reliable generally recognized statistical analysis methods, and setting up peer review analysis of data and conclusions. Reliable and unbiased research is central to the scientific method, the support of the hypothesis and the quest for truth in explaining natural phenomena.[7]

A little understanding of basic statistics can help medical professionals sift through the murky world of medical research and come to logical and reasonable conclusions of the data presented. P-hacking, cherry-picking and data dredging are more common ways of manipulating statistics to support the hypothesis presented. As the colloquial oft-quoted Mark Twain once said, "There are three kinds of lies; lies, damn lies and then there are statistics."

Dr. Douglas Lobay, BSc, ND

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Response to Moldy Buildings, CIRS, Sick People and Damaged Brains

The latest research is proving that mold mycotoxin exposure is a silent epidemic across much of the developed world. The reasons behind the increase in mold mycotoxin exposure and its increased pathogenicity are complex and beyond the scope of this letter, but the amount of research going into mycotoxins is immense. Since the year 2000 there have been over 22,000 articles on mycotoxins according to PubMed. Since expanding our environmental toxicant testing platform, we have endeavored to increase the field of research into how environmental toxicants cause injury by collaborating with multiple academic institutions. We have tested over 150,000 samples with various types of environmental toxicants, which have been shown to be underlying contributors to multiple chronic illnesses.

We are writing this letter in response to Dr. Shoemaker's five-part article seen last year in the *Townsend Letter*. While we greatly respect and appreciate Dr. Shoemaker's contributions to understanding and treating patients with water-damaged building syndrome, we respectfully wish to refute three points that he claims in his article: 1.) Dr. Shoemaker states "we find scores of papers regarding healthy people with markedly abnormal levels of mycotoxins in urine." 2.) Dr. Shoemaker downplays the need for anti-fungal therapy to treat mold exposure. 3.) Throughout the five articles Dr. Shoemaker advocates the need for expensive testing for genetic and chronic inflammatory response (CIR) markers. We advocate the need to find the underlying causes of mold-related illnesses, eliminate the mycotoxins derived from mold, and alleviate the cell danger response for proper treatment.

In part three of the series Dr. Shoemaker states "there is no published control group data (PubMed 4/9/2019) showing absence or simply a paucity of mycotoxins in urine in controls compared to cases." Even though we had not published our results by the time of Shoemaker's publication, our *Townsend Letter* article, "Biochemical Markers in the Urine Associated with Gastrointestinal Mold Overgrowth Are Associated with Elevated Urinary Mycotoxins in Patients with Suspected Mold Illness" shows that patients exposed to mold have significantly higher amounts of mycotoxins compared to healthy controls.[1] In addition, multiple papers had been previously published that demonstrate that mold-exposed patients have higher values than controls.[2-4] Without any citations by Shoemaker to back up his claim that normal individuals have elevated mycotoxins, it is possible that he is referring to the background amounts in the urine of normal people from exposure to mold in food sources or outside air. Such exposures may be especially common for mycotoxins such as ochratoxin, fumonisins, and deoxynivalenol.[5] However, from our published data we see a 23-fold increase in urine levels of aflatoxin M1, an 11-fold increase in urine levels of ochratoxin A, and a 38-fold increase in urine levels of sterigmatocystin in mold-exposed patients compared to controls.[1] These data indicate that mycotoxins are significantly elevated in patients that are exposed to water-damaged buildings.

In the first and third parts of the series Dr. Shoemaker argues against the importance of determining fungal infections and treatment in dealing with water-damaged buildings. His one point of evidence is a single study in Germany from 2003 which came to the conclusion that "Positive fungal cultures from nasal secretions have to be considered normal findings."[6] However, utilizing this one study simply ignores more recent studies which contradict this finding. One of the best recent findings was done by Joseph Brewer, which found multiple species of mold producing mycotoxins in chronically ill patients; but none in healthy controls.[2] In another study using an advanced DNA platform, the authors were able to determine that several species of *Aspergillus* were in significantly higher amounts in ethmoidal sinusitis compared to healthy controls.[7] Shaw et al's study on autism,[8] published nearly 20 years ago, showed much higher amounts of mold metabolites in urine samples of children with autism compared to normal control children; these mold markers decreased significantly after treatment with the anti-fungal drug nystatin, together with reduced autistic symptoms. The reduction of these metabolites by a drug that is not absorbed from the intestinal tract indicated a colonization of the intestinal tract by mold that would not have resolved without antifungal treatment. In addition, a very recent study confirmed that autistic children have a high prevalence of *Aspergillus fumigatus* in blood samples compared to healthy controls.

Our own data demonstrates that, using an organic acids test, we can determine if a patient is colonized with either *Fusarium* or *Aspergillus*. Using the markers 5-hydroxymethyl-2-furoic acid, furan-2,5,-dicarboxylic acid, and tricarballylic we were able to determine which patients are more likely to have high mycotoxins. Patients with these values had elevated mycotoxins over 97% of the time.[1] In addition, using antifungals has been shown to be an integral part of treatment.

Colonized patients could linger for years and rarely get better without antifungal treatment. After discussing treatment with hundreds of doctors and attending the International Society for Environmental Acquired Illness (ISEAI) conference, we believe it is a necessary part of treatment to check for colonization and to provide antifungals when necessary. Obviously, practitioners should be careful to only provide it when warranted to help prevent an increase in anti-fungal resistant species, but the agricultural use of anti-fungals is much more a driver of this phenomenon than medical use.[9]

The last point that we wish to make is to advocate against doing multiple tests to diagnose a chronic inflammatory response syndrome (CIRS). Many of the genes and cytokines upregulated in this pathway are very promiscuous and will be upregulated by a variety of stimuli. Some of these things include metals, pesticides, traumatic brain injury, and mycotoxins.[10-13] It seems better for the patient that practitioners determine the cause of upregulation rather than prove that upregulation exists. There seems to be at least three main parts of treatment that need to be followed: 1.) Identify if there is an environmental source of mold and, if there is, remove it. 2.) Assist in detoxification. 3.) Assist the body in eliminating the cell danger response.[14] Treatment that assists in identifying and assisting with these aspects will provide the most personalized and effective treatment for the patient.

Matthew Pratt-Hyatt, PhD, and
William Shaw, PhD

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Mind-Body Approach to Depression

review by Dr. Nasha Winters

Depression: The Mind-Body, Diet and Lifestyle Connection by Ray Griffiths
Clink Street Publishing, London, UK
ISBN 1912850982, 9781912850983; c. 2019; 150 pp; $12.99

After reading and reviewing Ray Griffiths' book, *Mitochondria and Health and Disease,* a few months back for *Townsend Letter*, I welcomed another opportunity to read the latest by this articulate author who can deliver up-to-date scientifically referenced material in an enjoyable and digestible fashion.

For the past three years and the first time in history, the United States is seeing a dip in survival rates, thanks to the exponential rise in opiate overdoses and suicides.[1] It is a call to action to ask WHY and to bring hope and support to the front lines and restore our rightful place at the table to enjoy improved longevity.

Ray Griffiths new book, *Depression: The Mind-Body, Diet and Lifestyle Connection,* offers light in the midst of the darkness by exploring a whole-body approach to mental health and calling out the triggers contributing to the rise in devastation and fall in both quality and quantity of life in the Western world.

Triggers such as stress, nutritional deficits, dietary indiscretions (namely sugar addiction), lack of exercise and time in nature, loss of community and purpose are discussed in detail with excellent references to lead the charge.

His take-home message is suggesting the wellbeing of our mental state depends on our brain's ability to adapt, grow, repair, and survive the threats of modern life. He places emphasis on the brain's central headquarters, the hippocampus, a small organ located in the temporal lobes of the brain, associated with mental health, memory, and emotion and how the structural integrity of that organ shrinks under duress and leads to depression and anxiety.

Roy discusses what activates that shrinkage, such as imbalances in the HPA axis (impact of stress), gut/brain axis (how the microbiome directs the show), hormonal influences (2:1 ratio of women to men experience depression), insulin resistance (depression and Alzheimer's risk go hand in hand and directly relate to blood sugar imbalance), inflammation (from traumatic injury, but also traumatic experiences, toxicants, infections, wrongful diet, poor sleep), environmental and social enrichment (impact of nature deficit and isolation), to name a few.

When functioning properly, our hippocampus is regenerating about 700 new cells per day. When damaged, malnourished, overwhelmed, or lacking in the proteins (BDNF and NGF) that stimulate neurogenesis and neuroplasticity, this important mood-stabilizing and adaptation-promoting organ shrinks and withdraws from its duties, leaving us lacking resilience, insight, hope, and motivation.

There were many pearls I took away from this simple but well-written book:

- All chronic illness, including diabetes, osteoporosis, cardiovascular disease, arthritis, obesity and cancer are strongly associated with increased levels of depression and anxiety—running parallel to, and not because of, these conditions.
- Adverse Childhood Events (ACE) shrink our hippocampus, and lack of connection with mother at a young age increases our susceptibility to depression and leaves us less prepared to deal with the experiences of life.
- Our hippocampus is "fertilized" and nourished by neurotrophin proteins, BDNF and NGF, which are the bridge builders, connecting our experiences to biological actions.
- Our neurotrophins depend on our diet, nutrition, exercise, and emotional fulfillment to do their job.
- Ray does a great job showing the reader what suppresses and boosts our neurotrophins and some basic dietary, nutrient, and lifestyle hacks that will increase our neuroplasticity and neuroregeneration to enhance our mental resilience and overall longevity.
- Addictions are a misplaced search for spirit (and trying to compensate a starving brain). Meditation, mindfulness, and spiritual practice enhance BDNF and our ability to emotionally cope.
- Community and finding joy, passion, purpose, and gratitude build the neurotrophins.
- Isolation, solitary confinement, and the era of technology over social interaction directly lower NGF and lead to aggressive and psychotic behavior.

I would have liked to see information on the impact of EMFs and screen time, specifically blue light and its impact on microglial immune and inflammatory triggers to the brain, as well as the increase in glucose uptake to the brain from technologies that further exacerbates the dopamine and insulin balance, leading to hippocampus shrinkage.

I also would have liked to see some discussion on impact of intermittent fasting on raising BDNF levels and the fact we are so enamored with the Mediterranean diet (MD) as the best diet for depression, when much of the reason the MD has been successful is because of the region's spiritual practice that includes upwards of 200 fasting days per year. Fasting, community, and closer connection to nature and circadian rhythms are becoming more evident as the real impact, along with the food choices, influencing our overall wellbeing today.

