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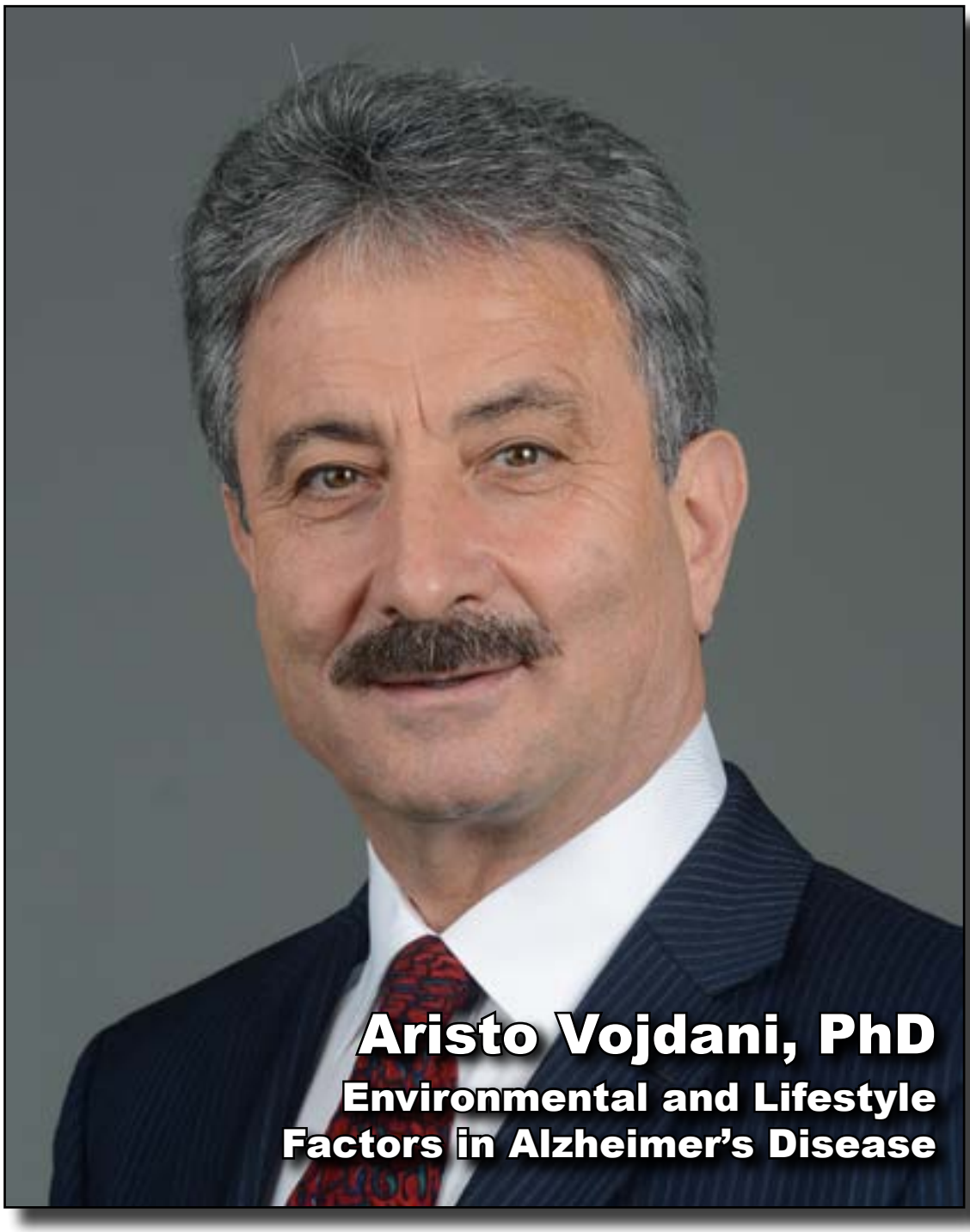

Aristo Vojdani, PhD

Environmental and Lifestyle Factors in Alzheimer's Disease

OCTOBER 2019
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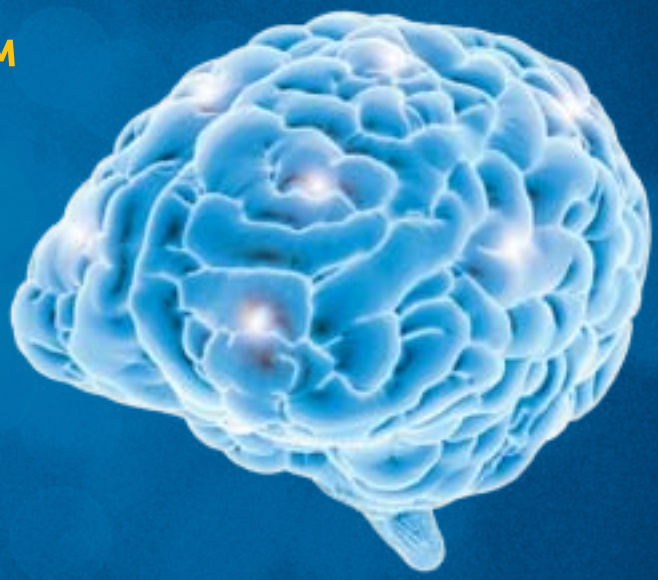

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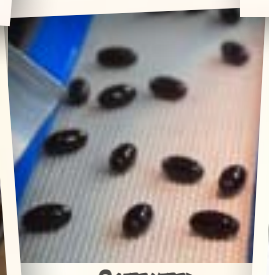
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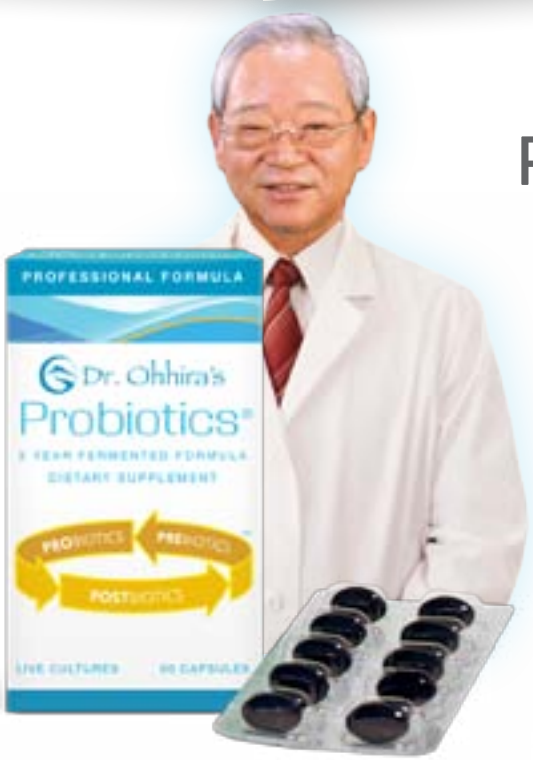

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Top/Left: Jonathan Collin, Sam Collin, Jeff Wellington
Bottom/Left: Deborah NissenCollin, Jacqueline and Affinity Wellington

From the Publisher

Why Shouldn't We Use LDN for All Neurological Conditions?

The medical profession cringes whenever a treatment is touted as a panacea, a cure-all. Such remedies are generally little more than snake oil offered by hucksters to a vulnerable and suffering population. Still most medications not only have limited benefit but usually are accompanied by minor and major adverse effects including, not infrequently, death. There is something to be said about a drug that has a broad range of symptomatic benefit with very few side effects, none of which are lethal. That Rx is naltrexone and the dosing of the pharmaceutical is low dose, hence low dose naltrexone (LDN). For a few individuals it may even be ultra-low dose naltrexone. Wouldn't that be a boon for medicine to have a medication that not only relieves symptoms, especially pain, and poses no ill effects? It is time that neurologists and physicians as a whole take LDN seriously and prescribe it not as a last resort, but as a first resort.

Linda Elsegood is one individual who has greatly benefitted from LDN when no other medication provided any relief at all. She developed the full range of symptoms characteristic of multiple sclerosis as a 40+ year old mother and wife. Her life was entirely hampered by physically disabling symptoms and cognitive impairment. She needed assistance with

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Letter from the Publisher

➤ *continued from page 4*

nearly all her day-to-day tasks, including clothing herself, going to the bathroom, and eating. Too weak to stand she became confined to a wheelchair – she barely made it through her daughter's wedding celebration. Medications for MS were limited in the late 1990s, and they offered very little to reverse her course. Pain medication lived up to its reputation and simply made her dopey. By chance she read of a promising treatment in the US that individuals were posting on some blogs. That treatment was LDN; and after much consultation and cajoling of her physicians in the British National Health Service, she succeeded in arranging a prescription for it. Within three weeks there was a major change in her symptoms; within two years the wheelchair was gone. Linda is now the chairperson of the LDN Research Trust and very actively providing patient and physician education about LDN internationally. Her MS has remained in remission now for more than 13 years!

Peripheral neuropathy is a debilitating and painful condition for most individuals. Despite the best efforts of individuals who have diabetes, neuropathy frequently complicates their condition. A patient who has type 2 diabetes had been opting to manage her condition without the use of medication. Unfortunately, her glucose control was sub-optimal with an elevated hemoglobin-a1c. She noted that her most difficult symptom had been insomnia caused by intractable foot pain. She agreed to abide by a much more restrictive, low-carbohydrate diet. Additionally, she was agreeable to using a substantial nutraceutical regimen both morning and night, intended to help control her glucose levels. She also elected to have i.v. chelation treatment as she did have a low-grade burden of toxic elements, including lead and mercury. As time proceeded, she did experience improvement in her diabetic control, hypertension, weight management, and general state of well-being. She was able to exercise with more vigor. However, her feet pain persisted despite several administration of herbals and homeopathics to abate the discomfort. Eventually she agreed to try LDN at a very low dose.

Within weeks there was a marked reduction in her discomfort and improvement in her insomnia. Dosing of the LDN was increased from once to three times daily. She experienced further pain reduction and less interrupted sleep.

LDN has not only been helpful in MS and peripheral neuropathy but in other neurologic conditions as well. For those who would like a primer on the topic read *The LDN Book* edited by Elsegood and published by Chelsea Green Publishing. Additional reading material and videos are available on the website, ldnresearchtrust.org.

How Safe Is that Avobenzone You Are Absorbing with the Sunscreen Spray?

The short answer is no one knows. According to Jo McGinty's August 3rd *Wall Street Journal* column ("The Numbers"), we do know, based on a study published in *JAMA* in May, that four commercial brands caused volunteers' blood levels of avobenzone to exceed "acceptable limits" after just one day of application. That limit is 0.5 nanograms per ml of the ingredient. In the products under study, which all listed the concentration of avobenzone to be 3%, the measured blood levels were 4.0 ng/ml for the spray, 4.3 ng/ml

for the lotion, and 1.8 ng/ml for the cream. Similarly, other sunscreen chemicals were determined to yield high blood levels after one day use. Oxybenzone demonstrated far higher blood levels measuring 200 ng/ml for the spray and 169 ng/ml for the lotion. Octocrylene had average levels of 5 ng/ml for the spray, 5.7 ng/ml for the lotion, and 5.7 ng/ml for the cream.

Now that we know that we absorb these chemicals quite nicely by spraying or slathering ourselves with these products, one needs to know what effect these chemicals are having on us. The industry would have us believe that they are inert but we know better. Anne Marie Fine, MD, wrote about the skin's role as an underappreciated route of entry for toxicants in the June 2019 issue of the *Townsend Letter*. Fine broadly considered how absorbed chemicals act as endocrine disruptors, neurotoxins, and carcinogens. Additionally, the chemicals might cause birth defects – think of all the pregnant women basking in the sun after carefully applying sunscreen. Any possibility that the avobenzone might be impacting the fetus?

Well the FDA wants to find out and find out this year. A rule set to go into effect this November is ordering manufacturers of all these sunscreen products to do the testing for each of the major chemicals. There are 16 of them; zinc and titanium oxide are deemed safe while PABA and trolamine salicylate are not. As you might imagine the industry is fighting back, seeking to avoid testing of their chemicals. This is a $2 billion industry so one can imagine the lawyers will be offering all sorts of reasons not to test.

Much as I don't like to concur with FDA policy making – the draconian restrictions it is imposing on compounding hormones and injectables are awful – this is one time when mandated testing for safety makes sense.

Fluoride and Brain Decay – No Problem as Long as We Prevent Cavities

Although I approve of the FDA investigating avobenzone in sunscreen lotions, I am not a fan of their ignorance or, would that be, denial of fluoride's toxicity. Ever since the dental profession joined forces with the aluminum industry who needed a good way to dispose of fluoride industrial waste, fluoride has become the central means to preventing cavities. We are encouraging young parents to use fluoride toothpaste on toddlers. Much worse, however, has been the widespread fluoridation of community water systems. Strangely enough, despite the herculean efforts and sanctimonious testimony

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of public health officials, nearly half the municipalities in the US have not signed on for water fluoridation. Of course, the need to fluoridate remains a mandate for these good doers – many non-fluoridating cities are besieged every five years or so by a full-tilt propaganda campaign to get on board with the fluoridators and stop threatening the dental health of children. Nevertheless, the large number of towns that don't fluoridate makes for an interesting comparison with those that do. And the difference is not only surprising but makes for a compelling argument to not fluoridate.

Researcher and citizen advocate, John MacArthur, who has written several times before about the mischief caused by fluoride in the *Townsend Letter*, writes in this issue about the devilry achieved by fluoride on the brain and its cellular functioning. The dental profession treats fluoride very cavalierly as though it is a knight in armor despite the fact that excessive fluoride application results in dental fluorosis. Chemically one of the harshest agents on the lab bench is hydrofluoric acid, which is capable of reacting with ordinary glassware. In the operating room the administration of a particular anesthetic, sevoflurane, is capable of rendering a patient delirious post-surgically. One of the most abrasive chemotherapy agents is 5-fluorauracil. You get the idea – fluoride transforms a compound that has a certain level of toxicity and amplifies that toxicity many-fold.

MacArthur examines the evidence of how the fluoride that we absorb from our toothpaste and, without consent, from our drinking water insults our brain cells and the blood brain barrier and the synaptic proteins that enable neuron communication. When you compare states that have the largest number of fluoridating cities to those that have the least, there is more neurological disease in the states that are heavy fluoridators. This includes that great scourge befuddling researchers and doctors, Alzheimer's disease. Shouldn't that be a reason to give the fluoridating stalwarts pause? Maybe a reason for the FDA to investigate? Yes, avobenzone may be harsh, but what about fluoride? And if Alzheimer's isn't your thing, MacArthur's examination of the statistics shows a similar picture of increased death from hypertension, stroke, and kidney disease in states that push fluoridation versus those that don't.

We have tests available that assess mercury and lead, pesticide and solvent, and mycotoxin levels. We need some tool capable of determining fluoride toxicity. Of course, that might be heckled by the dental profession.

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Clinical Study #1 (1999)

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

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

Clinical Study #2 (2007)

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

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

Clinical Study #3 (2014)

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

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

Clinical Study #4 (2016)

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

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

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Letter from the Publisher

➤ *continued from page 8*

We Don't Have a Treatment for Alzheimer's But We Might Have One to Prevent It

One of the most frustrating aspects of treating a patient with Alzheimer's disease is the paucity of treatment options. The pharmaceutical world offers several drugs, none of which leads to good control of the condition much less reversal. The progressive deterioration of dementia is heartbreaking for the patient and the family; it is so painful to experience a person's vitality and competency break down especially with the memory of someone so full of life and creativity. While researchers seek some remedy that may stop the B-amyloid deposition and the tau protein neurofibrillary tangles, we do have a remedy, a natural one at that, very likely to slow if not prevent the development of Alzheimer's. This is not new experimental work – but it is work that has been largely ignored by public health authorities despite its low cost and dearth of adverse effects.

James Greenblatt, MD, has a special interest in integrative medicine, especially in how it applies to managing psychiatric disorders. Greenblatt has written frequently about depression, anxiety, suicide prevention, attention deficit disorders, and optimizing brain health in this publication as well as in other journals and books. His most recent text is titled *Integrative Medicine for Alzheimer's.* His research reveals extensive evidence that individuals with higher nutritional intake of a "non-essential" nutrient have a far lower incidence of Alzheimer's than those with a lower intake of that nutrient. The need for it is not related to genetic errors of metabolism – it is simply those getting more of it have less Alzheimer's, those with less have more. If the evidence confirms that there is a reduction in Alzheimer's with intake of this nutrient, shouldn't it be a mandatory part of our dietary enrichment, just like fortifying white bread with thiamine and salt with iodine? I would think so, but you make up your own mind after reading this issue's article by Greenblatt.

When you are evaluating a new patient who is using ten different prescription medications, how many nutrients would you assume have been rendered deficient or ineffective? None, two, five, or twenty?

Read Ross Pelton, PharmD's report in the upcoming November *Townsend Letter.*

Cover Story: Assessing Non-Genetic Factors Leading to Alzheimer's Disease

Families with a high number of relatives having Alzheimer's disease at an early age clearly have a genetic basis for the disorder. Genomic testing has determined that certain mutations appear to increase the risk for developing Alzheimer's. However, the ever-increasing number of individuals succumbing to dementia in the elderly population suggests that genetics cannot be the key cause. Greenblatt's discussion of a nutrient deficiency may represent a major public health breakthrough in Alzheimer's prevention. The question remains, however, as to how one can assess the risk for developing Alzheimer's and would such information be useful in its prevention or at least in slowing its development.

Aristo Vojdani, PhD, director of Immunosciences Lab, would argue "yes" on both points. He would make the case that testing would be very useful in appraising one's risk for developing Alzheimer's and that such abnormalities would not depend on the disease imminently becoming symptomatic. Instead, immunologic abnormalities would be evident years, if not decades, before memory loss is prominent. It has long been acknowledged that there has been an association between aluminum and Alzheimer's. Yet the evidence remains weak that the two are directly tied together. Vojdani's work asserts that it is not the mere presence of aluminum that is the issue. Instead, it is the immune system's recognition of aluminum binding to tissue proteins, leading to antibody formation against the aluminum-tissue protein complex. Such antibodies cross react with amyloid precursor protein, a signaling peptide capable of producing fibril formations that result in amyloid plaque formation. Vojdani's article in this issue provides a detailed discussion of how not just metals, like aluminum, and chemicals, like phthalate, but also microbial infections are all capable of creating bound-tissue complexes, leading to immune system recognition and production of antibodies against these metal-tissue complexes or pathogen-tissue complexes. It is the cross reactivity of these antibodies with amyloid-beta peptide that leads to amyloid plaque deposition as well as tau neurofibrillary deformation. Testing to determine the presence of such antibodies offers important clues as to whether neurodegenerative changes are occurring and to what degree. Moreover, beyond chemical and microbial risk factors, foods form tissue-bound complexes also leading to antibody formation cross reacting with brain tissue. Not surprisingly, gluten is frequently found to have very high antibody formation.

Vojdani's treatise makes a compelling argument for the immunoreactivity of a variety of environmental toxins, pathogens, and food proteins contributing to the early development of dementia. The fact that these antibody abnormalities can be screened decades before cognitive impairment offers an important tool not just for risk assessment but also prevention.

Jonathan Collin, MD

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briefed by Jule Klotter
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Microbiota Transfer Therapy for Autism

Chronic gastrointestinal symptoms are common among people with autism and neurodegenerative illnesses like Parkinson's and Alzheimer's diseases. Because abnormal gut microbiota has been documented in those with autism, researchers at Arizona State University (ASU) decided to test a microbiota transfer therapy (MTT) program to see if it could improve GI symptoms and autistic symptoms. The MTT technique they are using is based on the work of Australian gastroenterologist Thomas Borody.

MTT treatment begins with a course of vancomycin for two weeks to reduce pathogenic bacteria followed by a bowel cleanse with MoviPrep to remove vancomycin and remaining bacteria. Then, patients receive high-dose fecal microbiota transplant (FMT) for one to two days, followed by seven-to-eight weeks of a daily maintenance dose. The FMT is given with Prilosec, a stomach-acid suppressant, to increase the survival rate of the FMT bacteria.

The initial ASU open-label study involved 18 children with ASD and chronic gastrointestinal problems. This Phase 1 study showed that MTT safely reduced GI symptoms by 80% and significantly increased gut microbial diversity, including potentially beneficial bacteria. Moreover, most of the children showed a slow, steady improvement in behaviors. Two years later, the researchers re-evaluated the 18 participants to see if the changes in the original study had persisted.

Two years after MTT, most children still had improvement in their GI symptoms compared to baseline (before treatment). "The improvement was on average 58% reduction in Gastrointestinal Symptom Rating Scale (GSRS) and 26% reduction in % days of abnormal stools relative to baseline... similar to what we observed at the end of treatment," according to the researchers. In addition, microbiota diversity was higher than at baseline. In fact, many children had greater diversity two years after treatment than they had at the week 18 follow-up in the original study – but the composition did not match the donor microbiome: "This suggests that the recipients didn't retain completely the donated microbiome, but rather retained some features of it such as increased overall diversity and increase in some important microbes such as Prevotella, while finding a new state."

Autism symptoms, assessed with the Childhood Autism Rating Scale (CARS) rated by a professional evaluator, continued to improve after the original study. Eighty-three percent of the children were in the severe category at the beginning of the original study. Autism severity decreased by 23% by the end of week 10 in the initial study. Two years later, severity was 47% lower than baseline; 17 % (instead of 83%) were in the severe range, 39% were rated mild to moderate, and 44% were below the ASD diagnostic cut-off scores. In addition, parents reported that social responsiveness had greatly improved. Whereas 89% of the children were in the severe range at baseline, using a parent-rated Social Responsiveness Scale (SRS), the percentile in the severe range dropped to 47% with 35% in the mild/moderate range, and 18% below ASD measures. These results are notable because autism symptoms tend to remain stable without major interventions.

This Phase 1 study and follow-up showed good safety and efficacy. According to information at the autism.asu.edu website, the ASU researchers are conducting a Phase 2 MTT involving adults with autism. This Phase 2 trial is randomized, double-blind, and placebo controlled. ASU researchers hope to perform a similar study with children when they have funding. Eventually, they hope these studies will lead to larger Phase 3 trials that result in FDA approval for the use of fecal microbiota transplants to treat autism. Right now, FMT is only permitted to treat people with life-threatening diarrhea due to recurrent *Clostridium difficile* infection.

On June 13, 2019, FDA released an important safety alert regarding use of fecal microbiota for transplantation after two immunocompromised adults, who had received investigational FMT, developed invasive infections and became seriously ill. One patient died. The fecal material came from the same donor. The FDA now requires that any potential donors whose medical history makes them at increased risk for multi-drug resistant organisms (MDRO) be excluded as microbiome

donors. Also, FDA scientists have determined specific MDRO testing protocols to implement to ensure that positive donor stool is not used.

FDA. Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms. June 13, 2019.
Price D. Autism symptoms reduced nearly 50% 2 years after fecal transplant. April 9, 2019.
Kang D-W, et al. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. *Scientific Reports.* 2019;9:5821.

MDMA-Assisted Psychotherapy for PTSD

In Winter 2018, Multidisciplinary Association for Psychedelic Studies (MAPS) began recruiting for Phase 3 clinical trials of MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD) (see https://mdmaptsd.org for details). The FDA requires Phase 3 trials before approving prescription treatments. FDA gave its Breakthrough Therapy Designation to the MDMA program in August 2017, based on the results of MAPS' six Phase 2 studies, and agreed to expedite its development and review.

The MDMA-assisted psychotherapy protocol consists of 18 hours of non-drug psychotherapy that supports two or three eight-hour sessions during which the participant receives MDMA, a psychoactive drug also known as Ecstasy. A supportive team of two co-therapists prepares each participant for the first MDMA session during three 90-minute psychotherapy sessions. The clinicians follow the participant's lead in determining the type of environment, music, etc. to be used during the MDMA sessions and remain with the participant throughout each eight-hour session. "MDMA-assisted psychotherapy is designed with the intention to create a space for a person to come back to recognizing their own power, their own capacity to heal, to love, and to live a full life. In a safe setting, supported by two clinicians and with ample time, participants are offered the chance to address the core issues of their trauma," explains Shannon Clare Carlin, MA. Each MDMA session is followed by an overnight stay onsite, seven days of telephone contact, and three 90-minute psychotherapy sessions aimed at integrating the experience.

One Phase 2 clinical trial, led by Michael C. Mithoefer, MD, involved military veterans, firefighters, and police officers with chronic PTSD (duration of 6 months or more) and a Clinician-Administered PTSD Scale (CAPS-IV) total score of 50 or more. The participants were randomized into one of three MDMA dose groups: 30 mg (control), 75 mg, or 125 mg. Masked independent raters assessed participants at baseline and at one month after the second MDMA session (primary endpoint). After this assessment, the blind was broken; then, open-label sessions using the full dose (100-125 mg) of MDMA were conducted with all participants, using the same protocol as described above. The 125 mg group received one session (their third at full dosage), and the other two groups received three MDMA sessions. A follow-up was conducted 12 months after the final full-dose open-label session.

"At the primary endpoint, the 75 mg and 125 mg groups had significantly greater decreases in PTSD symptom severity (mean change CAPS-IV total scores of -58.3 [SD 9.8] and -44.3 [28.7]; p=0.001)," the authors report. The improvement in the

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➤ *continued from page 15*

control group was not as great (-11.4 [SD 12.7]). Symptom severity did not significantly decrease further in the active groups after the open-label sessions. Symptoms in the control group, however, did significantly decrease.

Improvement remained after 12 months. PTSD symptoms were still significantly lower compared to baseline with mean CAPS-IV total score of 38.8 [SD 28.1] at follow-up compared to 87.1 [SD 16.1] at baseline ($p<0.0001$). In addition to lower CAPS-IV total scores, participants showed improvements in psychological, occupational, and social functioning measures.

A total of 85 adverse events – mostly mild or moderately severe – were reported. Anxiety, headache, fatigue, and muscle tension were the most common adverse events to occur during the MDMA session. Fatigue, anxiety, and insomnia were also reported with decreasing occurrence in the week following a session. Four serious events also occurred, one of which was apparently associated with the treatment. A participant with premature ventricular contraction at baseline developed an acute increase in premature ventricular contractions during the third open-label session. The problem was detected by one of the therapists during routine heart rate readings. The participant was admitted to the hospital for overnight observation and cardiac assessment and fully recovered.

Mithoefer MC, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomized, double-blind, dose-response, phase 2 clinical trial. *The Lancet.* May 1, 2018.

Phase 3 Trials: Study Initiation Visits for 8 Sites Completed. *MAPS 2018 annual report bulletin.* Winter 2018;20.

Carlin SC. Cultivating Inner Growth: The Inner Healing Intelligence in MDMA-Assisted Psychotherapy. *MAPS 2018 annual report bulletin.* Winter 2018;30-33.

Low-Dose Naltrexone for Multiple Sclerosis

On internet forums, people with multiple sclerosis (MS) report experiencing benefits, such as reduced relapse rate and slowed disease progression, when using low-dose naltrexone (LDN). Naltrexone binds to opioid growth factor (OGF) receptors, displacing the endorphin OGF, which regulates cell growth and immune function. The body's cells respond to this displacement by increasing receptor production, increasing receptor sensitivity, and increasing OGF production. Low-dose naltrexone blocks receptors for just a few hours before being excreted. Once LDN is out of the system, the body responds to the increased OGF and OGF receptors with a rebound effect, enhancing the regulation of cell growth and immune response. LDN's affect on OGF activity has led to its use as a treatment for cancer and autoimmune conditions, including multiple sclerosis. While a handful of clinical trials indicate that LDN is well-tolerated and safe for MS patients, data about its efficacy is hard to find.

Michael D. Ludwig and colleagues published a 2016 retrospective study that compared a group of patients with relapse-remitting MS who received glatiramer acetate

(Copaxone) and LDN as adjunct therapy (n=31) to a group of patients who refused the medication because of adverse effect concerns but agreed to take LDN (n=23). The researchers looked only at safety, not efficacy; they wanted to see if the LDN-only patients had a higher incidence of progression or exacerbation of the disease. The LDN-only group took 3 or 4 mg LDN for an average of 1095 days (about 3 years) with an individual range of 30-2169 days of use. The LDN-Copaxone cohort took LDN therapy for an average of 1418 days (about 47 months). Disease progression was assessed using MRI and timed 25-foot walks.

The authors stated, "Statistical analyses between the groups, and for each patient over time indicated no significant differences in clinical laboratory values, timed walking, or changes in magnetic resonance imaging." Yet, the details indicate that LDN-only participants seem to have fared somewhat better. Only one LDN-only patient had multiple flares during the study, compared to six patients with multiple flares in the LDN-Copaxone group; the remaining patients each had one flare during the study. About 50% in each group had stable disease, according to MRI, by study's end; but twice as many became "slightly worse" in the LDN-Copaxone group, and no LDN-Copaxone patient "slightly improved." In contrast, two LDN-only patients slightly improved. Also, patients in the LDN-Copaxone group showed a statistically significant decrease between timed 25-foot walking times (taken at baseline and every 6 months thereafter) between visit 1 and visit 4: 6.3 ± 0.5 (visit 1) and 5.1 ±0.3 (visit 4). The LDN-only remained about the same 6.2 ± 0.5 (visit 1) and 5.9 ± 0.4 (visit 4). The authors conclude "These data suggest that the apparently non-toxic, inexpensive, biotherapeutic is safe and if taken alone did not result in an exacerbation of disease symptoms" in people with relapse-remitting MS.

I was unable to find any clinical studies designed to look at efficacy. The clinicaltrials.gov website lists several LDN trials for cancer patients and for people with fibromyalgia, but none for patients with MS.

How does LDN Work? www.ldnscience.org/ldn/how-does-ldn-work
Ludwig MD, et al. Long-term treatment with low dose naltrexone maintains stable health in patients with multiple sclerosis. *Multiple Sclerosis Journal.* 2016; 2:1-11.

Bipolar Mood Cycles and the Moon

T.A. Wehr, an emeritus professor of psychiatry at the National Institute of Mental Health (Bethesda, Maryland), decided to investigate a possible relationship between lunar cycles and mood cycles in people with rapid cycling bipolar disorder after examining the records of a patient whose moods followed a 35.5-day cycle for years. Wehr conducted a retrospective study using records from 16 additional patients with rapid cycling bipolar disorder. The patients exhibited a cyclic illness pattern, exhibiting mania for several weeks, abruptly transitioning ("within a day or so") to an equal number of weeks with depression, and then abruptly transitioning back to mania. All 17 patients had "a frequency of 6 or more complete (mania+depression) cycles, that is, 12 or more affective episodes per year."

"'Because people differ in how they respond to these lunar cycles, even if you were to average together all the data I've collected, I'm not sure you would find anything," he told journalist Linda Geddes. "'The only way to find anything is to look at each person individually over time, and then the patterns pop out.'" In doing so, Wehr found that some mood swings followed a 14.8-day cycle (full moon to new moon) while others followed a 13.7-day cycle (declination cycle that drives daily tides, related to Moon's position relative to Earth's equator). While patients did not switch moods every 13.7 or 14.8 days, switches occurred only during a specific time in the lunar cycle. The Moon's elliptical orbit, which has a 206-day cycle, also played a role.

Wehr says, "If bi-weekly lunar cycles drive rapid mood cycles by entraining the circadian pacemaker to the 24.8-h lunar tidal day, how might one interfere with their influence? One approach would be to refrain from prescribing antidepressant medications while continuing maintenance treatment with lithium carbonate." Antidepressants are associated with rapid mood cycling. When antidepressants were discontinued, mood cycling slowed or remained in the depression stage in nine patients. Wehr says another approach is "to strengthen the pacemaker's entrainment to the 24.0 h solar day. This could be accomplished by exposing patients to longer periods of darkness at night, which have been shown to increase the amplitude of the pacemaker's phase-responses to light and strengthen its coupling to the light-dark cycle." In fact, one patient had a complete remission by staying in total darkness from 1800 hours (6 pm) to 0800 hours (8 am) every day.

Geddes L. The mood-altering power of the Moon. July 31, 2019. www.bbc.com.
Wehr TA. Bipolar mood cycles and lunar tidal cycles. *Molecular Psychiatry.* 2018;23:923-931.

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Next issue devoted to...

Fibromyalgia, Chronic Fatigue, Chemical Sensitivity, and Pain Management

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*

FCT® and the Brain: With an Approach Like This, Who Needs Neurotransmitters and Pills?

by Savely Yurkovsky, MD

"I agree 1000% with your article on dysfunctional medicine. I have questioned its lack of results for 23 years. Only FCT has provided a logical explanation to illness and tools to bring healing to patients. I thank you." Michael Corey, DC (Tustin, California).

As the epidemics of anxiety, depression, insomnia, OCD, addictions and all other brain disorders continue to skyrocket and consume even children and teens, the failed "scientific" approach toward them remains unfazed. It is based on chemical pharmaceutical medicine (CPM) with its always "logical" tests and treatments of targets that have something to do with disease. In brain disorders these are neurotransmitters. In conventional medicine, the treatments are drugs, in alternative, interesting substances. Yet, as both of these carry zero preventative and curative capacity and often fail, some "progressive" approaches such as integrative psychiatry, functional psychiatry and the like have been redressing this stillborn CPM in a different clothing. Surely, for brain chemistry one cannot find a more impressive target than neurotransmitters with their sophisticated lab profiles promising "better" treatments. Based on these and other nonspecific, wasteful tests, the claim package also includes "underlying causes" and "the root cause of the symptoms."[1] The same reference source presents an answer to "What is Functional Psychiatry" in which Dr. Mark Hyman, medical director at the Cleveland Clinic's Center for Functional Medicine, defines functional medicine as "…the future of conventional medicine – available now."

Sorry for spoiling the party but as far as an esteemed piece of real estate such as Cleveland Clinic validating any medicine…it itself represents a complete failure in reversals of chronic diseases, like CPM worldwide. And the happy idea of continuing to endure conventional medicine – even of the future – is enough to cause suicidal depression. The piece was a virtual infomercial between Dr. Hyman and an interviewed integrative psychiatry professor with an exchange of flattery as between a priest and a choir, with the inspiring claims of delivering root causes and "individualized treatment to a unique person." While suggesting a healthy diet for brain disorders may sound innovative, the great Hippocrates said this more than 20 centuries ago.

Everything is interconnected, interdependent, acting and changing all at once.

Concerning the idea of individual neurotransmitter assessments and treatments, like virtually all good ideas in CPM, this makes a lot of sense until one starts poking it a bit. Like all science-based speculations, it contains an element of truth where neurotransmitters do participate in all of the major functions in the brain from mood to sleep, memory and learning, addictions and neurological functions. There are between 30 and 100 neurotransmitters, formally registered, with 10 of these carrying out 99% of all brain-related functions. Among these the major and better-known groups – GABA, serotonin, dopamine and glutamate – have been targeted by pharmaceutical and alternative manufacturers. However, even as thousands of research papers in psychiatry and neurology impress their importance, their real value as the primary root or cause of disease is marginal to none. This can be better understood through the concepts of this nasty discipline – philosophy of science – whose major purpose is to preclude scientists from corrupting science or doctors medicine. Knowing well that scientists tend to fool through using fancy verbiage, or as noted by ingenious Hahnemann through "learned prating" in medicine, philosophy of science strips fancy prating down to meat and potatoes language by displaying similar logistics through simple examples from our ordinary life. By comparing this multibillion-dollar fancy neurotransmitter science to a simple example of a criminal using a computer to send malicious signals or messages to commit wire fraud, we can obviously conclude that neither signals nor neurotransmitters in our case, which are called messengers in neuroscience, nor computers are the real criminals and arresting them can't

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solve cybercrimes. The solution must come from neutralizing the criminals who program computers with criminal information. In our case computers are brain zones that were invaded by criminal or pathological information, which comes from our environment in the way of toxicological, infectious, and electromagnetic agents.