Perhaps the final two points I made warrant another book (hint, hint!) though I very much appreciate the thorough assessment and solution that Ray offers in these pages. I suggest you grab a copy of his book, a cup of organic coffee or tea, a handful of blueberries and walnuts, and find a sunny spot somewhere out in nature to literally expand your mind (specifically, the hippocampus), flood your brain cells with BDNF, and get a rush of connection, gratitude, and joy that will lift your spirits and rewire your brain.

Reference

1. Haskins J. Suicide, opioids tied to ongoing fall in US life expectancy: Third year of drop. *The Nation's Health.* February/March 2019;49(1):1-10.

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CALENDAR

Please visit TownsendLetter.com for the complete calendar

JANUARY 16-19: FREQUENCY SPECIFIC MICROCURRENT SEMINAR (CORE) in Cleveland, Ohio. Also, **FEBRUARY 20-23** in Phoenix, Arizona; **JUNE 13-17** in Italy; **JULY 23-26** in Iceland. CONTACT: https://frequencyspecific.com/

FEBRUARY 1-2: CHELATION WORKSHOP in Kuala Lampur. Malaysia. CONTACT: drmaung@hotmail.com

FEBRUARY 3-17: INTENSIVE CLINICAL TRAINING in India. 160+ live cases demonstrated in 2 weeks to show action of homoeopathy in gross pathologies. CONTACT: https://homoeopathy-course.com/courses/india

FEBRUARY 7-9: LABORATORY, ENDOCRINE, & NEUROTRANSMITTER SYMPTOSIUM in Las Vegas, Nevada. Practical and applicable advanced neuroendocrine training for your integrative practice. Earn up to 14.5 CMEs. CONTACT: www.fx-ed.com

FEBRUARY 7-9: GREAT PLAINS LABORATORY PRACTITIONER WORKSHOPS – Organic Acids Testing and Environmental Toxin Testing in Fort Lauderdale, Florida. Also, **APRIL** in Baltimore, Maryland; **JUNE** in Kansas City, Missouri; **JULY** in Portland, Oregon. CMEs available. CONTACT: 913-341-8949; http://www.gplworkshops.com/

FEBRUARY 29-MARCH 1: FREQUENCY SPECIFIC MICROCURRENT ADVANCED SEMINAR in Phoenix, Arizona. Also, **JUNE 20-21** in Tuscany; **AUGUST 1-2** in Iceland. CONTACT: https://frequencyspecific.com/

MARCH 5-7: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE SPRING MEETING – The Roots of Toxicity in Dallas, Texas. In collaboration with ICIM, IABDM, and IAOMT. AMA Category 1 credits available. CONTACT: http://aaemconference.com/

MARCH 7-8: ICIM STAFF TRAINING FOR IV THERAPY AND IV DISODIUM EDETATE CHELATION THERAPY in Dallas, Texas. CONTACT: https://icimed.com/conferences/?page_id=2993

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

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

APRIL 2-4: FREQUENCY SPECIFIC MICROCURRENT SEMINAR – PAIN/INJURY MODULE in Portland, Oregon. Also, **APRIL 24-26** in Denver, Colorado; **MAY 15-17** in Raleigh-Durham, North Carolina; **SEPTEMBER 18-20** in Chicago, Illinois; **OCTOBER 16-18** in Anaheim, California. CONTACT: https://frequencyspecific.com/

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

APRIL 2-5: ENVIRONMENTAL HEALTH SYMPOSIUM 2020 – Immunotoxicity: The Intersection Between Toxic Exposure, Infectious Disease, and Autoimmunity in Scottsdale, Arizona. CONTACT: https://environmentalhealthsymposium.com/

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

APRIL 5-7: FREQUENCY SPECIFIC MICROCURRENT SEMINAR – NEURO-VISCERAL MODULE in Portland, Oregon. Also, **JUNE 5-7** in Denver, Colorado; **JULY 10-12** in Philadelphia, Pennsylvania; **NOVEMBER 6-8** in Chicago, Illinois; **DECEMBER 4-6** in San Francisco, California. CONTACT: https://frequencyspecific.com/

APRIL 23-26: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING For Doctors, Dentists & Health Professionals: Detecting Parasites, Dental & Fungal in St. Louis, Missouri. Simon Yu, MD, CONTACT: www.preventionandhealing.com. 314-432-7802.

MAY 14-16: 29th ANNUAL A4M/MMI SPRING CONFERENCE in Orlando, Florida. CONTACT: 561-997-0112; https://www.a4m.com/

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

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

JUNE 12-14: INTERNATIONAL CONGRESS OF REGENERATIVE MEDICINE on Captiva Island, Florida. CONTACT: https://www.icrmconference.com/

JUNE 20-27: CLINICAL AND COMPARATIVE MATERIA MEDICA @ Allen College of Homeopathy in the United Kingdom. On-site or interactive online course. CONTACT: https://homoeopathy-course.com/courses/england/7-day-summer-school

AUGUST 27-30: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING For Doctors, Dentists & Health Professionals: Detecting Parasites, Dental & Fungal in St. Louis, Missouri. Simon Yu, MD, CONTACT: www.preventionandhealing.com. 314-432-7802.

SEPTEMBER 11-13: FREQUENCY SPECIFIC MICROCURRENT MASTER CLASS in London, United Kingdom. CONTACT: https://frequencyspecific.com/

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Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, MSW
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Rajan Sankaran: The Eight-Box Method

Commemorating 26 Years of Study with My Mentor

I was an avid homeopathic student from the moment I read *Kent's Lectures on Homeopathic Philosophy* shortly after beginning my ND degree in Bastyr's second graduating class – much to the consternation of some core faculty members who were less than enthusiastic about homeopathy, as compared to "science-based medicine." Not so Dr. Bastyr, who was a multi-modality doc who loved homeopathy. In fact, when I, suffering from a tenacious bronchitis, first saw him as a patient on my arrival in Seattle, I remember his sage drawl: "Why, that's a *Rumex* cough." And so it was!

Bastyr College had barely gotten off the ground in those early days. Our classes were hit and miss, and the homeopathy instruction left much to be desired. Plus, the new naturopathic college in Northern California went belly up, so our class doubled in size nearly immediately. Fortunately, my unquenchable thirst to learn the best of homeopathy along with being at the right time in the right place, pointed me towards my goal. Homeopathy happened to be enjoying a remarkable renaissance, especially in the Bay Area, after having been nearly dead in the water since the "modernization" of medicine in North America, thanks to the Flexner Report in 1910. So, the limited homeopathy that we were taught as ND students was supplemented by seminars with George Vithoulkas and excellent case conferences, right here in Seattle, offered by the IFH (International Foundation for Homeopathy), of which I eventually served as president.

The Evolution of the Sensation Method

For the first 10 years after becoming an ND, I studied with all of the foremost teachers of homeopathy. If there were someone teaching, I would be there. But I didn't come across anything that knocked my socks off until I happened upon *The Spirit of Homeopathy* by Rajan Sankaran in 1993. Bob and I wasted no time in attending Rajan's London seminar; and when we asked how and where to learn more, he invited us to join the first "Foreigner's Course" in Mumbai. Four of us from the US attended, along with about eight Europeans. The homeopathy practiced by Rajan and his colleagues was light years ahead of anything we were doing. They had memorized *materia medica* and repertory, and their understanding of casetaking and the relationships between remedies was far beyond anything I had previously learned. A number of those cases from 1993 are still indelibly imprinted on my memory! Immediately upon our return from India, our casetaking and grasp of remedy relationships had been so profoundly altered that we changed about 80% of our homeopathic prescriptions. We wrote a *Townsend Letter* article at the time, "Back from Bombay," which must still be available in the archives. That was the first of nine annual pilgrimages that we made over the subsequent years to fine tune "the method," as well as dozens of seminars with Rajan and his colleagues in the US, particularly Hawaii. Some other homeopathic practitioners at the time, like us, embraced these "new" ideas wholeheartedly. Others did, and still do, refer to themselves as true Hahnemannians and

eschew all that Rajan teaches. For me, the last two and a half decades have breathed new life, inspiration, and excitement into my practice.

The *Sensation Method* is all about eliciting the underlying sensation or thread, which is the underpinning of any homeopathic case. Understanding the unique sensation of each individual makes it possible to find the one homeopathic remedy (out of 5000+) that can profoundly help the patient. This is a far cry from my initial training, which taught that the 45 polychrest remedies were all we needed for most patients. Why would millions of patients need one of so few remedies? Only because of the homeopath's lack of familiarity with the rest of the *materia medica*!

But, as is the case with most genius teachers, the method evolved with the years as Rajan explored new angles, conducted a number of homeopathic provings, and began to evolve his methodology in an increasingly coherent and consistent way. Yet, the method was evolving so quickly that it could be hard to follow and reproduce. When Rajan took a "live case," then asked all of us what we would prescribe, the responses were all over the map! In 2004, in Mumbai, one of our North American colleagues showed us photos of her gorgeous piece of land in Chile. As fate would have it, we began our Chile land project the following year, after having embarked on a kayaking trip in Patagonia. And, though I have continued to use Rajan's methodology, we have not returned to India.

Fast Forward Fifteen Years to the Eight-Box Method

We didn't see Rajan again in person until three years ago at his San Anselmo seminar, then again, the following year. Thankfully, this recent seminar in Minneapolis was the third opportunity to study with him in as many years; but it wasn't like the concentrated dose in Mumbai, and I am tempted to go back for another training course at his school, *The Other Song.* Rajan chose Minneapolis because of the Northwestern Academy of Homeopathy. (I still don't understand the name, being located in what I call the northern Midwest of the US.) Minnesota has the most freedom of any state in the US for unlicensed practitioners. The school is flourishing, and there are a large number of successful homeopathic practices in the area. Nearly 90 avid students attended the seminar and about that same number came to Rajan's evening talk. Impressive!

Over the last several years, Rajan has developed what he calls the eight-box method. He was looking for a more dependable way to select and confirm the correct remedy for each patient, as well as the right potency. There are ➤

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many different ways to arrive at a homeopathic prescription for a given patient. That is what strikes some naysayers as unscientific, inconsistent, and unprovable. Rajan wanted to fine tune a system where many a homeopath, based on solid evidence, would come to the same prescription for a patient. The *ReferenceWorks and MacRepertory* computer programs are invaluable in this process. We are forever indebted to our dear friend and colleague, David Warkentin, who developed these brilliant programs, which are still the lifeblood of our remedy selection process. This method is carefully explained in *Exact, Complete, Depth: The Eight Box Method of Case Analysis* (2018) by Rajan.

The Eight Boxes – An Example (titles of the boxes vary some from case to case):

1. Pathology (diagnosis/es by name)
2. Local Symptoms (the specific local symptoms and their characteristics, modalities)
3. Physical Generals (including modalities – what makes each symptom better or worse).
4. Mental Symptoms
5. Dreams/Delusions/Fears
6. Could be Mother's History During Pregnancy or Past History
7. Sensation/Kingdom/Source
8. Genius/Pattern (What must be present, bottom line, that ties together the case?)

Then rubrics in the repertory are carefully chosen so that there is, in the end, little doubt that the particular remedy covers the entire case. Once the remedy is selected, it is important to corroborate the match through *materia medica*. The ultimate proof is, of course, a positive response in the patient's symptoms long-term. I don't present a case as "cured" unless there is at least two years of successful follow-up with the same remedy. We are talking about long-term improvement, hopefully in all the person's symptoms, not just an amelioration over a matter of months, since that could happen by chance. Rajan presented a number of video cases from his practice in India, explaining the use of his new method and showing the impressive changes as a result of the well-chosen remedy, or *similimum.* I refer readers who wish to learn more about the eight-box method read the compact, yet compelling book mentioned above.

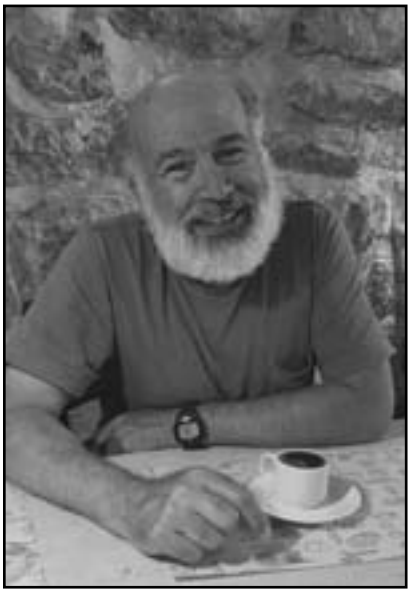
A Breakthrough in Remedy Plant Subclasses

The characteristics of a patient needing a plant remedy, as opposed to a mineral or animal, are sensitivity, adaptability, and one particular sensation, depending on the particular plant family, as well as its opposite. This sensation mimics the features of the plant family in nature. For example, the *Leguminosaes* in nature include various members who spread their seeds through the bursting of pods. I remember a vivid example of this while walking on a path in Southern Argentina on a hot day. The crackling sound in the air of the pods bursting in the head and scattering their seeds was nearly deafening. How fascinating that humans who need members of this family will describe feeling scattered, fragmented, and splitting apart! *Sankaran's Schema*, published in 2005, has been a godsend to help me and countless other homeopaths worldwide to differentiate between the different remedies belonging to 33 plant families and prescribe them for patients. Though *Schema* is clearly a preliminary work in progress, since there are tens of thousands of plants which are either existing or potential homeopathic remedies, it is a remarkable beginning.

Rajan, who is always looking to improve his method in order to help more patients profoundly, recently introduced a new chart of plant remedy subclasses based on whether they are Monocotyledons (monocots) or Aicotyledons (dicots), both of which fall under the category of Angiosperms (flowering plants) or Gynosperms. The dicots were then subclassified into six subclasses: Magnoliadae, Hamamelidae, Carophyllidae, Dellenidae, Rosidae, and Asteridae. This was the first time I had been exposed to this revised schema, and it will take some time to absorb and apply to my practice. When I think of the breadth of my homeopathic understanding when I first started studying with Rajan compared to now, coming upon three decades later, it is a quantum leap. At seventy-one-and-a-half and far from retiring, I can only imagine the leaps that lay ahead for me and for other classical homeopaths over the decades to follow! ◆

Judyth Reichenberg-Ullman is a licensed naturopathic physician, board certified in homeopathy. She practices with her husband, Robert Ullman. She sees patients in person at Serene Natural Health in Edmonds, Washington, as well as by phone consultation internationally. They live on Whidbey Island, Washington, and in Pucón, Chile. Please visit their website at www.healthyhomeopathy.com and Facebook at Healthy Homeopathy. She can be reached by phone at 425-774-5599 or through email at drreichenberg@gmail.com.

Together the doctors have written eight books on homeopathy: *Homeopathic Self Care, The Savvy Traveler's Guide to Homeopathy and Natural Medicine, Whole Woman Homeopathy, Ritalin-Free Kids, A Drug-Free Approach to Asperger Syndrome and Autism, The Homeopathic Treatment of Depression, Anxiety, and Bipolar Disorder,* and *Rage-Free Kids* as well as *Mystics, Masters, Saints and Sages – Stories of Enlightenment*. They have been columnists for the *Townsend Letter* for nearly thirty years! They also have an app: Natural Travel Doctor. Apple version: https://tinyurl.com/l7song8 and Android: https://tinyurl.com/m7cnexh .



Curmudgeon's Corner

by Jacob Schor, ND, FABNO
drjacobschor1@msn.com

Mean Platelet Volume

A rash of recently published papers suggest that the measurement of mean platelet volume (MPV), performed routinely in complete blood count (CBC) tests, is of greater prognostic value in a range of conditions than previously realized.

Truth be told, when I was new in practice some decades back, this test must have also been new. Although I clearly remember seeing MPV results on patient lab reports early in our practice, I was unsure as to what MPV stood for and clueless as to what the results meant. I had no memory of Dr. Kruzel teaching us about MPV in his lab diagnosis class at NCNM. Before suggesting any omission on his part, I readily admit that I may have dozed off during that segment of his lecture. Suffice to say, I recall clearly reading through lab results with patients and feeling relieved that the MPV results were within normal range, so not having to explain what a non-normal MPV might signify.

At some point though a patient's CBC did come back with a high MPV, throwing me into a semi-panic. There was no Google back then. My only option was a 1-800-call to the lab we used. I eventually spoke to the in-house-pathologist. I can still hear his side of the conversation in my memory; "Oh, MPV…that's an interesting test. The blood counters we use to count RBCs and WBCs and all that stuff are able to count and measure platelets as well. So, we report all those platelet numbers…. Do I know what they mean? No idea. We just report them. Yes, hopefully once doctors see these numbers often enough, they'll start to notice patterns and correlate them with disease…."

I remember his words well as I have often paraphrased them to patients over the years, saying, "The lab reports these MPV numbers, but no one knows what they actually mean."

My line is no longer true; and research on MPV interpretation is advancing, it seems, rather quickly.

Platelets, also called thrombocytes, are cytoplasmatic fragments of bone marrow megakaryocytes and are essential for normal blood clotting. They are tiny, having a diameter of 3-5 µm and a volume of 4.5–11 fL. A single megakaryocyte releases 1500–2000 platelets into the bloodstream, where they circulate for 7–10 days. Platelet cytoplasm contains three different types of granules (i.e. alpha granules, dense granules, and lysosomal granules), secretory vesicles that contain pre-formed molecules, and a complex membranous system. [1]

Platelets' primary function is clotting the blood to prevent unwanted bleeding. Platelets interact with each other, as well as with white blood cells and endothelial cells, searching the vascular bed for sites of injury, where the platelets become activated. When stimulated, platelets undergo a shape change, increasing their surface area; and the bioactive molecules stored within their alpha and dense granules are rapidly secreted.[2]

Newer evidence suggests that platelets contribute to the inflammatory process, microbial host defense, wound healing, angiogenesis, and remodeling.[3] Platelets release more than 300 proteins and other small molecules from their granules (including chemokines, cytokines like interleukin-1β, CD40 ligands, β-thromboglobulin, growth factors etc.) that influence the function of the vascular wall and circulating immune cells.[4] Platelets also secrete microbicidal proteins and antibacterial peptides.[5,6]

MPV is measured by the same machines that determine other CBC parameters. When the body produces platelets in large numbers, MPV can suggest information about platelet production or bone marrow or platelet destruction problems. MPV goes up when platelets are being destroyed faster than usual, for example in inflammatory bowel disease, immune thrombocytopenic purpura, and myeloproliferative diseases. Low MPV values are associated with thrombocytopenia from aplastic anemia.

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Since a platelet's lifespan is brief, only about 8-10 days, examining platelets provides a window on current function that can rapidly shift.

MPV also seems to take on varying roles in different inflammatory conditions. High MPV levels are associated with high-grade inflammation owing to the presence of the large platelets in circulation. Yet at the same time, MPV might decrease in high-grade inflammation due to the consumption and sequestration of these large platelets in the vascular segments of the inflammatory region. Low MPV is associated with low-grade inflammation, like rheumatoid arthritis and attacks of familial Mediterranean fever. As a generalization, MPV decreases in acute disorders and increases in chronic disorders.[7] But don't trust that statement too closely.

Conditions Associated with Decreased MPV:

Cytotoxic Chemotherapy
Hypersplenism
Reactive Thrombocytosis
Iron Deficiency Anemia
Hypothyroidism
Acquired Immunodeficiency Syndrome (AIDS)
Wiskott-Aldrich Syndrome
X-Linked Thrombocytopenia

Conditions Associated with Increased MPV:

Immune Thrombocytopenia
Disseminated Intravascular Coagulation
Myeloproliferative Disorders
Administration of Erythropoietin/ Thrombopoietin
Recovery from transient hypoplasia
Gray Platelet syndrome
GATA-1 mutation
vWD Type 2B
Platelet Type vWD
Paris-Trousseau Syndrome
Mediterranean Macrothrombocytopenia
Bernard-Soulier Syndrome
MYH9-related disorders
21q11 deletion syndrome
Acute & Chronic Myelogenous Leukemia
Post-Splenectomy
Vasculitis
Megaloblastic Anemia
Diabetes Mellitus
Pre-eclampsia
Chronic Renal Failure
Respiratory Diseases
Thrombocytopenia secondary to Sepsis
Hyperthyroidism
Myocardial Infarction
Prosthetic Heart Valves
Massive Hemorrhage[12]

In comparison with smaller ones, larger platelets have more granules, aggregate more rapidly with collagen, have higher thromboxane A2 levels, and express more glycoprotein Ib and IIb/IIIa receptors.