Once the integrity of brain zones has been compromised so has their receptors through which they must properly respond to messengers and messages, themselves, which they produce; any affective, mental, and neurological disorder follows the same general principle that operates with all somatic diseases where messengers (enzymes, hormones, immune regulators and others) become distorted and/or misinterpreted by organ receptors. That is why FCT (Field Control Therapy) primarily focuses only on the organs and their reasons or causes for producing distorted messages and applies this from head to toe diseases.

While this general focus has been confirmed by thousands of texts in neuroscience, referring to the brain zones as the sources of neurotransmitters and even to toxicological, infectious, and electromagnetic morbid agents that distort these zones, narrow CPM training precludes integrative and functional psychiatrists and neurologists from determining exact malfunctioned brain zones, their invaders, and effective treatments. FCT has overcome this key obstacle through body energy diagnosis and treatment, as based on physics – namely, through bioresonance testing that noninvasively tunes into any part of the brain and other organs to determine their malfunction and causes. This is followed by homeopathic-energetic remedies that stimulate the repair of malfunctioned brain zones and their release of the elicited invaders.

Based on FCT-cured cases, the latter are toxicological agents (with mercury being their leader), infectious agents, and electromagnetic fields. But what is even more impossible to establish through CPM, neurotransmitter, or any lab tests, is that all of these agents act together in mutually enhancing fashion. This has been confirmed by scientific literature. Furthermore, the agents and their interactions affect many somatic organs too, and their malfunctions further enhance brain pathology from the periphery and vice versa. This turns all of the sophisticated medical specializations on their head. The bottom line, chronic diseases have no borders. In light of this total pathophysiological chaos in which the neurotransmitter-based treatments are processed by confused brain and body receptors, not to mention how these drugs mesh with the other 30-100 neurotransmitters, they end up producing many side effects from impotence to suicides.

In light of CPM's methods and the pathological chaos in chronic diseases, functional psychiatry's and medicine's pledging to find "root causes" represents a scientific impossibility. This is impossible to establish with certainty by any method even bioresonance testing. Even though the test can overcome lab obstacles to determine morbid agents concealed inside the brain and other organs, this can only suggest root causes with a high degree, but not 100% certainty – even when diseases reverse, based on these findings.

The reasons are that, unlike acute diseases where a sudden change in health in AàB linear fashion can be clearly linked to a root cause such as a flu virus, food poisoning, ingesting or inhaling a toxic substance, chronic diseases play through different, very convoluted dynamics. Everything is interconnected, interdependent, acting and changing all at once. This creates thousands of abnormalities: metabolic, nutritional, immune, liver, colon, and others with most of these being secondary to, but not root causes themselves. Even a malfunctioning or mutated gene, per se, may not be a root cause at all since it is impossible to tell whether this is the real cause of illness; other interacting genes compensate for this malfunction; or a "bad" gene is just a red herring and disease is caused by an overlooked metal toxicity or an infection. While many patients have been sentenced to a "justified" suffering from chemical sensitivities or inability to detoxify metals due to a mutated detox gene (ie, MTHFR), some patients have told me that they have that mutation, yet no signs of chemical sensitivity. So, even when not having mutated genes, does it amount to being poisoned with mercury, lead, pesticides, and a myriad of other environmental pollutants? Toxicology has established that we cannot metabolize toxic metals, genes or no genes, and in virtually all of these MTHFR mutations it is not the gene but practitioners' fault for using ineffective treatments to detoxify metals.

Even when the tests detect agents of known high pathogenicity such as mercury and other heavy metals, yeast, or parasitic, viral, and bacterial infections, this does not automatically affirm these as root causes because their mere detection is no guarantee that other causes have not been overlooked. Likewise, when a treatment with chelators, nutrients, complex homeopathies, or sauna for established mercury or other metal toxicity makes a person feel better, this, per se, still does not seal a diagnosis of root cause, since we cannot know what other toxic agents these treatments might have decreased in the process – or that a person suffered more from an unknown infection or EMF sensitivity which have improved thanks to that decrease. Also, establishing root causes deductively – even if following an improvement in symptoms through pharmaceutical treatments, as used in functional and biomedical medicine – is virtually impossible since these represent "hairy" treatments; actions cannot be confined to specific toxins, receptors, proteins, enzymes, infections, organs or tissues.

Our bodies use similar receptors, including for neurotransmitters, and proteins in many different tissues. This is why a former Stanford University pharmaceutical researcher, Bruce Lipton, PhD, stated that side effects of pharmaceuticals are just their natural effects.[2] This further adds to the reasons for side effects of neurotransmitter-based pharmaceuticals. Based on all of these facts, no test has ever stamped any abnormal finding as "root

cause" or can prove it as such. Root cause is an interpretational entity by a practitioner with no existing list or book of their identity. The best we can do is to maximally narrow the treatment against a specific morbid agent, as used by FCT through specific homeopathic-energetic remedies, based on bioresonance testing, and avoid using piles of supplements or other treatments in order to avoid a confusion from "what did what?" In cases of a cure, the treated causes were only *likely* the root ones. In the absence of good progress, another important cause might have been undetected, or a patient lacked compliance or continued to be re-poisoned. Since neither functional psychiatry nor medicine has published any documented cured cases, how can one claim which causes are root or speculative? In case I misunderstood something about these speculations, I invite anyone to openly challenge me.

Certainly, if the main task – curing a patient – is accomplished, even without having an inkling of the real physical cause of disease, as through classical homeopathy, psychic or religious healing, so be it. Who needs an infomercial on root cause? Even academic psychiatrists got tired of all of their empty solutions and theories about brain chemistry and call for finally using patients' recovery as the main model for practice.[3] Speaking of classical homeopathy, in the assessment of brain function and health in general, it offers the most comprehensive assessment available in all medicine today.

However, short of clear, specific emotional and somatic states, for which it has good remedies, its success is not consistent; and other general healing practices work only sporadically in chronic diseases. Most of the examples below of successfully treated brain disorders were based on homeopathic-energetic remedies addressing alleged causes as suggested by bioresonance testing. Prudent environmental and lifestyle guidance such as a healthy diet and reduction of EMF exposure and stress through Memon technology were offered also. It is only through a narrow, specific testing and treatment of potential causes of diseases that FCT has compiled its own database regarding which of these can be considered more, less, or not a root cause at all. Also, the sicker a patient who responded to a remedy, addressing a specific morbid agent, the more likely that the agent was the real cause. This experience serves as a very useful base to lead to a quick, reliable, and low-cost overall assessment and treatment. A few cases were cured through classical homeopathy.

A Case of OCD, Hyperactivity, and Aggression in a "Difficult" Teen

This case is noted for a detailed description by the mother for every FCT specific remedy aimed at a cause or rather multiple causes of pathology. This girl was deemed hopeless by a child psychologist who recommended psychotropic drugs. In an email, dated February 12, 2015, the mother wrote:

FCT® and the Brain

> I'd like to provide Dr. Yurkovsky with some information/insights about what I have observed about my daughter Claire during the 5 weeks of treatment she has just completed.
>
> As a whole, I have a witnessed a dramatic change in her behavior - it was almost immediate. The absence of certain behaviors have highlighted just how intense they actually were. Her first drop was Strep A.

The lengthy report thoroughly describes the girl's reaction to each subsequent remedy for Lyme infection, mercury toxicity, and malfunctioning in the brain zone that regulates emotions. The end result is presented in this section.

> Her entire being/energy felt altered. Calm.
>
> In short, she has:
>
> - stopped moving/flipping/ cartwheeling so often/intensely
> - stopped restless activity/starting a new project what seems like every 20 min
> - stopped lashing out in frustration
> - almost completely stopped fighting with her sister. This is a HUGE change. They started playing together for the first time in months without huge fights
> - become much calmer, absolutely more patient, absolutely more cooperative.
>
> The change is dramatic – so much so that I can see in retrospect that she was in a "frenzy" working up to what felt like some sort of crisis....

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She coincidentally is having a growth spurt; she's taller and very thin.

The mentioned bone spurt often follows when children are treated for worms, as in this case, which also greatly contribute to emotional and mental problems. Worms are often missed by stool tests. Another interesting common observation, reported by the mother, is that many parents get used to their children's pathological behaviors as 'norm,' until they see it ceased. The same holds true for many of our own mental, emotional, and physical disorders

A Case of Cured PANDAS, Tourette's Syndrome, with Hundreds of Daily Tics, Headaches, Fears and Depression.

His mom's testimonial:

Our son, Zane had been diagnosed with PANDAS and seen three neurologists, including the head of epilepsy at NYU, an immunologist and infectious disease specialist and two pediatricians before seeing Dr. Yurkovsky. He also tried fifteen months of antibiotic therapy as well as essential oils which did not help.

While a patient of Dr. Yurkovsky, no other treatments were used other than those prescribed by Dr. Yurkovsky, which have led to his complete healing. The effectiveness of the treatment was dependent on addressing toxic mold in our attic and basement as well as replacing our oil burner with a closed end propane unit.

While the aforementioned specialists were relying on his blood tests and were bombarding the only detected Strep A with pharmaceuticals, the boy's brain, according to bioresonance testing was the proverbial toxic dumpster and zoo. It seemed to carry mercury, lead and other toxic metals. Detected infections, besides Strep A, were Lyme, *Babesia microti*, influenza, helminths, mold, and secondary to prior heavy antibiotic use mutated Strep A, mutated Lyme, and candidiasis. The detailed testimonial is on our website.

Parkinson's Disease and Cognitive Ability

A man in his early 50s came with progressive neurological symptoms of Parkinson's disease for years, fatigue, poor memory, rapid 30-pound weight loss, chocolate, alcohol, and cannabis addiction. In just a few treatments, there was at least an 80% decrease in Parkinson's symptoms, energy and memory were restored, addictions gone, 10 pounds gained, and he looked 5-10 years younger: "My friends and family comment that I look and act much better, healthy. Even my vision is better where I can read now without eye lenses. My overall cognitive ability is much better. My family feels relieved."

Speaking of cognitive ability, I have a number of elderly patients who reported far better memory, word search, even analytical function and creative writing enhanced through just "vacuuming" their brains from poisons. It is the lifetime accumulation of the latter that was the root cause. Not old age, brain plaques and hardening of the arteries "all needing better dementia and Alzheimer drugs and more research."

- "Doctor help! I am having severe head pain, brain fog and anxiety as if I am going out of my mind." One drop of a specific EMF remedy made all these vanished.
- "When I am exposed to computer, or fluorescent light I feel like I disappear. My brain becomes completely shut, I hardly know where and who I am." After FCT treatment "vacuumed" her brain to remove mercury, toxic metals, Lyme and other infections: "I still don't like computer and fluorescent light, but they are no longer a problem, as day and night."

Does Insomnia Really Need More Sleep Studies and Drugs?

A typical case of a child having difficulty falling asleep and waking up at night was cured by treating his worms with remedies. Another child's insomnia was cured by addressing fossil fuel fumes in the house. A middle-aged woman who was terrorized by repeated adrenaline rush at night awakening her in fear was cured with just one drop of candida remedy. A postmenopausal woman with insomnia "because of menopause" was cured by a few remedies cleaning her ovaries from mercury and infection. Another postmenopausal woman has solved her insomnia by plugging Memon in her bedroom. Speaking of sleep studies, it is one of the biggest jokes and rip-offs in medicine as to the causes of insomnia. This mere lodging of people overnight is followed by the same sleeping pills.

Savely Yurkovsky, MD, is board-certified in internal medicine and board-eligible in cardiovascular medicine who undertook a particular interest in mercury toxicity as both its victim and a clinician managing a busy private practice. Shortly after moving to the US from the former Soviet Union, he received several silver amalgam fillings, which he recognized later as the cause of his mounting health problems. These problems persisted, despite removal of fillings that prompted him to explore various mercury detoxifying approaches: oral, intravenous, homeopathic. After observing their corresponding partial benefits, limitations, and aggravations on himself and his patients, he resorted to bioresonance testing and causative homeopathy, based on relevant knowledge from physics and toxicology, to optimize benefits and safety of the detoxification. The guidance of his physics consultant, the Stanford University materials science Professor William A. Tiller, PhD, was instrumental in enhancing diagnostic ability of bioresonance testing to address the known limitations of lab tests to detect the presence of toxicants in the internal organs. This testing also was used to draw a better comparative capacity between various mercury detoxifying treatments as well as to evolve a safer therapeutic strategy leading to minimize the re-intoxication or dumping effect, which are common to these treatments. It also guided to optimize an unlimited therapeutic potential of homeopathy that has a unique capacity to therapeutically connect with any organ and tissue, via specific signals, as no other treatment can.

His book, *Biological, Chemical, and Nuclear Warfare – Protecting Yourself and Your Loved Ones: The Power of Digital Medicine* has been endorsed by Professor Emeritus William A. Tiller, PhD, of Stanford University and IT Physics Professor George Pugh, PhD. He presented this system at the Combating Bioterrorism Conference in 2005, sponsored by the Office of Homeland Security.

Dr. Yurkovsky founded a teaching organization, *SYY Integrated Health Systems, Ltd.*, in 1999, which is dedicated to training health practitioners in this biophysical system under the concept of FCT – Field Control Therapy®. He has lectured extensively in the US and Europe.

Do Addictions Need Better Drugs and Rehab Programs?

A woman, addicted to cannabis for 35 years, lost any interest in it after homeopathic energetic cannabis. An FCT practitioner cured his brother, a hard-core heroin addict who had bounced through many rehabs in vain, by cleansing his brain from heroin and other hallucinogens.

Classical Homeopathy in Brain Affections

- A chronic depression for years in a middle-age woman following a divorce. One pellet of *Natrum muriaticum*, cured.
- "I just can't stop crying. Anytime I hear some sad stories, children or someone hurting, I cry." In the office she was bursting in tears just mentioning this. One pellet of *Pulsatilla,* cured.
- "Yelling at someone was so easy, I just couldn't wait." Later, "It's amazing but after that little pellet (*Staphysagria* remedy) I have lost any desire to yell."
- "I have a heavy heart. Anytime I see bad news on TV or in newspapers I get a heavy heart. "Why? I just feel so burdened for the entire world and its problems." One pellet of *Carcinosin*, cured.
- In spite of having been adopted into a loving family who provided everything, a seven-year-old girl was never happy. She demanded extra attention and was throwing tantrums. A remedy prescribed by a very experienced classical homeopath did not work. Even though she has never verbalized missing her biological mother, as she was adopted from day one, yet bioresonance testing indicated that the corresponding brain zone was traumatized by the separation on a subconscious level and matched it with the right remedy, *Ignatia amara*. It cured.
- A case of a college campus rape. A very depressed and malfunctioning college student since an assault was cured by one pellet of *Natrum muriaticum*.
- Suicidal depression cured without Prozac. A young banker with suicidal depression, rages with hitting and destroying furniture and attacking his dad for f…… up his childhood. *Aurum metallicum*, one pellet, cured.
- A demon turned angel. A normally mild and well-mannered woman would turn vicious at handling even minor disagreements with her husband. She would curse, scream, and deliberately "stick" into him by reminding him of his old mistakes because these still troubled him. It had nothing to do with infidelity; yet he admitted and apologized many times. Afterwards, she would regret it; yet the next argument would release the same demon. One pellet of *Hyoscyamus niger* cured.

Which exact neurotransmitters became balanced in all of those cured cases? Is it really important?

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2. Lipton, Bruce. *Biology of Belief*. Mountain of Love: 2005.
3. Barber M. Recovery as the New Medical Model for Psychiatry. *Psychiatric Services*. March 2012; 63 (3).

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An exploration of why and how things happen.

GENERATIVITY

PETER D'ADAMO, ND

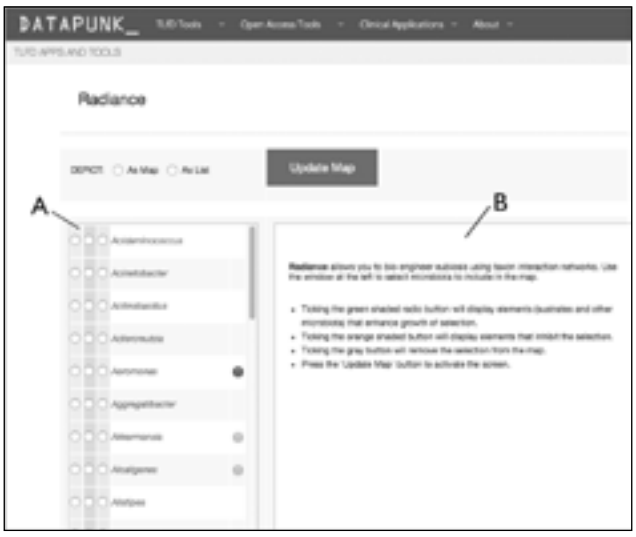
***Radiance*: Engineering Eubiosis**

It's time for another episode in our continuing adventures in generative paradigmatics. I hope you enjoyed the last installment (*TL*, June 2019), where we investigated using graph theory to develop an interactome crawler that allowed us to surf up and down the protein-protein interactome (PPI) and identify natural products capable of exerting effects in concert on high-value gene/molecular targets. For this we developed a generic open-source app ('Psychic') based on a similar app in the *Opus23™* program that works on client raw genomic data. This kind of bioinformatics holds great promise for a more robust polypharmacy, since we are (at least computationally) within the realm of the cybernetic axiom of *requisite variety* (the variety of a system's control mechanism must be greater than or equal to the variation in the system being controlled.)

Flocking and the Homeless

Most of you will recognize the image of flocking birds that I use as a logo for the column – a capability that they share with many self-organizing functions found in nature, such as termites that build mounds without blueprints, and even the detachment of metastatic cells from the surrounding extracellular matrix (ECM). These complex actions can be modeled by particle swarm optimization (PSO) algorithms (more on this in a later column.)

Figure 1: The main *Radiance* screen.
A: The selection frame. B: The depiction frame.



Dr. D'Adamo's article and all figures will be available on the website http://www.townsendletter.com.

PSO modeling has been used to study how swarming behavior renders metastatic cells immune to *anoikis* (programmed cell death due to 'homelessness'). Swarm behaviors are considered 'weak emergence,' new properties arising in systems as a result of the interactions at an elemental level that can be computationally modeled. 'Strong emergence,' on the other hand, are new qualities produced that are irreducible to the system's constituent parts. There are very few true examples of strong emergence in nature; the consciousness you're using to read this article being perhaps the only widely accepted example.

In the June column I introduced the concept of a directed acyclic graph network (DAG,) where things (nodes) get connected to other things by lines (edges) possessing directionality (an arrow at one end or the other). The order, direction, and degree of connectedness confer considerable insights and values to a network; and with the right tools, we can do some surprising work. For example, DAGs are crucial to much of today's machine learning and probabilistic AI, such as seen with Bayesian networks. We'll build a Bayesian-inspired tool for differential diagnosis based on user-selected medical subject headings (MeSH) symptoms and probabilities in an upcoming column.

DAGs can also be used to quantify causality from correlation. This will be critical in the evolution of AI to beyond human capabilities. When is something clearly the cause of something else? Not easy for humans, let alone machines! To do this we can employ DAGs to identify 'causal inference,' by first looking at the data for associations (observing what is), then proposing some sort of 'do' intervention (changing what one sees; 'If I take a baby aspirin, will my risk of heart failure reduce?') and finally hypothesizing 'counterfactuals' (estimates of the unobserved outcomes; 'If I had arrived on time.') A fascinating and readable introduction to causal inference is Judea Pearl's *The Book of Why: The New Science of Cause and Effect* (Basic Books, 2018).

Hating Your Friends and Loving Your Enemies

Today's exercise harkens back to the old proverb that 'the enemy of my enemy is my friend' suggesting that two opposing parties can or should work together against a common enemy. The earliest evidence of authorship traces back to the Indian teacher, philosopher, and royal advisor Kautilya, also known as Chanakya or Vishnugupta (fl. c. 4th century BCE). We'll use this aphorism to structure an interactive tool ('Radiance') that will allow us to engineer microbiome eubiosis via the selection of either the enhancement or inhibition of specific genera of microbiota.

As part of the *Opus23 ™* bonus module 'Utopia', *Radiance* allows clinicians to structure nutraceutical approaches to the microbiome raw data results of specific clients, typically from

reporting services such as uBiome. In the *Townsend Letter* version of *Radiance*, we'll have full functionality; we just won't be able to work with the added insights of what needs to be done for a specific client.

Building this type of bioinformatics program requires three types of data.

1. **A database (*Substrata*) profiling all known genera known to populate the human microbiome.** This was not as easy as one might expect. Many commensal microbes have not been extensively studied and reported upon. Searching the traditional electronic reporting sources (such as PubMed) yielded some punctuated information; but general information, if available at all, was best found via traditional microbiology textbooks. This database is online and searchable at https://www.datapunk.net/substrata/.
2. **Binary microbiota relationship/interaction data**. Here we were much more fortunate. Professor Pål Trosvik and his team at the University of Oslo have recently published interaction data by genera as heatmaps (*Microbiome*. 2015; 3:44. PMID 26455879. PMC4601151). Upon contact, Professor Trosvik most generously permitted the use of his data, and in true scientific spirit provided the linear regression contouring needed to allow us to construct the binary relationships, which, as will be seen below in a small section of the data file, are quite simple and straightforward:

   Bifidobacterium|1678|Roseburia|841|+
   Bifidobacterium|1678|Lachnospiraceae|186803|-
   Bifidobacterium|1678|Peptococcaceae|186807|+
   Bifidobacterium|1678|Ruminococcaceae|541000|-
   Bifidobacterium|1678|Ruminiclostridium|1508657|0

   Each line is a record in the database; each field is separated by the pipe ('|') character. In this case, growth of genus *Bifidobacterium* (taxon id 1678) is
   - Enhanced by genus *Roseburia* (taxon id 841)
   - Inhibited by genus *Lachnospiraceae* (taxon id 186803)
   - Enhanced by genus *Peptococcaceae* (taxon id 186807)
   - Inhibited by genus *Ruminococcaceae* (taxon id 541000)
   - Not influenced at all by genus *Ruminiclostridium* (taxon id 1508657)

Figure 2: The *Radiance* results frame

3. **A binary database of natural products, foods, and medications ('agents') shown to enhance or inhibit growth of specific microbiota genera.** Fortunately, this data was an inevitable consequence of building the main microbiome ('Substrata') database. Like the interaction binaries, this database links genera taxon id numbers to tagged agents, either via their role as inhibitors or enhancers of growth.

Radiate the Microbiome

The rest of this column is best appreciated by direct hands-on mucking with the software. *Radiance* is available at https://www.datapunk.net/tlfd/radiance/. So, go over to your computer and fire up your browser with this URL. I'll wait. Once here, you'll be greeted by the screen in Figure 1.

The screen is actually comprised of two frames. The selection frame on the left lists all the microbiota genera for which we have interaction data and some form of expression control by agent (herb, food, etc.). Clicking on any name fires up an information popup window with all sorts of data on that genus (the same data displayed by the aforementioned 'Substrata' program).

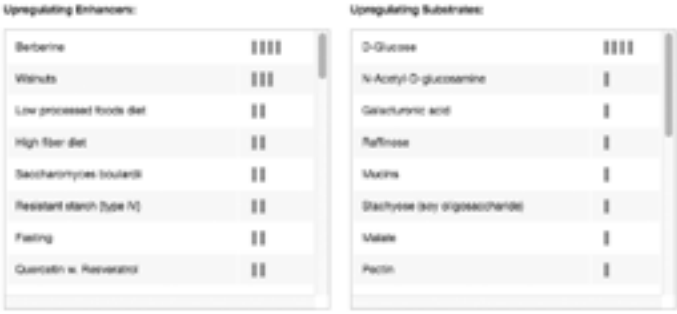
To the left of each genus name are three radio buttons, colored green, orange, and grey. If your goal is to identify ways to increase growth of that genus, tick the green box; to explore ways to inhibit, tick the orange box. If you decide that, after ticking either the green or orange box, you'd rather not include that genus in the analytics after all, tick the grey box.

To the right of certain genera appear colored icons with an exclamation point. These are clues to the genus' known pathological significance: red indicates a well-known pathobiont; yellow a more situational pathobiont. Green indicates that it is one of the good guys.

The larger frame is the depiction frame, and it's where all the alchemy occurs. After setting up your selections, this frame will update when you press the 'Update Map' button. Let's go ahead and set up some imaginary goals for an imaginary client with a 'hot' gut and low overall diversity. We'll tweak *Radiance* to

- **Enhance *Akkermansia* and *Faecalibacterium*:** These two genera are typically overall 'good guys' in the human microbiome. *Akkermansia* is a mucin degrader, and because of that occupies a 'keystone' role in the microbiome. *Faecalibacterium* is a genus thought to be anti-inflammatory via its modulation of IL10.
- **Diminish *Collinsella* and *Bilophila:*** *Collinsella* is considered an 'inflammatory pathobiont' and is linked to the progression of rheumatoid arthritis. *Bilophila* likes leftover bile and its overgrowth has been linked to an increased risk of colon cancer. ➤

Figure 3: The *Radiance* results frame as tabular data



➤

To do this we tick the green boxes next to *Akkermansia* and *Faecalibacterium* and the orange boxes next to *Collinsella* and *Bilophila*; then press the 'Update Map' button. Now, as they used to say, *through the magic of television*, we see the main screen come to life (Figure 2).

The main *Radiance* results screen depicts the interaction network involved in the regulation of the four genera we specified and submitted. As with tradition, arrow-tipped edges indicate stimulation/enhancement; and T-bar tipped edges indicate inhibition. Agents that directly impact the selected genera link to its main node. For example, *Radiance* tells us that *Faecalibacterium* can be enhanced with arabinoglactan, whilst *Collinsella* can be inhibited by beta-sitosterol. Useful information in its own right, but we can add more to the mix: network relationships. Because we have data on interacting genera, we can also develop recommendations for agents that enhance genera exerting similar desired secondary effects on our selected microbe targets, a gambit termed *The Indirect Approach* and summarized by the strategist B.H. Liddell Hart as "The longest way round is often the shortest way home."

For example, *Collinsella* can be indirectly inhibited by fostering *Blautia* with type III resistant starch and *Bifidobactrium* by adding Jerusalem artichoke to the diet. We could possibly enhance *Akkermansia* by increasing opportunities for *Oscillospora*, but since this genus tends to inhibit *Faecalibacterium* we'd probably not want to do that.

The default results frame depicts the relational data as a directly acyclical graph (DAG). You can also view the therapy options as tabular data by ticking 'As List' for the DEPICT option, then pressing the 'Update Map' button one more time. *Radiance* then updates the screen (see Figure 3).

Looks like this exercise in eubiosis engineering might respond positively to some well-known agents and protocols.

Well, there you have it, my second *TL* column. I hope it proves helpful. Feel free play with the software. You can't break anything! Email me (peter@dadamo.com) with comments, questions, bug reports, and suggestions.

As previously mentioned, next time we'll investigate how to use a common algorithm for spam detection (Naive Bayes), along with NCBI Medical Subject Headings (MeSH) symptom data to develop a probabilistic tool (*Candidate,* an AI-powered differential diagnosis (DDx) engine).

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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

Possible Impediment of b-Amyloid-Facilitated Alzheimer's Disease Progression with Amycenone (AMY) Isolated from Mushroom

by Sensuke Konno, PhD

Introduction

Alzheimer's disease (AD) is a devastating, progressive disease, which can affect anyone who becomes older than 60 years of age.[1] In fact, AD is the most prevalent progressive neurodegenerative disease, responsible for 75% of all dementia cases today.[2] The specific causes are unknown but a physical build-up of beta-amyloid protein (bA) in the brain is believed to eventually lead to AD.[1] Such bA plaques can exert oxidative stress on synapses and neurons, subsequently leading to progressive synapse and nerve cell damage.[3,4] That also modulates signal transduction pathways (involving kinases, phosphatases etc.), resulting in neurofibrillary tangles.[5,6] These events can further lead to a deficiency of neurotransmitters, general loss of neural functions, and death of neural cells.[7] It is thus plausible that these complex cellular events will be ultimately attributed to the development of AD.

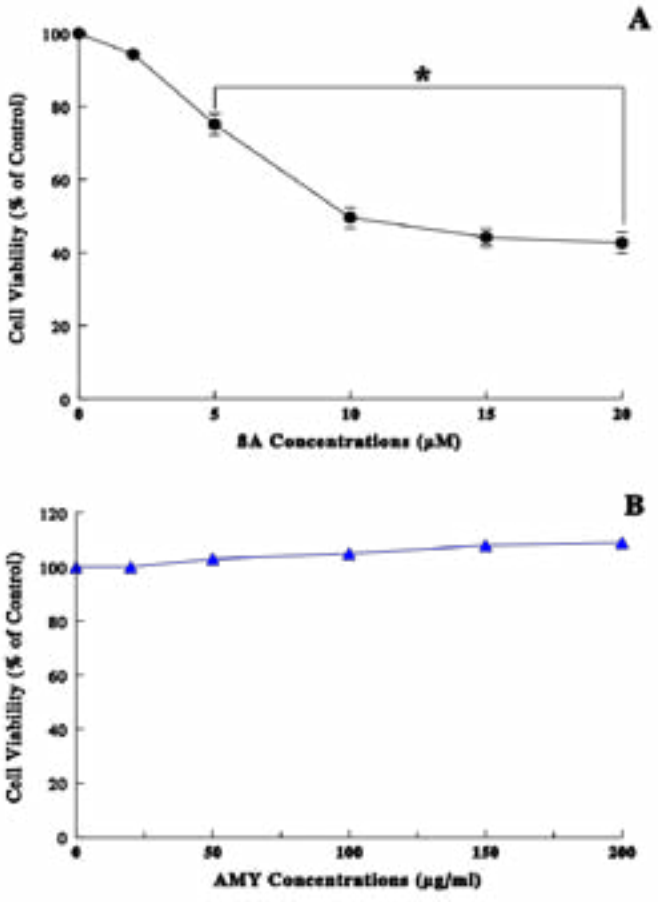
When we were searching for any compound(s) that might work for AD, we came across amycenone (AMY; Mushroom Wisdom, Inc., East Rutherford, New Jersey), a proprietary extract from a mushroom called Lion's mane or *Hericium erinaceus. H. erinaceus* has been reported to display a variety of pharmacological activities in the prevention of dementia such as AD and Parkinson's disease.[8] *H. erinaceus* extracts generally have antioxidant, antitumor, anti-inflammatory, and immunomodulatory properties;[9] more interestingly, it also displays neuroprotective properties such as facilitating nerve growth factor (NGF) expression.[10] This implies that *H. erinaceus* may have beneficial effects on neurodegenerative diseases, including AD. Hence, we were interested in studying this unique AMY to see if it would have any positive effects against AD, focusing on bA-mediated cyto/neurotoxicity *in vitro*. We hypothesize that alleviating or neutralizing such neurotoxicity at the early stage of AD may effectively impede or slow down further progression of neuronal damage, eventually reducing a risk of AD development.

Accordingly, we investigated if AMY would alleviate bA cytotoxicity and also explored the potential cytotoxic mechanism of bA. Such study was specifically carried out in terms of oxidative stress (OXS), endoplasmic reticulum stress (ERS), cell cycle, and apoptosis.

Effects of bA or AMY on Cell Viability

Neuron-like PC12 cells were employed as our *in vitro* model because they have been widely used for the similar neuronal (including AD) investigations.[11] Effects of bA or AMY on PC12 cells were assessed by cell viability test. Cells were first seeded for 24 hours and treated separately with varying concentrations of bA (bA25-35, 0-20 mM) or AMY (0-200 mg/ml) for another ➤

Figure 1. Effects of bA or AMY on PC12 cell viability. PC12 cells were separately treated with given concentrations of bA (**A**) or AMY (**B**) for 24 h and cell viability was determined by MTT assay. All data are mean ± standard deviation (SD) from three independent experiments (*p <0.05).



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24 hours; and cell viability was determined by MTT assay. bA ≥5 mM had a significant cytotoxic effect on PC12 cells and the ~50% reduction in cell viability was led with ~10 mM (i.e. IC_{50}) as shown in Figure 1A. Such a *reduction* in cell viability by bA, compared to control cells, is due to cyto/neurotoxicity of bA, resulting in loss of viable (live) cells. Hence, this 10 mM of bA was used in the rest of our study.

In contrast, AMY (0-200 mg/ml) by itself had little effect on PC12 cell viability (Figure 1B), indicating no cytotoxic or adverse effects of AMY.

Protective Effect of AMY Against bA Cytotoxicity

We next examined if AMY would protect PC12 cells from bA cytotoxicity. Cells were treated with bA (10 mM) in the presence of three different concentrations of AMY (50, 100 or 150 mg/ml) for 24 hours. As shown in Figure 2, a ~50% cell viability reduction with bA drastically declined to merely ~15% (i.e. ~85% cell viability) in the presence of AMY (150 mg/ml). Thus, these results suggest that AMY appears to effectively protect PC12 cells from bA cytotoxicity.

Diminution of bA-Exerted OXS with AMY

To address whether cytotoxicity of bA could be attributed to oxidative stress (OXS), we performed lipid peroxidation (LPO) assay[12] to assess the severity of OXS. The amount of malondialdehyde (MDA) that is formed as a by-product of OXS reflects the OXS severity: *the more MDA formed, the severer OXS*. As shown in Figure 3, compared to controls, about two-fold more MDA was formed by bA, indicating that bA exerted nearly twice the OXS formed with the control. However, AMY (100 mg/ml) was capable of diminishing such elevated OXS by ~30%, demonstrating its antioxidant activity.

Diminution of bA-Exerted Endoplasmic Reticulum Stress (ERS) with AMY

Besides OXS, another factor closely linked to AD is endoplasmic reticulum stress (ERS),[13] which could be exerted by bA. ER is a vital organelle involved in protein folding and secretion; but accumulation of unfolded/misfolded proteins in ER, due to a variety of pathophysiological insults, would lead to ERS.[13] Under ERS, the unfolded protein response (UPR) is activated to adapt cells to such a stress condition to recover homeostasis or induce apoptosis of damaged cells.[13,14] Particularly, two key factors, GRP78 and CHOP, play an important role in ERS. GRP78 is the central regulator of ERS,[15] and CHOP is a participator in the initiation of apoptotic or organ regeneration and is activated in the temporal cortex of AD brains.[16,17] Both GRP78 and CHOP have been also shown to be up-regulated under ERS.[13]

Western blot analysis (Figure 4) revealed that both GRP78 and CHOP were notably upregulated by bA, compared to those in control. However, AMY was capable of preventing the upregulation of those regulators, indicating diminution or suppression of ERS. Thus, these findings suggest that bA-exerted ERS appears to be effectively diminished with AMY.

Reversal of bA-Mediated Cell Cycle Arrest with AMY

Moreover, it was possible that bA-induced growth inhibition or cell viability reduction was due to a cell cycle arrest. Although a completion of "cell cycle" through the various cell phases is required for continuous cell proliferation, such a cell cycle

continud on page 30 ➤

Figure 2. Protective effect of AMY against bA cytotoxicity. Cells were treated with bA (10 mM) in the presence of indicated concentrations of AMY for 24 h, and cell viability was determined. All data are mean ± SD from three separate experiments (**p* <0.05).