MPV may shift in systemic inflammation, acute pancreatitis, unstable angina, and myocardial infarction.[8] MPV can be used as a marker in following patients with active ankylosing spondylitis[9] and rheumatoid arthritis.[10] In patients with septic shock, a rise in MPV, indicates a worse prognosis.[11]

As mentioned there has been recent growth in knowledge about using MPV as a prognostic indicator in disease. MPV is prognostic for mortality from sepsis, lung cancer prognosis, heart disease, gestational diabetes, and diabetic retinopathy.

MPV may provide useful information on erectile dysfunction. In a meta-analysis of seven studies including 795 patients and 524 healthy controls, MPV was significantly larger in patients with ED than in controls. The MPV of those with ED was about 0.596 fL greater than the control patients. The mean difference between vasculogenic ED patients and non-vasculogenic ED patients was 0.706 fL.[13]

Tumors can produce cytokines, such as interleukin interferon-gamma and tumor necrosis factor, which in turn affect platelet production in bone marrow. Researchers reported that cytokines such as interleukin-3 or interleukin-6 influence megakaryocyte ploidy and can lead to the production of more reactive and larger platelets.[14,15]

Shifts in MPV appear related to many tumor types, including colon,[16] thyroid,[17] and renal cell.[18] But this gets confusing; MPV elevates in colon cancer but decreases in thyroid and renal. Elevated MPV is neither good nor bad…. It appears to vary with cancer type.

Usually MPV and platelet count (PC) are inversely associated. So, using the ratio, MPV/PC may be more helpful because it exaggerates shifts in platelet indices to allow diagnosis of malignant tumors.[19]

This MPV/PC ratio was used in a retrospective clinical study aimed to evaluate its diagnostic value in colorectal cancer in a study by Wu et al, published in April 2019. Blood parameters were compared in 186 patients with colorectal cancer, 132 with adenomatous polyp and 108 healthy controls. MPV was significantly lower in colorectal cancer patients than in adenomatous polyp ($p = 0.002$) and healthy controls ($p < 0.001$). MPV did not differ between healthy controls and those with polyps. The MPV/PC ratio was also lower in colorectal cancer patients. But MPV/PC significantly differed between TNM stages and the presence/absence of lymph node metastasis. MPV/PC was negatively correlated with the neutrophil to lymphocyte ratio (NLR) ($p = 0.002$) and platelet to lymphocyte ratio (PLR) concentration ($p < 0.001$). Thus, MPV may help differentiate between polyp and colon cancer patients and aid initially in staging.[20]

MPV also correlates with lung cancer development and metastasis. Kurteglu et al reported in January 2019 that the platelet related numbers including MPV were useful in evaluating the prognosis of resectable lung cancers. A total of 101 patients took part in this study. Higher pretreatment platelet count levels were associated with larger tumor size. These Chinese researchers used a value to assess patients called plateletcrit (PCT)(where PCT = PLT × MPV/10).[21] They suggest that this is a more comprehensive measurement to follow.

High pretreatment plateletcrit level were associated with more metastasis. Patients with high pretreatment plateletcrit levels also had worse overall survival. Other platelet indices were not significantly correlated with outcome.[22] Let's do the math here. As MPV decreases, plateletcrit should increase.

In a second recent study also published in 2019, Li et also looked at platelets in lung cancer patients. This study retrospectively compared 232 NSCLC patients with brain metastases against 244 NSCLC patients without metastases. MPV was reduced in NSCLC patients with brain metastases

compared with NSCLC patients without metastases. Platelet count was increased and mean platelet volume (MPV) was reduced in NSCLC patients with brain metastases compared with NSCLC patients without metastases. After adjusting for other risk factors, the ORs (95% CIs) for NSCLC brain metastases according to MPV quartiles were 1.757 (1.024-3.015), 2.097 (1.209-3.635), 1.517 (0.874-2.635), and 1.000, respectively. MPV is found to be independently associated with the presence of NSCLC brain metastases.[23]

These aren't the first suggestions that MPV might be useful for lung cancer patients. Going back to September 2018, Watanabe et al suggested that MPV might be useful in monitoring response to EGFR tyrosine kinase inhibitor treatment in lung cancer patients. Progression free survival was 14.7 months in patients with low MPV and only 8.2 months in the high group.[24]

In another April 2019 study, Tham et al looked at the use of platelet count and MPV as a prognostic indicator for head and neck cancer but did not find the ratio of value for these types of cancer.[25]

In a study published in April 2, 2019, Pafili and colleagues reviewed the medical literature that has described links between MPV and cardiovascular disease (CVD). As MPV is routinely measured as part of CBC, data on MPV can be found retrospectively on large numbers of patients. The authors write:

> There is accumulating evidence showing that the MPV may predict CVD, as well as outcomes in patients with CAD. There is also evidence linking MPV and comorbidities (e.g. diabetes mellitus and impaired glycemic control) that are expected in patients with CAD. The effect on MPV of drugs commonly used to treat CAD has not been clarified, but there is some evidence that they may exert a beneficial effect on the MPV. More specifically, the MPV may predict the effect of antiplatelet drugs (e.g. clopidogrel). There is also evidence relating MPV to stroke, atrial fibrillation, coronary artery ectasia and periprocedural outcomes after percutaneous coronary intervention (PCI).[26]

In a study published April 1, Ding and colleagues reported that, in a study designed to detect and compare changes in platelet parameters in patients with acute myocardial infarction (AMI) and stable coronary artery disease (SCAD), MPV levels were significantly higher in the AMI (n=31) and SCAD (n=34) groups ($p < 0.05$), compared with the control group (n=50), while PLT was significantly lower ($p < 0.05$).[27]

A study by Avci et al, published all the way back in December 2018, tracked 480 patients hospitalized with ST segment myocardial infarcts (STEMI) seeking prognostic significance in changing MPV. In total 23% of these patients died. Those patients with a greater increase in MPV had a 30% greater risk of mortality.[28]

Going all the way back to 2014, we find rather similar conclusions in a meta-analysis by Sansanayudh et al that combined findings from forty earlier studies that provided data on MPV and measured CAD outcomes. MPV was significantly larger in patients with CAD than controls with a mean difference of 0.70 fL. The mean MPV in patients with acute coronary events was 0.84 fL compared to 0.46 fL in patients with chronic stable angina. Patients with MPV greater than ≥7.3 fL) were more than twice as likely to have CAD than patients with smaller MPV (OR 2.28 (95% CI: 1.46, 3.58).[29]

Testing MPV in pregnant women may prove useful as a screening test for gestational diabetes. Colak reported on April 4, 2019, that they had compared 200 women with gestational diabetes (GDM) against 200 normal pregnant women. Women with GDM had higher MPV value compared with the control group ($p < .001$). The cutoff value of MPV was 7.38 fL with 70% sensitivity and 60% specificity.[30]

MPV may also be a potential screening test for diabetic retinopathy. In mid-March 2019, Ji et al reported results from a systematic review of 14 studies. MPV values in diabetic retinopathy patients were significantly higher than healthy controls [SMD (95% CI) = 0.92 (0.60-1.24)] or in type 2 diabetics who did not have diabetic retinopathy. MPV values might even reflect the severity of the disease.[31]

Somewhere it should be mentioned that there is a strong association between low vitamin D levels and high MPV. Researchers from Turkey first reported this in 2014[32] and a Korean group confirmed this finding in 2017.[33]

Right about here we should provide a list of dietary and nutritional interventions that change MPV, but I am hesitant; up until now scant attention has been paid to whether a supplement changes MPV.

A 2014 paper from a Turkish researcher reported that 500 mg/day of vitamin C lowered MPV in young soccer players.[34] Chinese researchers reported in 2016 that drinking green tea has a similar effect at reducing MPV.[35]

We've known since 2008 that using rosuvastatin seems to lower MPV,[36] but no evidence has been found to suggest that red rice yeast will do the same. Niacin may actually increase MPV.[37]

Two separate Turkish studies and one from India all suggest patients suffering from panic disorder have altered MPVs. The Turkish studies report increased MPVs while the Indian study suggests panic disorder is associated with lower MPV.[38-40]

If all this strikes you as confusing, then you've been paying attention. It seems that changing platelet volumes tell us something is going on. Whether the mean volume is increasing or decreasing almost doesn't seem as important as the fact that it is changing. This feels important enough that we should be paying attention and be seeking ways to stabilize platelet volumes. Of course, it may not be the platelets themselves that matter as much as underlying shifts in function. Shifting MPV may provide a window to a great many metabolic processes occurring within the body. The striking thing about this is that the test is already being run on our patients, the information is already in their charts. It's just that no one has been paying much attention to MPV. It won't cost anything to change this.

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Curmudgeon's Corner

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The Perfect Storm: Explaining the Loss of Microbiome Diversity and the Epidemic of Chronic Degenerative Diseases

by Ross Pelton

The Perfect Storm, which was originally a book, and eventually a movie, was based on a true story. However, the "perfect storm" has now become a metaphor that refers to a rare combination of events or converging forces that result in a devastating outcome.

I propose that there is a "perfect storm" of conditions that is responsible for the current and growing epidemic of dysbiosis. These conditions are directly related to the global epidemic of chronic degenerative diseases.

For centuries, plagues and infectious diseases were the primary causes of death. However, medical records show that over the past 100 years, improved living conditions, vaccines, and other medical advances have resulted in the near elimination of infectious disease epidemics in most parts of the world.

Although infectious diseases have largely been eliminated, mankind is now experiencing an epidemic of chronic degenerative diseases.[1] Mankind is now experiencing epidemics of cancer,[2] cardiovascular disease,[3] inflammatory bowel diseases,[4] metabolic syndrome,[5] obesity,[6] arthritis,[7] Alzheimer's disease,[8] autism,[9] ADHD,[10] nonalcoholic fatty liver disease (NAFLD),[11] depression, anxiety, and other forms of mental illness.[12] It is unprecedented to have so many types of chronic degenerative diseases escalating to epidemic proportions all at the same time.

In this article, I will review some critical changes that have taken place since the end of World War II, which are responsible for our current epidemic of chronic degenerative diseases. The key factor I will emphasize is how these changes all contribute to disrupting the microbiome and that the resulting dysbiosis causes intestinal permeability, which promotes the development of chronic degenerative diseases.

Nutrient Decline in Food

Over the past 50-70 years, there has been a substantial and continual decline in the nutritional content of the commercially available food supply in the US. Donald Davis and his team of researchers from the University of Texas at Austin's department of chemistry and biochemistry published a landmark study in the *Journal of the American College of Nutrition* (Dec. 2004) titled "Changes in USDA food composition data for 43 garden crops, 1950 to 1999."[13] They reported finding significant declines in the amount of protein and essential vitamins and minerals over the past half century. According to Dr. Davis, the primary cause of the declining nutritional in our US food supply is due to changes in agricultural practices such as the use of mono-cropping, artificial fertilizers and antibiotics, which are designed to improve traits such as the size, growth rate, pest resistance in plants rather than focusing on maintaining healthy soil and growing healthy plants with nutrition.

Industrial Farming: Before World War II, the family farm population in the US exceeded 30 million people, which accounted for 23 percent of the total population.[14] In the decades after World War II, a "system" of industrial agriculture evolved which relies on chemically intensive food production that features massive single-crop farms and animal production facilities. Today, the majority of American farmland is dominated by large agribusiness farms. Many agribusiness farming practices have negative consequences for the quality of food and the health of humans, animals, and the environment. "Industrial" agribusiness farms produce approximately 98% of America's food supply.[15]

Artificial Chemical Fertilizers: Farming income is not based on micronutrient density, but rather on the size of the crops they grow. Rather than focusing on the quality of the food, farmers have become increasingly concerned with the volume of food they can produce.

Plants need at least 16 nutrients to be healthy. However, after World War II, farmers learned that the addition of only three nutrients, namely nitrogen, phosphorus, and potassium could significantly increase crop yields. Within a relatively short period of time, most farmers abandoned the centuries-old tradition of fertilizing their crops with organic manure and switched to the widespread use of artificial chemical fertilizers.

Studies now show that long-term application of chemical fertilizers leads to serious acidification of the soil, nutritional imbalance, deterioration of the microbiome in the root system of plants and an increase in the level of toxic metal ions in soil.[16]

Monocropping: Another big change resulting from industrialized farming was a switch from regular annual crop rotation to mono-cropping. Monoculture farming utilizes large areas of available land to grow a single crop. This method of farming became increasingly popular with large agribusiness farming companies. Large tractors, weighing as much as 15 tons, can easily work thousands of acres. However, these large tractors cause severe compaction of the soil. Subsequent plowing breaks down the surface characteristics of the soil, which leaves the soil susceptible to wind and water erosion.

Monocropping with huge expensive equipment became increasingly popular with large agribusiness farmers because it significantly reduces costs. However, when large areas of farmland are used to grow a single crop, it leads to a loss of environmental biodiversity. Connecting the dots, we see that monocrop farming leads to loss of biodiversity, which weakens the plant's immune system and makes the crop more susceptible to pests and diseases. Enter the era of pesticides, insecticides and herbicides.[17]

Pesticides and Herbicides: Monocrop farming damages the farmland, by reducing the amount of water and nutrients the soil can retain and accelerating the loss of topsoil.[18] Monocropping also dramatically reduces biodiversity. Plants grown in a monoculture environment have weakened immune systems and do not possess the necessary defense mechanisms to withstand the impact of pests and other predators such as fungus and blight.[19] To combat these problems, farmers began steadily increasing their use of pesticides, insecticides, and herbicides. In addition to being used in agriculture, these toxic chemicals are also widely used in non-agricultural areas such as public parks, golf courses, and urban lawns and gardens.

Although use of these chemicals increased yields, there is growing global alarm about the damage they cause to the health of animals, humans, and the environment. There is a concern that exposure to trace amounts of agricultural pesticides and herbicides can damage our human microbiome, which increases the risk of developing numerous other chronic degenerative diseases.[20,21]

A healthy microbiome protects against intestinal permeability and chronic degenerative disease.

Glyphosate/Roundup: In my opinion, glyphosate poses a serious health risk to mankind because its widespread use throughout the world is killing the microbiome on Earth. A recent study reported that levels of glyphosate found in humans have increased by more than 1,000% in just the last 20 years.[22] A study just published in March 2019 reported that glyphosate in rats, at levels of glyphosate determined safe by the US EPA, had negative effects on sexual development and disruption of the microbiome.[23]

The results of the following study are incredibly frightening. Scientists conducted a study which showed that when bacteria are simultaneously exposed to herbicides like glyphosate and antibiotics, mutants with higher levels of resistance to antibiotics can evolve. The scientists conducting this study stated, "In some cases, resistance evolved 100,000 times faster."[24] This discovery may explain why the emergence of antibiotic resistant superbug infections has developed so rapidly. International health experts are calling this a global threat to mankind.[25]

Metaorganism (Plant + Soil microbes)

In *The Human Superorganism,*[26] author Rodney Dietert stresses the relatively new concept that humans are a symbiotic superorganism consisting of the individual *and* the approximately 100 trillion bacteria that make up his/her microbiome. Similarly, an increasing number of scientists are utilizing the term *metaorganism* to express the importance of plant-microbiome interrelationships.[27]

It takes more than a bunch of chemicals in the soil (artificial chemical fertilizers) for plants to be healthy. Plant health depends on soil fertility, and soil fertility depends on the health of soil microorganisms as much as the chemical makeup of the soil itself. The degradation of organic matter in soil (humus) is the source of nutrients for plants. But this process cannot happen without the action of "microbial middlemen." Soil microorganisms (bacteria and fungi) play a critical role in the health of plants. We must stop the application of artificial fertilizers and toxic pesticides such as organophosphates and herbicides such as glyphosate on plants and the soil on planet earth. They *kill* soil bacteria. Maintaining soil fertility with healthy microbes is the key to plant health and their resistance to bugs and diseases.

The destruction of life in the soil is the primary cause of plant diseases, and it is also contributing to the epidemic of chronic degenerative diseases in humans. The poisoning of life in the soil by applying artificial fertilizers and toxic agricultural chemicals is one of the most serious risks to the health of humans and nature in the history of mankind. It is imperative for the health of humans and all of nature that we develop methods of sustainable agriculture.

One of the best sources of information on organic gardening and sustainable agriculture is Howard Garrett, who is known as *The Dirt Doctor*. Information about Howard's radio show, thousands of topics, podcasts, his FREE weekly newsletter, online courses and books is available at https://www.dirtdoctor.com.

Antibiotics

The modern-day discovery of antibiotics (sulfa drugs in the 1940s and penicillin, erythromycin, tetracycline and others in the 1950s) ranks as one

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of the most important discoveries of all time. However, what was initially a life-saving miracle has now developed into a critical global health crisis. In addition to disrupting the microbiome in animals, humans, and the soil (pesticides are actually antibiotics) the overuse of antibiotics is resulting in the rapid development of antibiotic-resistant superbug infections.

The Centers for Disease Control and Prevention (CDC) has reported that nearly 99,000 people die each year in the United States from antibiotic-resistant bacterial infections.[28] That is more deaths than breast and prostate cancer combined. In 2014, England's Prime Minister David Cameron commissioned a Review on Antimicrobial Resistance (AMR). Based on the results of the commission's report, Cameron stated, "If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work, and we are cast back into the dark ages of medicine."[29] If serious action is not taken, experts predict that by 2050, antibiotic-resistant infections may overtake cancer and kill over 10 million people per year.

The over-prescribing of antibiotics by physicians and dentists is one part of the problem. In 2016, over 270 million outpatient antibiotic prescriptions were prescribed in the United States.[30] A 2016 Centers for Disease Control and Prevention (CDC) report estimated that at least 30% of antibiotics prescribed in US outpatient settings are unnecessary.[31] Another study published in *JAMA* reported that 81% of antibiotic prescriptions prescribed by dentists are not needed.[32]

Antibiotic use plays a major role in the emerging global health crisis of antibiotic resistance 'superbug' infections. Approximately 80% of the antibiotics sold in the United States are used in animals, primarily to promote growth and prevent infections.[33] Although the majority of antibiotic use occurs in agricultural settings, very little attention is being paid to how antibiotic use in farm animals contributes to the emerging problem of antibiotic resistance infections.

Ingestion of antibiotics is the most serious cause of microbiome disruption and dysbiosis. However, as I reported in last month's issue of the *Townsend Letter* ("Microbiome-Disrupting Drugs"[34]), there are many other classes of drugs that disrupt the human microbiome.

The Fiber Gap

An article titled "The Fiber Gap and the Disappearing Gut Microbiome: Implications for Human Nutrition" discusses how low fiber diets are affecting people's microbiome and, ultimately, their health. The authors of this study report that 90% of children and adults in America *do not* consume the recommended amount of daily dietary fiber.[35]

One of the most important reasons the Standard American Diet (SAD) causes human health problems is due to its low fiber content. Highly processed foods lack fiber. Fiber is the required food for your probiotic bacteria. There is increasing evidence that a lack of dietary fiber, referred to as the Fiber Gap, is one of the most critical factors contributing to the epidemic of gut dysbiosis in humans.[36]

It takes more than probiotic supplements to create and maintain a healthy microbiome. People must learn how to feed their probiotic bacteria well. If probiotic bacteria are not supplied with a diverse, fiber-rich diet, they will not thrive and survive. Thus, millions of people probably do not get much benefit from the probiotics they take because they are not consuming a wide range of fiber-rich foods.

It is essential to realize that the quantity of fiber in the daily diet is not the only fiber issue. A diversity of different kinds of fiber-rich foods is required to promote the growth of a diverse microbiome. How many different kinds of colored, fiber-rich fruits and vegetables are you feeding your probiotic bacteria today?

For an easy way to increase the diversity of fiber-rich foods in your daily diet, I suggest you Google my 8-minute YouTube video which teaches people how to save time when making salads. Just Google "Ross Salad Buzz."

This concludes my summary of the major issues that are altering human microbiomes, which results in dysbiosis, intestinal permeability and, ultimately, chronic degenerative diseases. The factors I've discuss are changes in farming practices such as mono-cropping, the use of artificial fertilizers, pesticides, insecticides and herbicides, antibiotics used in animals and humans, other microbiome-disrupting drugs discussed in the December 2019 issue of *Townsend Letter*, and the lack of adequate fiber in American diets. Now I will continue with an explanation of how and why disruption of the microbiome and the resulting dysbiosis are largely responsible for our epidemic of chronic degenerative diseases.