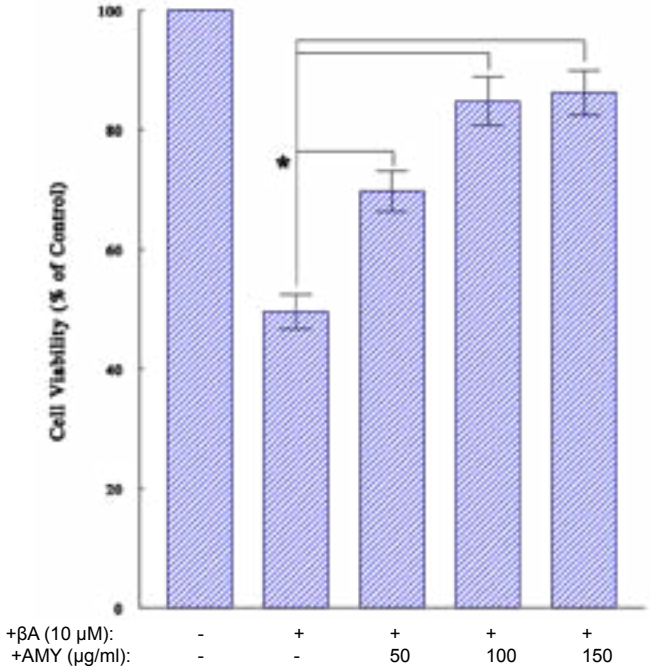
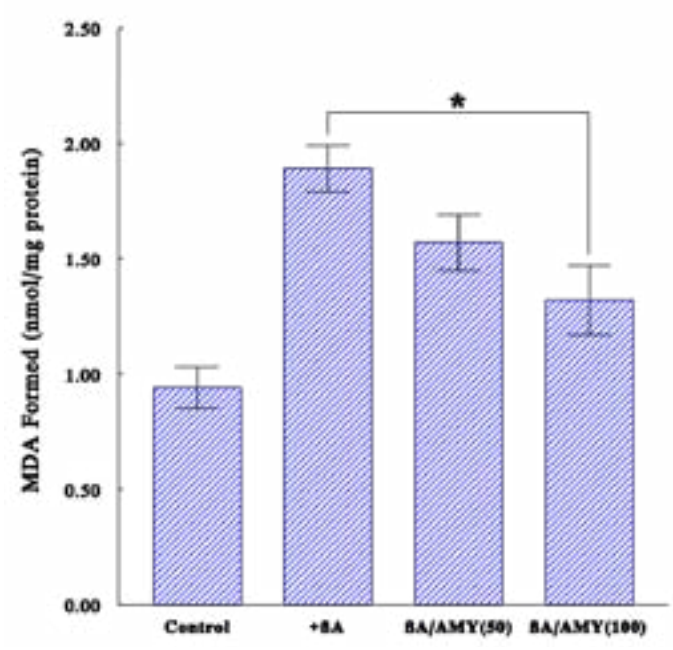


Figure 3. Severity of OXS. Cells were exposed to bA (10 mM) alone or in combination with either 50 or 100 mg/ml AMY for 6 h and subjected to LPO assay to assess severity of OXS. All data are mean ± SD from three independent experiments (**p* <0.05 compared bA alone with bA/AMY combinations).



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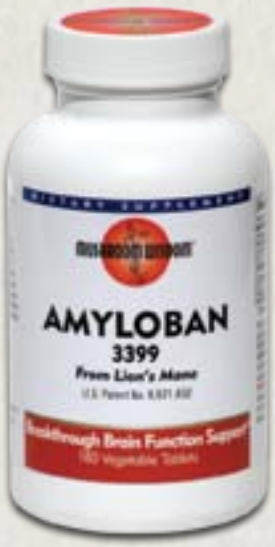

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➤ *continued from page 28*

progression to the next phase could be interrupted or blocked by certain drugs, chemicals, or biologicals.[18] As a result, the cell growth is ceased, due to an incompletion of cell cycle, leading to the cell viability reduction. As shown in Figure 5, compared to controls, the G_1-phase cell population was significantly increased while the S-phase population was decreased by bA. This accumulation of cells in the G_1 phase is known as a G_1 cell cycle arrest[18] that will subsequently lead to a growth cessation.

However, this G_1 arrest (induced by bA) was substantially *reversed* with AMY, resulting in the decreased G_1 and increased S populations. This *reversal* of G_1 arrest indicates that cells are proliferating again as the cell cycle progression has resumed.

Anti-Apoptotic Effect of AMY

Lastly, whether the cell viability reduction due to bA-induced OXS, ERS, and cell cycle arrest might ultimately result from apoptosis (programmed cell death) was examined. The status of two key apoptotic regulators, bcl-2 and Bax, was assessed by Western blot analysis. Such study (Figure 6) revealed that bA led to a down-regulation (reduced expression) of bcl-2 but an up-regulation (elevated expression) of Bax, indicating induction of apoptosis because bcl-2 is anti-apoptotic while Bax is pro-apoptotic.[19] This finding was consistent with a previous report.[20]

Nevertheless, when bA was combined with AMY, bcl-2 was up-regulated while Bax was down-regulated, indicating the *inhibition* of apoptosis. Thus, the cell viability reduction induced by bA is more likely attributed to apoptosis, but AMY appears to considerably inhibit such induction of apoptosis, demonstrating its anti-apoptotic effect.

Conclusions and Comment

Alzheimer's disease (AD) has become the fifth leading cause of death in people ≥65 years old in the US as it is a complex disease involving pathophysiological and biochemical factors.[21] The present study indeed showed that b-amyloid (bA) could exert oxidative stress (OXS) and endoplasmic stress (ERS) on neuronal cells and also induce a cell cycle (G_1) arrest and apoptosis. These findings are consistent with bA-associated pathogenesis described elsewhere.[13]

However, despite numerous studies conducted on AD, it is a fact that pathogenesis of AD has not yet been fully understood and few effective therapeutic options are currently available. We thus urgently need to establish or find the improved option to at least slow down the disease progression. It may not be fully effective, but we desperately need "something" to slow it down.

We have investigated herein one of such candidates, amycenone (AMY) isolated from a mushroom, to see if it would have positive and beneficial effects against bA-induced

Figure 4. Status of ERS. Cells were treated with bA (10 mM) alone or in combination with AMY (100 mg/ml) for 24 h, and the status of ERS was assessed by Western blot analysis. Autoradiographs of GPR78 and CHOP expressed in three experimental conditions are shown for comparison. Beta-actin is also shown as a protein loading control.

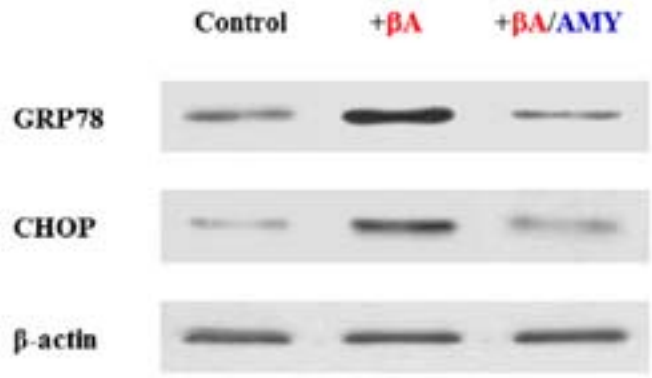


Figure 5. Cell cycle analysis. Cells were treated with bA (10 mM), AMY (100 mg/ml), or bA/AMY combination for 24 h, and cell cycle analysis was performed to determine distribution of cells in 3 different cycle phases. Only mean values (without SD) from three separate experiments are shown for a better comprehension (*p<0.05 compared with controls).

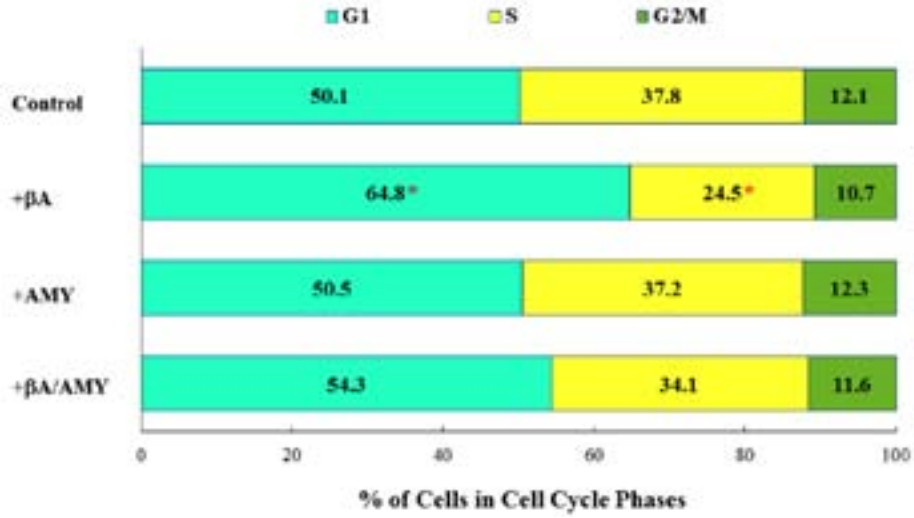
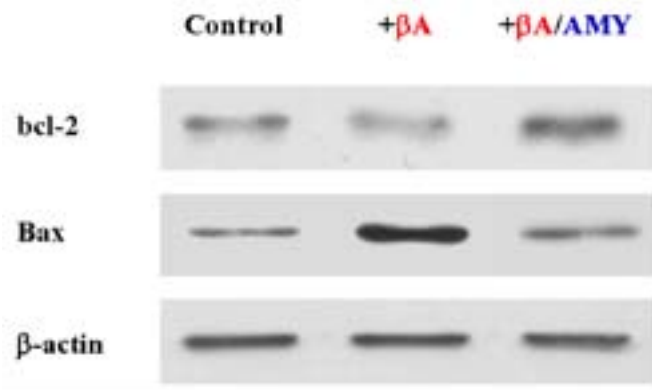


Figure 6. Anti-apoptotic effect of AMY. Cells treated with bA (10 mM), AMY (100 mg/ml), or bA/AMY combination for 24 h. Autoradiographs of bcl-2 and Bax expressed in three experimental conditions are shown following Western blot analysis. Beta-actin is a protein loading control.



cytotoxicity *in vitro*. We found that bA was indeed highly cytotoxic to neuronal cells, mediated through OXS and ERS. Cells subsequently experienced a cell cycle arrest (ceasing cell growth) and ultimately resulted in apoptosis. However, AMY was capable of effectively diminishing or preventing all these adverse effects, led by bA, to protect neuronal cells. Although it looks like an oversimplified scheme, it accounts, at least in part, for how neurodegeneration in AD takes place and how AMY may impede or slow down the bA-facilitated disease progression. We understand that this is yet the *in vitro* study and more studies are required for assessing the actual efficacy of AMY and its safety *in vivo*. Thus, the animal (mice) study is under consideration and would be carried out in the near future.

After all, AMY appears to be a promising agent against AD, and further investigations are certainly warranted for the future clinical trial.

Acknowledgement

I would like to personally thank Ms. Donna Noonan (Mushroom Wisdom, Inc.) for a generous gift of AMY and her devoted support.

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On the cover

Environment and Alzheimer's Disease

by Aristo Vojdani, PhD, MSc, CLS

Abstract: Alzheimer's disease is a chronic neurodegenerative disease that is the most common cause of dementia. Many people mistakenly believe that genetics is the sole cause of Alzheimer's, but research accumulated over the years has shown that environmental factors actually have a greater role in the development of the disorder. In this review we show that infectious agents, the toxic chemicals in our environment, even the food we eat daily, and the composition of the bacteria in our bodies can increase the risk of developing Alzheimer's disease. By their reaction with brain tissue antigens such as amyloid or tau protein, these environmental triggers or antibodies produced against them contribute to the pathophysiology of this disorder. Although statistics show that about 6,000,000 people in the US do suffer from mild cognitive impairment or the advanced stages of Alzheimer's disease, roughly 47,000,000 people may actually already be in the preclinical stage of the disease. It is important to use reliable and accurate testing such as Alzheimer's LINX™ to identify the specific triggers that are involved in the development of this disorder, so that medical practitioners can remove these triggers and implement lifestyle modifications to prevent Alzheimer's disease in the more than 50,000,000 individuals in the preclinical and early stages of the disorder.

For years, like many, I believed that genetics was the cause of Alzheimer's disease (AD) and other neurodegenerative disorders. Many times I had heard that since my mother got AD at the age of 71 that I was sure to get it as well. However, the latest research indicates that environmental factors such as certain pathogens, toxic chemicals, undigested food antigens, and alterations in gut microbiota can increase the risk of developing AD.[1-4] About 6,000,000 people in the US and more than 47,000,000 people worldwide live with AD, and by 2050 this number may exceed 120,000,000 if no effective prevention strategies are used.

AD is divided into two main categories: early and late onset. The early onset of AD occurs between the ages of 30-60 and is almost 100% due to genetics. It is due to mutation in several genes such as APP, $PSEN_1$ and $PSEN_2$ that are involved in the production of amyloid-beta. These mutations are responsible for the accumulation of amyloid plaques and neurofibrillary tangles, neuronal and synaptic loss in the brain. Only about 300,000 out of around 6,000,000 AD sufferers in the US or about five percent suffer from early onset AD. The other approximately 5,700,000 sufferers in the US are afflicted with late onset AD, which occurs after the age of 60.[5] Furthermore, according to Brookmeyer et al., in 2017, 46,700,000 Americans, who were in one of the preclinical stages of AD, may or may not develop full-blown AD, depending on their lifestyle.[6]

Based on this, the changes from normal to full-blown AD are classified into three major stages:

- First stage of AD – Preclinical (46,700,000 in the US)
- Second stage of AD – Mild cognitive impairment (2,500,000 in the US)
- Third stage of AD – AD with dementia (3,500,000 in the US)

ApoE Is Not a Gene for Alzheimer's Disease

Apolipoprotein E (ApoE) is a lipid carrier, a protein involved in the metabolism of fats in the body. ApoE has been implicated in innate immunity, inflammation, atherosclerosis, and AD.[7] There are three common ApoE alleles in the human population: E2, E3 and E4, with ApoE4 present in about 10% of the population. In late-onset AD, the apolipoprotein E4/4 (ApoE4) variant plays a significant role as the risk factor for the disease. Although not every individual positive with ApoE4/4 will get AD, overall the E4 allele is significantly enriched in patients with AD, and E4-carrying patients show heavier amyloid-β plaque load in the brain and

earlier disease onset. This is why ApoE was initially identified as an amyloid-β binding protein. Interestingly, substantial evidence has demonstrated a relationship between ApoE and amyloid-β deposition in a dosage-dependent and isoform-specific fashion, with ApoE4 the strongest and ApoE2 the least.[7] This function of ApoE is likely linked to receptors, such as the low-density lipoprotein receptor, heparin sulfate, that are expressed on the membranes of microglia cells, to which they tend to bind. In addition to ApoE binding to microglia cells, in the initiation stage of plaque formation, ApoE may participate as an opsonin to enhance the microglia-plaque interaction. It seems that the effects of ApoE isoforms on the deposition of plaques may be related not only to their capacities for mediating microglial cell activation but for opsonization as well. Similarly, ApoE may directly regulate tau pathogenesis and induce neurodegeneration. This integrated view of ApoE involvement in different stages of AD is shown in Figure 1.

Figure 1. Immunomodulatory functions of ApoE in the neurodegenerative process involved in Alzheimer's disease.

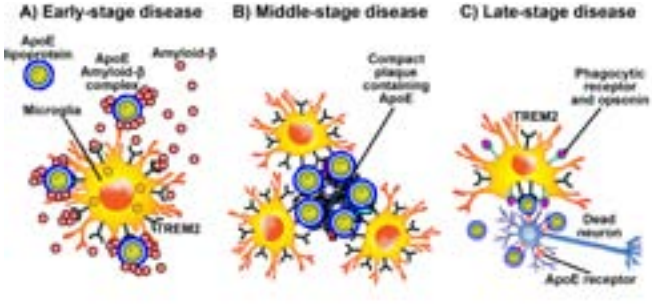

Figure 1 shows the three different stages of Alzheimer's disease: A) Early-stage disease. Apolipoprotein E (ApoE) exacerbates amyloid-β pathology during the initial amyloid-β seeding stage. This is likely partially due to a direct pro-aggregating effect of ApoE on amyloid-β through ApoE-amyloid-β interactions. In addition, ApoE may serve as an opsonin bridging microglia with amyloid-β seeds by binding to triggering receptors expressed on myeloid cells 2 (TREM2) on microglia. This may result in recruitment of more activated microglia to amyloid-β seeds that promote plaque formation. B) Middle-stage disease. During the plaque accumulation phase, disease-associated microglia surround the ApoE-containing plaque, contributing to the neurodegenerative process. C) Late-stage disease. Intracellular pathological tau accumulation and other factors result in more neuronal injury and death. ApoE, via interaction with the TREM2 receptor, may attract neurons to the microglia and may opsonize these neurons for phagoptosis first, followed by apoptosis or neuronal cell death.

It is due to this mechanistic action of ApoE that individuals with one copy of E4 may have a greater risk of developing AD by two-to-four fold, while those with two copies of E4 have their risk increase to 10-12 fold.[8] However, Alzheimer's disease only occurs in a small percentage of ApoE4/4 carriers during their lifetime because lifestyle plays a very significant role. This is according to the World Health Organization; while the rate of ApoE may not be that different from country to country, there is more than a 160-fold difference between different countries in the rate of AD. This rate of AD per 100,000 people in 20 representative countries out of 183 is shown in Table 1.

Table 1. Number of Alzheimer's cases per 100,000 in different countries, ranked

Country	Numbers	Rank	Country	Numbers	Rank
Finland	65.7	1	Germany	17	97
Turkey	51.1	3	India	15.6	124
United Kingdom	49.1	5	South Africa	13.3	133
United States	44.4	8	Austria	10.9	147
Lebanon	41	10	Costa Rica	9.9	153
Canada	22	32	Japan	7.2	158
Iraq	25	40	Russia	6.7	159
Thailand	21.8	56	Romania	4.8	164
Slovakia	20.8	64	Colombia	2.4	177
Israel	18.8	84	Singapore	0.4	183

Data extracted from World Health Organization 2017 statistics

The information in Table 1 indicates that even in an individual who is an ApoE4/4 carrier, environment and lifestyle play significant roles in the development and prevention of AD. This is why the title of this article is "Environment and Alzheimer's Disease."

The Role of Environmental Factors in Alzheimer's Disease

It has been shown that AD can be caused by various factors: genetic, environmental (infections, toxic chemicals, food antigens, etc.), head injuries, and other existing medical conditions. Its main characteristic is the breakdown of function and communication within the brain. This breakdown is caused by the buildup of neurofibrillary tangles and plaques within the brain that lead to neuronal degeneration and the brain's deterioration. These tangles and plaques contain protein remnants of environmental factors and brain proteins such as amyloid-β, tau-protein, and α-synuclein, which are generally recognized as the hallmarks of Alzheimer's and Parkinson's disease.

Infections and Alzheimer's Disease

Among the environmental factors that contribute towards Alzheimer's disease, infectious diseases have garnered the lion's share of attention.[9-11] One source of infectious pathogens is the oral microbiome, the bacteria or specific antibodies of which have been found in the brains and blood of patients with AD.[12] When compared to individuals without AD, the amount of bacteria in the brains of those suffering from AD was found to be seven times greater.[12] Elevated levels of antibodies against periodontal bacteria such as *Porphyromonas gingivalis* have also been found in the blood of AD patients. The same patients also had increased levels of the proinflammatory cytokine tumor necrosis factor alpha, a protein that affects the permeability of the blood-brain barrier; this is the vital structure that keeps harmful molecules from penetrating into the circulatory system and eventually reaching the brain.[12] In fact, periodontitis has been associated with a six-fold increase in the rate of cognitive decline in AD sufferers.[13]

Aside from the oral microbiome, the gut microbiome has also been shown to have a role in AD. The Gram-negative bacteria *Escherichia coli* and *Salmonella typhosa* have both been found in amyloid deposits.[14] Lipopolysaccharide (LPS) has been shown to interact with and help to form amyloid fibrils, producing aggregates of amyloid-β.[15]

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Additionally, infections such as *Borrelia burgdorferi, Chlamydophila pneumoniae, Cytomegalovirus* (CMV), *Helicobacter pylori*, and *Herpes simplex* virus type 1 (HSV-1) have been linked to the progression of AD and dementia.[16] Unsurprisingly, recent studies have shown that compared to healthy controls, patients with AD had a greater infectious burden, higher amyloid-β levels, and suffered from lower cognition.[17] These and other pathogens that trigger AD are summarized in references 3 and 17. The mechanisms by which these pathogens and their antigens contribute to AD pathology are yet to be fully understood. Overall, it is postulated that immune response to bacterial amyloids that lead to the production of cross-reactive antibodies, proinflammatory cytokines, immune complexes, and oxidative stress may be responsible.[18,19]

To further clarify this point, our 2018 study published in the *Journal of Alzheimer's Disease*[1] investigated whether antibodies made against amyloid-β would react both with other brain proteins as well as pathogens associated with AD as a result of molecular mimicry or the binding of bacterial toxins to amyloid-β-42 (Aβ-42). The study used a specific monoclonal antibody made against Aβ-42, which not only reacted strongly with Aβ-42, tau protein, and α-synuclein, but also had from weak to strong reactions with 25 different pathogens or their molecules, some of which have been associated with AD (see Figure 2).

Figure 2. Degree of reactivity of rabbit monoclonal anti-β-amyloid peptide 1-42 with different bacterial antigens and toxins measured by ELISA. Compared to the reaction of anti-Aβ-42 with Aβ-42 peptide as 100%, *C. jejuni* BCdT was extremely strong (98%), *E. coli* BCdT was very strong (79%), rabies was strong (53%), *C. jejuni* was moderate (33%), *C. pneumoniae* was low (13%), and any reactivity below the red line is insignificant. *Modified from Vojdani et al., J Alzheimers Dis. 2018;63:847–60.*

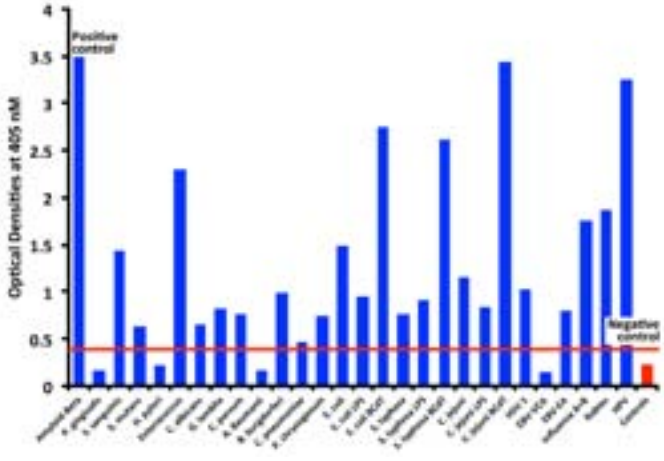


Figure 2 compares the reaction of monoclonal antibody made against amyloid-β to amyloid-β with the antibody's reaction against various infectious pathogens and their toxins. The reaction was extremely strong with HPV and the bacterial cytolethal distending toxins (BCdT) of *Campylobacter jejuni*; very strong with *E. coli* BCdT, *Salmonella typhosa* BCdT, and *Enterococcus*; strong with rabies, influenza A+B, *E. coli,* and *Streptococcus sanguinis;* moderate with *C. jejuni,* HSV-1, *B. burgdorferi, E. coli* LPS, *S. typhosa* LPS, *C. jejuni* LPS, *Giardia lamblia,* Epstein-Barr Virus early antigen, *Cryptosporidium parvum, S. typhosa, Penicillium chrysogenum, Candida albicans,* and *Streptococcus mutans;* low with *C. pneumoniae*; and insignificant with *H. pylori,* EBV-VCA, *Acenitobacter baumanii,* and *P. gingivalis.* Interestingly, the same Aβ antibody reacted not only with *E. coli, S. typhosa* and *C. jejuni* whole bacterial antigens, but also with their pure LPS and particularly with their BCdTs.

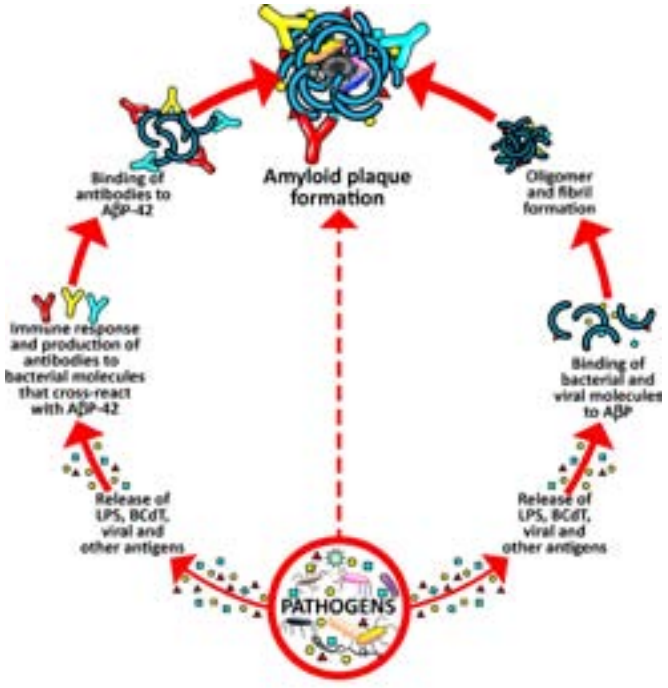
These results indicate that, due to molecular mimicry, different pathogens, their antigens, and antibodies that are produced against them in the context of breakdown of blood-brain barriers, plus inflammatory cytokines, play a significant role in plaque and tangle formation. In fact, it has been established that the GI tract epithelial and blood-brain barriers become more permeable with age. As we grow older, then. our protective barriers wear thin, and our central nervous system (CNS) becomes more vulnerable to potential neurotoxins (LPS, BCdT) generated by the resident microbes, making it easier for these pathogens or their antigens to colonize the brain.[20] Amyloid-β-peptide (AβP) is also released defensively as an anti-bacterial peptide, but in this process it may bind to LPS, BCdT or other pathogenic antigens. This leads to Aβ fibril formation, but it may also induce the production of antibodies against both amyloid peptide and bacterial toxins. The measurement of antibodies against LPS and BCdT is imperative. Simply measuring levels to bacterial toxins such as LPS is not accurate because of their short shelf-life and the fluctuations to which they are subject. The measurement of antibodies produced against them is thus more reliable. For this reason, the measurement of antibodies against LPS is included in an intestinal barrier permeability screen, and antibodies against BCdTs are included in an irritable bowel/SIBO screening through Cyrex Laboratories, LLC (see the Array 2 – Intestinal Antigenic Permeability Screen™ and Array 22 – Irritable Bowel/SIBO Screen™ respectively).

Figure 3 shows how pathogens can release toxins and other antigenic molecules that bind directly to amyloid-beta peptides (AβPs), forming small oligomers, then fibril formations that result in amyloid plaque formation. Immune response against pathogens and their antigens that have known cross-reactivity to AβP results in the production of Aβ cross-reactive antibodies. The binding of these microbe-cross-reactive antibodies to Aβ may block its anti-bacterial activity and result in AβP aggregation, which further contributes to amyloid plaque formation, the hallmark of Alzheimer's disease. Thus, one strategy for the prevention of AD is the treatment of infectious agents with all available means, especially the enterobacters that produce both LPS and BCdT toxins, as the antibodies produced against these toxins may contribute to leaky gut, leaky BBB and, eventually, amyloid plaque formation. As discussed above, reliable tests for detecting LPS and BCdT antibodies are available at Cyrex Laboratories, LLC. Additional testing for BBB permeability is also available (see the Array 20 – Blood-Brain Barrier Permeability Screen™).

Toxic Chemicals and Alzheimer's Disease

As was discussed in the earlier section, starting from the mid-1980s the role of infections in Alzheimer's disease has been well-established by hundreds of articles.[9,17] However, with the exception of a few chemicals, the role of environmental contaminants and dietary proteins in AD has been largely neglected.[19] Toxic metals

Figure 3. The direct and indirect roles of pathogens in Alzheimer's disease. *Modified from Vojdani et al., J Alzheimers Dis. 2018;63:847-860.*



such as aluminum, mercury and lead are among the few that have been relatively extensively studied; they are known to cause toxicity to the brain and other organs and have been linked to numerous neurodegenerative diseases, including AD.[21-23]

In search of a mechanism for chemical-induced autoimmune reaction, in one of our recent studies[2] we reacted antibody made against AβP-42 with many different haptenic chemicals bound to human serum albumin (HSA). We found that monoclonal anti-AβP-42 reacted from moderately to strongly with several chemicals bound to HAS (Figure 4); it did not react significantly to many other chemicals bound to HSA, nor to HSA alone. With reaction against AβP-42 as 100%, aluminum (32%), dinitrophenol (30%), protein disulfide isomerase (26%) and mercury (20%) reacted moderately with AβP-42 antibody, while phthalate reacted strongly (50%).

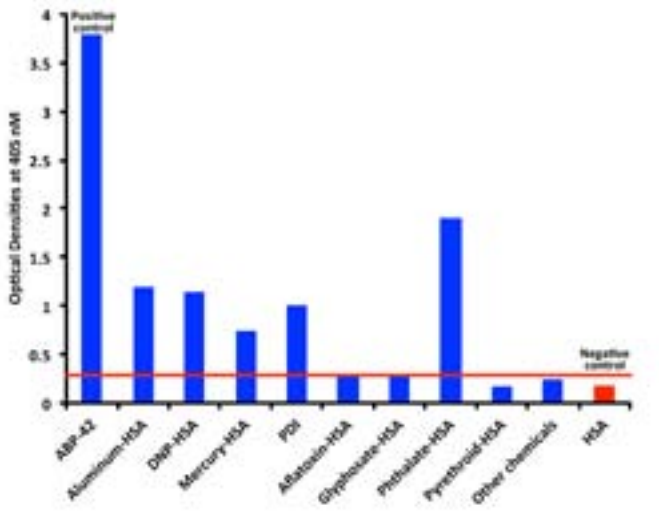
Aluminum compounds are added to a large number of commercially prepared products, such as cheese, candies, coffee whiteners and even drinking water. Its use is so common that aluminum uptake into the bloodstream begins in the womb and continues throughout an individual's lifetime.[19] Most absorbed aluminum is excreted, but some of it still manages to bind to different tissue proteins, particularly in the intestinal mucosa and the brain. The accumulated aluminum in the brain affects memory, cognition, and synaptic activity. It activates microglia and promotes the aggregation of amyloid-β and neurofilaments, which are all characteristic of neurodegenerative disorders.[24]

Phthalates are esters of phthalic acid used primarily as plasticizers to increase the flexibility, transparency, durability and longevity of plastics.[25] Using molecular modeling, the binding of phthalate plasticizers to HSA was examined *in vitro*. The interaction of phthalate with HSA was shown to have resulted in alterations in the conformational and secondary structures of HSA. It was also shown that hydrophobic sources were the main interaction for phthalates with HSA-protein.[25]

Environment and Alzheimer's

Mercury has been reported by many epidemiological and demographical studies to have a strong association with AD.[26] Autopsy studies in one review found increased levels of mercury in the brain tissues of AD patients, but not in their blood, urine, cerebrospinal fluid or hair.[26] It has been demonstrated in *in vitro* and animal studies that mercury causes tau protein phosphorylation and the increased formation of AβP aggregates. Similar structural changes in HSA molecules due to mercury binding could explain the immune reactivity between AβP-42 antibody and mercury-HSA that was detected in our study. The selectivity or specificity of certain chemicals binding to HSA and their effect on AβP aggregation is supported by the findings that the same antibody did not react with HSA alone, formaldehyde-HSA, aflatoxin-HSA, or many other chemicals used in our study (Figure 4). Based on the information presented here, the most effective measure for the prevention of AD and other neurodegenerative disorders would be the elimination of mercury, aluminum, plasticizers, and other toxic chemicals from human contact as much as possible. Although the biggest chemical culprits are listed above, there may be others playing a role in the individual patient. Additional testing for antibodies against chemicals bound to human tissues (or body burden) is available through Cyrex Laboratories, LLC (see Array 11 – Multiple Chemical Immune Reactivity Screen™).

Figure 4. Reaction of monoclonal anti-AβP-42 antibody with various chemicals bound to HSA. Note that the reaction of AβP-42 antibody with aluminum (32%), dinitrophenol or DNP (30%), protein disulfide isomerase or PDI (26%), an enzyme that is important in α-synuclein function in the brain, and mercury (20%), is moderate, but is strong with the plasticizer, phthalate (50%). Anything below the red line is insignificant. *From Vojdani et al., J Alzheimers Dis Parkinsonism, 2018;8:441.*



Food and Alzheimer's Disease

Many of the published articles about food and Alzheimer's disease are usually about proper diets for preventing or minimizing the risks of AD, such as the "Mediterranean-dash Intervention for Neurodegenerative Delay" or MIND diet.[27] However, in one of our own recent studies,[2] we investigated

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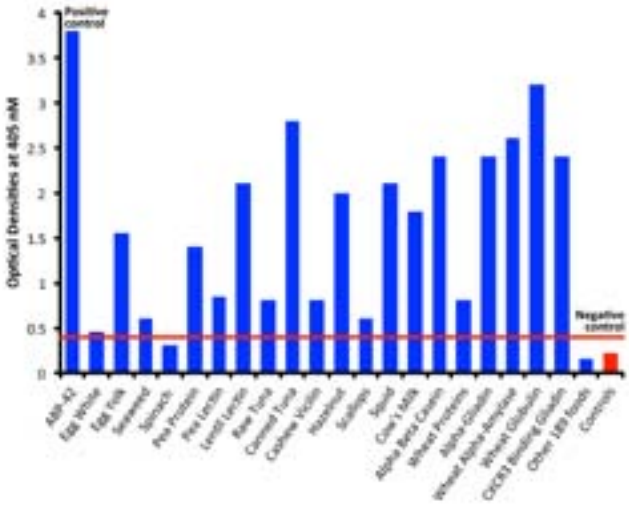
the immunoreactivity of AβP-42 antibody, one of the hallmarks of AD, with 208 different raw or heat-modified food extracts to explore the same approach we applied in our studies on the cross-reactivity between food antigens and brain proteins.[28,29] We found that 19 out of the 208 food extracts demonstrated moderate to strong immune reactivity with AβP-42 antibody (see Figure 5). Using the reaction of AβP-42 antibody with pure Aβ-42 peptide with an index of 3.8 as 100%, we obtained results ranging from egg white with an index of 0.45 (12%) to wheat globulin with an index of 3.2 (84%). This means that, in the real world, if the egg white antibody should cross the BBB, it may react with AβP-42 by 12%, and wheat globulin antibody may react by 84%. This shows that certain foods may cross-react with neuronal cell antigens, which we have already demonstrated in our own past articles, and which other studies have touched on as well. Wheat peptide has been shown to share significant homology with cerebellar tissue and synapsin,[30-32] casein and butyrophilin, myelin basic protein, and myelin oligodendrocyte glycoprotein.[33] Plant aquaporins from tomato, spinach, corn and soy have been shown to share up to 70% homology with human aquaporin proteins expressed in astrocytic foot processes.[34,35] The demonstrated homology indicates that these foods may be associated with gluten ataxia,[36] multiple sclerosis,[35] and neuromyelitis optica.[34]

Next to wheat globulin, the most reactive food with anti-AβP-42 was canned tuna (74%), but raw tuna did not react as significantly (21%). We repeated the experiment with the tuna three times, beginning with the tuna in the can to protein extraction all the way to ELISA assay, performing all in quadruplicates. With less than 20% variation in ELISA ODs, all three canned tuna preparations gave strong reactions (a mean OD of 2.8 ± 0.36, or 74%) with AβP-42 antibody. With raw tuna, the result was OD 0.80 ± 0.13, or 21% (Figure 5). As opposed to actual raw tuna, canned tuna, of course, goes through many modifications as it is processed. The mercury in the tuna, and possibly the aluminum and plasticizers used in the can, may have changed the molecular structure of one or more tuna proteins, resulting in a strong reaction with the AβP-42 antibody. Kawahara has shown that aluminum is an excellent cross-linker of proteins through three different metal-binding amino acids, namely, arginine, thyrosine, and histidine.[37]

In our earlier research, we already investigated the possible difference in reactivity between raw and processed/modified/cooked foods.[38] Using ELISA as the gold standard to detect IgG, IgA, IgM and IgE antibodies against different raw and modified foods, we showed that certain foods after cooking and processing do undergo some kind of structural change and become more antigenic, so that an individual may react to the cooked or modified food extract, but not to the raw version of the same food. The proteins of canned tuna have been cooked and additionally are exposed to the chemicals involved in canning; therefore, we believe that this enhanced immune reactivity of processed tuna with AβP-42 antibody is the result of the combined effects of aluminum, plasticizer, mercury, and perhaps other chemicals, compounded by the processes of cooking. These may have changed the protein molecular structure of the canned tuna, making it more easily recognized by the AβP-42 antibody.[2] This means that measurement of IgG, IgA or IgE antibodies against commercially available raw food antigens is simply not good enough for cross-reactivity studies or even for the detection of food allergies as currently performed in many laboratories. This is what makes Cyrex' Array 10, the most comprehensive real-world food immune reactivity test available, so unique. For more information on this matter, you may consult the Cyrex Array 10 Clinical Application Guide or the author's most recently published book.[39]

We have already mentioned earlier in this section that some foods have been associated with certain disorders, including autoimmune diseases.[34-36] The reaction between food antigens and the immune system leading to autoimmunity is the subject of our aforementioned book.[39] This interesting subject, in fact, is considered a new field of study and has been given the name "immunodietica" in a very recent article published in the *Journal of Translational Immunology*,[40] which set the stage for an infusion of greater interest in the impact of diet on the pathogenesis and progression of autoimmune diseases.