Zonulin

Dr. Alessio Fasano discovered a molecule named zonulin, which is expressed during inflammation and regulates the permeability of the tight junctions in the intestinal tract. I would not be surprised if Dr. Fasano wins the Nobel prize for discovering zonulin because I think it is one of the most important health discoveries in our lifetime. I highly recommend reading Dr. Fasano's book *Gluten Freedom,*[37] which provides a good summary of his discovery of zonulin and all of its implications for health.

Dr. Fasano states that the two prominent factors that cause gastrointestinal (GI) inflammation and cause zonulin to be expressed are bad bacteria and gluten.[38] One of the most important aspects of Fasano's discovery is the fact that GI inflammation and zonulin-induced intestinal permeability allows antigenic food particles, toxic agents, microorganisms, and bacterial byproducts such as highly pro-inflammatory lipopolysaccharides (LPS) to cross the gut barrier. When any of these agents enter into systemic circulation, they can induce immune responses that causes the development of diseases.

We now know that gut dysbiosis and intestinal permeability are

associated with an alarmingly wide range of systemic diseases, including autoimmune diseases such as celiac disease, type-1 diabetes, IBD, colitis, multiple sclerosis; metabolic disorders including obesity, insulin resistance, Type-2 diabetes and polycystic ovary syndrome; and other conditions such as asthma, coronary artery disease, and cancer.[39]

Zonulin is the only human protein discovered to date that has been shown to reversibly regulate intestinal permeability by modulating intercellular tight junctions in the intestinal tract.[40] Dr. Fasano believes that reducing inflammation and down regulating zonulin can reestablish healthy gut tight junctions.

Dr. Fasano's new theory suggests that when these pathological disease processes are activated, they are *not* necessarily auto-perpetuating. He believes these disease processes can be arrested and, in some cases, even reversed by reducing inflammation and healing the gut.[41]

Healing the gut requires reducing inflammation. While there are many triggers that can cause inflammation, Dr. Fasano's research suggests that the two most important factors to address are avoiding gluten and correcting bacterial imbalances or dysbiosis.

Since much of my work is focused on how to create and maintain a healthy microbiome, that is the topic I will address in regard to healing the gut. The *Townsend Letter* archives contain excellent articles on gluten-related issues.

Postbiotic Metabolites Accelerate Gut Healing

In my article titled "Postbiotic Metabolites: The New Frontier in Microbiome Science" (*Townsend Letter*, June 2019), I introduced the topic of postbiotic metabolites and the important roles they play in regulating both GI and systemic health.

Hallmarks of dysbiosis include harmful bacteria, inflammation, an alkaline pH, poor digestion and absorption of nutrients, poor detoxification, dysregulated gut-brain communication, and compromised immune function. Various types of postbiotic metabolites help to address and improve all of these issues in the microbiome ecosystem. For example, some postbiotic metabolites are classified as antimicrobial peptides (AMPs) that directly kill pathogens. Others like short-chain fatty acids (SCFAs), organic acids, amino acids and fulvic help to establish the optimal GI pH, which is slightly acidic. Butyric acid is a SCFA metabolite that accelerates the growth of healthy new epithelial cells to replace cells damaged by inflammation.

The examples above are just the proverbial tip of the iceberg. In the book *The Mind-Gut Connection*, author Emeran Mayer, MD, states that your bacteria use the information in their millions of genes to produce hundreds of thousands of metabolites. That's why I call this the New Frontier in Microbiome Science.

Conclusion

In all ecosystems, greater species diversity creates a more stable, healthier environment. The same holds true for the human microbiome. It is critical to understand that dietary fiber is the required food for your probiotic bacteria. Ingesting a wide range of different kinds of dietary fiber is absolutely essential for a healthy, diverse microbiome. Diverse dietary fibers support the growth of a diverse range of probiotic bacteria, which will in turn produce a wide range of health-regulating postbiotic metabolites. Direct ingestion of postbiotic metabolites is the fastest way to initiate healthy improvements in people suffering from dysbiosis-related GI problems.

Some commercial probiotic products are produced utilizing a multi-year fermentation process. In these fermentation production processes, organically grown fiber-rich foods are shredded and added to large fermentation vats along with starter strains of probiotic bacteria. The bacteria spend several years fermenting the food fibers to produce postbiotic metabolites. Products produced utilizing these fermentation production processes contain probiotic bacteria, prebiotic foods and hundreds of postbiotic metabolites. Directly delivering postbiotic metabolites elicits positive changes in the microbiome ecosystem much faster than just delivering probiotic bacteria.

Free Offer: Healthcare professionals**,** I urge you to educate yourself and your patients about the importance of postbiotic metabolites. If you would like a copy of my article "Postbiotic ➤

The Perfect Storm

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Metabolites: The New Frontier in Microbiome Science," email a request to me at ross@naturalpharmacist.net.

Taking Action

Speak Up: In 2015, the International Agency for Research on Cancer (IARC), which is the specialized cancer agency of the World Health Organization (WHO) announced that glyphosate is a probable carcinogen.[42] To see a state-by-state listing of more than 100 cities in the US that have banned glyphosate, go to https://www.dirtdoctor.com/garden/Glyphosate-Where-is-Glyphosate-Banned_vq13726.htm.

If your city is not on this list, I urge you to speak up and make your voice heard. Do what you can to get your community to ban glyphosate. Contact your political representatives and urge them to ban glyphosate and support sustainable agriculture. One of the best websites for information about the health risks of both GMO foods and glyphosate is Moms Across America: https://www.momsacrossamerica.com/.

Urban Farming/Victory Gardens: During World War II, many people planted small gardens and grew food to help prevent food shortages because many farmers had left their farms to fight the war. These small garden plots were called Victory Gardens.

We no longer have an agricultural food supply. We have a nutrient-deficient industrial food supply dependent on artificial fertilizers and toxic chemicals. As people become increasingly concerned about the quality of food in America, there is a reemergence of Victory Gardens. It is called the Urban Farming movement. People are growing food in backyards, rooftops, balconies and in community garden plots. If you don't have the space or time to grow a garden, consider joining a Community Supported Agriculture group (CSA), which is a popular way for consumers to buy local, seasonal food directly from local farmers: https://www.localharvest.org/csa/.

The goal of healthy aging is to reduce and postpone age-related diseases. Centenarians are frequently used as a model for healthy aging studies because of their ability to delay, or even avoid, chronic diseases. Studies of centenarians have consistently shown that the microbiome of these long-living people is more diverse compared to the microbiome of younger groups of people.[43,44]

The bottom line: Do everything you can to purchase and consume nutrient dense fiber-rich food that is grown on healthy soil and…do everything you can to create and maintain a healthy microbiome.

Free Copy: If you would like a free copy of my "Quick Reference Guide to Drug-Induced Nutrient Depletions," send an email request to ross@naturalpharmacist.net.

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

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

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

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

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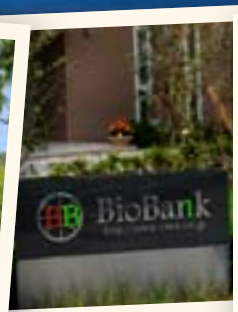
Dr. Iichiroh Ohhira: A Pioneering Genius in Probiotic Science

Malaysian Mystery – 'drinking fermented elixir'

Advanced Research – Okayama University



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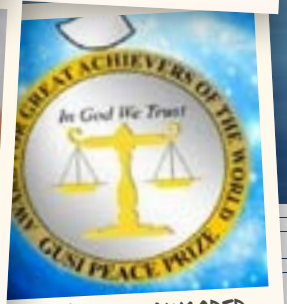
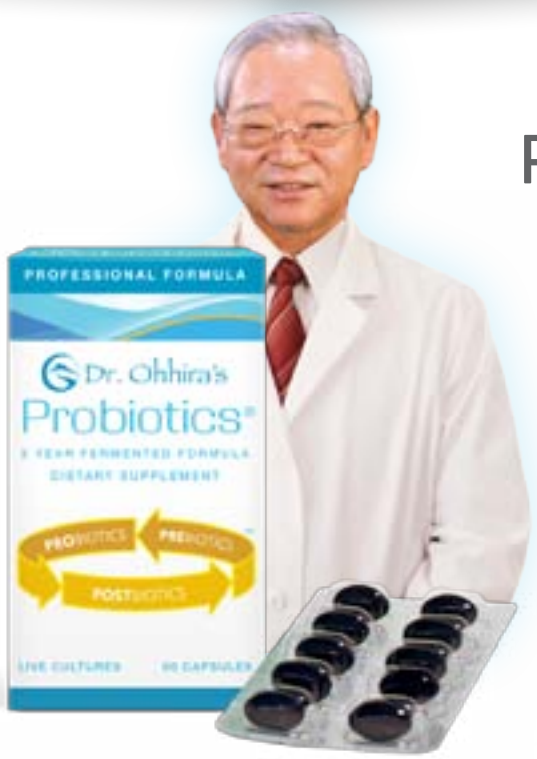


Dr. Ohhira awarded GUSI Peace Prize



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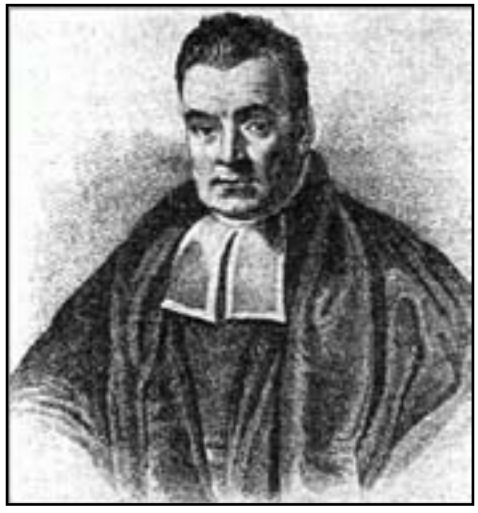
GENERATIVITY

Peter D'Adamo, ND

Machines That Learn: Differential Diagnosis and Botanical Insights

Certain words have particular probabilities of occurring in a spam email versus a legitimate email. For instance, most email users will eventually receive an email from a diplomat or princess asking for a small donation guaranteed to let loose the floodgates of embezzled riches, a common event in spam email, but seldom seen in other emails. To me this begs the question of just how a princess or diplomat manages to use email, but that is a question for their respective internet service providers to answer. Maybe they just have other people do it for them.