Figure 5. Reaction of monoclonal anti-AβP-42 antibody with various food antigens. Results ranged from egg white (low, 12%) to wheat globulin (extremely high, 84%). The canned tuna was much more reactive (OD 2.80, 74%) than the raw tuna (OD 0.80, 21%). All results below the red line were insignificant *From Vojdani et al., J Alzheimers Dis Parkinsonism, 2018;8:441.*



Toxic chemicals or their metabolites bind to different tissue proteins, such as albumin or hemoglobin, changing their tertiary structures so that they resemble that of amyloid precursor protein (APP). Immune response against these chemical-tissue protein complexes results in antibodies cross-reactive to AβP-42, which contribute to Aβ plaque formation. The toxic chemicals can directly affect the brain, or form neo-antigens, inducing the production of antibodies against the chemicals that bind to tissue proteins. If the tissue protein is amyloid-β, then the chemical or antibody binding can result first in the misfolding of the Aβ-42 peptide, then in amyloid fibril formation. For their part, the food antibodies that penetrate the BBB can cross-react with AβP-42, and, like the chemicals, can also bind to an AβP-42 monomer, resulting likewise in the misfolding of the Aβ-42 peptide and further contributing to amyloid fibril formation. Furthermore,

continued on page 38 ➤

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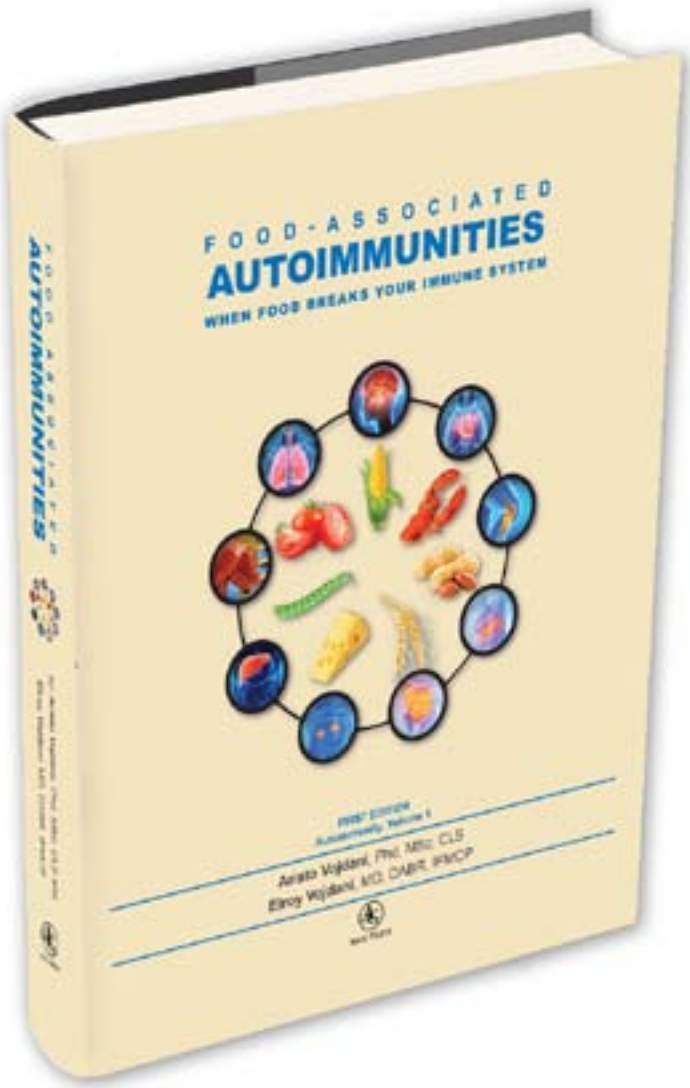


The original inventor of food IgG testing breaks decades of silence regarding the prevalence of innacurate food testing and reporting in many laboratories.

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.

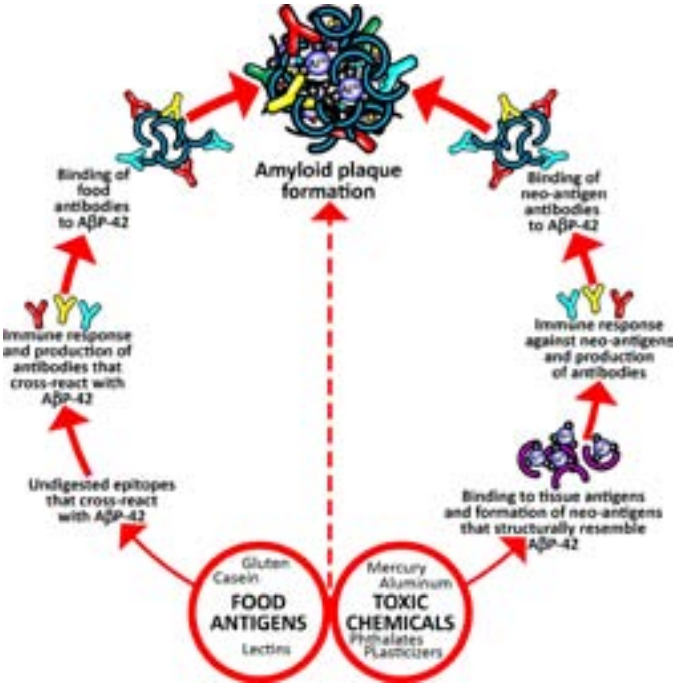
The growing scientific interest in the interaction between diet and autoimmune disorders has created the new field called immunodietica, which is the subject of this book.

Environment and Alzheimer's

➤ *continued from page 36*

immune reaction against the undigested peptides of these foods (gluten, casein, lectin, many cooked food components) can result in the production of antibodies that trigger friendly fire attacking amyloid-β peptides and other brain proteins (see Figure 6). This, in conjunction with the formation of immune complexes, the release of cytokines, activation of the complement cascade, and other inflammatory factors promotes the aggregation of the senile plaques that are characteristic of Alzheimer's disease.

Figure 6. Contribution of toxic chemicals and food antigens to amyloid plaque formation via two different mechanisms. *Modified from Vojdani et al., J Alzheimers Dis Parkinsonism. 2018;8:441.*



Based on the results of our studies and the existing accumulated lore, it is possible to hypothesize a mechanism that takes into account the effects of toxic chemicals, the binding of pathogens with brain amyloids, the molecular mimicry and the ability of certain food antibodies to cross-react with AβP-42, and integrate these factors into the amyloidogenesis that is the hallmark of AD. The key to understanding this antibody immune reactivity is the blood-brain barrier (BBB).

The BBB is the all-important structure that prevents infectious agents, undigested food molecules, and toxic chemicals from gaining access to the circulatory system, and from thence into the brain. A number of various types of brain-reactive autoantibodies have also been shown to be ubiquitous in the serum of both healthy humans and patients with AD, although the levels are noticeably higher in AD patients.[41] In a person with an intact BBB all of these molecules may safely stay on their side of the wall, so to speak. But there are any number of events or conditions that can render the BBB more permeable, and a compromised BBB may then allow all these unwanted molecules to reach the neurons within the brain tissue (see Figure 7).[41,42]

Figure 7. The fortress of the brain is guarded by astrocyte warriors, preventing the entry of unwanted molecules into the brain.

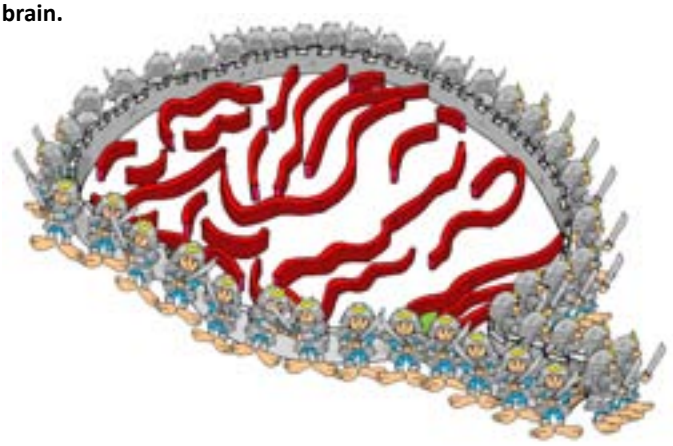
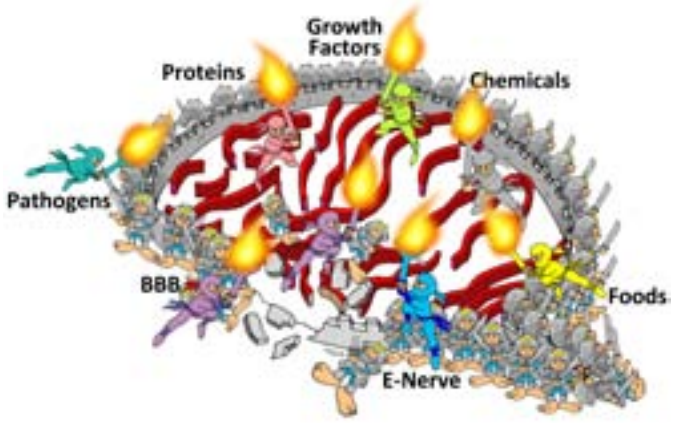


Figure 8. Assault on the fortress of the brain. There are many environmental factors that can facilitate the entry of unwanted molecules into the brain like a swarm of ninjas; if they breach the defenses and reach the brain tissues, they can set fire to the neurons and unleash the conflagration of inflammation, possibly leading to neurodegeneration.



We believe that the information presented here shows enough indications for immunoreactivity between infectious agents, food proteins, toxic chemicals, and AβP-42 cross-reactive autoantibodies in conjunction with a compromised BBB as having a role in the pathogenesis of Alzheimer's disease. We may conclude that for early detection of the risks associated with AD and other neurodegenerative disorders, environmental triggers together with brain proteins (amyloids, tau, α-synuclein, neurofilaments, BBB proteins) should be necessary components of blood tests for Alzheimer's. Accurate testing can show if a person has been exposed to these environmental factors, and if antibodies produced against them are reacting with amyloid-β or other neural tissues. This kind of reliable information can help us to prevent AD or its progression if we catch it early enough. We need to get to the cause of cognitive decline and fix any imbalances before the situation becomes irreversible. Therefore, it is necessary to identify and remove the triggering factors that are causing the brain's defenses to malfunction and produce a harmful instead of a protective amyloid response. The necessary actions can be summarized in these three steps:

1. Identify and remove the triggers.
2. Remove the amyloid clusters.
3. Rebuild the synapses destroyed by the disease.

Thus, the first step is to identify and remove the triggers of AD, such as pathogens, toxic chemicals, food antigens that cross-react with AβP-42, tau protein, α-synuclein, and other brain proteins.[1,2] These may be divided into the following categories:

- Brain proteins and peptides involved in AD;
- Growth factors involved in neuronal regeneration;
- Enteric nerve, enzymes and intestinal peptides;
- Gut microbiome, oral pathogens, and other organisms that are known to cross-react with proteins involved with AD;
- Toxic chemicals that induce modification of brain proteins;
- Specific raw and cooked or modified food that cross-reacts with brain proteins; and
- Blood-brain barrier proteins.

These blood-based biomarkers are available as the Alzheimer's LINX™ panel from Cyrex Labs LLC. They can help practitioners to identify and remove specific environmental triggers and decrease or halt the immune system's production of antibodies that contribute to the formation of amyloid plaques and tau tangles. This removal of triggers, coupled with maintaining the health and integrity of the BBB, can reduce the risk of autoimmune reactivity and development of AD in the approximately 50,000,000 Americans who are in the preclinical or mild cognitive impairment stages of Alzheimer's disease.

In fact, a lifestyle modification program based on the identification of such triggers was already demonstrated by Bredesen et al. in two different studies on 110 different patients.[43,44] Dr. Bredesen's protocol uses a comprehensive, precision medicine approach that involves determining the potential contributors to Alzheimer's cognitive decline (such as activation of the innate immune system by pathogens, change in intestinal permeability, exposure to toxins, or other contributors) using a computer-based algorithm to determine subtype, and then addressing each contributor or trigger with a personalized, targeted, multi-factorial approach dubbed ReCODE (Reversal of COgnitive DEcline). This lifestyle modification approach for AD is in line with the May 2019 WHO guidelines for "Risk reduction of cognitive decline and dementia."[45]

We believe, whole-heartedly, that testing at-risk individuals before the onset of disease is the first step in combating cognitive decline. Using the personalized information obtained from the results of an accurate and reliable Alzheimer blood test panel such as Alzheimer's LINX™ and following WHO recommendations will help many individuals, especially those in the preclinical stages of Alzheimer's disease.

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Pathways to Healing

by Elaine Zablocki

The Hidden Power to Heal

This week I've been reading a book by Wayne Jonas, MD, that looks at health and healing from an unfamiliar angle. *How Healing Works: Get Well and Stay Well Using Your Hidden Power to Heal* challenges us to look at human beings as whole systems, including the physical body, social and emotional connections, thoughts and intentions. "Whole systems science showed us that a person is an ecosystem – more like a garden to be cultivated than a car to be fixed," he writes. "In systems science, the safest and greatest effects occur when the whole person is nudged towards a meaning response, using the universal need to maintain dynamic stability as the healing force....We strengthen our network links and stimulate our own healing capacity in nonspecific ways to achieve a deeper and more lasting healing."

Jonas was the director of the NIH Office of Alternative Medicine and the director of the World Health Organization Center for Traditional Medicine. From 2001 to 2016 he was the president and chief executive officer of the Samueli Institute, a nonprofit research organization.

In this book, he discusses general principles and then describes specific cases showing how these ideas play out in the lives of individuals. For example, a Mexican woman diagnosed with diabetes refused insulin treatment and decided to put herself on a strict diet. She lost weight and her blood sugar levels improved, but she lost her role as a provider of tasty food for her family. She found a long-term solution when she adapted favorite recipes to provide a healthy diet that also met social needs.

In another case, Bill was coping with severe back pain. Several conservative treatments hadn't helped, and he opted for surgery. It worked – but after nine months the pain returned. At this point he began working with Jonas to find a combination of processes that would sustain self-healing. He kept a journal and uncovered traumas from his childhood that were sabotaging his efforts. "I stopped seeking a single fix," he told Jonas. "When I decided to find out what I needed for a better life in general, that is the moment I began to really heal from my pain."

The Headlines Missed the Real News

You may recall seeing headlines about an NIH study that showed St. John's wort wasn't effective for depression. Jonas helped design that study, and in a chapter called "How Science Misses Healing," he tells us about the hidden maneuvering that led to this study, and the results no one noticed.

The study compared Zoloft, St. John's wort, and placebo. It was carefully designed to use the right doses, appropriate patients, and proper blinding so no one knew who was getting which substance. The study found all three groups got better at the same rate, and the herb and the placebo had fewer side effects. "Sales of the herb dropped further," Jonas writes. "What few people picked up on, however, was that the proven drug had also not worked any better than placebo. This was the most important finding of the study, and it was totally missed."

The St. John's wort story is just one example of a general issue. Our current research develops medications with one intended effect, to cure one specific problem. "Proven treatments that target specific molecular pathways and so create their intended effect usually also have effects on unintended targets, producing unwanted side effects," Jonas writes. "These unwanted effects frequently impact 50% to 70% of those who take them, including when the treatment did not work. In short: in complex systems like the human body, specific treatments have a higher probability of causing harm rather than good."

Practical Knowledge in Usable Chunks

Nowadays Jonas serves as the executive director of Samueli Integrative Health Programs, an effort to empower patients and physicians with solutions to enhance health and prevent disease. Through his book, his website (drwaynejonas.com) and speeches, Jonas shares practical ideas directly with consumers and practitioners.

His website offers an array of practical information for consumers and practitioners in well-defined, usable formats. Look for the Resources/Tools button to download pocket guides on breathwork, Mediterranean diet, coping with depression, moving meditation, and many other topics. "A Guide to Optimizing Treatment Through Integrative Health for People Living with Pain" offers tips on how to navigate the healthcare system.

One of the best downloads on the website is the "Guide to Nutrition for Chronic Pain." This 35-page booklet summarizes nutritional information in clear language, with pages on foods that can reduce inflammation, limit the need for medications, and improve a person's mood.

Another valuable resource is the "Guide to Developing an Integrative Health Model." It is designed to help MDs understand the benefits of therapeutic yoga, acupuncture, chiropractic, nutritional counseling and other modalities. For each of these options, the guide offers a summary of scientific research, how to find a qualified practitioner, which patients could benefit, and insurance information. It is a useful resource for MDs who want to expand referrals to alternative practitioners but need additional authoritative information to get started.

Wayne Jonas, MD

A Gap Between Two Systems

In his book, Jonas describes two very different healthcare systems we all experience today. One focuses on acute problems such as injuries and heart attacks. One focuses on prevention and health promotion through vaccinations, sanitation, lifestyle changes, and similar methods. "The two systems operate in virtual isolation from each other, as if they were in separate buildings," Jonas writes. "Once you have been labeled with a disease and have crossed the diagnostic threshold to enter the world of acute care, an entire industry awaits you. It's an industry that thinks in terms of single causes for disease, applies narrow remedies, and ignores the importance of nutrition, social support, and a healing environment."

He offers suggestions for ways each of us can support our own innate healing abilities. "The first step in creating a personal environment that promotes healing behavior is awareness of this gap and exploring ways to fill it in your life," he writes. "If you find yourself crossing the diagnostic threshold into the acute care system, you can ask your doctor to help you bridge the gap between prevention and treatment....armed with this information, you can then find lifestyle changes that will prevent future problems."

Every chapter of this book is filled with new information that can help us all find ways to enhance our health and cope with a dysfunctional healthcare system. It includes examples of what it could be like if our healthcare system aimed at supporting health rather than curing disease. This is a book to read slowly.

Resources

How Healing Works: Get Well and Stay Well Using Your Hidden Power to Heal by Wayne Jonas, MD.

Website: http://drwaynejonas.com/

Elaine Zablocki is the former editor of CHRF News Files.

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Literature Review & Commentary

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

Can Diet Help Prevent Age-Related Cognitive Decline?

The association between long-term intake of vegetables and fruits and late-life subjective cognitive function (SCF) was examined in a prospective cohort study of 27,842 male healthcare professionals (aged 40-75 years; mean age, 51 years at baseline in 1986). Average dietary intake was calculated from food frequency questionnaires collected every four years until 2002. SCF was assessed twice (2008 and 2012) using a six-item questionnaire, and the average of the two scores was categorized as good, moderate, or poor. Higher intakes of total vegetables, total fruits, and fruit juice were each significantly associated with lower odds of having moderate or poor SCF, after adjustment for major non-dietary factors and total energy intake. The association with total fruit intake was weaker after further adjustment for major dietary factors. In this model, the multivariate odds ratio for vegetable intake (top vs. bottom quintile) was 0.83 for moderate SCF (p for trend < 0.001) and 0.66 for poor SCF (p for trend < 0.001). For orange juice, compared with less than one serving per month, daily consumption was associated with a lower odds of poor SCF (0.53; p for trend < 0.001).

Comment: In this study, higher consumption of vegetables, orange juice, and possibly total fruit were each associated with a lower risk of age-related cognitive decline. While observational studies cannot prove causation, a number of nutrients found in vegetables and fruits (such as magnesium and B vitamins) are known to play an important role in cognitive function. In addition, fruits and vegetables contain abundant amounts of beta-carotene. In a randomized controlled trial, supplementation with 50 mg of beta-carotene every other day for 18 years slowed the rate of age-related cognitive decline, compared with placebo, in middle-aged and elderly male physicians.[1] That amount of beta-carotene can be readily obtained by consuming a diet high in vegetables and fruits.

Yuan C, et al. Long-term intake of vegetables and fruits and subjective cognitive function in US men. *Neurology*. 2019;92:e63-e75.

Is Thiamine Useful for Essential Tremor?

Two patients (aged 73 and 75 years, respectively) with essential tremor and a normal plasma thiamine concentration experienced rapid and marked improvement after beginning treatment with thiamine at a dose of 100 mg intramuscularly twice a week. At the time this report was written, thiamine treatment had been continued for approximately three years, and the improvements were maintained.

Comment: Essential tremor (also called benign tremor or familial tremor) is a slowly progressive disorder characterized by a tremor of the upper extremities and occasionally other parts of the body. A tremor is considered essential if is not associated with known causes such as Parkinson's disease, vitamin B_{12} deficiency, hyperthyroidism, stroke, use of certain medications, or consumption of (or withdrawal from) alcohol. Essential tremor is inherited in some cases and occurs randomly in other cases.[2]

The doctor who wrote this report has also reported that high-dose thiamine (given orally or intramuscularly) is beneficial for a wide range of other neurological conditions, including Parkinson's disease, spinocerebellar ataxia type 2, Friedreich's ataxia, myotonic dystrophy, fibromyalgia, and fatigue associated with multiple sclerosis or following a stroke. The patients who improved did not typically have thiamine deficiency before receiving high-dose thiamine. There has

been no confirmation from other investigators with regard to most of these clinical observations. Follow-up studies by other research groups would therefore be welcomed.

Costantini A. High-dose thiamine and essential tremor. *BMJ Case Rep*. 2018;2018:bcr-2017-223945.

Docosahexaenoic Acid for Attention-Deficit/Hyperactivity Disorder

Fifty children (aged 7-14 years) with attention-deficit/hyperactivity disorder (ADHD) who were not taking psychotropic medication were randomly assigned to receive, in double-blind fashion, 500 mg per day of docosahexaenoic acid (DHA) from an algal source or placebo for six months. The primary outcome measure was the change in the ADHD rating scale IV Parent Version-Investigator (ADHD-RS-IV) after four and six months. There was no significant difference between groups with respect to the primary outcome measure. With regard to secondary outcome measures, compared with placebo, there were small but statistically significant positive effects of DHA on psychosocial functioning, emotional problems, and focused attention. No significant side effects were reported.

Comment: Studies on the effect of omega-3 fatty acids (eicosapentaenoic acid [EPA], DHA, or both) in children with ADHD have produced conflicting results. A meta-analysis of 10 randomized controlled trials found that omega-3 fatty acid supplementation resulted in a small but statistically significant improvement of ADHD symptoms.[3] The effect of such treatment presumably depends both on the patient's habitual intake of omega-3 fatty acids (from fish and other sources) and on individual differences in fatty acid metabolism. One study in which the combination of EPA and DHA was ineffective was conducted in Japan, where fish consumption is high and children were probably already consuming abundant amounts of omega-3 fatty acids.[4] The available evidence suggests that supplementation with DHA or the combination of EPA and DHA may provide modest benefits in children with ADHD, particularly those with low dietary intake of omega-3 fatty acids.

Crippa A, et al. Behavioral and cognitive effects of docosahexaenoic acid in drug-naive children with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled clinical trial. *Eur Child Adolesc Psychiatry*. 2019;28::571-583.

High-Dose Methylcobalamin for Amyotrophic Lateral Sclerosis

Three hundred seventy-three patients with definite or probable amyotrophic lateral sclerosis (ALS), with disease duration of 36 months or less were randomly assigned to receive placebo or 25 or 50 mg of methylcobalamin intramuscularly twice a week for 3.5 years. The study was apparently single-blind, and the injections were given in such a way that the patients and their caregivers could not see the red color of the active treatment. The primary endpoints were the time to the composite outcome of death or full ventilation support, and changes in the Revised ALS Functional Rating Scale (ALSFRS-R) score from baseline to the end of the trial. Two hundred sixty patients completed the trial. There was a nonsignificant trend toward a beneficial effect of both doses of methylcobalamin for each of the two primary endpoints. In post hoc analysis, when considering only those patients who had been diagnosed early (i.e., they entered the study 12 months or less after the onset of symptoms), methylcobalamin-treated patients had a longer median time to the primary event ($p < 0.025$) and less decrease in the median ALSFRS-R score ($p < 0.025$), compared with those who received placebo. No significant adverse effects were observed.

Comment: These results suggest that high-dose vitamin B_{12} in the form of methylcobalamin may prolong survival and slow disease progression in patients in the early stages (but not the later stages) of amyotrophic lateral sclerosis. The mechanism of action is not known, although vitamin B_{12} is known to play an important role in the functioning of the brain and central nervous system.

Kaji R, et al. Ultra-high-dose methylcobalamin in amyotrophic lateral sclerosis: a long-term phase II/III randomised controlled study. *J Neurol Neurosurg Psychiatry*. 2019;90:451-457.

N-Acetylcysteine and Bipolar Disorder

Eighty patients with bipolar disorder (type I or II) with a current depressive episode lasting at least four weeks, who were being treated with antidepressants, antipsychotics, and/or other psychotropic medication were randomly assigned to receive, in double-blind fashion, 1.5 g of N-acetylcysteine (NAC) twice a day or placebo for 20 weeks. The primary outcome measure was the change in the Montgomery Asberg Depression Rating Scale (MADRS) score over the 20-week treatment period. The mean MADRS score at baseline was 30.1 and 28.8 in the NAC and placebo groups, respectively. The mean decrease in the MADRS score at 20 weeks was 13.8 in the NAC group and 13.2 in the placebo group ($p = 0.88$ for the difference in the change between groups).

Comment: This study failed to confirm the results of a previous trial conducted by the same research group, in which NAC given as an adjunct to conventional medication improved symptoms of depression in patients with bipolar disorder.[5]

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The conflicting results might be explainable at least in part by the large placebo response in the present study. In the earlier study, the MADRS score decreased in the placebo group by 21%, as compared with a 55.6% decrease in the present study. A large placebo response in the new study may have made it difficult for the active treatment to demonstrate efficacy.

Ellegaard PK, et al. The efficacy of adjunctive N-acetylcysteine in acute bipolar depression: A randomized placebo-controlled study. *J Affect Disord*. 2019;245:1043-1051.

Acetyl-L-Carnitine for Dementia Associated with Cerebrovascular Disease

Fifty-six Korean patients (mean age, 73 years) with dementia associated with cerebrovascular disease were randomly assigned to receive, in double-blind fashion, 500 mg of acetyl-L-carnitine (ALC) three times per day or placebo for 28 weeks. The primary outcome measure was the Korean version of Montreal Cognitive Assessment (MoCA-K). The mean MoCA-K score increased (improved) from 17.3 to 17.6 in the ALC group and decreased from 16.7 to 15.9 in the placebo group ($p = 0.01$ for the difference in the change between groups). ALC was well tolerated.

Comment: ALC is structurally similar to acetylcholine and functions as a cholinergic neurotransmitter. In addition, as a source of L-carnitine, ALC may help prevent the decline in brain mitochondrial function that typically occurs with age. In studies in rodents, ALC counteracted the age-related decrease of several receptors in the central nervous system. In randomized controlled trials, administration of ALC in doses of 1.5 g to 3.0 g per day for periods of six weeks to 12 months improved various measures of cognitive function in elderly people with mild-to-moderate age-related cognitive decline.[6] ALC has also been reported in double-blind trials to slow the deterioration of mental function in patients with Alzheimer's disease.[7-9] The results of the present study indicate that ALC can also prevent the progression of dementia associated with cerebrovascular disease.

Yang Y, et al. A multicenter, randomized, double-blind, placebo-controlled clinical trial for efficacy of acetyl-L-carnitine in patients with dementia associated with cerebrovascular disease. *Dement Neurocogn Disord*. 2018;17:1-10.

Acetyl-L-Carnitine for Carpal Tunnel Syndrome

Eighty-two patients with carpal tunnel syndrome of mild-to-moderate severity in a total of 120 hands received acetyl-L-carnitine (ALC) for 120 days (500 mg twice a day intramuscularly for 10 days followed by the same dose orally for 110 days). Seventy-three patients completed the trial. Compared with baseline, a significant improvement was seen in the mean sensory conduction velocity of the median nerve and in symptoms as assessed by the Boston Carpal Tunnel Questionnaire ($p < 0.0001$ for each). A significant improvement was also seen in nine measures of pain as assessed by the Neuropathic Pain Symptom Inventory ($p < 0.0001$).

Comment: ALC is known to exert a neuroprotective effect in patients with various types of peripheral neuropathy. ALC has also been shown in animal studies to have an anti-nociceptive effect (i.e., it blocks the perception of pain by sensory neurons). In the present study, treatment with ALC was associated with both subjective and objective improvement in patients with carpal tunnel syndrome. Controlled trials are needed to rule out the possibility of a placebo effect.

Cruccu G, et al. L-Acetyl-carnitine in patients with carpal tunnel syndrome: effects on nerve protection, hand function and pain. *CNS Drugs*. 2017;31:1103-1111.

Coenzyme Q10 for Nephrotic Syndrome

A four-year-old girl was diagnosed with glomerulopathy (proteinuria with hypercholesterolemia) at two years of age. Treatment with glucocorticoids produced no improvement, and subsequent treatment with cyclosporine A resulted in only partial remission. She was found to have a mutation in a coenzyme Q complex gene (a CoQ6 defect). Previously described patients with this mutation typically had sensorineural deafness and various neurologic abnormalities in addition to progressive steroid-resistant nephrotic syndrome, and almost half of them died in early childhood. This patient in this report did not have any of those manifestations. She was treated with coenzyme Q10 at a dose of 30 mg per kg of body weight per day. Within one month she was in complete remission, which enabled reduction and discontinuation of cyclosporine A over a three-month period.

Comment: Mutations of various CoQ genes are associated with steroid-resistant nephrotic syndrome, with or without neurologic or other manifestations. The dramatic response to coenzyme Q10 in the present report raises the possibility that other patients with steroid-resistant nephrotic syndrome have an unrecognized defect of a CoQ gene. The authors of this report suggested that practitioners should consider genetic testing and/or an empirical trial of coenzyme Q10 supplementation in all patients with steroid-resistant nephrotic syndrome, regardless of whether or not they have other manifestations of a defective CoQ gene.

Stanczyk M, et al. CoQ10-related sustained remission of proteinuria in a child with COQ6 glomerulopathy - a case report. *Pediatr Nephrol*. 2018;33:2383-2387.

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Childhood Nature Exposure Predicts Adult Mental Health

by Kurt Beil, ND, LAc, MPH

There is an old adage in medicine about whether health conditions are the result of "nature" or "nurture." However, a recent pair of unrelated recent studies is leading researchers to ask "what if nature *causes* nurture?" In particular, what if exposure to nature as a child impacts health (specifically, mental health) as an adult?

Childhood Nature Exposure

In one of the studies, published in the *Proceedings of the National Academy of Sciences*,[1] researchers at Aarhus University in Denmark accessed Danish census database and found all people born between 1985 and 2003 that lived in Denmark until at least the age of ten years. For each of these almost one million people (n=943,027) an assessment was made of the amount of green space (GS) in an approximately 100-yard radius around their home for each year of life age 0-10 years, using satellite data that measures vegetation density. This GS data was categorized into 10 deciles from least- to most-green, and these deciles were the basic units of analysis for the study.

Researchers then reviewed records from the Danish Psychiatric Central Research Register (PCRP) to assess any psychiatric diagnoses (both in-patient and out-patient) that study individuals had received since reaching adolescence. The list of assessed mental disorders was taken from the International Classification of Diseases (ICD-8 and ICD-10) and included substance abuse, schizophrenia, schizoaffective disorder, mood disorders (including bipolar disorders and depressive disorders), neurotic stress-related and somatic disorders (including obsessive-compulsive disorder), eating disorders (including anorexia nervosa), and personality disorders (including borderline type).

For each person in the study (remember, that is all people born in Denmark between 1985 and 2003, living there until the age of 10), their childhood GS deciles were compared to prevalence of psychiatric diagnoses as an adolescent and/or adult. In order to rule out potential confounders, the data analyses adjusted for factors known to also influence mental health, such as urbanization (i.e. population density), household socioeconomic status, family history of mental illness, year of birth, and parental age at time of birth.

In the other study,[2] conducted across four diverse cities in Europe, adult participants (n=3,585) completed a survey assessing the frequency of their childhood nature experiences and compared these results to those from a standardized questionnaire commonly used in mental health assessments (SF-36). Current adult residential green space was determined by similar satellite methods, as in the Danish study, to see if this was an influencing factor.

The question of interest in both of these studies was "Does the amount of green space exposure in the childhood impact mental health as an adult?"

Results

Results from both of these studies provided a very robust answer: Yes. In the Danish study, on average the amount of GS around the child's home accounted for 27% of the likelihood that a person as an adult has had a diagnosis of mental illness (See Table 1). The more green the surroundings as a child, the less likely that they have mental illness later in life. Conversely, being raised in an area with very little childhood GS produced the greatest risk of having some type of mental illness in adulthood. Across the different diagnosis categories measured, risks varied from 12% for borderline personality disorder to 37% for substance abuse disorder. Common diagnoses such as depression and anxiety had a 26% and 33% risk related to childhood GS, respectively. In addition to the control group of intellectual disabilities, only schizoaffective disorder and anorexia nervosa did not meet the criteria for achieving statistical significance.

On average, these changes in relative psychiatric risk across childhood GS density grouping were comparable in size to other measured mental health risk factors, such as family history of mental illness or parental age at time of birth. Certain psychological disorders (i.e. mood disorders especially depressive disorder, and neurotic stress-related and somatic disorders) were more influenced by vegetation density than by any of the other predictive factors measured.