Thomas Bayes, maybe. Although commonly thought to be his likeness, nobody is actually sure it is him.

In this column we'll be exploring artificial intelligence (AI) modules from the Comprehensive Perl Archive Network (CPAN), a great resource for legally appropriating very useful tools made by people far better at this than me. One of their featured machine learning modules is also one of the simplest. It's called the Naive Bayes algorithm.

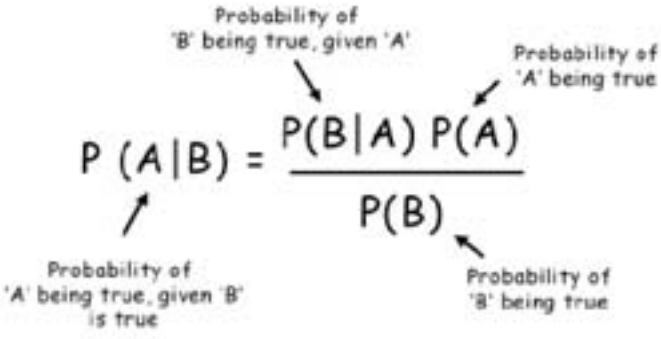
The Naive Bayes algorithm is what is known as a classifier-type algorithm. You'd probably know it best as the mechanism by which your email program decides whether to show you an email or just shunt it to your junk mail folder. It has a memory comprised of training data (classes of things, in this case words, that either define spam or not); and based on what criteria it is presented with (in this case the email in question), it calculates a probability (odds) that it is spam. If that number is high enough, off it goes to the junk folder.

The algorithm earned this name because it is based on a type of probability known as Bayesian, named after the Reverend Thomas Bayes, an early math nerd who came up with it while trying to use probability to prove the existence of God.

The Naïve Bayes algorithm is based on Bayes Theorem for calculating probabilities and conditional probabilities. The algorithm is naive because the events it models are independent; the occurrence of one event does not affect the probability of the occurrence of another. We make it initially 'smart' by supplying it with *training data*: a model of the known stuff about the world that the algorithm can learn from and make predictions on.

Bayes Theorem describes the probability of an event, based on prior knowledge of conditions that might be related to the event. For example, if osteoporosis is related to age, then a person's age can be used to more accurately assess the probability that they have osteoporosis, compared to an assessment made without knowing the person's age. Bayes Theorem is a tool that converts human belief, based on evidence, into predictions.

Bayes Theorem is commonly expressed as the formula:



With Bayes Theorem we can use the probability of one thing to predict the probability of another thing. And because of this, Bayes Theorem has become one of the great statistical sausage machines that scientists can ratchet-up to make better predictions as new evidence surfaces. Although it hasn't proved the existence of God, Bayes Theorem has proved useful in other ways: from testing new medicines, to weather forecasting, and even helping to improve mobile-phone reception.

Differential Diagnosis

If you hear the sound of hoofs, don't expect to see zebras. Unless, of course, zebras be nearby. As most of the readers know, differential diagnosis (DDx) is a method used to identify the presence of a disease entity where multiple alternatives are possible. Evidence suggests that the association between physicians' diagnostic accuracy and their confidence in that accuracy may be quite poor.[1] The likelihood of an accurate DDx is dependent on inclusion of candidate conditions that are responsible for as large part as possible of the probability of having developed the condition. If an important candidate condition is missed, no method of differential diagnosis will supply the correct conclusion.

With this in mind, I coded *DDx Pinpointer,* a Perl script that uses the Naive Bayes machine learning algorithm to classify possible candidate conditions based on a training dataset of weighted symptomatology data that I'd previously extracted from PubMed (Medical Subject Headings) MeSH datasets (https://www.ncbi.nlm.nih.gov/mesh)

To run DDx Pinpointer, fire up your favorite browser and point it to https://www.datapunk.net/tlfd/bayes_ddx. Don't worry, I'll wait. You're back? Good!

You are presented with a query screen (Figure 1):

Using the scrollable window on the left, simply tick off a few favorite symptoms, and optionally give them some 'weight' (weight would correspond to symptom severity in an actual patient). To factor in occurrence data, (puts emphasis on more common presentations) tick the 'Factor Occurrence' checkbox. Don't remember what 'Drug-Induced Akathisia' is? Then click on any hyperlinked symptom to trigger a small descriptive popup. We'll tick 'Constipation,' 'Abdominal Pain,' and 'Nausea.' When ready, pressing the *Run DDxPinpointer* button will take you to the results screen.

Figure 2 shows the probable diagnostic considerations rated from highest to lowest probability. 'Intestinal Obstruction' comes in at number one, which sort of makes sense; followed by the somewhat unhelpful 'Gastrointestinal Diseases,' 'Irritable Bowel Syndrome,' 'Colonic Neoplasms,' and then everything else. To my way of thinking it is the 'Everything Else' that will be most helpful to the clinician in real-time, the stuff we just don't think of at the time – the weirdo rule-outs.

Figure 3 provides an additional deep-dive for those interested in genomic/molecular links to pathology. If desired, you can tick off a few of the winning diseases and the app will respond with a probability-based guess at what genes/molecules are likely to be of interest. It's just an illustration of the power of bioinformatic mash-ups: taking disparate data and making them play together.

Bayes' Leaf

Recently, I was in the applications directory of my Mac and saw an icon for an app called *Bountiful Herbs* (https://www.bountifulherbs.net/) that I must have downloaded years ago. Clicking on it I discovered a fairly robust herbal database that had enough weighed information to provide some good ➤

Figure 2

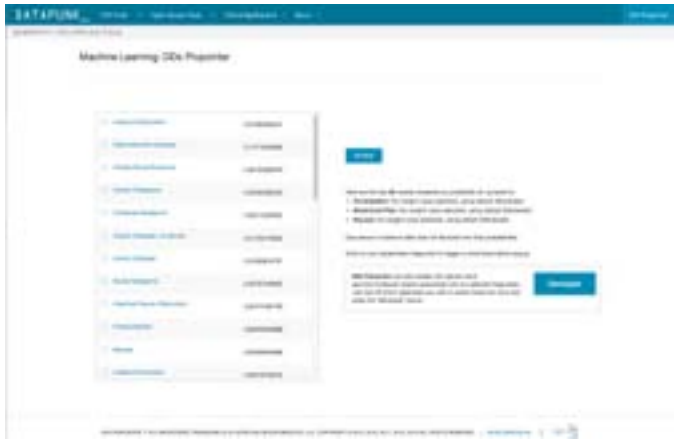


Figure 1

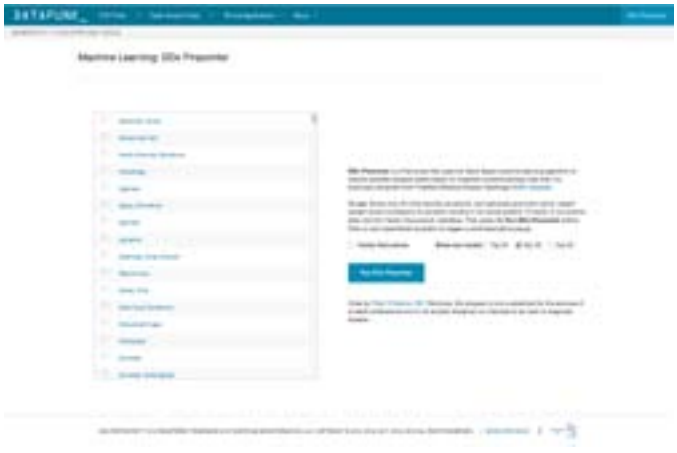
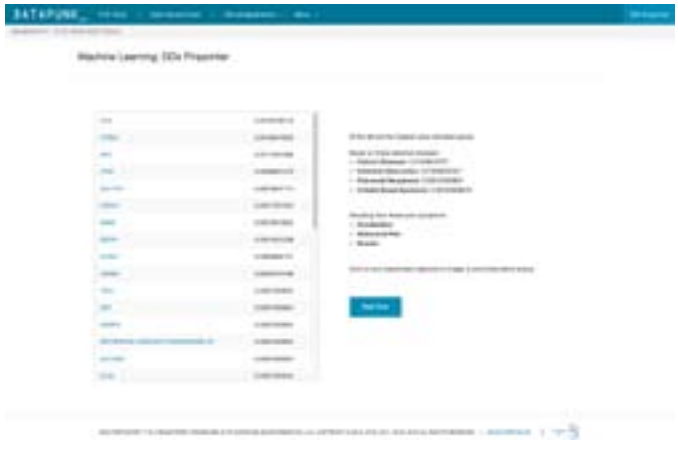


Figure 3



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training data. The program allowed for the export of data; and after massaging it so much that I could probably get a certificate from the Swedish Institute, I was able to feed it into the Perl Naive Bayes module.

Since you're already on the website, to fire up the *Phyto Pinpointer,* just select it from the *TLfD Tools* pull-down menu on the bar at the top of the page (Figure 4).

With *Phyto Pinpointer,* you select a combination of desired medicinal actions you want to explore, and the program will use Reverend Bayes' algorithm to return a graduated list of botanicals that probability-wise best fit those selected actions. For each selection you can optionally add an indication 'strength' (a weighted value of just how important that particular action should factor in the overall classification).

For example, if I select the actions 'Alterative', 'Anodyne' (mild) and 'Anti-rheumatic while also setting the strength of 'Anti-rheumatic to 'strong' when I press the Pinpoint button, the script returns with results (Figure 5). In this case, *Phyto Pinpointer* responds with three very good suggestions (*Smilax spp., Harpagophytum procumbens and Phytolacca Americana*).

Like all machine-learning algorithms, what makes the Naive Bayes algorithm so powerful is its ability to gauge the probability for submitted groups of criteria that do not have an exact representation in the training data. That is the big difference between encyclopedia-type lookups and AI. The first can only retrieve what it knows, the second can make a pretty good guess about what it doesn't.

I'm not a big herbal energetics guy, but, hey, data is data; and these often factor in traditional medical type prescribing, so I added the ability to weave this type of criteria into the AI training knowledge set. You can choose both an 'energetics' and a 'taste' setting and give it some weight as well.