In the other European study, analysis also demonstrated a strong relationship between reported childhood nature exposure and adult mental health. Individuals that reported low amounts of time in nature as children were four times more likely to have poor

mental health as adults (β-Coefficient −4.13; 95% CI −5.52, −2.74. p < 0.001). Conversely, spending time in nature as a child seemed to have a protective and preventive impact on adults' mental health status. These results remained after adjusting for factors like current use of nature, perceived importance of nature, and amount of nature surrounding the current living residence.

One important additional finding of this European study showed that people with lower exposure to nature as children placed less importance on the value of nature as adults, which supports evidence research found in other research studies.[3,4]

If the findings of both these studies hold true, they could significantly alter our understanding of the factors that cause and prevent mental illness, and lead to novel approaches to both clinical and public mental health.

Green Space and Mental Health

These two studies are far from the first to look at the impacts of green space on mental illness and mental health. Research in this area began in the 1980s[5] and has increased in recent years. Specific studies have assessed the impact of adults' residential green space on rates of depression,[6] and other studies have explored the mental health effects of living in and moving to/from areas with greater green space access.[7,8] There are now systematic reviews and meta-analyses demonstrating the beneficial effects of outdoor natural environments for the mental health of adults and children, making the connection between the human mind and the surrounding environment undeniable.[9–11]

There are multiple proposed mechanisms to explain how or why this relationship may exist.[12] Two of the most well-researched and supported are the "stress reduction theory" (SRT) proposed by Roger Ulrich,[13] and the "attention restoration theory" (ART) proposed by Stephen and Rachel Kaplan.[14]

- SRT suggests there is a positive *psychophysiological response* to natural environments that *reduces* stress and associated allostatic load, with resultant neurological, hormonal and immunological effects that impact overall health, including mental health.[15]
- ART suggests that *cognitive processing* of natural stimuli requires less "direct attention" than modern industrial stimuli and is *restorative* to mental processes thus reducing effort and strain that can lead to mental illness.[16]

Both SRT and ART are based on a concept of *biophilia*, proposed by the famous biologist and author E.O. Wilson to describe the "inherent human affinity for other natural, living things" that arose in our prehistoric ancestors via millions of years of evolutionary adaptation to natural surroundings.[17] Over this extended period our bodies, brains, nervous and endocrine responses developed in ways that processed natural settings as a restorative *baseline* to which we are best suited (or, in evolutionary terms, "fit") to inhabit. According to biophilia, the more green space in our surrounding environment, the easier and more effectively our brains and nervous systems can function, and the less opportunities there are to generate *dis-ease*.

For many people, including children, modern living does not provide regular opportunities to experience these biophilic environmental benefits, leading to what author Richard Louv has called a modern epidemic of "nature deficit disorder."[18] People often live their lives disconnected from the natural world, isolating themselves in houses, offices, cities, and other *un*natural (i.e. human-made) places. Without regular exposure to the natural world, some vital part of human functioning suffers in ways that are similar to deficiency of an essential vitamin. The greater the absence in our lives of this "vitamin N" as Louv calls it (N for "Nature"),[19] the greater the likelihood that illness (including mental illness) will occur. In contrast, the more time people spend in nature, the greater the preventive and therapeutic dose of vitamin N they receive, and the healthier they are in mind and body. It is very difficult to prove this directly, but evidence such as the findings in this current study provide support that these theories are valid.

There are many other additional possible mechanisms that could be contributing to the effect that green space has on mental health. These include the following:[12]

- Increased **physical activity** around the house and in nearby parks, leading to improved mental health.[20] Physical activity is a well-established method for improving mental health

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Table 1. Incidence Relative Risk (IRR) of Psychiatric Diagnoses for Lowest-to-Highest Childhood Green Space (GS) decile

Psychiatric Disorder	ICD-10 code	IRR	95% CI
Any Psychiatric Disorders	F00-F99	1.27	1.24-1.30
Substance Abuse	F10-F19	1.37	1.29-1.46
Schizophrenia	F20	1.19	1.09-1.30
Schizoaffective Disorder	F25	1.16	0.84-1.61*
Mood Disorders	F30-39	1.26	1.21-1.30
Bipolar Disorders	F30-31	1.17	1.03-1.34
Depressive Disorders	F32-F33	1.26	1.21-1.32
Neurotic, Stress-Related and Somatic Disorders	F40-F48	1.33	1.29-1.37
Obsessive Compulsive Disorder	F42	1.21	1.13-1.31
Eating Disorders	F50	1.18	1.11-1.26
Anorexia Nervosa	F50.0	1.11	0.99-1.24*
Personality Disorders	F60	1.14	1.08-1.20
Borderline Disorder	F60.31	1.12	1.03-1.22
Intellectual Disability (control)	F70-79	1.01	0.92-1.11*

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and addressing negative moods and behaviors.[21]

- Mitigation of **noise pollution** through buffering of absolute and perceived sound levels,[22] as well as reduction of total noise levels, which impact mental health.[23]
- Reduction of **ambient temperature and humidity** through vegetation buffering,[24] which has been associated with decreased prevalence of mental health conditions.[25]
- Moderation of **air quality**, especially particulate matter and airborne toxins that adhere to/are absorbed by vegetation and are thus filtered out of the air.[26] These toxins have been shown to impact mental health conditions such as schizophrenia and depression.[27,28]
- Modulation of **immune system response** with potential mental effects similar to other known cytokine impacts.[29] These immunoregulatory mechanisms include
  - greater physical contact with flora and fauna,[30,31] leading to a more robust and diverse bacterial microbiome which has been shown via the "**hygiene hypothesis**" to benefit health[32];
  - inhalation of aromatherapeutic "**phytoncides**" produced by vegetation, altering chemical cytokines known to regulate inflammation and mood[33]; and
  - observation of natural scenes producing states of awe and gratitude, aspects of "**positive psychology**" that are preventive and therapeutic measures against mental illness.[34,35]
- Enhanced personal, emotional, and self-developmental skills as a result of "**place attachment**" to preferred outdoor green spaces, resulting in greater mental health.[36]
- Increased **social interaction** and **sense of community**, which are both increased with greater amounts of green space and are known to affect mental health.[37]

According to biophilia, the more green space in our surrounding environment, the easier and more effectively our brains and nervous systems can function...

These mechanisms have all been extensively studied in adults. It will take a great deal more research to determine if any of them are relevant to childhood exposures, much less how exposure at this age range could be influencing psychopathology later in life. However, it is difficult to view the vast breadth and variety of published evidence and not conclude that environmental factors like green space have a large impact on mental health.

Urban Stress

One of the most important implications of this research is the relationship between green space,

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mental health, and urban development. In the Danish study mentioned above, green space had a greater impact than degree of urbanization. However, green space was more relevant in determining mental health risk when analyzed *in combination* with urbanization. Those kids who grew up in the most urban, population-dense areas had higher risk for psychiatric disorders than those who grew up in rural, population-sparse areas, even if the amount of green space around their home was the same. This suggests that it is not just the amount of nature outside a person's front door that matters; it is also what is occurring in the greater surrounding area beyond what can immediately be seen and heard.

The results of this study were most pronounced in more densely-populated urban regions. This data supports dozens of other studies detecting a large discrepancy in urban vs. rural rates of mental illness.[38] A study utilizing the same datasets as the current study demonstrated a 40% increased risk of psychiatric disorder for urban adults compared to rural adults, with rates for conditions such as schizophrenia as much as 86% increased.[39] Meta-analysis has confirmed this urban association with schizophrenia,[40] and measurable neuro-anatomical and neuro-functional differences in brain structure predictive of schizophrenia have been detected in children raised in urban environments.[41] This type of evidence has prompted some researchers to propose a study of "neurourbanism" to identify ways in which the "new" environment of modern cities may be altering brain development. Our brains may simply be better suited for a traditional "biophilic" world in which exposure to green space is more abundant.[42]

These issues are important to consider as urbanization accelerates in our modern society. In the United States, population is >80% urban and rising.[43] Since 2008, the global population is more than 50% urban with projections of 65% urban population by the year 2050. Based on the material presented in this short article, it is no coincidence that mental health issues are also rising, currently reported by the WHO as the #1 cause of health-related disability in the world.[44] Almost one in every five people in the United States live with a diagnosed mental illness, and these numbers are increasing.[45]

While decline of available green space in urban (and rural) areas is likely not the only cause of these rising rates of mental ill-health, we must consider it a contributing component. Fortunately, evidence also shows that increasing green space and green space experiences can decrease some psychopathologies such as depression and PTSD.[46,47] These benefits often occur in a dose-dependent manner, with threshold "doses" of green space being easily feasible in those cities willing to make the investment.[48] Many municipalities are actively engaging in "urban greening" efforts to improve ➤

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the health, both mental and physical, of their residents as well as the health of the local environment.[49,50]

Conclusions

Given the prevalence of mental ill-health in society, it may be beneficial to investigate the incorporation of environmental approaches for these conditions to address prevention and possible treatment. Exposure to green space in the area surrounding a child's household may protect against a range of mental illnesses later in life. Conversely, absence of green space during childhood may be a significant risk factor for the development of these conditions. To address this, clinicians could begin promoting time outside in nature for pediatric patients (and their parents) as much as possible. Individuals wanting to reduce the risk of psychiatric disorders in their own children may want to consider living in neighborhoods with sufficient green space. Multiple stakeholders including individuals, communities, public health workers, city planners, and municipal administrators may want to support local efforts for developing, maintaining, and/or restoring local greenery options for their mental health-promoting benefits.

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Fluoride and Mental Decay: Causation and Correlation

by John D. MacArthur

Back in the stone age of neuroscience, a controversial public health intervention was implemented. In 1945, because of its ecological association with decreased dental decay, fluoride was added to US drinking water. Now, fluoridation must end because of its many causative biochemical links to increased mental decay.

Well-established molecular mechanisms of fluoride toxicity are oxidative stress and inflammation, whose role in the initiation and pathogenesis of Alzheimer's disease is now being recognized.[1]

More recently, increasing scientific evidence reveals fluoride's pathological role in major neurodegenerative pathways: arterial stiffness, endothelial dysfunction, endoplasmic reticulum (ER) stress, and microglial activation.

Arterial Stiffness

The biological aging process is always associated with arterial stiffness, which is emerging as an important risk factor underlying the effect of blood pressure on the brain. Arterial stiffness correlates with the pathogenesis of a large spectrum of vascular disorders: hypertension, stroke, kidney dysfunction, cerebrovascular disease, dementia, and Alzheimer's disease. Arterial stiffness is associated with the extent and progression of β-amyloid deposition in the brain.[2]

When arteries lose their elasticity, it impairs their ability to absorb the increased pressure generated as the heart ejects blood into them. This arterial-pressure pulsatility is instead transmitted to smaller blood vessels. The brain's hippocampus is particularly vulnerable because its capillaries are located close to large vessels. Swedish researchers have outlined a sequence of vascular events, connecting arterial stiffness to damaged hippocampal capillaries and impaired memory in older adults.[3]

In people with fluorosis, the elastic properties of the ascending aorta are impaired.[4] Fluoride accelerates arterial calcification and stiffening that lead to hypertension. When fluoride levels in drinking water increased from 0.84 to 1.55 mg/L, hypertension prevalence increased 22%.[5]

Impaired elasticity of the ascending aorta is associated with subclinical hypothyroidism. Higher TSH levels, a measure of hypothyroidism, correlate with aortic stiffness.[6] Data from nearly 8,000 medical practices in England revealed a positive association between patients diagnosed with hypothyroidism and fluoride levels in their drinking water. Those living in a fluoridated region had twice the hypothyroidism prevalence as those in a non-fluoridated one.[7] This study did not include undiagnosed subclinical hypothyroidism.

Fluoride exposure … increase[s] inflammation in the central nervous system, which leads to neurodegeneration.

Not only is subclinical hypothyroidism associated with "cognitive dysfunction," the US National Research Council (2006) also said that in pregnant women, it is associated with "decreased IQ of their offspring."[8] In August 2019, *JAMA Pediatrics* published a carefully researched and meticulously peer-reviewed study linking maternal exposure to optimally fluoridated water with lowered IQ in their children – confirming other recent findings that low levels of fluoride during fetal development can cause cognitive impairment.[9]

Subclinical hypothyroidism is also associated with increased cholesterol concentrations.[8] In May 2019, *JAMA Neurology* reported a link between high LDL cholesterol levels and early-onset Alzheimer's disease.[10] Several animal studies have shown that fluoride exposure increases LDL cholesterol levels.

Endothelial Dysfunction

Endothelial cells line the inside of blood vessels from the aorta to microvessels, where they form a selective blood-tissue barrier that protects every organ system. Microvascular endothelial cells play a critical role in brain development, maturation, and homeostasis. Endothelial cell dysfunction in the blood-brain barrier is the first pathological change in the development of small vessel disease (SVD), the leading cause of vascular dementia. SVD contributes to and worsens the symptoms of Alzheimer's disease; triples the risk of stroke; and is responsible for up to 45% of dementias.[11]

Researchers at Johns Hopkins University School of Medicine demonstrated that sodium fluoride causes "dramatic" endothelial barrier dysfunction, as evidenced by marked increases in macromolecule endothelial cell permeability.[12]

"Sevoflurane" is a general anesthetic that significantly increases blood fluoride levels. After exposure to Sevoflurane, the blood-brain barrier is compromised due to "flattening of endothelial cell surfaces."[13,14] Sevoflurane is associated with high rates of post-operative delirium, a common and often fatal disorder affecting as many as 50% of older people during surgery or hospitalization. The severity of this delirium correlates directly to the severity of later cognitive impairment and decline.[15]

Another fluorinated drug that increases blood levels of fluoride and causes endothelial cell dysfunction is 5-fluorouracil.[16,17]

African Americans have reduced endothelial function – and greater arterial stiffness – compared with whites, even after adjusting for traditional cardiovascular risk factors.[18]

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ER Stress

Within a cell, the endoplasmic reticulum (ER) is the site where proteins are synthesized and folded. ER function is highly sensitive to toxins that can overwhelm the cell's folding capacity and cause misfolded proteins to accumulate – a condition known as ER stress.

Chronic ER stress is responsible for neurodegeneration in numerous human diseases whose pathology includes accumulation of misfolded proteins in the brain. In Alzheimer's disease, the ER is "drastically affected."[19,20] In addition, mounting proof indicates that ER stress is incriminated in psychiatric diseases like major depressive disorder, bipolar disorder, and schizophrenia.[21]

Fluoride exposure induces excessive ER stress and associated cell death in the hippocampus of rats, resulting in histological and ultrastructural abnormalities that impair learning and memory capabilities.[22]

Damaged tooth enamel is called dental fluorosis, because it is caused by fluoride, which initiates an ER stress response during tooth development. Beginning with the lowest dose tested, researchers at the Forsyth Institute observed an increase in the magnitude of ER stress with increasing doses of fluoride.[23]

In skeletal fluorosis, fluoride causes ER stress during osteoblast maturation. The severity of osteofluorosis is associated with accumulation of fluoride in bone in a dose-dependent manner.[24,25]

Microglial Activation

Microglia are a type of immune cell that account for about 10% of all brain cells. An essential function of microglia is to defend the brain against toxins. When activated, microglia produce neuroinflammation that can damage and kill neurons. Microglial activation is involved in the development and progression of a variety of neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, and Lou Gehrig's.[26] Only recently is it becoming clear that brain microglia are also key regulators of the developing brain.[27]

Fluoride is able to cross the blood-brain barrier and accumulate in neurons, affecting many biochemical mechanisms. Fluoride exposure has been shown to activate microglia and increase inflammation in the central nervous system, which leads to neurodegeneration.[28]

Microglial activation decreases levels of postsynaptic density protein-95 (PSD-95), which is concentrated in the trillions of tiny synapses that allow neurons to communicate with each other. Research demonstrates that PSD-95 orchestrates synaptic development and plays an important role in synaptic plasticity, the basis of learning and memory.[29]

When rats were sub-chronically exposed to fluoride in their drinking water, researchers found that fluoride activated microglia and decreased PSD-95 protein levels in the brain's hippocampus. The fluidity of synaptic membranes and the expression level of PSD-95 decreased gradually with increasing fluoride concentration – suggesting a molecular basis of central nervous system damage caused by fluoride.[30,31]

Rats anesthetized for four hours with 2.5% Sevoflurane showed decreased PSD-95 expression and long-term deficits in hippocampal function. Seven weeks after exposure, they had significant spatial learning and memory impairment.[29]

Fluoridation's Ecological Correlations

Fluoride's multiple causative links to mental decay are reinforced by multiple ecological associations with leading causes of death and with prevalence rates of neurodevelopmental disorders.

Alzheimer's Disease. Death rates in 2013 from Alzheimer's disease (sixth leading cause of death) averaged 9% higher in the 20 states whose public water supplies were more than 80% fluoridated (avg. 93% in 2012), compared to the 30 states fluoridated below 80% (avg. 58%).[32,33] In the 10 most fluoridated states (avg. 97%), Alzheimer's death rates averaged 25% higher than in the 10 least fluoridated states (avg. 35%).

Hypertension and Stroke. Hypertension is a major cause of vascular cognitive impairment and is the single most important modifiable risk factor for adult stroke (cerebral vascular disease). Stroke doubles the chances of developing dementia.[34,35] In the 10 most fluoridated states, death rates from hypertension (thirteenth leading cause of death) averaged 13% higher, and death rates from stroke (fifth leading cause of death) averaged 6% higher than in the 10 least fluoridated states.[32,33]

Kidney Disease. The US Public Health Service has long known:

> Subsets of the population may be unusually susceptible to the toxic effects of fluoride and its compounds. These populations include the elderly, people with osteoporosis, people with deficiencies of calcium, magnesium, vitamin C, and/or protein, and people with kidney problems.[36]

The number of Americans unusually susceptible to fluoride now far outnumber children with developing dentition, the claimed beneficiaries of fluoridation.

Cognitive decline is one of many manifestations of brain damage that clearly accompany the decline of kidney function, even in early stages.[37]

Kidney disease death rates (ninth leading cause) averaged 13% higher in the 20 states more than 80% fluoridated, compared to the 30 states fluoridated below 80%.[32,33] In the 10 most fluoridated states, death rates from kidney disease averaged 26% higher than in the 10 least fluoridated states.

Preterm Birth. A well-designed New York state public health study found that water fluoridation was independently associated with a 15% increased risk of preterm birth. No follow-up research was done, although two years earlier the US Institute of Medicine reported: "Those born preterm have an appreciable risk of long-term neurological impairment."[38,39]

Since 2009, a team of researchers at the EPA's Neurotoxicology Division continues to find substantial evidence that fluoride is a "developmental neurotoxicant," one of 22 gold standard chemicals "well documented to alter human neurodevelopment." Others include aluminum, arsenic, ethanol, lead, and methylmercury.[40]

Attention-Deficit Hyperactivity Disorder (ADHD). The most common neurodevelopmental disorder of childhood is ADHD. Each one-percent increase in artificial fluoridation prevalence in the US was associated with 67,000 to 131,000 additional ADHD diagnoses (2003 to 2011).[41]

In 2011, rates for youth (aged 4-17) currently diagnosed with ADHD averaged 25% higher in the states fluoridated at

80% or more, compared to those below 80% in 2010.[32,42]

Mental Retardation/Intellectual Disability. In 1993, mental retardation prevalence rates averaged 33% higher for children (aged 6-17) in the 26 states fluoridated above the national average (62% in 1992) compared to the 24 states fluoridated below it.[43,44]

By 2012, it had nearly doubled. The prevalence rates of "intellectual disability" (the new term for mental retardation) averaged 57% higher for students (aged 6-21) in the 26 states fluoridated above the national average (75% in 2012) compared to the 24 states fluoridated below it.[32,45]

In the 10 most fluoridated states, intellectual disability prevalence averaged 84% higher than in the 10 least fluoridated states.

Fluoridation Must End

In 2019, a large longitudinal study found a dose-response association between dementia in women and men who consumed relatively low drinking-water levels of fluoride. The dementia risk more than doubled in the highest quartile compared with the lowest.[46]

It's important to minimize fluoride consumption, but this is very difficult because fluoridation chemicals (increasingly from China) are intentionally added to about 75% of US tap water. An EPA-regulated water contaminant, fluoride now contaminates the nation's processed food-and-beverage chain, essentially making the US artificially fluoride endemic. Products produced in a fluoridated city still contain fluoride even if the label says "filtered water" (unless specifically filtered by reverse osmosis).

The amount of fluoride we consume is unknown because manufacturers and producers still do not provide information on the fluoride content of commercial foods and beverages, even though in 2006 the National Research Council said they should. This extremely comprehensive report's dozens of recommendations have been ignored, including: "Studies of populations exposed to different concentrations of fluoride should be undertaken to evaluate neurochemical changes that may be associated with dementia. Consideration should be given to assessing effects from chronic exposure, effects that might be delayed or occur late-in-life, and individual susceptibility."[47]

The annual cost of neurological diseases and disorders to American society is approaching $1 trillion. Even if ending water fluoridation reduced mental decay by merely 10%, not only would this be incalculable benefit to millions of families but would save $100 billion a year.

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John D. MacArthur's previous contributions to the *Townsend Letter* include five reports: "Too Much Copper, Too Little Zinc, and Cognitive Deterioration in Alzheimer's Disease" (with George J. Brewer, MD), and "Fluoride and Preterm Birth" (October 2013); "Overdosed: Fluoride, Copper, and Alzheimer's Disease" (November 2013); "Placental Fluorosis: Fluoride and Preeclampsia" (May 2015); and "Prenatal Fluoride and Autism (April 2016).

Safe, Effective, Natural Solutions to Mood Disorders

by Todd A. Born, ND, CNS

Mood disorders are mental health issues that primarily affect a person's emotional state, in which a person experiences long periods of extreme happiness, extreme sadness, or both.[1] In the fifth addition of The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, the list of mood disorders and their diagnostic criteria are exceedingly lengthy; but the most common include major depression, dysthymia, bipolar disorder, seasonal affective disorder (SAD), and depression related to an illness, substance abuse or medication.[2] For simplicity of this article, I will refer to these issues collectively as mood disorders unless otherwise indicated.

The 2001-2003 National Comorbidity Survey Replication shows an estimated 9.7% of US adults (anyone over 18) had any mood disorder in the past year, with a higher prevalence in females (11.6%) than males (7.7%); and an estimated 21.4% of US adults will experience a mood disorder at some point in their lives.[3] Please note that these figures are a combination of mood disorders; frequently updated individual statistics may be found by accessing the National Institute of Mental Health Statistics website at https://www.nimh.nih.gov/health/statistics/index.shtml.

Depression alone affects more than 300 million people worldwide.[4] Bipolar disorder affects more than 60 million, and SAD can affect up to 10% of the population, depending on geographical location.[5] The direct and indirect costs of these health issues are immense. For example, in 2008, the World Health Organization (WHO) ranked major depression as the third leading cause of burden of disease worldwide and projected that the disease will rank first by 2030.[6] In 2015, it was estimated that bipolar I disorder (BDI) total costs were $202.1 billion (US dollars), an average of $81,559 per affected individual.

Sadly, the aforementioned numbers of afflicted individuals, as well as cost burden, are likely underestimates because many of the individuals that struggle with mood disorders go undiagnosed. At times, they may be reluctant to seek help due to the social stigma associated with these conditions. In practice, mood disorder detection, diagnosis, and management also pose many challenges for clinicians because of various presentations, unpredictable course and prognosis, as well as variable response to treatment.[7,8]

There is an urgent need for safer and more efficacious alternatives to medications. Medications certainly have their role in mood disorders, when used judiciously. It has been well established in mild to moderate depression, for example, that medications are no more effective than placebo.[9] In manic and depressive states of bipolar disorder, the data is mixed on how efficacious medications really are.[10]

The extensive laundry list of side effects of mood disorder medications is so vast, it makes one's head spin. In clinical practice, it seems the side effects tend to be so intolerable for patients, they would many times rather suffer from their illness than deal with the negative consequences of the medications. Antidepressants, anxiolytics, stimulants, antipsychotics and mood stabilizers are typically used with mood disorders; but a full discussion of their efficacy and potential side effects is beyond the scope of this article.

To better understand mood disorders and provide more effective treatment interventions, it is beneficial to look at underlying etiologies, risk factors, and genetics (encompassing family history). Each particular mood disorder has its own unique set of etiologies, but commonalities amongst all of them include brain structural changes (not yet well understood) compared to those without mood disorders, neurotransmitter alterations, and hormonal imbalances. Risk factors include low self-esteem, being highly self-critical, traumatic and stressful events (e.g., physical or sexual abuse, loss of a loved one), comorbid mental disorder (e.g., schizophrenia or anxiety disorders), alcohol and recreational drug abuse, chronic illness, and side effects of certain medications (e.g., sleeping pills and anti-hypertensive drugs).[11]

An enormous risk factor is genetics[12] and even epigenetics.[13] Research into the role single nucleotide polymorphisms (SNPs) play in mood disorders has exploded in the last 15 years or so and offers promise to help improve people's lives through nutritional and botanical interventions.[14,15] Indeed, even pharmacogenetic testing is finally becoming more mainstream in clinical practice, offering safer, more specific, personalized pharmaceutical options.[16-18]

A comprehensive, integrative approach to mood disorders works very well in clinical practice.[19] This may include all or most of the following: lifestyle and dietary modifications, constitutional homeopathy, botanical medicines, nutraceutical support, psychotherapy, and occasionally pharmaceutical interventions. Again, given space limitations, this article will focus on evidence-based botanical and nutraceutical interventions.

Studies are consistent that up to half of all individuals diagnosed with a mood disorder use one or more complementary and alternative medicine (CAM) therapies.[20,21] It has been shown that diet,[22] exercise,[23] sleep, a strong supportive social network, and low stress environment reduce relapses in mood disorders.[24] Even targeting the proverbial "gut microbiome" can have a tremendous positive impact![25,26]

Given all of the aforementioned information and dire need of safe and effective alternatives, are there really any nutraceutical and/or botanical interventions that work? The answer is yes, definitely.

Vitamins and Minerals

Vitamin B12 (cobalamin) is involved in DNA synthesis, red blood cell formation, homocysteine metabolism, and synthesis of S-adenosylmethionine (SAMe). It also is heavily involved in the proper function of the nervous and immune systems.[27] Observational studies have shown that as many as 30% of patients hospitalized with depression are deficient in this vitamin.[28] Depression can be induced by B12 deficiency, even with normal hematological and blood parameters,[29] so a therapeutic intervention of 1000 mcg (1 mg) daily, orally, has been suggested.[30] The forms of B12 in these studies have varied.

It has been shown that individuals with psychiatric conditions either have impaired transport across the blood-brain barrier and/or an accelerated catabolism, hence the need for increased requirements.[31] When these individuals were treated with a therapeutic trial of B12, clinical improvement was noted.[32]

Folate is a generic term referring to both natural folates in food and folic acid (the synthetic form used in many supplements and fortified food). Folate is critical in the synthesis of DNA and RNA, several amino acids, methylation reactions, homocysteine and B12 metabolism, and assists in the proper functioning of the central nervous and immune systems.[33]

Like B12, low red blood cell folate levels have been detected in 15–38% of adults diagnosed with depressive disorders.[34] Efficacious doses have ranged from 200 mcg to 15 mg of folic acid, along with medication(s), depending on the mood disorder.[35,36] Do note, most trials have been conducted on folic acid, not its biologically active forms of 5-methyltetrahydrofolate (5-MTHF, the major circulating form in the body) and 5,10-methylenetetrahydrofolate. In individuals with methylenetetrahydrofolate reductase (MTHFR) polymorphisms and/or on medications that inhibit dihydrofolate reductase (by reducing interactions), along with those having compromised gastrointestinal function, folinic acid and 5-MTHF may be the preferred forms.[37,38]

Vitamin B6 (pyridoxine, pyridoxal and pyridoxamine) and its coenzyme form, pyridoxal 5'-phosphate (PLP), are essential to over 100 enzymes, affecting lipid, amino acid, and carbohydrate metabolism, along with the action of steroid hormones.[39] It cannot be synthesized in the body and must be obtained from the diet. In the brain, PLP is necessary to metabolize serotonin from tryptophan and dopamine from L-3,4-dihydroxyphenylalanine (L-Dopa). Other neurotransmitters and amino acids that are PLP-dependent include glycine, D-serine, glutamate, histamine, and γ-aminobutyric acid (GABA).[40] PLP also plays a role in the metabolism of homocysteine.[41] Typical dose ranges are from 10 to 200 mg/day, but anyone taking more than 200 mg/day should be monitored for neurotoxic symptoms.[42]

Vitamin D3 (cholecalciferol) is a fat-soluble vitamin that functions as a hormone precursor. It is biologically inactive and must first be hydroxylated in the liver to 25-hydroxyvitamin D (25[OH]D), with further hydroxylation in the kidneys to its active form, 1,25-dihydroxyvitamin D, the form that acts as a steroid. In this form it suppresses prostaglandin action; inhibits p38 stress kinase signaling, tumor angiogenesis, invasion and metastasis; and inhibits NF-κB signaling.[43,44]

Doses of 500 mg to 10 grams of EPA and DHA, with many trials using 1 to 2 grams daily, have been shown to be effective in prevention and treatment of depressive disorders, with EPA having better data for efficacy than DHA.

Many studies have seen a correlation between low serum concentrations of 25(OH)D and mood disorders.[45] While the exact mechanisms of action haven't been fully elucidated, vitamin D supplementation has been shown to improve mood in both depression and SAD.[46,47] It should be noted that "optimal" serum levels of 25(OH)D are around 40 ng/mL.[48,49]

Magnesium insufficiency and frank deficiency are rampant in the US and most industrialized nations. More than half of the populous (ages ≥ 4 years) is considered to be under consuming this vital mineral.[50] Chronic diseases, medications, decreases in food crop magnesium content, and the availability of refined and processed foods[51] have all contributed to this epidemic.

Magnesium is the second most abundant cation in soft tissues (behind potassium) and is a cofactor for more than 300 enzymes. It plays a role in adenosine triphosphate (ATP) production, neuronal activity, cardiac function, electrical properties of cell membranes, has antispasmodic effects, and assists in glutathione synthesis.[52,53] In addition to all of these accolades, it has anxiolytic properties, increases stress tolerance, and is a great antidepressant.[54-56] The recommended daily allowance (RDA) varies by age and gender, ranging from 360 to 420 mg of elemental magnesium daily.

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Zinc, well known for its immune properties, also plays an important role for mood, as it is essential for over 300 enzyme-dependent reactions.[57] The RDA for males 19 years and older is 11 mg daily and for females, 8 mg daily. Therapeutically, trials have shown efficacy at much higher doses, although this depends on the condition being addressed. In many of the depression trials, a dose of 25 mg daily of elemental zinc was utilized.[58,59] Excessive zinc intake can have toxic effects, as well as deplete copper, so the US Food and Nutrition Board has set the tolerable upper limit for those 19 years or older at 40 mg/day.[60]

Omega-3 Fatty Acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are well known for anti-inflammatory affects[61,62] via suppression of NF-κB, cyclooxygenase (COX)-2, tumor necrosis factor (TNF)-α, and interleukin (IL)-1β. They also have a solid reputation for assisting those afflicted with mood disorders. Doses of 500 mg to 10 grams of EPA and DHA, with many trials using 1 to 2 grams daily, have been shown to be effective in prevention and treatment of depressive disorders,[63-65] with EPA having better data for efficacy than DHA.[66] In bipolar disorders, there is strong evidence that omega-3 fatty acids are helpful in depression but not for attenuating mania.[67]

S-Adenosylmethionine (SAMe)

SAMe is produced *in vivo* from homocysteine and 5-MTHF, and also is available as a supplement. It is the body's major methyl-group donor and is vital for membrane function and neurotransmission.[68] In divided doses totaling 800 to 1600 mg daily, SAMe has been shown to be just as effective as tricyclic antidepressants with a lower side effect profile.[69] It also has been shown to have a beneficial effect in depressed individuals where medication was not fully resolving their symptoms.[70] It should be used with caution in bipolar disorder, as it can trigger mania.[71]

References will be posted online only

Amino Acids

5-Hydroxytryptophan (HTP) is the rate-limiting intermediary in the synthesis of serotonin from L-tryptophan. The dosage of 5-HTP depends on condition, ranging from 50 mg to 3 grams daily in short studies.[72-75] Commonly, it is dosed at 50 to 100 mg, one to three times daily, with some of the best evidence at this dose seen in anxiety.[76,77] For depression, clinical trials have used 400-900 mg per day in divided doses.[78-80] Caution is advised for those on selective serotonin reuptake inhibitors (SSRIs).

N-Acetyl-L-cysteine (NAC) a derivative of L-cysteine, but more stable,[81] is well known for its function as an antioxidant and precursor to glutathione,[82] acts as a mucolytic,[83] has anti-inflammatory properties[84] and is the treatment of choice for acetaminophen-induced hepatic necrosis.[85] At 1000 mg, two to three times daily, this sulfhydryl molecule also possesses efficacy in numerous neuropsychiatric conditions.[86-88] It appears to increase the uptake of cysteine, which activates a reverse transport of glutamate into the extracellular space. Restoring glutamate to the extracellular space *inhibits* more glutamate release, thereby improving compulsive behaviors.[89]

Taurine can be synthesized *in vivo* from cysteine. It stabilizes cell membranes, is an osmoregulator, assists in bile acid conjugation, contributes to cardiac contractility, inhibits platelet aggregation, is an antiarrhythmic and anticonvulsant, and last but not least, also functions as a neurotransmitter.[90,91] Albeit, direct clinical trials of taurine on mood disorders may not exist, it has been shown to inhibit the release of excitatory neurons, like glutamate, act as a GABA agonist, inhibit TNF-α, and increase ATP production.[92,93]

Botanicals

Hypericum perforatum (St. John's wort) is a highly revered botanical medicine with antibacterial, antiviral, anticancer (*in vitro*), antioxidant, neuroprotective, anti-inflammatory, and vulnerary (wound healing) properties.[94] It is probably most well-known for its antidepressant effects, showing equal efficacy to tricyclic antidepressants and SSRIs, but with higher tolerability.[95-97] The constituents hyperforin and adhyperforin appear to modulate the effects of serotonin, dopamine, and norepinephrine, as well as inhibit reuptake of these neurotransmitters. Most studies in individuals with depression, anxiety, and SAD show improvement with 300 mg, three times daily.[98,99] Caution should be used in those on medications that interact with cytochrome P450 (CYP1A2, 2C9, 2C19, & 3A4) inducers, monoamine oxidase inhibitors (MAOIs), P-glycoprotein inducers, photosensitizers, and serotonergic agents.[100]

What doesn't *Curcuma longa* (turmeric) do? Its virtues are endless, but one may not be aware of its efficacy in depressive disorders. Studies have shown that just 1000 mg of the herb daily is as effective as 20 mg of fluoxetine; and when used in combination with the medication, response rates for those with major depression rose from 65% to 78%.[101] A 2017 meta-analysis showed again, its efficacy in depression.[102] It also has been shown to reduce anxiety.[103] It is postulated that it inhibits the activity of both monoamine oxidase (MAO)-A and MAO-B, increases the levels of neurotrophic factors (particularly brain derived neurotrophic factor [BDNF]), and modulates the serotonin and dopamine neurotransmission in the brain.[104]

Rhodiola rosea (rhodiola) is a wonderful plant that thrives in cold regions and high altitudes and is notorious for its ability to increase resistance to physical, chemical, and biological stressors.[105] *In vitro* and animal studies have shown

the constituents rhodioloside, salidroside, and tyrosol regulate the activity of serotonin, dopamine, and norepinephrine, as well as inhibit MAO-A.[106-108] In depressed individuals, 340 mg one to two times daily has been shown to decrease overall depressive symptoms, emotional instability, insomnia, and somatization.[109,110] Typically, dosages range from 200-600 mg daily, depending on the percentage of active constituents. Caution should be used in those with bipolar disorder, who are prone to manic episodes when given antidepressants or stimulants.[111]

Crocus sativus (saffron) is a well-known, brilliant yellow-red, precious spice that mostly grows in Iran, Greece, Morocco, and India and is one of the most expensive botanicals in the world.[112] It has a long history of traditional use and is considered to be an antispasmodic, thymoleptic, carminative, cognition enhancer, aphrodisiac, and emmenagogue.[113] This revered spice also has been shown clinically to benefit attention-deficit/hyperactivity disorder,[114] Alzheimer's disease,[115,116] anxiety[117] and depression.[118] It is theorized that safranal, a carotenoid found in saffron, interacts with the GABAergic system,[119] modulates levels of serotonin (possibly by inhibiting reuptake),[120] as well as alters levels of dopamine and norepinephrine.[121] Standardized extracts containing 2% safranal, 2% crocin and small amounts of picrocrocin (% in studies unspecified), dosed at 15 mg twice daily have been shown to significantly reduce numerous parameters of depression.[122-124] It is very safe and has no known drug-herb interactions.[125]

Hormones

The use of pharmaceutical hormone replacement therapies (estrogen, progesterone and testosterone) will not be discussed in this article, but the prudent use of dehydroepiandrosterone (DHEA) and pregnenolone will be.

Pregnenolone is a ubiquitously produced endogenous neurosteroid, mostly made in the brain and adrenal glands from cholesterol. It is known as the master steroid hormone, since all steroid hormones, including cortisol, aldosterone, allopregnanolone, DHEA, progesterone, and testosterone, are made from it.[126] Pregnenolone is thought to interact with the endocannabinoid (CB1) receptor, exerting antidepressant effects.[127] Pregnenolone and its metabolites have also been shown to modulate GABA-A, N-methyl-D-aspartate (NMDA), cholinergic, dopaminergic, and neurotrophic systems, thus affecting neuronal excitability.[128,129]

In individuals with mood disorders, doses have ranged from 5 to 500 mg daily, with typical dosing of 50 to 100 mg daily. Monitoring serum pregnenolone levels every three to six months is advisable. Studies in both bipolar disorder and depression have shown significant improvements in symptoms.[130,131]

DHEA is the most abundant neurosteroid hormone in the human, secreted by the adrenal gland and produced in the brain.[132] As a precursor to male and female sex hormones, DHEA has been shown to be effective in many health conditions; but germane to this paper, doses of 30 to 500 mg daily have been shown to be helpful in depression and dysthymia.[133,134] DHEA-S, the major circulating metabolite of DHEA, is not subject to day-to-day and diurnal changes that DHEA is.[135,136] For this reason, DHEA-S should be tested prior to administering the hormone to ensure it may be of benefit, as well as monitored every three to six months. Excessive administration of DHEA can cause acne and hirsutism; and as a precursor to estrogen and testosterone, there is a theoretical risk that long-term use could lead to hormone-sensitive cancers, especially if DHEA-S becomes elevated.

The aforementioned text is not an exhaustive list of safe and effective interventions to mood disorders, but rather a consolidation of what has better evidence clinically, both from published human studies and this author's personal experience. As with any health condition, individuals should not self-treat, but rather seek out a qualified healthcare professional to discuss their health concerns and options. ◆

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Dr. Born's clinical focus is utilizing integrative medicine to treat chronic diseases. He has a strong interest in difficult and refractory cases, allergies, gastrointestinal issues, neurological and neurodegenerative disorders, endocrinology, cardiovascular disease and diabetes, autoimmune disease, development and behavioral issues, HIV/AIDS, and geriatrics.

Advanced Nutrient Therapy For ADHD, Mood, and Behavioral Disorders

by Dr. Jason Loken, ND, DOMP, RMT, PhD (cand)

There is no debate that attention deficit and hyperactivity disorder (ADHD) diagnoses have skyrocketed over the past decade, but why? Are we really living in a time where such a large percentage of our children are unable to manage their behavior, their temperament, their focus, their impulsivity, and their ability to learn?

Let's take a look at the prevalence of ADHD diagnoses in the United States. According to the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013), 5% of children have ADHD.[1] However, other studies in the US have estimated much higher numbers. For example, in a 2016 Centers for Disease Control and Prevention study, scientists found that 6.1 million children (9.4%) aged 2-17 years living in the US had been diagnosed with (ADHD).[2]

In a recent study published in 2018, researchers reviewed data on 186,457 children and adolescents aged 4 to 17 years. The data was collected from the National Health Interview Survey, an in-person interview that the Centers for Disease Control and Prevention conducted annually from 1997 to 2016. It was found that the rate of ADHD diagnoses in this group of children and adolescents rose from 6.1% in 1997-1998 to 10.2% in 2015-2016.[3]

Between 2003 to 2011 the prevalence of ADHD increased by 42%,[4] with increases in nearly all demographic groups in the United States regardless of race, sex, and socioeconomic status. Eleven percent of school-age children in the United States now meet the criteria for the diagnosis of ADHD; one in five boys and one in 11 girls meet the criteria.[4]

There is no question that the data supports a dramatic increase in the prevalence of ADHD but why? In my opinion there are generally three accepted explanations for the explosion of ADHD diagnosis over the past two decades. These explanations include the following:

1. An increased awareness of ADHD and better case finding.
2. An over-diagnosis and misdiagnosis of ADHD based on heuristics, unclear rules of thumb, rather than adhering to recognized diagnostic criteria. Boys in particular are substantially more often misdiagnosed compared to girls.[5]
3. A real problem due to factors that are affecting our children's health and making them sicker and more susceptible to ADHD.

Although there is much debate as to which of these factors or combination thereof are responsible for the rise in ADHD diagnoses, what I can tell you is that, clinically I have seen a significant increase over the past 17 years in the number of children I see that do have challenges managing their behavior and attention. I have also spoken with many teachers who have been in the field for fifteen to twenty years or more who often tell me exactly the same thing. So, what's in the proverbial water that's impacting all of our kids in such a negative way?

There is an ever-growing list of theories for the rise in ADHD. You may have heard everything from changes in home and family dynamics and parenting, both parents working, less focused attention to our children, the increase in screen time, and the fast-paced nature of our modern world, the refinement of our foods, the increases in chemicals, GMOs, glyphosate, sugar, and the ever increasing food sensitivities we see.

We also can't forget the sedentary nature of our kids' lives, less physical activity, obesity, video games, the increase in EMF pollution, as well as the substantial increase in vaccinations. This potential list of possible contributing factors could go on and on depending on which expert you decide to talk to.

What I have become extremely curious about over the past several years in regards to ADHD is whether or not there are any measurable changes in the pathways that govern how people think, feel, and act—in a nutshell, our brain chemistry. The problem I kept coming up with was finding a reliable way to clinically assess which pathways were out of balance, why they were out of balance, and ultimately how to correct it so these children can get their brain chemistry back in check and improve the trajectory of their life.

It was about four years ago that I was sitting in my car listening to a podcast on Bulletproof Radio. Dave Asprey was interviewing a legend in the world of orthomolecular psychiatry, Dr. William Walsh of the Walsh Research Institute (WRI). I was elated when I heard Dr. Walsh talk about the biochemical therapy that the WRI teaches doctors. Dr. Walsh's research

suggests that mental illnesses are largely epigenetic in origin. It has been discovered that environmental factors such as toxic exposures and nutrient imbalances can cause genes to express themselves improperly and influence many psychiatric disorders.[6] Research in epigenetics has discovered several nutrients that have profound effects on the transporters at neurotransmitter synapses leading to too little or too much available neurotransmitter.[7,8]

The WRI is founded on over 35 years of clinical research and a massive database containing millions of chemical factors in blood, urine, and tissues in patients challenged by behavior disorders, ADHD, autism, anxiety, depression, bipolar disorders, schizophrenia, and Alzheimer's disease. There are over 1.5 million chemical assays from testing over 10,000 patients with behavioral disorders and 5,600 patients with ADHD alone.[9,10] It has been discovered that approximately 90% of these individuals have significant imbalances in brain chemistry that can often be corrected using advanced nutrient therapy. By the end of the podcast I had already contacted the Walsh Research Institute and signed up for my first practitioner-training program.

Advanced nutrient therapy offers an alternative treatment approach to pharmaceutical medications. Through the targeted prescription of vitamins, minerals, and amino acids, a natural method of correcting imbalances in neurotransmitter activity can be attained. The clinical challenge is to determine biochemistry of each patient and to develop an individualized treatment plan aimed at normalizing brain chemistry. For most patients, the benefits of advanced nutrient therapy result from the following[11]:

- Normalizing the concentration of nutrients needed for neurotransmitter synthesis;
- Epigenetic regulation of neurotransmitter activity; and
- Reducing free radical oxidative stress.

What I have found most impactful from this training is that we can now narrow down with accuracy which

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Case Report of a 12-Year-Old Male Diagnosed with ADHD and Anxiety Disorder

Primary symptoms:

- Diagnosed with anxiety disorder and ADHD;
- Doctor wanted to put him on stimulant medication to assist with ADHD symptoms;
- Extremely poor stress control;
- Very sweet kind child most of the time;
- Extreme mood fluctuations often triggered by stress, changes in routine, and socially fitting in at school;
- Academic underachievement;
- High anxiety, addicted to video games and screens;
- Began biting himself and self-harming when he was in a meltdown;
- Very sensitive and emotional child;
- White spots on fingernails.

This child has a very sweet disposition with caring parents. It was suggested by his GP to start a trial of Ritalin for ADHD and see how he improves. The parents wanted to try other treatment options first before resorting to medications.

His diet has been well balanced, and he has a good appetite other than morning nausea on occasion. He seemed to be generally sensitive to brighter lights and gets overwhelmed and distracted when there are more stimuli in a room such as noises, lights, and additional people. He was very sensitive to the feelings of others and picks up quickly on the emotional climate around him. He loves animals and finds much comfort just playing with his dog.

Lab Results

Initial lab results revealed that this patient had several imbalances at the same time. He had extremely low levels of zinc, was overmethylated, and had very high levels of pyrroles.

Pyrroles are assessed through a urine test and done at a specific lab that is very familiar with testing pyroluria. Normal levels are between 0-10 and his levels were 93.79. This was a very elevated level and likely the reason for his very low zinc levels. Levels this high it would make it virtually impossible for him to be able to self-regulate, and he probably had never known what is has felt like to be calm in his body.

Treatment

The main treatment to address the elevated pyrrole included zinc picolinate and high levels of B6 and P5P, vitamin C, selenium as well as biotin, borage oil, and vitamin E.

The treatment for overmethylation included niacinamide, folinic acid, and sublingual B12.

Once treatment started the biggest difficulty was consistency with the nutrient therapy; but once the family got into a routine, he was able to commit to a relatively consistent daily schedule.

The family started to notice that within a month his stress response was improving. He was no longer biting or hurting himself; his episodes that were described as severe meltdowns started to be less intense and less frequent. His social anxiety at school decreased, and he was interacting in more social events, including hip hop classes and performing at a school talent show. His ability to focus on schoolwork also started to improve little by little as the weeks and months went by. White spots on the fingernails disappeared, and medications were never required.

I encouraged the family to see an occupational therapist to assist with developing more social skills now that the biochemistry was more in balance.

It took a while to get his labs rechecked as this child had a strong aversion to getting needles; but when we re-checked his pyrrole levels, which was the main imbalance, his levels reduced from 93.79 down to 17.51. He still feels best when he is maintaining his regime of supplements. The dosages for the specific nutrients will vary depending on his future lab results.

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pathways are not functioning properly and, with precision, know how to treat it with targeted nutritional therapy. In order to do this, a detailed clinical intake is required as well as specific labs through blood and urine. Both the clinical symptoms and labs are weighted equally in making the diagnosis. There can be several different imbalances, sometimes referred to as biotypes, at play causing a child to display behavioral and ADHD symptoms. Each biotype is treated uniquely; this is why it is vastly important to figure out the root imbalance. For example, when we look at ADHD there are actually seven different chemical imbalances that are often at the root of the problem.[10] According to an outcome study from 2004,[12] involving 207 patients diagnosed with a behavioral disorder at the Pfeiffer Treatment Center over a 10-year period the imbalances discovered were as follows:

1. Elevated copper/zinc ratio: 75.4%
2. Overmethylation: 29.5%
3. Undermethylation: 37.7%
4. Pyrrole disorder 37.7%
5. Heavy metal overload: 17.9%
6. Glucose Dyscontrol: 30.4%
7. Malabsorption: 15.5%

A child may have any one or combination of them. Each biotype has its own set of unique symptoms based on the way that it is affecting brain chemistry.

According to the WRI some of these imbalances affect brain chemistry in the following ways.[10] An elevated copper:zinc ratio can lead to depleted levels of dopamine and elevated levels of norepinephrine causing symptoms such as episodic rage, poor attention, and hyperactivity. A pyrrole disorder may cause a severe deficiency of zinc and B6 leading to decreased levels of serotonin and dopamine causing the child to have symptoms such as poor stress control, sensitivity to lights and sounds, and explosive anger. Undermethylated individuals, aka histadelia, have too little methyl and will have elevated blood histamine and low serotonin levels. They are more likely to suffer with symptoms such as depression, perfectionism, seasonal allergies, defiance, and obsessive-compulsive tendencies. Whereas overmethylated, aka histapenia, patients would have low histamine and elevated levels of dopamine, serotonin, and norepinephrine and be more prone to anxiety, panic attacks, paranoia, and depression. All of these patients may be diagnosed with ADHD, but the treatment is unique to the underlying biochemistry that is out of balance. Not only can the improper treatment be useless, it could aggravate the condition and make things far worse.

I love this approach because it is very individual, systematic and clinically reliable. In my opinion every child struggling with symptoms of ADHD or a behavioral disorder should get tested first to see if there are any brain chemistry imbalances at the root of the problem. For certain biotypes, medications such as Ritalin or a serotonin reuptake inhibitor may be quite effective; for others it could be devastating. If we understand the root imbalance, we can often address the underlying cause through nutritional therapy with little to no side effects.

The research suggests that there are a number of factors, both biophysical and psychosocial that can have a powerful influence on epigenetic tags and disease susceptibility.[13-15] For example, emotional or physical trauma, nutritional imbalances, and toxin exposure may all alter epigenetic gene expression potentially setting in motion brain chemistry imbalances. Once the epigenetic imbalance has been established, we need to assist the patient in switching it back off. Advanced nutrient therapy is a very viable solution for ADHD, mood and behavioral imbalances that may be epigenetic in origin.

I am a firm believer in the need for good parenting and a loving environment, teaching kids ways to self-regulate, getting them to move their bodies and become more active, and eating healthy foods; yet if there is a chemical imbalance, all of these strategies are limited. For example, imagine being asked to do mindfulness techniques or cognitive/behavioral therapy if your body is biochemically elevating your norepinephrine levels, or if you don't have enough serotonin or dopamine to actually focus or feel good; it is virtually impossible. Once the underlying imbalance is supported then the child can more fully embrace all of these wonderful strategies and move towards a life that is much less struggle and much more fulfilling.

Dr. Loken, ND, DOMP, RMT, PhD (cand) is passionate about transforming our beliefs around healing and embracing our limitless potential. With over 20 years in natural health care, he has founded the Centre For Integrative Medicine, a healing center that amalgamates his training in integrative medicine, naturopathic medicine, osteopathy, applied kinesiology, registered massage therapy, and the Walsh mental health approach.

Dr. Loken is the former professor of Orthopedics and Physical Medicine at the Canadian College of Naturopathy. He lectures internationally and has appeared on both television and radio discussing topics such as disease prevention, optimal health, stress management and mental health.

In his expanding efforts to bring care and ease into people's lives and ultimately this world, Dr. Loken has co-created a support organization called GlobalShifts, He is the author of two books including the inspirational book, *Letters that Move the World; intentional acts of gratitude*. The vision of this book is to create a focused moment for positive change in our world. His most recent book, *Understanding to Knowing: Unlocking Your Path to Optimal Health*, assists individuals back into the driver's seat of their own health and offers practical solutions to a myriad of health problems. It is his sincere belief that when we take the time to truly care for ourselves, we ignite our innate capacity to care for others and ultimately our world.

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Alzheimer's Redefined:
Nutritional Lithium as the Foundation for Prevention

by James Greenblatt, MD

Adapted from his book *Integrative Medicine for Alzheimer's*
(Victoria, BC: FriesenPress; 2018)

In the time it has taken you to read the title of this article, someone somewhere in the world has developed dementia. Approximately 50 million people on the planet currently live with some form of this neurodegenerative disorder, and epidemiologic data reveal incidence rates to be on a meteoric rise.[1] Projections from the WHO forecast the number of cases to rise to 152 million by 2050, meaning that the global dementia burden will more than triple within the span of a single generation and leave an unprecedented population of sufferers to battle an invisible and, ultimately, lethal foe for which there is no cure.[1] Alzheimer's disease (the most common form of dementia) ranks sixth amongst the top ten leading causes of death in the US and is the only physiologic ailment amongst the top ten that cannot be remedied through pharmaceutical intervention. Attempts to find a cure for Alzheimer's and other neurodegenerative illnesses have thus far been met with stoic failure; and despite decades' worth of research and billions of dollars invested, viable solutions continue to elude the medical community.

Progressive memory loss that interferes with the tasks and activities of daily living is *not* considered to be a normal part of aging. In fact, the latest research demonstrates that the biologic processes that precipitate cognitive decline may commence decades before symptoms begin to manifest.

From one perspective, the discovery that Alzheimer's has a lengthy prodromal period is truly frightening. The knowledge that the biologic processes underlying Alzheimer's can in some be active up to four decades *before* cognitive deficits are observed adds a "Sword of Damocles-esque" facet to what is already a devastating disease. The plaques and tangles characteristic of Alzheimer's may accrue silently for years, until the day comes that the scales of neuronal health and degeneration tip irrevocably towards decline. And, as so many pharmaceutical studies have shown, once a person begins to exhibit functional cognitive deterioration, little can be done: symptomatic presentation remains a tragic point of no return for Alzheimer's sufferers and the basis for what is justifiably termed a public health crisis.

From another perspective, however, the knowledge that Alzheimer's develops slowly over a long period of time is cause for hope. A prodrome presents a window of opportunity, a chance to modify certain etiologic factors while they remain modifiable. And, as a growing body of scientific evidence suggests, many of the processes underlying Alzheimer's pathogenesis are indeed modifiable. Factors such as these are tools than can be wielded to potentially significant effect in a treatment approach centered upon *prevention* and may have the power to turn the tide in our battle against Alzheimer's and dementia. No longer must we approach neurodegenerative illness as a foregone conclusion; the newest model of disease pathogenesis offers us a chance to proactively steer neurologic aging along a course toward health.

Amidst a flurry of new research geared towards substantiating and operationalizing this new Alzheimer's prevention model, one remedy shows potential above the rest. From a long and controversial past, the mineral **lithium** has lately emerged as one of the most powerful and promising treatments available for neurodegenerative illness.

Understanding Alzheimer's Disease

Alzheimer's is a tragic neurologic malady characterized by a progressive and irreparable shrinkage of brain tissue, which leads inevitably to declines in memory, social communication and, eventually, to death. This slow, progressive, and cumulative patterning explains why most Alzheimer's patients don't present with symptoms until over the age of sixty-five.

Pathologically, Alzheimer's is the product of two trademark lesions that occur at the cellular level: plaques and tangles. **Plaques** are formed by deposits of small protein fragments called amyloid-β (or β-amyloid) peptides, which choke the synapses through which signals are transmitted between neurons and effectively block cell-to-cell communication in certain regions of the brain. Often simultaneously, other lesions called **neurofibrillary tangles** develop within the neurons themselves. These tangles result from a disruption in the production of a different protein called **tau**. Normally, tau filaments

help to circulate nutrients and other essential supplies throughout the cell. In Alzheimer's disease, however, these strands destabilize, becoming twisted or 'tangled.' Without a functional tau system to circulate vital compounds, the neurons starve or die. The result? The cellular and intracellular processes required for the creation, storage, and retrieval of memory are disrupted, the biologic process of learning is halted, and cognition deteriorates.

There is evidence to show that plaques and tangles may actually be a common malformation in the aging human brain. New research has revealed that plaques can appear a full thirty to forty years before symptoms of cognitive decline begin to manifest.[2] A recent study published in the *Journal of the American Medical Association* presented the following statistics: ten percent of *healthy* fifty-year-olds have detectable amyloid deposits; this figure swells to thirty-three percent by age eighty, and forty percent by age ninety.[3] Individuals with a mental illness – specifically, patients with depression or bipolar disorder – are at an even greater risk of developing amyloid precursors.[4]

Nutritional Lithium: The Unlikely Treatment

The mineral lithium has shown tremendous promise for the treatment and prevention of Alzheimer's disease. This humble element has an extensive history of medicinal use, founded in its long-established benefits for a range of physical, emotional, and mental ailments.

By the time lithium was first isolated as a mineral salt by Swedish chemist Johan August Arfvedison in 1817, its use in traditional medicinal preparations had already spanned millennia. The Greek physician Galen (130-200 C.E.) advised patients suffering from disorders of the spirit to bathe in and drink the waters of the natural springs located in Ephesus – which, we know now, had a high lithium content. These lithium-rich mineral springs, and others throughout the world, remain and continue to be sought-after health destinations, frequented through the ages by rulers and commoners alike.

Throughout the 19th and early 20th century, lithium was used as a supplement to fortify a variety of foods and beverages. The third edition of the *Merck Index*, published in 1907, listed forty-three different medicinal preparations containing lithium[5]; the following year, the *Sears, Roebuck & Co. Catalogue* advertised Schieffelin's Effervescent Lithia Tablets for a variety of afflictions.[6] These formulations were evidently very popular, inspiring soft drink inventor Charles Leiper Grigg to create a new "lithiated" beverage in 1929. Leiper called it Bib-Label Lithiated Lemon-Lime Soda, and it was marketed for its potential to cure hangovers and lift mood.[7] This drink, better known to us today as 7-Up, contained lithium citrate until 1950.

The more lithium in the groundwater, the healthier was the population.

As lithium is distributed throughout the earth's crust, it is found naturally in food and water as a consequence of its presence in soil and bedrock. The US Environmental Protection Agency has estimated that the lithium intake of the average adult ranges from approximately 0.65-3.0 mg/day. Grains and vegetables are the primary sources of lithium in the standard Western diet, with animal products like eggs and milk providing the rest. As the human body cannot synthesize lithium on its own, consistent dietary intake is important. The WHO added lithium to its list of nutritionally essential trace elements in 1996, and in 2002 an article published in the *Journal of the American College of Nutrition* established a recommended daily allowance for lithium – thus cementing lithium's status as an essential mineral.[8,9]

In modern medicine, lithium is most well-known and frequently utilized for its ability to stabilize mood in individuals with affective disorders. A substantial body of strong empirical evidence, derived from research and clinical use, demonstrates that high-dose pharmaceutical lithium restores brain and nervous system function through a variety of biologic pathways. Lithium's demonstrated efficacy is such that it is considered a first-line intervention for bipolar disorder, and it is thanks to its extensive history of use for bipolar disorder that we have learned of its potential as a treatment for cognitive decline.

Researchers working with bipolar patients began to suspect that lithium may confer more than balanced mood when longitudinal and retrospective analyses revealed that subjects taking lithium displayed lower rates of dementia than did those taking other medications. In an attempt to validate this finding, one study compared Alzheimer's prevalence in sixty-six elderly bipolar patients on chronic lithium therapy with forty-eight patients who were not being treated with lithium.[10] The results were staggering: lithium therapy reduced the prevalence of Alzheimer's to levels observed in the general elderly population, with just five percent of patients in the lithium group presenting with Alzheimer's as compared to thirty-three percent in the non-lithium group. A research series conducted in Denmark explored the lithium-Alzheimer's association using differential study designs and achieved strikingly similar results: a survey of the records of over twenty-one thousand psychiatric patients revealed that lithium therapy was associated with a decreased prevalence of dementia and Alzheimer's.[11, 12]

Bolstered by findings such as these, many within the scientific community were eager to explore the utility of lithium as a treatment for neurodegenerative illness in experimental settings. Unfortunately, the first clinical trials testing lithium with dementia patients proved disappointing, likely owing to the fact that researchers have thus far attempted to incorporate lithium into the same ameliorative model employed by pharmaceutical companies, i.e. testing lithium on patients who have already developed

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Alzheimer's. As pharmaceutical trials have demonstrated time and again, there is little that can be done to correct the damage to a brain in the advanced stages of neurodegenerative illness, and in this respect lithium appears to be no different.

In 2011 a team led by O.V. Forlenza turned away from standard ameliorative paradigms and instead examined lithium's potential as a prophylactic.[13] In a study designed to determine whether long-term lithium treatment could *prevent* Alzheimer's in high-risk individuals, forty-five subjects with mild cognitive impairment (MCI, a precursor to Alzheimer's) were randomized to receive lithium or placebo for twelve months. Over the course of the trial, lithium doses were maintained at sub-therapeutic levels (150-600 mg/day) to minimize the risk of potential side-effects. Analyses conducted at study conclusion revealed that subjects in the lithium group displayed a decrease in levels of tau proteins as compared to pre-trial levels. This finding came in stark contrast to that of the placebo group, in which overall tau levels rose steadily throughout the study. Equally as impressive, lithium treatment was associated with performance improvement on the cognitive subscale of the Alzheimer's Disease Assessment Scale test and in various attentional and memory-related tasks.[14] Lithium tolerability was determined to be good as patients reported limited side effects, and the overall adherence to lithium treatment was an impressive ninety-one percent. The researchers concluded that lithium had a significant preventative impact on Alzheimer's when administered in early stages of disease pathogenesis.

The Promise of Low-Dose Lithium

Evidence corroborating the efficacy of low-dose lithium has come primarily from epidemiologic studies in which groundwater assays have uncovered stunning correlations between lithium levels and psychiatric disorders. Between 1970 and 2013, eleven different studies involving over ten million subjects examined lithium levels in drinking water from regions around the globe and compared them to rates of suicide, violent crime, psychiatric hospital admissions, substance abuse, and overall mortality in the same locales.[15-20] Nine of the eleven studies revealed significant inverse associations between lithium and rates of adverse health outcomes; in other words, the more lithium was present in the groundwater supply, the healthier the local population was found to be.

Inspired by these incredible findings, two recent studies narrowed the scientific gaze on associations between groundwater lithium and rates of dementia and Alzheimer's. The first, a nationwide study conducted in Denmark, explored whether dementia incidence in the general population was correlated with long-term exposure to lithium in drinking water.[21] Lithium exposure was significantly different between participants who received a diagnosis of dementia or Alzheimer's during the study period (January 1, 1970 and December 31, 2013) and healthy controls: the median level of exposure for the former was determined to be 11.5µg/L, whereas the median level of exposure for controls was 12.211.5µg/L.

The second study, published in 2018 by the *Journal of Alzheimer's Disease*, examined the relationship between levels of lithium in drinking water and variance in rates of Alzheimer's mortality across Texas.[22] Lithium levels were assayed from 6,180 water samples collected from public wells since 2007, and averaged for 234 Texas counties. These levels were compared to Alzheimer's mortality rates while adjusting for a variety of environmental and physiologic risk factors (e.g. gender, air pollution, obesity, type II diabetes). Results were stunning: not only was Alzheimer's mortality significantly and inversely correlated with lithium levels, but the correlation remained significant even controlling for most risk factors. In fact, higher lithium levels were associated with lower rates of obesity and type II diabetes – both of which are independent risk factors for Alzheimer's disease.

While these findings are remarkable and have spurred global interest in the clinical applications of low-dose lithium, the transition from evidence to real-world application has been slow. As lithium is a naturally occurring mineral and cannot be patented (and is thus not profitable), financial investments into trials exploring the viability of low-dose lithium for dementia and Alzheimer's have generally been few and far between.

The magnitude of what we are all facing when it comes to Alzheimer's and dementia and the incredible, empirically corroborated potential of lithium as neuroprotective agent should trump any and all proprietary considerations, however. Additional large-scale, high-quality clinical trials using low-dose lithium are essential.

Key Neuroprotective Mechanisms

Not only is there a significant and still-growing body of evidence demonstrating that lithium is neuroprotective, but biomolecular research has shed light onto the very mechanisms through which lithium confers its protective effects. Most significantly, lithium has been found to disrupt the key enzyme responsible for the deposition of amyloid plaques and neurofibrillary tangles – the biologic hallmarks of Alzheimer's. This enzyme is glycogen synthase kinase-3 (GSK-3), which normally plays a major role in neuronal growth and development. In the healthy brain, GSK-3 is critically important, as it helps to drive the synaptic remodeling necessary for the formation of memory.

In the Alzheimer's brain, however, GSK-3 becomes hyperactive in regions that control behavior and cognition, including the hippocampus and frontal cortex. When in such a state, GSK-3 can itself activate proteins within neurons – proteins that shouldn't be activated – such as amyloid-beta and tau. Eventually, these proteins are synthesized and activated faster than the normal processes of metabolic degradation can clear them, and they build up to form the signature plaques and tangles that disrupt brain function and result in a progressive cognitive decline. Lithium

functions as a direct GSK-3 inhibitor to prevent this overexpression, halting inappropriate amyloid production and tau activation before these proteins become problematic.[23,24]

In addition to protecting the brain from the development of plaques and tangles, lithium has been shown to repair existing neuronal damage caused by Alzheimer's. For example, lithium ions encourage the synthesis and release of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), which in turn stimulate neuron growth and repair.[25] Neuroimaging studies have shown that the brains of patients taking lithium have significantly higher gray matter volumes, suggesting that lithium has powerful stimulatory effects on processes relating to neurogenesis. One study has even directly demonstrated that damaged neurons exposed to lithium respond with increases in dendritic number and length.[26]

Lithium's story certainly does not end here, and we likely have only scratched the surface as far as elucidating the mechanisms through which it supports brain health. Beyond promoting neurotrophin synthesis and inhibiting GSK-3, recent studies have confirmed that lithium influences NMDA receptors, protein synthesis and modification, transcription factors, cellular autophagy and apoptosis, inflammatory mediators, glutamate excitotoxicity, microglial activation… and the list continues to grow.[27] The more we seem to learn about lithium, the more powerful the argument for its continued research and incorporation into Alzheimer's prevention strategies becomes.

Conclusion

As we have explored, the numbers associated with Alzheimer's disease are staggering. Countless hours, decades of research, and millions of dollars have been poured into global efforts to combat this disease; and yet we are hardly better off today than we were 10…30… even 50 years ago. While we know more about the biologic mechanisms underlying Alzheimer's than ever before, incidence rates continue to climb. Pharmaceutical companies have invested billions in the hopes of finding a cure and have little to show for it but a string of abandoned drug trials.

Instead of viewing Alzheimer's through a lens of inevitability, we can accept that Alzheimer's susceptibility lies along a continuum of risk which is dynamic *and thus alterable*. Instead of taking reactionary steps to an already-established case, we can focus our efforts on *prevention*. Instead of focusing on one singular disease pathway and trying to arrest it, we can use low-dose lithium to foster brain health through a variety of pathways.

An impressive body of scientific research confirms that lithium bestows powerful neuroprotection through a multitude of biologic mechanisms, many ➤

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of which directly slow or inhibit the pathologic cellular cascades from which Alzheimer's emerges. Furthermore, it has been shown to decrease levels of existing amyloid plaques and neurofibrillary tangles which for at-risk individuals is an enormously significant discovery.

In addition to its established efficacy as a neuroprotective agent, lithium's strong safety profile makes it a particularly attractive treatment, as prevention strategies for dementia are most efficacious when initiated early and continued over a long period of time. And it doesn't take a lot of lithium: studies have shown that lithium may in fact be most effective in preventing age-related neurologic decline when used at safe, affordable micro-dose levels; studies have confirmed that doses as low as 300 µg/day exert measurable neuroprotective and cognition-enhancing effects.[28]

Low-dose lithium offers the best strategy currently available to protect the brain from the devastation of neurodegenerative disease. This strategy, in concert with a shift in focus towards prevention, offers patients and medical practitioners, worldwide, legitimate hope that the tide of Alzheimer's disease can be turned.

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A pioneer in the field of integrative medicine, James M. Greenblatt, MD, is dually board-certified in adult and child and adolescent psychiatry with over three decades of experience treating clients with mood disorders, eating disorders, and other mental illnesses. His knowledge in the areas of biology, genetics, psychology, and nutrition as they interact in the treatment of mental illness has made him a highly sought-after speaker, and he has lectured internationally on the scientific evidence for nutritional interventions in psychiatry. Dr. Greenblatt has also published multiple books and articles for professional and consumer audiences on how to employ a comprehensive approach toward mental health treatment. His book series *Psychiatry Redefined,* which includes *Integrative Medicine for Alzheimer's* from FriesenPress, draws upon his many years of experience treating complex and diverse patient populations. Dr. Greenblatt currently offers online courses for medical and health professionals as well as specialized fellowship programs in integrative psychiatry.

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Moldy Buildings, CIRS, Sick People, and Damaged Brains: 25 Years of Research Brought Us to the Cure Word, Part 3

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Editor's Note: Exposure to mold in water-damaged buildings causes a frustrating number of puzzling symptoms and eventually leads to chronic inflammatory response syndrome (CIRS), as explained in the first article of this five-part series, published in the July 2019 issue. In Part 2 (August/September 2019), the authors explained the importance of maintaining the building envelope in order to prevent health-damaging mold from infesting buildings.

CIRS Diagnosis

When we think of chronic inflammatory response syndrome (CIRS) in 2019, our initial case definition has been expanded to include not only

1. abnormal proteomics;
2. abnormal regulation of immune functions and hormonal feedback loops;
3. loss of neuropeptide regulation of the above;
4. but also, abnormal transcriptomics;
5. together with suppression of ribosomal and nuclear encoded mitochondrial genes.

In the text that follows these terms will hopefully become clear and begin to act as your friend. Suffice to say, these CIRS illnesses are all around you; but of possible greater importance, the concepts of (6.) dysregulation of inflammation and (7.) dysregulation of gene transcription set the precedent for looking at underlying inflammatory bases for other illnesses, including autoimmune problems, diabetes, obesity, atherosclerosis, and neurodegenerative processes in a new light.

Clinical Case Definition: Chronic inflammatory response syndrome (CIRS) is a chronic illness acquired following the exposure to the interior environment of a water-damaged building (WDB) with resident microbes including, but not limited to, filamentous fungi, bacteria, including actinomycetes and mycobacteria; and their toxins and inflammagens, including, but not limited to, hemolysins, beta glucans, mannans, and spirocyclic drimanes. Cases with CIRS-WDB will have multisystem, multi-symptom illness. Presence of multiple reliable objective biomarkers, taken as a group but not individually, will aid in diagnosis and in monitoring therapy. Markers include genetic haplotypes, innate immune inflammatory elements, deficiency in neuroregulatory peptides or their receptors, dysregulation of pituitary and end organ endocrine factors, as well as clearly defined abnormalities in transcriptomics.