All in all, I'm pleased and somewhat surprised at just how perceptive and useful these simple machine learning apps are. The Naive Bayes algorithm has numerous applications in medical AI, so future applications are essentially endless, given the appropriate training data. For example, I'll probably do a future column on how AI can help clinicians predict the odds of specific Phase I detoxification compromise, based on published cytochrome interactions and specific client polymorphisms. In a world of patients increasingly characterized by an intake of multiple drugs, supplements, herbs and foods, this type of vigilance is essential to the practice of safe medicine.

Reference

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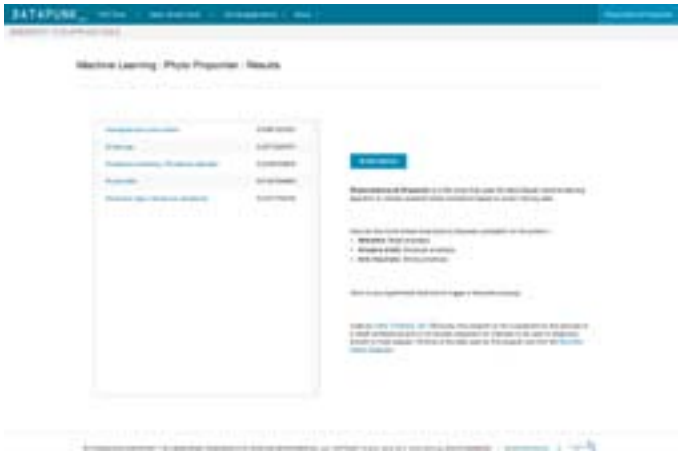
Figure 4

Figure 5



Peter D'Adamo is a distinguished professor of clinical medicine at the University of Bridgeport School of Naturopathic Medicine. His *New York Times* bestselling books have sold over 8 million copies and have been translated into over 75 languages. He is the developer of the acclaimed *Opus23* genomic software suite and a variety of other generative apps that can be explored at www.datapunk.net. In his spare time, he brings old VW Beetles back to life at his garage on www.kdf20.com.

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Researched Nutritionals Product Discussion: BDNF Essentials™, BioDisrupt®, and HistaQuel®

by Debby Hamilton, MD, MPH

BDNF Essentials™

The concept of neuroplasticity has given us hope that we can heal and repair the brains of our sickest patients from autism to Alzheimer's. Neuroplasticity is the ability of the brain to grow, change, and repair. Brain derived neurotropic growth factor or BDNF is the critical brain compound that fosters neuroplasticity. Chronic conditions with neurologic impairment from dementia to traumatic brain injury and even to our ever-increasing prevalence of mood disorders are often associated with low levels of BDNF. Finding ways to increase levels of BDNF is important in treatment of many of our patients with cognitive impairment.

BDNF Essentials™ is a product designed to improve BDNF levels and foster healing of the nervous system. Improving BDNF and healing the cells involves supporting two different mechanisms. The first is the use of supportive herbs that have been shown to increase BDNF in research studies. The second is the use of phospholipids to support repair of the cell membranes. The NeuroCytoProtect™ blend contains lion's mane mushroom, *Scutellaria lateriflora* (skullcap), bilberry, bacopa, and ashwagandha. These herbs were found to increase BDNF in research studies. With the increasing levels of BDNF, patients were also found to have cognitive improvement in memory, attention, and processing along with decreases in depression and anxiety. The Cognition Blend™ contains a combination of CDP-choline or citicoline and phosphatidylserine. These phospholipids are important components of cell membranes and needed for repair of these membranes. Equally important is research showing cognitive improvement with these phospholipids. Overall BDNF Essentials™ offers nutritional support to encourage neuroplasticity through supporting BDNF and cell membrane function.

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Many microbial communities exist in a structure called biofilms. These biofilms serve a protective function for the bacteria and yeast by the formation of a physical barrier to antimicrobials. This structural barrier is made by the microorganisms and contains primarily proteins along with carbohydrates and lipids. Chronic infections from the intestine to the sinuses are often difficult to treat because of biofilms. In order to treat these chronic infections, the biofilm needs to be broken down for the antimicrobials to reach the bacteria and the yeast.

BioDisrupt® is a product designed to target and break down biofilms. Treating infections caused by biofilms involves three mechanisms. To treat biofilms, the biofilm needs to be disrupted, the microbes need to be treated, and formation of new biofilms needs to be prevented. Quorum sensing is the communication between microbes that allows them to form biofilms, and inhibiting this mechanism helps prevent biofilm formation.

The structural matrix of the biofilm needs to be broken down first by enzymes to allow the antimicrobials to reach the microbes. The EnzymeDisrupt™ blend contains multiple enzymes targeted to treat the different components of the biofilm, including lysozyme, serratiopeptidase, beta-glucanase, lipase, protease 4.5, cellulase, and hemicellulase. In order to target multiple bacterial and fungal species, an herbal blend called HerbDisrupt™ was created, including cranberry, berberine, rosemary and peppermint. These herbs in research have been found to be anti-microbial, anti-quorum sensing, and anti-adhesive. These functions are needed to treat the infection and prevent the formation of new biofilms. N-acetylcysteine (NAC) is the final component of BioDisrupt®. NAC is a mucolytic and has been shown in research to aid in biofilm disruption. Since chronic infections are known to have biofilms, BioDisrupt® offers a tool that targets both facets needed in fighting these infections, including breaking down the structural matrix and having antimicrobial properties.

HistaQuel®

Mast cell activation has increasingly been found to be a factor in chronic disease promoting an ongoing cycle of inflammation and oxidative stress. Multiple environmental factors can trigger mast cell activation, including infections, inflammation, food, and toxins. One of the primary compounds released by mast cells is histamine. In addition, mast cells release tryptase, pro-inflammatory cytokines, and other inflammatory mediators. Once released from the mast cell, these mediators cause symptoms that impact all body systems and can be very disabling. As we are learning more about mast cell activation impacting chronic illness, finding ways to target this is crucial.

HistaQuel® is a formulation designed to inhibit mast cell activation and block histamine 1 receptors to help both mast cell activation syndrome and allergic conditions. MastCell Secure™ is a group of flavonoid herbs, including luteolin, Quercefit (enhanced form of quercetin for increased absorption), perilla, and fisetin. These herbs have been shown in research to inhibit mast cell activation, including release of histamine throughout the body. Clinical research on these herbs has shown improvement for allergic conditions and mast cell activation. Nettle leaf is also part of the supplement, which has been shown in research to block the histamine 1 receptor. When histamine binds to this receptor, it activates allergic responses. HistaQuel® offers a dual mechanistic approach to decrease mast activation and allergies. ◆

➤ *continued from page 104*

was conducted on 10,631 patients in a large urban healthcare system in Philadelphia who had been hospitalized for heart failure between April 1, 2016, and April 1, 2017. Adequate tests of iron status were conducted during hospitalization in only 158 patients (1.5%; or 1 of every 67 patients). Of those 158 patients, 109 (69%) had iron deficiency as defined by the American Heart Association/American College of Cardiology guidelines.[5] Of the 109 patients diagnosed with iron deficiency, only 23 (21.1%) received intravenous iron, which is considered the standard of care for the treatment of iron deficiency in heart failure patients. Of the iron-deficient patients who did not receive intravenous iron, only 19.8% were prescribed oral iron upon hospital discharge. The authors of this study concluded that iron deficiency, despite having major implications in heart failure, is not being adequately evaluated or treated during hospitalization for heart failure.[6]

As noted previously, identifying and treating iron deficiency resulted in a 47% reduction in the composite endpoint of heart failure hospitalizations and cardiovascular mortality. It is uncommon for a single intervention to have such a large effect size. The fact that this relatively simple, safe, and inexpensive treatment is largely being overlooked represents a system failure in modern medicine. As medical care continues to become more complicated and more specialized, we must remember not to forget the basics.

Alan R. Gaby, MD

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Modern Medicine Neglects the Basics

A couple of years ago, an elderly family member was hospitalized because of heart failure. After he was discharged, I saw a printout of the lab tests that had been done during his hospital stay. Although he was not anemic, his serum iron concentration was below normal. The cardiologist apparently did not consider the low iron level to be important since no further tests of iron status were ordered and the possibility of iron deficiency was not mentioned in the discharge summary.

While a low serum iron level by itself is not diagnostic of iron deficiency, I was concerned that a potentially significant factor was being overlooked. Like many other patients with heart failure, my family member had several risk factors for iron deficiency. First, he avoided red meat because of its potential adverse effects on the cardiovascular system. Second, his diet was high in fiber, and fiber is known to inhibit iron absorption. Third, patients with heart failure often have bowel-wall edema (secondary to the backup of fluid from the heart), which can impair nutrient absorption. Fourth, gastric acid plays a key role in iron absorption, and he was on long-term acid-suppressive medication (a proton pump inhibitor).

Research conducted over the past decade has shown that the prevalence of iron deficiency in heart failure patients is as high as 50%. Moreover, iron deficiency, even in the absence of anemia, is a strong and independent predictor of mortality in these patients. In randomized controlled trials, correction of iron deficiency significantly improved functional capacity, symptoms, and quality of life; significantly decreased the number of hospitalizations for worsening heart failure; and nonsignificantly reduced mortality.[1-3] A meta-analysis of four randomized controlled trials found that in heart failure patients with iron deficiency, compared with placebo, intravenous administration of iron resulted in a 47% reduction in the composite endpoint of heart failure hospitalizations and cardiovascular mortality ($p = 0.01$).[4] These benefits are apparently related to the fact that iron is a component of cytochromes in the electron-transport chain and therefore plays a key role in mitochondrial energy production.

I asked the cardiologist if he would order more definitive tests for iron deficiency when my family member came to the office for his follow-up visit. Surprisingly, the cardiologist stated that he did not know which lab tests to order and that testing for iron deficiency is the job of the patient's internist. I contacted the internist, who agreed to measure serum iron, total iron-binding capacity, and ferritin. These tests demonstrated severe iron deficiency, and iron supplementation resulted in clinical improvement.

I was rather surprised that a heart specialist did not feel well versed in an area so fundamental to the practice of medicine – assessing iron status – particularly since it had been seven years since a landmark study in the *New England Journal of Medicine* demonstrated the importance of identifying and treating iron deficiency in patients with heart failure.[1] Recently I learned that this "non-well-versedness" regarding iron deficiency was not unique to this particular doctor but is endemic among doctors that treat heart failure. A retrospective study

continued on page 103 ➤

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