There are at least 30 entities found inside WDB that individually and collectively can set off innate immune responses.[1] Indoor exposure will perpetuate these responses with eventual differential gene activation providing a mechanism for inflammatory compound production in the absence of ongoing exposure. Some of these inflammatory elements are well known. Endotoxins made by Gram-negative rod bacteria and actinomycetes, long overlooked but of marked importance and second only to endotoxins as activators of dysregulated gene activity, all cause differential gene activation.

We also know there is a pathogenic role for mycotoxins, albeit much smaller than thought just a few years ago. As additional research is becoming clear, mycolactones, made by mycobacteria, also have an inflammatory role. Of importance, are beta glucans, mannans, hemolysins, proteinases as well as cell wall fragments, hyphal fragments, and particulates found in reservoirs in air, including small, fine and ultra-fine particulates. We have not yet defined adequately a pathogenic role for mVOCs (microbial volatile organic compounds), but consensus opinion supports mVOCs having some ill-defined role in creating adverse human health effects. References for these important entities are found in the 2015 Medical Consensus Report on the Surviving Mold website.

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Differential Diagnosis, Other CIRS: Even though CIRS caused by exposure to the interior environment of WDB remains the most important source of CIRS, there are other important exposures that must be included in differential diagnosis. These include consumption of ciguatoxic fish found on tropical reefs. We must also look to see if there is exposure to freshwater bodies with resident blue green algae (cyanobacteria), found in every state of the Union. CIRS is also found in post-Lyme syndrome[2] and the rarely observed bites from recluse spiders. Of interest, is the discussion coming from the chronic fatigue syndrome (CFS) community commenting on CFS as a CIRS as well. Traumatic brain injury, including concussion and repetitive head injury from either concussive force such as firing artillery weapons or athletic competition with head contact, can set off innate immune responses that appear similar to CIRS is some ways.

Federal Agency Case Definition: In 2008, the US GAO provided us with a federal agency approved case definition that includes (1) potential for exposure; (2) symptoms like those seen in published, peer-reviewed literature; (3) laboratory findings similar to those seen in published, peer-reviewed literature and (4) response of objective parameters to treatment. This case definition provides flexibility for the clinician but also demands a benchmark of documentation of objective parameters to be found before a person can be labeled as having CIRS or an illness caused by exposure to a wet building.

In **differential diagnosis**, a process that sorts illnesses from non-illnesses, we will see normal laboratory findings of ESR, CRP, CBC and CMP. In addition, CIRS usually has normal thyroid functions, ANA, total IgG, total IgE and IgM. Cholesterol will be normal, and serum protein electrophoresis is normal. Viral studies are often thought to be indicative of ongoing viral infection but according to transcriptomic data are just telling us about intercalation of viral DNA into our own DNA. CIRS cases will usually have a normal EKG, normal pulse oximetry, and normal chest x-ray. There are interstitial lung disease findings less commonly found in CIRS so that chest x-ray must be obtained and reviewed. Of possible interest is the finding that certain cancers are under-represented in CIRS compared to the normal population. These include colon cancer, adenocarcinoma of the lung, and breast cancer (unpublished clinic data).

Looking for biomarkers, VCS (visual contrast sensitivity) deficits are found in 92% of CIRS cases. Analysis of symptoms, using cluster analysis (see Table 1), shows unique findings of 8 of 13 clusters found in adults with CIRS. Children are less often found to have distinctive clusters but finding 6 of 13 is consistent with CIRS in pediatrics. As an aside, reliable peer-reviewed literature[3] has shown that CIRS can extend to single symptoms in children with an emphasis of chronic headache and chronic abdominal pain.

Table 1. Cluster Analysis of Symptoms
Individual categories:

1. Fatigue
2. Weak, assimilation, aching, headache, light sensitivity
3. Memory, word finding
4. Concentration
5. Joint, AM stiffness, cramps
6. Unusual skin sensations, tingling
7. Shortness of breath, sinus congestion
8. Cough, thirst, confusion
9. Appetite swings, body temperature regulation, urinary frequency
10. Red eyes, blurred vision, sweats, mood swings, icepick pains
11. Abdominal pain, diarrhea, numbness
12. Tearing, disorientation, metallic taste
13. Static shocks, vertigo

A positive cluster analysis for biotoxin illness is presence of 8 or more of 13 clusters.

Finding a combination of VCS deficits and positive cluster analysis results in a 98.5% accuracy shown for CIRS with a 1.5% total source of abnormalities in false positives plus false negatives.

On physical exam, it is common to find a resting tremor in cases with this finding best observed by having the patient hold their hands out straight with palms facing down to the floor, spreading fingers as wide as possible. Then a single sheet of paper is placed on the outstretched hands; the fine tremor is easy to see. Hypermobility is commonly seen as well, particularly in those with antigliadin antibodies and anticardiolipin antibodies.

Additional laboratory findings include a distinctive HLA-basis of susceptibility with increased relative risk (RR >2.0); levels of MSH lower than 35 pg/ml; high levels of C4a, TGF beta-1 and MMP-9; with dysregulation of ACTH relationship to cortisol and antidiuretic hormone (ADH) relationship to osmolality. Commonly, there will be either low or high VEGF with one-third of cases each being under 31 or over 86. An abnormal von Willebrand's profile will be found in approximately 66% of patients. Nasal culture showing multiple antibiotic-resistant coagulase negative staph (MARCoNS) will be found in the deep aerobic nasal space in over 80% of cases with low MSH. Of these MARCoNS, over 60% will be resistant to methicillin.

An aside about mycotoxicosis: Since the advent of the shotgun use of antifungal medications to treat "mycotoxin illness," a re-run of what we saw in the ENT literature of the early 2000s, there has been an explosion of creation of frightening antibiotic resistances found in these MARCoNS, known promiscuous exchangers of plasmids and circular DNA, especially when antibiotics and antifungals are used together. Our antibiotic, biofilm-busting nasal sprays that worked wonders with "pre-2015 MARCoNS," no longer worked when azoles were added to sprays. These resistances include resistance to vancomycin and gentamicin! There are multiple additional reasons ***to not use*** **antifungals indiscriminately**, as will be discussed.

Our concerns about unwarranted use of antifungals for mycotoxicosis go to more than the current explosion of deaths from multi-azole resistant

Candida auris, called a "serious global health threat by the CDC" (CBS News 4/9/19); it goes to claims of illness using findings of mycotoxins in urine to diagnose the condition. Yet, there is no published control group data (PubMed search 4/9/2019) showing absence or simply a paucity of mycotoxins in urine in controls compared to cases. Moreover, when we look at the world's literature on urinary mycotoxins, we find scores of papers regarding healthy people with markedly abnormal levels of mycotoxins in urine.

As one reviews findings in CIRS beyond symptoms, VCS, and laboratory findings, depressed VO2 max and reduction reduced anaerobic threshold stand out. These findings, with low VO2 max thought to be related to ME/CFS,[4] are typically found in all sources of CIRS. Simply stated, if one is given capillary hypoperfusion, as seen in CIRS, reduced VO2 max will invariably be found. One must also review the section below on hypometabolism, as our thinking on VO2 max has been radically modified by new data coming from transcriptomics.

We also see elevated pulmonary artery pressure at rest (≥ 30 mm Hg) in CIRS but more often we can confirm that in exercise, PASP pressure usually rises more than 8 mm over baseline in CIRS patients.[5] This problem is called acquired pulmonary artery hypertension.

"Of all the things I have lost, I miss my brain the most." There is a uniquely abnormal fingerprint for CIRS-WDB found on NeuroQuant (NQ) with published evidence so strong that NeuroQuant is now one of the primary ancillary studies that should be done in all patients over age 7 and under age 92.[6-8] We have come to conclude that NQ is uniquely able to demonstrate the dreaded complications of multinuclear grey matter atrophy.

Of significant concern is the increased incidence in CIRS of lateral ventricle enlargement suggesting normal pressure of hydrocephalus but also suggesting atrophy of cortical grey matter. This atrophy extends to grey matter nuclei, which will have a mean incidence of 2.4 out of 6 grey matter nuclei in CIRS-WDB. Post-Lyme syndrome patients show mean atrophy of 3.0/6.

For those patients who have been treated with antifungals, a total of 4.5/6 atrophic grey matter was confirmed.[9] I don't understand taking medications that are optional at a cost of structural brain integrity.

Perhaps of greatest diagnostic and therapeutic importance is the finding of a marked suppression of (1) ribosomal; and (2) nuclear encoded mitochondrial genes in CIRS patients before treatment.

With an eye towards defective antigen presentation, we know that there is no protection from other sources of CIRS provided by a given source of CIRS. Our concepts of an active and effective adaptive immune response don't necessarily apply to CIRS.

Transcriptomics: Perhaps of greatest diagnostic and therapeutic importance is the finding of a marked suppression of (1) ribosomal; and (2) nuclear encoded mitochondrial genes in CIRS patients before treatment. Recovery with use of a published, peer-reviewed protocol (the Shoemaker protocol) has brought new hope that we will finally be able to put aside the longstanding dogma that these illnesses are never cured.

Because of the common findings of CIRS, with over 50% of buildings in the US reportedly having water intrusion and microbial growth, it is a tautology that CIRS doesn't hide.

Unfortunately, CIRS is uncommonly diagnosed outside of the communities dedicated to CIRS. It is quite rare, however, to find patients or providers who don't know someone who is chronically ill from fibromyalgia or CFS. Those diagnoses are ones without objective diagnostic biomarkers; not to mention none that also guide therapy. Once physicians can fill in the CIRS gap that is missing from medical schools and post-graduate CME, they will rapidly learn just how simple diagnosis is and how effective treatments are.

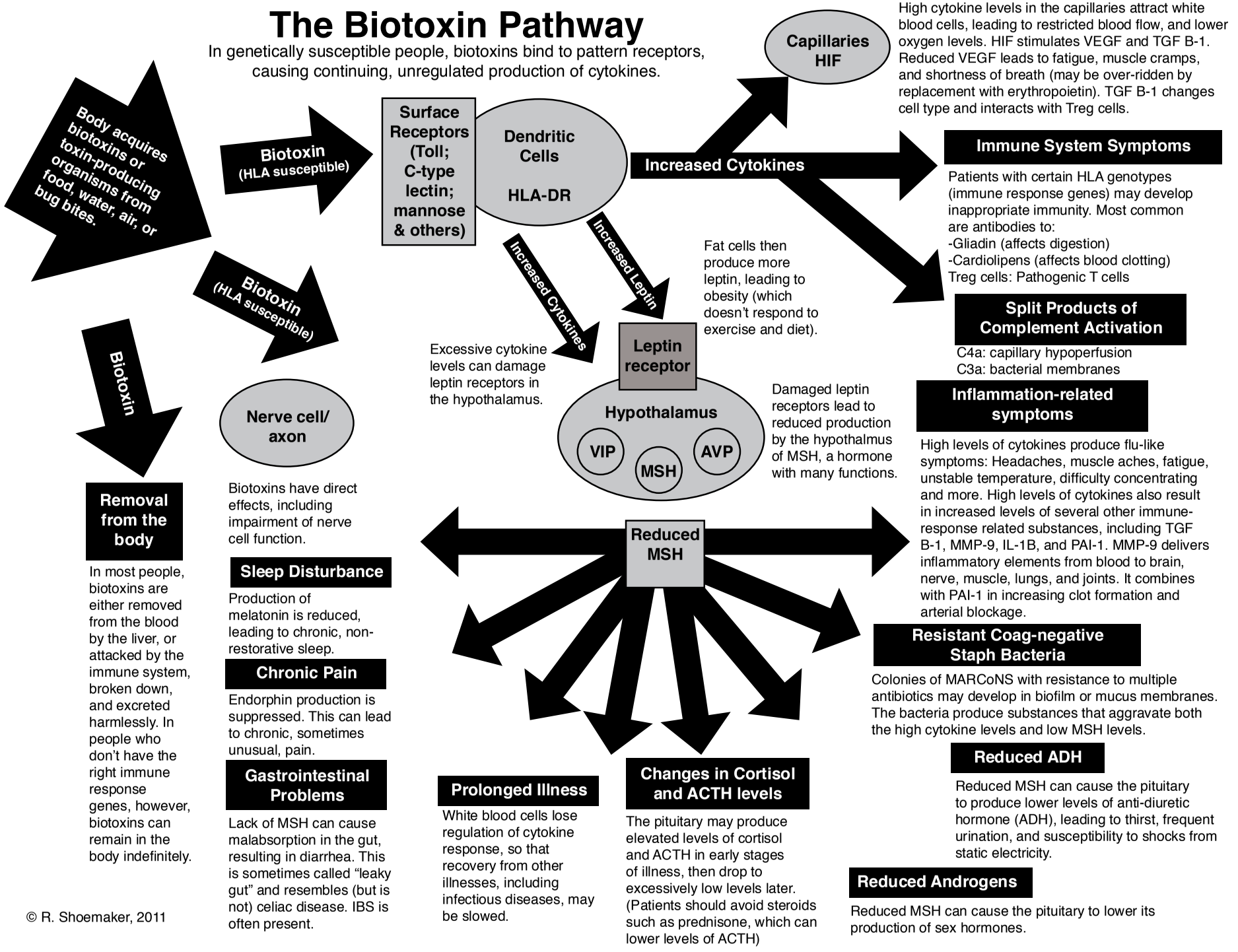
Confirming CIRS: Homing in on the case definition, what does potential for exposure mean? Potential for exposure demands objective findings showing microbial amplification with (1) visible mold; (2i) or presence of musty smells; (3) or determination of the types of molds found by DNA testing. We now add measurements of endotoxins and actinomycetes in modern labs with top-flight molecular methods to diagnostic criteria as these sophisticated assays are now readily available. Remember that musty smells, usually stemming from geosmin made by actinomycetes and occasionally by bacteria, are often used (curiously) to support a diagnosis of a *mold* problem. Use of accurate mold specific QPCR testing is readily and inexpensively available.

Unfortunately, some practitioners still think that air sampling has a role in the medical work-up of CIRS patients. Use of air samples for diagnosis is worse than worthless in that sampling air for spores, at least three microns in diameter or greater ignores ***99.8% of the total amount*** of fragments that cause inflammatory responses! These fragments are so small they pass right through the spore trap devices. Spore trapping then can't possibly be used to look for disease-causing inflammation. Don't forget, exposure to small particles, really just biochemicals, means that the bulk of bad actors in WDB are *not alive*. Please don't tell me to remediate a damp home by killing spores!

Even though spore sampling provides flawed information, that procedure is still widely used. Even worse than wrong-headed data generated by spore traps is the problem that occurs when people *believe that spore trapping makes sense* and that spore counts are indicative of something real in nature. Of note, air samples (1) only done for 5 or 10 minutes in a single-center location in a room do not tell us what has happened to bacteria or fungal spores that have settled out before the sampling; (2) don't tell us what particulates were missed by sampling in the center of a ➤

The Biotoxin Pathway

In genetically susceptible people, biotoxins bind to pattern receptors, causing continuing, unregulated production of cytokines.



High cytokine levels in the capillaries attract white blood cells, leading to restricted blood flow, and lower oxygen levels. HIF stimulates VEGF and TGF B-1. Reduced VEGF leads to fatigue, muscle cramps, and shortness of breath (may be over-ridden by replacement with erythropoietin). TGF B-1 changes cell type and interacts with Treg cells.

Immune System Symptoms

Patients with certain HLA genotypes (immune response genes) may develop inappropriate immunity. Most common are antibodies to:
-Gliadin (affects digestion)
-Cardiolipens (affects blood clotting)
Treg cells: Pathogenic T cells

Fat cells then produce more leptin, leading to obesity (which doesn't respond to exercise and diet).

Excessive cytokine levels can damage leptin receptors in the hypothalamus.

Damaged leptin receptors lead to reduced production by the hypothalmus of MSH, a hormone with many functions.

Split Products of Complement Activation

C4a: capillary hypoperfusion
C3a: bacterial membranes

Inflammation-related symptoms

High levels of cytokines produce flu-like symptoms: Headaches, muscle aches, fatigue, unstable temperature, difficulty concentrating and more. High levels of cytokines also result in increased levels of several other immune-response related substances, including TGF B-1, MMP-9, IL-1B, and PAI-1. MMP-9 delivers inflammatory elements from blood to brain, nerve, muscle, lungs, and joints. It combines with PAI-1 in increasing clot formation and arterial blockage.

Removal from the body

In most people, biotoxins are either removed from the blood by the liver, or attacked by the immune system, broken down, and excreted harmlessly. In people who don't have the right immune response genes, however, biotoxins can remain in the body indefinitely.

Biotoxins have direct effects, including impairment of nerve cell function.

Sleep Disturbance

Production of melatonin is reduced, leading to chronic, non-restorative sleep.

Chronic Pain

Endorphin production is suppressed. This can lead to chronic, sometimes unusual, pain.

Gastrointestinal Problems

Lack of MSH can cause malabsorption in the gut, resulting in diarrhea. This is sometimes called "leaky gut" and resembles (but is not) celiac disease. IBS is often present.

Prolonged Illness

White blood cells lose regulation of cytokine response, so that recovery from other illnesses, including infectious diseases, may be slowed.

Changes in Cortisol and ACTH levels

The pituitary may produce elevated levels of cortisol and ACTH in early stages of illness, then drop to excessively low levels later. (Patients should avoid steroids such as prednisone, which can lower levels of ACTH)

Resistant Coag-negative Staph Bacteria

Colonies of MARCoNS with resistance to multiple antibiotics may develop in biofilm or mucus membranes. The bacteria produce substances that aggravate both the high cytokine levels and low MSH levels.

Reduced ADH

Reduced MSH can cause the pituitary to produce lower levels of anti-diuretic hormone (ADH), leading to thirst, frequent urination, and susceptibility to shocks from static electricity.

Reduced Androgens

Reduced MSH can cause the pituitary to lower its production of sex hormones.

room and not in boundary layers on the bottom and sides of a room; (3) do not separate benign versus pathogenic species of both *Aspergillus* and *Penicillium* (these two very large genera are lumped as Asp/Pen!); (4) will rarely show presence of heavier particulates such as those made by *Stachybotrys*; (5) will never show presence of xerophilic organisms such as *Wallemia sebi*; and (6) without repetition of air sampling findings, multiple times per day in a given room for each of multiple days per week, multiple weeks per month and multiple months per year, the World Health Organization has declared that air sampling is of no benefit.[10]

One reason for the commonality of microbial findings in water-damaged buildings being similar in each of our states, together with foreign countries, is that the indoor ecosystem of a wet building is uniquely similar across all climates. There rarely is any wind, and there certainly is not any rain or frozen precipitation. There is only a narrow range of temperature in an occupied building and only limited diversity of visiting or exotic organisms will be found. Often there will be limited movement of fixed objects in a room, setting up areas of reduced ventilation ("still air"). Fixed walls (not to mention floors and ceilings) create boundary layers of both air and particulates.

MSQPCR (Mold Specific Quantitative Polymerase Chain Reaction) is a marker of presence of different species of filamentous fungi found inside homes, both water-damaged and not. The fungal DNA present *tell us much about the activity of water* found inside the building. The EPA-developed ERMI (Environmental Relative Moldiness Index) purports to quantify an index of microbial contamination in a building from assessment of MSQPCR measured on dust samples. Initially done on vacuumed samples, ERMI was done later using Swiffer cloth wipe samplings, with comparable validity comparing Swiffer to vacuum.

Proper ERMI testing demands accurate use of high-quality probes and primers for detection and reporting. Laboratories that license the ERMI technology from the EPA must be able to show accurate and ongoing quality control. Never send a sample off to a lab that does not have ongoing EPA licensing, as errors are routinely seen with faulty use of primers or inexpensive, inadequate reagents. If a MSQPCR lab won't tell you the quality control methods they use over the phone, don't use it.

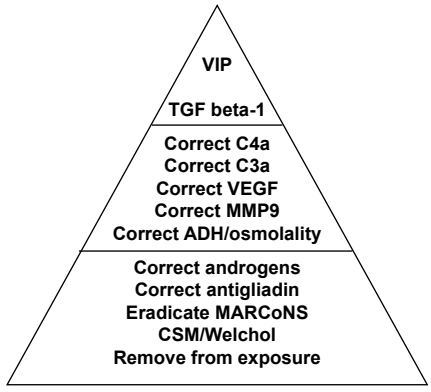
A lab test far more useful than ERMI and more accurate as a measure to show risk of recrudescence with re-exposure of CIRS patients to WDB is the Health Effects Roster of Type Specific (Formers) of Mycotoxins and Inflammagens, Version II (HERTSMI-2). HERTMSI-2 has been in increasingly wide use since its inception in 2011. Its accuracy is based on sorting health abnormalities associated with exposure to WDB to yield five species of fungi that (1) "span the globe," of $A_{(w)}$ from the driest to the wettest organisms; and (2) show the overwhelming increase in CIRS when these specified organisms are found. By relying on correlation of spore equivalents/mg dust with risk of acquisition of adverse human health effects, we finally have a measure that predicts safety (or not) for over 95% of CIRS patients entering schools, workplaces and residences.

We need to remember that MSQPCR will not report bacteria, endotoxins, mVOCs or any other of the inflammagens found in WDB.

The scoring system for HERTMSI-2 weighs severity of contamination from 0-10 points for given organisms. When we sort these organisms by $A_{(w)}$, we find that the drier-loving species of *Wallemia* and *Aspergillus penicillioides* are routinely found in $A_{(w)}$ of 0.65-0.8 but are rarely represented by air samples. The common species of *Aspergillus versicolor*, usually found in higher $A_{(w)}$ of 0.8 to 0.9, are reported by ERMI but are never reported at the species level by spore traps. Presence of *Chaetomium* and *Stachybotrys* reflect environmental conditions with an $A_{(w)}$ of 0.9-1.0 are only detected infrequently in air samples using spore traps.

A word regarding dust collection. Swiffer cloths and vacuum samples are equally useful. If you use a Swiffer cloth, routinely available in a grocery store, use a new Swiffer, one cloth per sample. Put a glove on your left hand and wipe in one direction, either left to right or right to left. Use one cloth for all the sampling. We want you to sample for dust on the back of a shelf and not on the front where it might be more commonly dusted. Don't use window sills or "public" areas, like hallways. I suggest avoiding shoes on closet floors, but closet shelves are fair game. Bathrooms are best avoided because of the role of water saturation following showers or bathing. If there is evidence of obvious microbial growth, resist the temptation to swipe it, as sampling the black patch on the bedroom wall, for example, will skew your sample to render results less reliable. If there is a crawlspace or a sump pump or a basement or an indoor spa or areas in bathrooms that are hampered by low air flow with inadequate exhaust, be sure to test for endotoxins with the same sample used for HERTMSI-2. Testing for abundance of *Actinomycetes* species is of tremendous value, especially when *Aspergillus penicillioides* or *Wallemia a*re predominant. This is not to say that actinomycetes won't grow in wetter environments, but they are more commonly found in drier environments indoors. They also like more alkaline surfaces like concrete that is chronically moist.

Figure 2. The Treatment Pyramid



We have seen that the causation of illness from water-damaged buildings is multi-factorial. We can't just rely on fungal DNA because in a way, what we ➤

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are asking is, "Can we identify specific (only one thing causes the illness) causation of human illness found from water-damaged buildings?" The answer is NO!

Countless different measurements, mostly not available (think about spirocyclic drimanes, known to cause inflammation but for which there are no commercial test available), are needed for 100% surety. We are less able to measure beta glucans and mannans. Moreover, microbial V0Cs are showing great potential to be a biomarker for water-damage, but the human health effects data associated with mVOC exposure is not confirmed. Please note that transcriptomics is changing the "no specific causation" idea. Differential gene activation can tell us if it is likely that reactivity to mycotoxins, actinomycetes, or endotoxins has occurred.

Symptoms

When we look at specific symptoms in CIRS, using a list of 37 symptoms (the same symptoms as seen in Table I, but separated by organ system this time) that have been collated from charts of thousands of cases and each found in more than 30% of cases, we find fatigue and weakness together with headaches, aches, and muscle cramps, defining involvement of three separate organ symptoms. Unusual pains, sharp stabbing pains, clawing pains, electrical pains, comprise their own category (possibly due to activity of transient potential receptor vanilloid (TRPV) activity on sensory neurons). Here we will also find sensitivity to the light touch, especially from water droplets in a shower or rainstorm. Our ophthalmic findings (in addition to visual contrast sensitivity, VCS) are light sensitivity, redness, blurred vision, and tearing. Respiratory issues are shortness of breath, cough and sinus congestions; abdominal pains and secretory diarrhea comprise our abdominal findings. Musculoskeletal problems are quite common with joint pain, especially with morning stiffness, being routinely found in patients over age 25. Of note is that ESR is invariably low normal. Perhaps of greatest importance are the symptoms suggestive of brain injury with executive cognitive dysfunction represented by deficits in recent memory, concentration, difficulty with word finding, assimilation of new knowledge, confusion, and disorientation leading the list. If present, think "brain fog," and get a NeuroQuant.

Hypothalamic symptoms include mood swings, appetite swings, unusual sweats, and difficulty with normal temperature regulation. Our renal findings are excessive thirst, frequent urination, and curiously, increased susceptibility to static shocks, but not just in dry environments. Neurologic findings of numbness, tingling, and taste abnormalities (metallic taste, especially) are common in CIRS. Additional neurologic problems include vertigo and skin tremor (get a NQ!).

Given that symptoms and VCS taken together (see cluster analysis, Table 1) are so accurate, one might reasonably ask, "Why do we need laboratory findings?" The answers are straightforward: (1) we must have an accurate ongoing differential diagnosis; (2) laboratory changes will show interval improvement with therapy or worsening with re-exposure (often not obvious!); (3) findings objectively demonstrate the physiology to interested third parties; and (4) provides opportunity for further study.

Figure 1 is the Biotoxin Pathway. This graphic has stood the test of time. Schematically, it represents the linkage of exposure and illness to laboratory findings. It can be applied to non-CIRS illness, especially Th17/T-reg imbalance.

Figure 2 is the Treatment Pyramid. The Treatment Pyramid has also stood the test of time with a 12-step protocol providing predictable improvement as shown in at least 30 countries around the world and in all 50 United States.

Ritchie C. Shoemaker, MD, remains active in the field of biotoxin-associated illnesses, the focus of his practice since 1997. At that time, an outbreak of unexplained human illness, associated with exposure to blooms of a dinoflagellate, *Pfiesteria piscicida*, attracted his attention and interest. Pfiesteria was the first example of an acute and then chronic biotoxin-associated illness recognized and published in peer-reviewed literature. Shoemaker's two papers on diagnosis and then treatment were the first in the world's literature on acquisition of illness from Pfiesteria in the wild. Since that time, other sources of biotoxin-associated illnesses have come forward including other dinoflagellates, cyanobacteria and, most importantly, organisms resident in water-damaged buildings.

Shoemaker has spent the last 22 years treating patients and conducting research that unveils the extraordinary complexity of these illnesses, now called chronic inflammatory response syndromes (CIRS). Starting with no biomarkers and now progressing to over 25, CIRS has been shown to have abnormalities in proteomics and transcriptomics with differential gene activation, the final ultimate pathway of disease production in the world of chronic fatigue.

His collaboration with Dr. James C Ryan, transcriptomist, has led to multiple publications that have application, not just to chronic fatiguing illnesses but to the inflammatory illnesses of the 21st century including atherosclerosis, diabetes, obesity, and autoimmune illness.

As Shoemaker's work has progressed on the complex problems of grey matter nuclear atrophy, a small but growing cohort of patients with multinuclear atrophy and cognitive impairment have led to improvements that may have application to illnesses such as Alzheimer's disease.

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Probiotics: The Cart Before the Horse?

by Dr. Douglas Lobay, BSc, ND

As a practicing naturopathic physician, I recommend probiotics to patients on a daily basis. I must admit, however, that I am still confused and unsure as to what the proper recommendations are. I am still addled by questions, such as do probiotics really help? What is the best probiotic? What species is better for which conditions? Should I recommend *Lactobacillus, Bifidobacterium, Enterococcus,* or *Streptococcus*? Should I recommend yeast such as *Saccharomyces boulardii*? When should I take them and for how long? How many billions of bacteria should you take? What about prebiotics? I discovered that medical database sites such PubMed, Medline and Cochrane have conflicting information on the benefits of probiotics. I also learned that many of the questions posed do not yet have reliable, empirical and scientific answers. Many unanswered questions about probiotics remain.[1-3]

I was returning with my family from a Christmas vacation to Varadero, Cuba, on a Sunwing 737-800 airplane in December 2018. The flight was uneventful except for the last hour before landing. A stewardess came on the intercom and calmly said there was a medical emergency and asked for any medical personnel to go to the back of the plane. I, along with a retired nurse, volunteered and went to the back of the plane. In the lavatory was a middle-aged woman in some distress. She was vomiting and had diarrhea. She had a decreased level of consciousness and was writhing around with abdominal pain. I asked her some pointed questions. I learned that she had an autoimmune disorder and was on several different medications, including high-dose prednisone and a biological immune suppressor. She told me she was feeling sick and nauseated for about two days. I deduced that she had probably contracted a stomach bug at the buffet food bar at her all-inclusive resort. She was travelling with her mother who also had gotten sick but was feeling better. I measured her vital signs. Her radial pulse was slightly erratic but palpable. Her breathing was shallow and rapid. I could not get a measurable blood pressure. There was no pulse oximeter on board. Her eyes were glazed and would roll back periodically. I continually monitored her vital signs and practiced basic first aid. Paramedics were alerted and would be waiting for her when the plane landed. The plane landed and after a brief consultation with the paramedics she was whisked off the plane to the hospital. Would she benefit from probiotic supplementation?

Probiotic supplementation is not that simple and straightforward.

I recalled one morning in July of 2018 as I was driving to a tennis match at the Parkinson's Recreation Centre. I was listening to the *Garden Show* on the AM 1150 radio station with Don Burnette and Ken Salville. They were discussing lawn seeding and green grass. They were talking about how to seed bald patches of lawn that had no growth. They suggested seeding the area with a high-quality lawn seed for the appropriate sun exposure containing a mixture of several different species. Preparing the soil by tilling, aerating, and applying a good fertilizer was necessary. Then, unbeknown to me, they suggested that the next step was the most important and neglected of getting good germination of the seed. You should water the seeded patch in earnest for about two weeks as this was vital for good growth. Without this watering your efforts would be futile. Water was vital for good implantation, germination, and growth. This got me thinking about probiotics, the human biofilm, and what should you do to ensure optimal results with supplementation.

Later in October 2018, I attended a small lecture on the human microbiome at the Manteo Resort in Kelowna. The ND was preaching on the value of probiotic supplementation to the already converted flock of naturopaths and chiropractors. Dinner was excellent, and the mood was like a Trump rally. Yes, probiotics were great, and they helped a myriad of disorders and ailments, but what was the scientific evidence? Researching and writing about the human microbiome and the effects of probiotics would be a daunting task.

There is a profound interest in the human gut microbiome as it relates to health. In the last twenty years there has been an explosion of scientific interest in understanding what is really going on inside our digestive systems. Until recently, nobody has been sure what is actually going on in the human intestinal microbiome. Partially due to the lack of external viability of these anaerobic bacteria, true sampling has been difficult and challenging. Now some recent studies have given us some clues and insight into the true nature of what is actually occurring there, and it is perhaps not what we have been taught to believe.

As a naturopathic physician, we were taught in school and pontificated by supplement companies that probiotics are

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all safe and good for the intestinal milieu. And of course, more is always better. In a pragmatic and linear approach, we were taught that a capsule of lactobacillus and other commensal probiotic bacteria, orally consumed, would bypass the strong stomach acid. They would then be released and free to implant in the internal lumen of the intestines and protective biofilm, primarily in the large intestine or colon. They would then multiply and help re-establish a healthy microbiotic environment. This sounds like a reasonable explanation of what was occurring with probiotic supplementation.

However, recent research from the two studies performed at the Elinav Lab reveals that the long-held beliefs of probiotic supplementation is not quite that simple and straightforward. The explanations that I was indoctrinated with may be more like a children's fairy tale than truth. There still remain many unanswered questions about the use of probiotics in health and medicine. Some recent scientific research reveals the truth about probiotic supplementation and the human intestinal microbiome.

A recent study by researchers at the Elinav Lab in the Weizmann Institute of Science in Israel revealed some interesting results about probiotic supplementation in humans. In the first study published in *Cell* in September 2018, it was discovered that post-antibiotic gut mucosal microbiome reconstitution was impaired by probiotics and improved by autologous fecal microbiome transplantation. Twenty-one healthy volunteers took the prescription antibiotics ciprofloxacin and metronidazole for seven days. Then six individuals had an autologous fecal microbiome transplant, seven individuals took no treatment and had what was called a spontaneous microbiome reconstitution, and eight individuals took an 11-strain probiotic consisting of different species of *Lactobacillus acidophilus*, *L. casei*, *L. paracasei*, *L. plantarum, L. rhamnos, Bifidobacterium longum, B. breve, B. infantis, Lactococcus lactis*, and *Streptococcus thermophilus*. The autologous fecal microbiome transplant group had a very marked improvement of post-antibiotic reconstitution of the indigenous microbiome. The probiotic-treated group showed a marked delay in reconstitution of the indigenous microbiome.

Compared to the spontaneous post-antibiotic recovery group, probiotics induced a marked delay and persistently incomplete microbiome reconstitution recovery. The autologous fecal microbiome group had a rapid and near complete recovery within days of administration. The authors concluded that the post-antibiotic probiotic benefits may be offset by a compromised gut mucosal recovery. This highlights the need for developing autologous fecal microbiome transplantation or individualized probiotic supplementation approaches when treating post-antibiotics recovery.[4]

In a second study also published in *Cell* in September 2018, personalized gut mucosal colonization resistance to empiric probiotics was associated with unique host and microbiome features. The authors reminded us that the evidence of probiotic gut mucosal colonization efficacy remains sparse and controversial. Most of the current evidence is made from stool sampling. The authors were right to point out that stool sampling often does not accurately reflect the true gut mucosal microbiome. Most of the research about the effects of probiotics is based in patient symptomology and stool sampling and not direct gut mucosal microbiome sampling. In this study, fifteen healthy volunteers underwent two separate colonoscopy and endoscopy procedures before and after treatment with an 11-strain probiotic or placebo. The researchers found that the majority of examined probiotic strains were transiently enriched in feces during the consumptive period and shortly thereafter. There was a clear washout of probiotics that were supplemented. They also discovered that there was marked person to person, strain to strain, and gut region specific mucosal probiotic colonization pattern. The effects of probiotic supplementation varied widely from person to person, from permissive to strong resistance of implantation. The authors concluded that probiotics transiently colonize the human gut mucosa in a highly individualized pattern and reminded us that stool sampling does not accurately reflect the true gut mucosal microbiome. The authors also pointed out that a "one size fits all" probiotic is probably not the best approach for each person.[5]

These studies highlight that the effects of probiotic supplementation are not as simple and straightforward as taking a few billion bacteria by mouth in the hopes they will attach, implant, and multiply in the intestinal biome. There appears to be more to this story than at first revealed. Maybe the probiotic bacteria stimulate the resident bacteria to competitively inhibit other dysbiotic bacteria from implanting and residing in the host. There are other mechanisms at work here. In the intestinal milieu, *Lactobacillus* and *Bifidobacterium* are relatively minor players. This would appear to be the case in the aforementioned studies.[4,5]

No one would deny that the use of probiotic foods and cultures has been used in human societies for health benefits for thousands of years. Foods like yogurt, kefir, sauerkraut, miso and others have been a staple in many cultures.[6,7] Harvesting the bacterial species used in these food preparations is a more recent development. Using probiotic supplements in the maintenance of a healthy digestive system and the treatment of disease is still controversial and largely unproven and unsubstantiated

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in the scientific literature. The use of probiotics in the treatment of specific disease like diarrhea, irritable bowel syndrome, dysbiosis and other digestive issues appears to be safe and effective. The use of probiotics also appears to be generally safe. The benefit of the use of probiotics over probiotic cultures has yet to be proven. I still like to consume yogurt and sauerkraut over taking a probiotic supplement unless in certain circumstances. New research regarding the relationship of the human microbiome and the immune system and central nervous system is emerging. Using bacteria to manipulate the immune system is very interesting. Using bacteria in the treatment of mental health issues like anxiety, depression and other neurological issues is fantastic.[8] The future of probiotics is exciting and thrilling.

Like the idiom of the cart before the horse, the use of probiotics exemplifies the use of something that occurs before all is known about what it does and how it works. Probiotics are generally regarded as safe for the general population by most health authorities. Minimal side effects are known to occur. Patient feedback is an indispensable resource to discover what works and what doesn't. Also, an informal review of Amazon and Iherb is revealing. Approximately 50 to 70% of probiotic consumers give a four- or five-star rating to various probiotics sold on these sites. Many people write that probiotics help improve overall digestion while decreasing gas and bloating and improving constipation and diarrhea. Approximately 5 to 12% of consumers give a one- or two-star rating complaining that the product simply didn't work, made digestion worse, and didn't improve gas and bloating or constipation or diarrhea. Researchers say that probiotics should be used with caution in severely immune compromised individuals, advanced leaky gut, or critical illness.

As an addendum to the story of the sick passenger on the airplane returning from Cuba with gastro-intestinal distress, here is how it ended. As she was leaving the plane with paramedics, I told her to get some probiotics or at least food cultures with good bacteria. I myself took a blended probiotic with 100 billion Lactobacillus and Bifidobacterium to help prevent contracting the same illness. It seemed to work. I also learned that sometimes it is okay to put the cart before the horse.

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Letters to the Editor

Re: "Homeopathy or Psychotherapy with Props"

I find it also necessary to respond to Dr. Douglas Lobay's negative comments concerning homeopathy [*Townsend Letter*, June 2018]. While I certainly don't feel myself at the level of the Ullmans as a homeopath, it has been an integral part of my veterinary practice for many years.

Many of you hopefully read my article on the use of tautodes a while back, but I'd like to, in this letter, relate my story with homeopathy and a couple of cases.

In mid-1984, a colleague of mine from the West Coast called to tell me that he was going to see something interesting about this medical therapy called homeopathy the next weekend and it was not very far away from me and could I make it. I told him I couldn't on Saturday because I was fully booked on appointments, but I could come up for the Sunday. At that time I didn't even know what the word meant, but the speaker was going to be a veterinarian from the UK who had even written a couple of books.

So, I went and was intrigued enough that I bought a kit that had 144 homeopathic medicines and a bunch of books. As serendipity tends to rear its head in my life, the Monday after, my new 28-year-old technician came in and looked like death warmed over. I asked her what was wrong, and she said she had severe menstrual cramps. She related that she had suffered with them since the initiation of her menstruation, and at times they had been so severe that she couldn't even go to work She had tried everything available without significant success. So, I said let's look at one of the little books I had gotten and see what we can find. As it turned out, homeopathic *Phosphorus* fit her symptom pattern and I opened the first container in my kit. Talk about placebo (which I prefer to use as opposed to "Psychotherapy and Props") effect – by the time she walked to the end of the hall the cramps had stopped and her color came back, to the incredulity of both of us. Later in the afternoon, the cramps began to start again, and she took a second dose and that was the end of her problems for that cycle. Homeopathic *Phosphorus* totally controlled her cramp problems until she had a baby and her whole hormonal pattern changed.

So that was an exciting and somewhat brain-rattling start. The one remedy I remembered specifically from that day's lectures was the use of homeopathic *Ignatia* at a 1M potency for grief. I'll report one case of many successes with that remedy.

An older lady came in with her dog that I had seen over the years with a history that her happy little dog was suddenly just totally depressed, not wanting to eat or do much of anything. A physical examination showed nothing of consequence and after asking her if something had happened recently in her home, she said her husband had just died. He had died at home with a moderately extended illness and toward the end was totally bedridden. At that time the dog spent all of its time, with the exception of eating, drinking and excretory functions in the bed with him. She had gotten like this after he died. I gave a dose of the remedy to the dog and a dose to the owner. The owner reported rather excitedly the next day the dog was totally normal. About two weeks later the owner's niece was in with her dog and told me she didn't know what I had told her aunt but that suddenly she was dealing with her husband's death so much better.

Probably the most extraordinary story is that of Rocky, an 18-month-old great Dane. The history was that he had had multiple episodes of infection starting at his lateral two digits and

going all the way up to shoulder. At the time I saw him, he had recently finished a one-month course of injectable penicillin and gentamicin, thankfully with no toxicity, but things were starting all over again. Also, in the history had been attempted cultures and even a biopsy which had been not useful. Since the owner hadn't come to me for anything conventional, and I had absolutely no argument with anything that had been done except the worry of the gentamicin, and I was just beginning to feel energy disturbances, it was apparent that there was an energetic disturbance where the dewclaw (the residual thumb on the medial side of the paw) had been removed at probably two days of age leaving just a small clean scar. My comment to the owner is that I thought he had somehow gotten an infection which had gotten deeper into his tissues even though it had not manifested at the time. She was dumbfounded by my speculation, particularly since all of his problems had been on the lateral side of his leg.

Nonetheless, I treated him with homeopathic *Silica* in a 30C potency to drive out unwanted material and a dose of homeopathic *Staphysagria* for "resentments from surgery" and she went home. She called back the next day to report an astonishing experience. She lived about 60 miles away from my practice, and on the way home she suddenly smelled something terrible in her van. It didn't smell like stool, so she stopped and looked in the back, and Rocky was sitting there with the old dewclaw incision having opened and a teaspoon to tablespoon of pus on the floor of the van. He drained for several days, and then was well and went on to finish his championship, which he had been trying to do since he was a puppy

I'll share one other case that also defies any Newtonian description, but even more lies in the realm of quantum physics and perhaps even trans/inter universe or dimensional shifts. A golden retriever that I had seen for a number of years after, incredibly, a successful chiropractic experience stopped all back pain and most of its urinary incontinence came in for her every six months or so check-up. The owner (a very astute lawyer and sister of a veterinarian) described a new phenomenon, that her dog had an exceptionally smelly and greasy coat, which was quite evident in the exam room. She related that she had bathed the dog the prior day and that it was getting so severe in her home she had to figure out something. Since the odor was somewhat sulfurous, and because sulfur is a commonly useful homeopathic medicine for retrievers, I decided to give the dog a dose of *Sulfur* in a 200X potency. We were in the exam room for about a half an hour and as we left the owner said that she couldn't believe it, but it seemed the odor had disappeared. It had, incredibly, and the greasy feel of the coat had also disappeared. Anybody that can explain that, to me, in Newtonian terms or placebo terms is welcome to. By the way, it wasn't a perfect cure, because the owner would have to repeat the dose every month or two, which she did when symptoms started to recur.

My approach to homeopathy – even though I've had lots of classical training – is distinctly eclectic, including the fact that I do use a fair amount of homotoxicology and other homeopathic prepared substances. For those in this readership with professional degrees that use homotoxicology in their practices, I have negotiated a nice relationship with the Bio Pathica company in the UK. This is important after the Heel Corporation closed BHI in this country, and a large number of products were no longer available. Some products are available here, but at significantly higher prices than from Bio Pathica. For anyone interested, please contact me by e-mail and I will send you the current pricing and ordering information since I have also negotiated that 10% of all orders will go into a research fund.

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Re: Kidney Disease

I read with great interest, Jenna C. Henderson, ND's excellent article called, "Is This Actually Chronic Kidney Disease, and What Can Be Done About It" (*Townsend Letter*, June 2019). The article was informative and well developed, offering valuable information about kidney disease and how it should be approached. She offers a list of kidney-supportive supplements, herbs, and mushrooms. However, I would like to delve deeper and make an effort to explain that chronic kidney disease is additionally associated with two main factors that I would like to describe. With the author's kind permission, I would like to share some of my knowledge, based upon my half decade of clinical experience. This may interest the reader in offering some treatment enhancements. In the last part of the article (page 24), she mentions that antioxidant status and mitochondrial support are essential to nephroprotection but also in clinical applications. Here I agree with the author.

First, reactive oxygen species (ROS), resulting in chronic oxidative stress, is an important causal factor of kidney degenerative disease. In fact, motor neurons degenerative disease is caused by the toxic effect of ROS metabolites due to impaired CuZn-SOD. Endogenous antioxidant enzymes are an essential defense system against oxidative injury to the kidney. EC-SOD (SOD 3) is expressed in high levels in normal adult kidneys together with the liver, respectively 60.2+8.9 and 66.7+8.9 nmol/g Hb. The lungs, for instance, are much lower, which could explain the incidence of cancer. Additionally, SOD is the only antioxidant enzyme synthesized in the mitochondria, making it easy to understand how important it is for protection against deleterious effects from free radical activity--an example is the hydroxyl radical, which comes from a very toxic family of damaging free radicals.

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Coenzyme Q10 is a transporter of electrons in the mitochondria respiratory chain, but also a strong antioxidant. Coenzyme Q10 level is highly expressed in the kidneys at 66 mcg/g while in muscles only 40 mcg/g. In the heart, it's even much lower at 14 mcg/g, showing coenzyme Q10 could definitely be an important supplement for not only patients with heart dysfunction but also kidney disease. We may also come to the conclusion that renal dysfunction is caused by increased ROS formation from lower antioxidant induction from various lifestyle stressors.

The possible cause of kidney failure could be associated with mitochondrial dysfunction and excessive free radical activity that damages mitochondrial components that in turn disturb or block the electron chain transport, which as a consequence may dangerously decrease ATP production, vital for kidney function. I believe that mitochondria (MT) and loss of ATP energy may be key factors that start kidney dysfunction. MT deficiency can be implicated in many organ dysfunctions from decreased ATP production, vital for all the body's organs.

What about having an iridology examination? For a naturopath, this should be the first approach to examine a patient. See my article, "Health and Diseases by Iridology Examination" (*Townsend Letter*, January 2017). Even better, read my book *Health and Disease Begin in the Colon*. I have been using iridology with my patients for over 50 years and still use it today. An iris examination of a chronic kidney disease patient may indicate various signs such as deep contraction furrows (previously called the nerve ring) passing through the kidney area, an indication of high stress. Collarette shape observation is also important. If inflammation is localized above the kidney area or the collarette or distended going in a zig-zag covering the kidney area, you have here an association between disturbed nerve and kidney function. You may also observe lesions with dark or brown toxemic spots covering the kidney area. These show the risk of kidney disease from family inheritance status. Often, we find an association between the collarette, the brain, and the kidney. So, you see we cannot be limited just to prescribing a kidney supplement, not in naturopathic medicine. Of course, the colon area needs careful examination as well since it also creates a state of pathological reflex to the kidneys, especially at the terminal end of the sigmoid colon.

Now we can quickly address doctors using the oxidative dried blood test. After taking a drop of blood from the small finger and transferring it to a glass slide in seven layers, we then let it dry for observation. Upon observing the 6th or best the 7th layer under a microscope, this will indicate chronic inflammation and excessive free radical activity. (See my book *Health and Disease Begin in the Colon*, pages 78-79). This is a unique way to immediately monitor oxidative injury in the kidneys in your office or clinic.

While I am now specializing in integrative oncology, in the past I have treated a number of kidney failures with success, some about 38 years ago at a time when there was no dialysis. The reader can see in my blog an article called "A Case Where I Reverse Kidney Atrophy with a Patient of 31 Years and Now He is 69 Years and Still Here" (Blog Archive 2017). A couple of years ago I had to treat him again because his creatinine urea and albumin were increasing, but again they came down to normal range with my treatment.

Now at this point in my life, I am pleased to share some of my personal experience as to which supplements I used, which can be added to the list suggested by Dr. Jenna C. Henderson.

Chlorella Growth Factor (CGF) is essential to help restore kidney function via mitochondrial and tissue repair. CGF is not a single substance but contains DNA/RNA, nucleic acids, a nucleotide peptide complex too long to describe, amino acids, manganese, glutathione in a very high level, sulfur, cysteine, and adenosine nucleotide. It contains all the necessary ingredients for DNA/RNA synthesis making new cells in the body every minute of our life. During an oxidative stress condition, cells activate repair mechanisms after injury, increasing the need for nucleotides. Therefore, CGF meets these requirements. CGF also functions as a strong antioxidant. I have used it with remarkable results in cases of chronic kidney disease, especially with juveniles, even those with severe kidney disease, not to mention proteinuria and reduced serum creatinine albumin.

Curcumin, as mentioned in the article, is a strong antioxidant that reduces the inflammatory process. CoQ10, SOD, and glutathione should be also included in such treatment, being strong antioxidants as well as for mitochondrial support.

Enzyme yeast cells preparation (Zell-Oxygen) is one important supplementation that I have already discussed several times in the *Townsend Letter.* Zell-Oxygen is a perfect natural combination to restore the respiratory chain of the mitochondria and increase ATP production.

Dr. Henderson does mention on page 23 of the article that the kidney's ability to recover from damage is limited, but I have accomplished such recovery with patients even with cases as far back as 38 years ago. Sometimes you have to use your intuition; experiment and you may achieve an unexpected positive result. You cannot always depend on references and wait until publications decide to look at some product that you may think will work.

My treatment for kidney failure came from my case 38 years ago. It was based on a special cell therapy that I have already spoken about in one of my articles published in *Townsend Letter*, "The Clinical Evidence of Cellular Respiration in the Treatment of Cancer." The product is called Regeneresan RN13, which contains ribonucleic acid

from 13 organs, that regenerates the whole body and also the kidneys. This product is only available in ampoules for i.m. injection. In my clinic, it is one of the most important treatments we use in a variety of diseases, including kidney disease and cancer, of course.

Alone we use the kidney ampule containing ribonucleic acid from these specific organs. Both applications include CGF, CoQ10, and SOD. But remember CGF is very powerful to use in cases of kidney disease. This should be the key treatment basis together with the other supplements as referred by Dr. Jenna C. Anderson.

I already have over 38 years of clinical experience using Regeneresan RN13 with a myriad of diseases. If simply used to restore a weak body, I can assure the reader that we have here a powerful therapy for kidney disease with which I have frequently treated both juvenile and adult patients in my clinic. Other naturopathic interventions that cannot be neglected should include hydrotherapy which I have utilized with so many patients over the past 52 years. Examples are a sitz bath, half bath, cold effusion on the back and kidneys, application on the kidneys via a wrap with clay or specific herbs, but clay alone is excellent. A juniper herbal bath is useful to detoxify the skin and kidneys. Unfortunately, naturopathy concentrates too often on supplements readily available on the market while forgetting about the basis of this medicine.

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Suggested Supplementation

Chlorella growth factor (CGF) in liquid and Sun Chlorella tablets developed by Sun-Chorella Ltd. (Japan). Available in the US at Sun-Chorella (Torrance, CA), (toll free) 1-800-829-2828, Ext 2455; Tel. 310-891-0600; Fax 310-891-0621.

Zell-Oxygen (developed in Germany in 1967 by Siegfried Wolz). Available in the US from www.back2nature.net; also Dr. Wolz Zell GmbH, (fax) 062722\561020; e-mail : info@wolz.de (Germany).

Coenzyme Q10 from www.mitoq.com. A very efficient coenzyme Q10 that quickly penetrates the mitochondria membrane.

Curcumin, Meriva SF by Thorne. A curcumin phytosome quickly absorbed by the intestine and delivered in the blood.

RN13 (ampule 5 ml. i.v. i.m.) from Schoss Apotheke, team@schloss.apotheke-koblenz.de (Germany).

Organic whole juniper berries (from Croatia) from Starwest Botanicals (Sacramento, CA) Order online: https://www.starwest-botanicals.com/ or call 1-800-800-4372.

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Our Overtaxed Systems

review by Katherine Duff

Toxic: Heal Your Body from Mold Toxicity, Lyme Disease, Multiple Chemical Sensitivities, and Chronic Environmental Illness
by Neil Nathan, MD
Victory Belt Publishing Inc., Las Vegas, Nevada, info@victorybelt.com
Softcover, ©2018, 336 pages, $29.95.

The new book, *Toxic: Heal Your Body from Mold Toxicity, Lyme Disease, Multiple Chemical Sensitivities, and Chronic Environmental Illness*, by Neil Nathan, MD, represents a giant leap for patients seeking help and healthcare providers who are open to learning about and treating these illnesses. This author has synthesized the research, results from his own practice, and a deep understanding of what his patients have been through to produce an outstanding text for physicians and patients.

Nathan sets the stage for this unique class of illnesses, demonstrating the difficulties in making progress. Patients present with multiple symptoms, and standard testing fails to find a cause. Healthcare providers deduce that the patient's symptoms are the result of mental issues when those tests do not reveal abnormalities. Having been rejected by doctors, these people know it is not "all in their heads" and may spend years without finding relief or may even get worse. Nathan tells us their bodies are experiencing the effects of toxicity and/or sensitivities.

The book takes us closer to understanding what is occurring in the bodies of people experiencing toxicity and sensitivity. He gives comprehensive details about how the body responds to toxins at the cellular level and the effects our genetic differences may have on the process. It begins when all the incredible systems in the human body that are tasked with removing toxins have been overwhelmed and can no longer do the job. Genetically speaking, 25% of the population who are unable to produce antibodies, such as to mold, must use those over-taxed systems to expel toxins. Sensitivity occurs when the nervous system becomes hyper-reactive to certain stimuli, usually a result of toxicity. Sensitivity and toxicity are often considered the same, but the author cautions that different treatments are necessary for each.

As tempting as it may be to treat the immediate symptoms, Nathan insists that the initiating cause be identified for success. This can be any number of instigators such as bacterial infections and environmental toxins, but he has found most of the cases stem from mold, Lyme disease, and its opportunistic infections such as *Bartonella* and *Babesia.* For all of these, the underlying factor is inflammation. Far from being a psychological condition, we now see that an immune response to the toxins is to release inflammatory cytokines that do not turn off. The result is chronic illness.

It is evident Nathan's decades of experience can save time and cost for providers who use his lists of symptoms, appropriate testing, and even the most accurate labs he has found. There are chapters for mold and *Bartonella* that detail the steps necessary to identify and treat these conditions. In the case of mold, he takes us through the steps the inhaled mycotoxin goes through when it binds with a receptor on the outside of the cell, and after a few more steps to end in the nucleus of the cell. It then turns on a gene transcription for a DNA segment that codes for the production of cytokines and additional immune cells that can be called into action. When the threat is gone, all should subside. For 75% of the population that will be the case; but for the other 25%, the inflammatory response continues. When there is persistent mold exposure, the patient will have to clean up the mold or move away from it to rebuild a healthy system again through treatment.

"My job as a physician is to elucidate the causative factors that are making them so sensitive and to treat those factors in proper order. This is not an easy task, and it is not for the faint of heart or those without patience."

We learn another important player in the mystery of these illnesses is mast cell activation. Mast cells form a bridge between the immune and the nervous systems. They coordinate a response with more than 200 biochemical mediators, histamine being the most familiar. This process operates correctly in most; but when an overloaded immune system combines with certain genetics, mast cells can become over reactive. This is when the patient can react to anything, such as light, sound, and chemicals. The list of symptoms from mast cell activation syndrome is long and varied, which is another reason most physicians label the symptoms psychosomatic. These reactions may appear to be allergic but are different in that it is activation of the mast cells, not IgE antibodies.

Throughout these discussions there are suggestions for testing and treatment, including what may be new information for many. He turns to Dr. Robert Naviaux and his model of cell danger response (CDR). Cells have evolved over time to protect themselves from threats such as toxins, bacteria, and viruses. In ultra-simple terms, once the cell has been penetrated and there is a reduction of electron flow in the mitochondria, it reacts by reducing its oxygen consumption. The resulting increase in oxygen concentration makes cellular redox more oxidizing. Eight events then are triggered that produce chemical reactions with the goal of defeating the invader.

One of these biological shifts involves the metabolism of vitamin D, which manages inflammation and prevents autoimmunity. Nathan points to the enzyme 24-alpha hydroxylase which may be increased by toxins, leading to a decrease in active vitamin D and resulting in more inflammation.

For keys to diagnosis, Naviaux tested patients with chronic fatigue syndrome (CFS) for 612 chemical substances in the blood against controls. They found the CFS patients consistently showed a few deficiencies. They found 25 percent of the deficiencies

were shared by all with CFS but the remainder differed from patient to patient. They also found the abnormalities in metabolic pathways have some overlap but are mostly different for males and females. Simply put, CFS affects individuals differently. By identifying several of the shared deficiencies, it was possible for Naviaux to diagnose CFS with high accuracy.

More than half of the book is directed to "rebooting" one's impaired systems. Chapters are dedicated to how the systems are affected and specifically how they can be treated. Starting with the nervous system, he describes the reverberating loop that has a pain signal entering the spinal cord to be sent to the brain. With nerves tightly packed in the spinal cord, the signal can stimulate neighboring nerves, sending more signals to the brain. Even though the painful event has passed, this looping process can turn into chronic pain.

To reboot the nervous system, he offers discussions of over ten therapies that can be tried. Of these he has preferences, one of which is frequency specific microcurrent therapy (FSM). Originally developed for patients with cervical trauma fibromyalgia, Nathan has found it produces rapid results and says it can be used for any traumatic injury to the nervous system.

Another therapy he has found valuable is Annie Hopper's dynamic neural retraining system (DNRS). The therapy uses meditation and mental exercises to retrain the brain in how it reacts to stimuli. For a patient who is stuck in a state of reacting, Nathan has found this to be helpful in calming the system enough to be able to move on to other targeted systems and therapies.

There is no stone left unturned in this book because the author addresses all the systems that can be affected and possible treatments. These may include supplements, pharmaceuticals, dietary advice, and physical therapies. Patients will see themselves in some but not all of the thirteen chapters. They will also see that more is now known about these conditions, and treating them is not a quick and easy endeavor. These are complex conditions. My hope is that readers fully appreciate the orderly treatments recommended in this book and seek professional guidance if at all possible.

The physician who chooses to help people with these chronic illnesses is indeed accepting a challenge. *Toxic* is a guide for physicians willing to accept the challenge and help patients who are by and large without help. Dr. Nathan has found this work rewarding, and he has seen its success. He knows there is a growing population of people who have reached their toxic limits and are going to need this kind of help.

This is an impressive book that should serve to usher in a new chapter in medicine – one that recognizes that our environment affects our very cells and genome. Set up for education and reference, it is well organized, beautifully printed, and replete with the science, resources, and a most comprehensive index. This book is truly a gift. May all physicians hear his call to action so the insurance/medical complex will eventually have to abandon the "all in the head" diagnosis.

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Optimizing Metabolism

by Ingrid Kohlstadt, MD, MPH
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Strengthen Your Ability to Predict If an Integrative Therapy Will Help Your Patient, Part 2: Caveat "mTOR"

Caveat emptor, the Latin phrase for buyer beware, has typically been used to describe used cars and imported appliances. Now the phrase seems apt to US healthcare with its deluged marketplace and overwhelmed Federal Trade Commission. Some products make inaccurate claims as addressed in Part 1, BLUF (bottom line up front). Other products are therapeutic for only a few people and potentially unsafe for the rest of the population. Given that health and safety may be at stake, it's wise for patients to seek their doctors' guidance. "Which treatment is right for me?" This column proposes a way we might be able to change "beware" to "physician-informed."

The desire to know the right treatment for each patient compels me into J.K. Rowling's imaginative world of Harry Potter. Suppose the practice of medicine had what J.K. Rowling calls a Sorting Hat? Wear the hat, and you'll be quickly placed in the right treatment group. The following steps bring this inventive concept into the medical treatment realm.

Step 1 – Split More and Lump Less

Most medical studies such as clinical trials and meta-analyses aggregate data. They apply a therapy to large studies to measure treatment effect. The larger the study size, the more power it has to detect a benefit. This study approach is sometimes called "lumping" because it combines those who benefit together with those who don't.

Lumping has a downside, which is not considered as often as it might be. Lumping uses the law of averages, a one-size-fits-all approach. That means that lumped data doesn't guide clinicians as to which patients will benefit from therapy and which patients will experience adverse effects such as therapeutic failure.

Lumped studies have a work-around, but it's not adequate. Separating the participants by age, gender, and one or two medical variables is an attempt to use the research to guide clinical decision-making. However, in metabolic therapies these common strata seldom split the study participants into clinically meaningful groups. Rapidly emerging science from the microbiome research and the fields of science called the 'omics are revealing many flaws in our assumptions about stratification. Science needs more studies to split the lumps.

Well-designed simple physiologic studies split data into biologically meaningful data. Step 1, therefore, is to find studies to help us split the data, to help us personalize our patient advice and sew our Harry Potter-style Sorting Hat.

Step 2 – Use Genomics

Genomic testing is a giant advance. Unlike epidemiologic data, which excels at lumping, metabologenomic data excels at splitting. It categorizes patients based on genetic variants called single nucleotide polymorphisms (SNPs).

The SNPs are already used clinically. For example, the field of pharmacogenomics tests patients for a handful of SNPs in order to select and dose pain medications, anesthesia, and blood thinners. The US Department of Defense is using SNPs to understand illness in returning soldiers and to prevent illness by strategically assigning soldiers to duty stations fitting their genetic susceptibilities. Personalized medicine has led the adoption of genomics into integrative therapies.

Genomics gives us the ability to split data in the powerful way folkloric Paul Bunyan splits wood. So, what's holding us back? Many of genomics findings are poised to unseat current medical practices. So, resistance to change is probably the biggest roadblock. But there's another reason, one feasible for us to address. Even those who are early adopters of integrative therapies think the voluminous 'omics data requires artificial intelligence (AI) tools. They are awaiting "Dr. Bot." AI may be tomorrow's answer, but today's patients can benefit from our existing understanding of metabolic pathways and the genomic road signs unique to each of us.

Step 3 – Sort Patients by Metabolic Differences such as mTOR

'Omics data informs us on how patients differ in the metabolic pathways influencing the mammalian target of rapamycin (mTOR). The long and short of it is as follows.

The long: mTOR is a kinase that in humans is encoded by the mTOR gene. mTOR links with other proteins and regulates many cellular processes. mTOR regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. It also functions as a tyrosine protein kinase that promotes the activation of insulin receptors and insulin-like growth factor 1 receptors. mTOR influences autophagy in a way that when mTOR is active, autophagy is suppressed.

The short: mTOR predicts longevity! Help patients keep their mTOR low, and your medical guidance is life-extending.

Figure 1 depicts mTOR with its metabolic influencers. Figure 1 is reproduced with permission from the NutriGenetic Research Institute. Another reason mTOR is important is that it blocks autophagy, the process by which the body clears infections and cellular debris. How autophagy fits into the mTOR pathway is depicted in Figure 1.

Step 4 – Assign Patients to Treatment Categories

Modern living revs mTOR production in all of us. To get a sense for the pervasiveness of the impact consider a breakfast with coffee and toast. Today the breakfast is enjoyed while reading something electronic rather than the newspaper. The bread is iron- and folate-enriched. The jam has added fructose. The coffee, unless organic, contains more pesticides, and plastics were used in its preparation. EMFs, iron, folate, pesticides, fructose, and xenoestrogens all promote mTOR. It's no longer feasible to avoid the myriad factors raising mTOR. What is possible is recognizing and avoiding the exposures to which each of us is most sensitive.

I therefore use Figure 1 to help my patients identify what they might do to strategically lower mTOR. Addressing genetic issues can further guide treatment.

Iron accumulation. People with HFE variants want to avoid iron from fortified foods. Some practitioners recommend the herb skullcap. Women with HFE variants may become more sensitive to iron after menopause and may benefit from donating blood. Inadequately researched is how magnetic iron increases susceptibility to EMFs. Also little-understood is how supplemental chromium may reduce iron absorption since they compete for the same transporter in the gut lumen.

EMF susceptibility. Anyone who perceives physical effects of EMFs should avoid them. So should others. Some individuals have generic variants in their calcium voltage genes that may make them more susceptible to electromagnetic fields from electrical devices and cell towers. EMFs raise insulin levels based on new research, so lowering EMF exposure to the extent possible is important in the setting of insulin resistance. A tip for patients is to avoid EMF exposure before their next blood test.

Protein drinks and amino acid supplements can be pro-inflammatory and raise mTOR. Therefore, I recommend non-caloric amino acid products and supplemental resveratrol or turmeric. Good Idea® is a non-caloric beverage that combines five amino acids, chromium, and natural flavors.

The amino acid glutamine has been shown to raise mTOR the most in people with variants in GAD and DAO genes. These patients are likely to find benefit from avoiding monosodium glutamate (MSG) and excess glutamine. A magnolia bark supplement may add support.

Pesticides are more harmful to people with PON1 variants. People with this genetic susceptibility may want to prioritize pesticide avoidance, organic foods, and supplementing with polyphenols, such as quercetin, and carotenoids such as astaxanthin and zeaxanthin.

Weakened autophagy. Those with genetic issues in the ULK1, ULK2, and ATG13 genes may already be predisposed to weakened autophagy. Supplemental berberine and lithium are thought to exert their desired effects by raising AMPK in support of autophagy. Eating less, intermittent fasting, and adhering to a modified ketogenic diet also support autophagy.

Summary

If only doctors' bags came equipped with a Harry-Potter-style Sorting Hat, right? In a way, they do. Understanding genomic variation in the metabolic pathways such as mTOR can help doctors and their patients personalize therapies. Metabolic pathways such as Figure 1 serve as roadmaps for today's patients. Eventually these pathways will come down from the clouds as AI. Whoever is already using the metabolic pathways for clinical decision-making will be at an advantage. The AI will merely be the systems engineers' way of making our Harry-Potter-style Sorting Hats more efficient.

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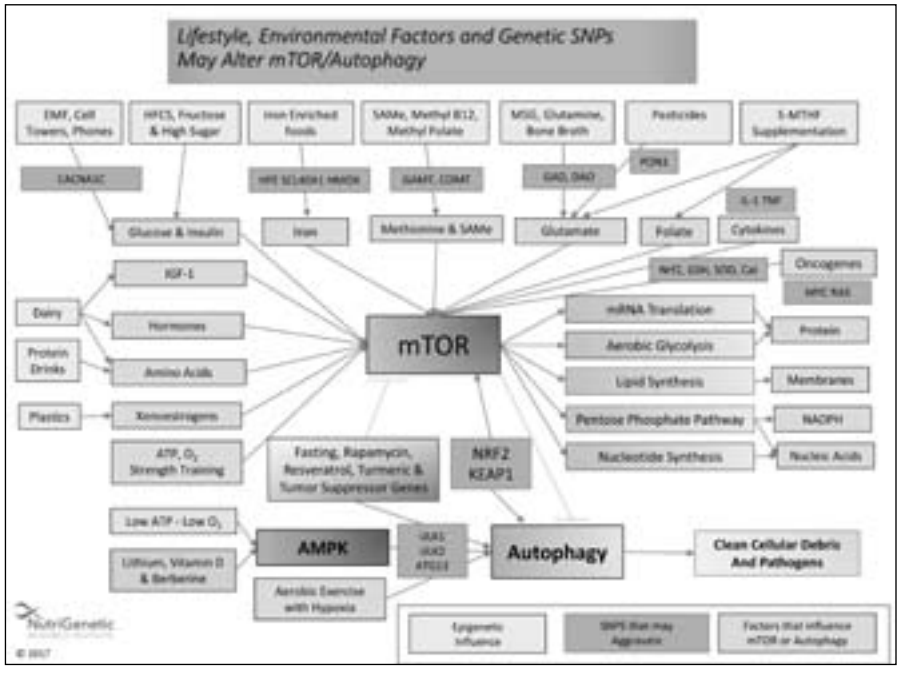

Ask Dr. J

by Jim Cross, ND, LAc
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How's Your Cognitive Dexterity?

Does your mind have the cognitive dexterity to be able to see through the attempted demonization of the sun by the various aspects of our society who make stupendous financial sums through the fear that is generated in the public eye of skin cancer, specifically melanoma?

Since the focus of this month's *Townsend* is on mental/brain health, let's start with how the sun marvelously enhances mood. I and probably around 99% of the world feel great when we venture outside and feel the sun hit our bodies. Is this some kind of cognitive delusion? I tend to think not because, as far as I'm concerned, very little improves my wellbeing like walking outside on a bright, sunny day or going to my summer swimming hole and taking off my shirt and feeling the sun hit my body before jumping in. So let's see if science can lead us in the correct direction.

My mother was an RN, so I tend to love nurses. Plus, she taught me early on that nurses really take care of the patients. I have always wondered why many studies involve nurses. I guess they are more reliable than most groups of people. So, one of the best studies involving light from the sun streaming through windows and its impact on the physiological, psychological, and behavioral health of nurses took place in a community hospital in Texas. The study was conducted in two nurses' stations on the north and south wards of the hospital. The nurses' station in the north ward had no access to daylight, whereas the nurses' station in the south ward had windows that looked out onto portions of the hospital building, the sky, and a courtyard. The north ward used T8 fluorescent ceiling mounted lamps as the only sources of light available. The same lamps were also present in the south ward.

The south ward nurses had statistically: lower blood pressure, lower heart rates, less sleepiness, and a superior mood.[1] They also laughed much more, and communication between them was improved. In addition, caffeine intake was reduced. There was also a non-statistically reduced frequency of medication errors. I hope to never be a patient in a hospital again, but I hope these south ward nurses or nurses like them will be taking care of me if I ever must be in a hospital.

Another study that supports the nurses' study above found 141 nurses in Turkey reported higher job satisfaction and less occupational stress when exposed to daylight for greater than three hours per day.[2]

One more study found nurses exposed to exterior nature views reportedly improved their perceived alertness and reduced acute stress. Nurses with no view or non-nature views reported deteriorated perceived alertness and increased acute stress.[3]

I don't want to write an over-long article; but there is also compelling evidence that the sun's exposure can enhance treatments for other brain diseases such as Parkinson's disease, ADHD, Alzheimer's disease, bipolar disorder, depression, and seasonal affective disorder/SAD. (Maybe they're just sad that there is no sun for them to walk or be out in!).

The imagination can only ponder the potential benefits if unencumbered sun could flow into hospitals and/or clinical workplaces. Patients, nurses, and doctors would have improved mood, which could lead to overall better health outcomes for their patients, higher safety, and increased overall quality levels. Intelligently designed clinical workplaces need to become not a future goal but a present reality. To put it succinctly: get out of little dark boxes and, as they sang in the musical *Hair*, let the sunshine in!

One last, final, stray thought: as long as it doesn't involve alcohol, a pharmaceutical drug, or a street drug, any substance that makes us feel as overwhelmingly good as the sun does probably doesn't need scientific evidence backing its claims for us to incorporate it thoroughly into our lives. This corroborates what every human being understands intuitively.

In the end, though, remember that the sun and what it physiologically induces in our bodies can never by itself reverse the negative effects of industrial food, an unclean environment, sedentary living, and unkind/negative thoughts. It can, however, totally accentuate the positive attributes of nutrient-rich food, living in a sustainably/environmentally conscious world, movement of our bodies, and kind/positive thoughts. So, use your richly earned cognitive dexterity and wisely embrace the sun!

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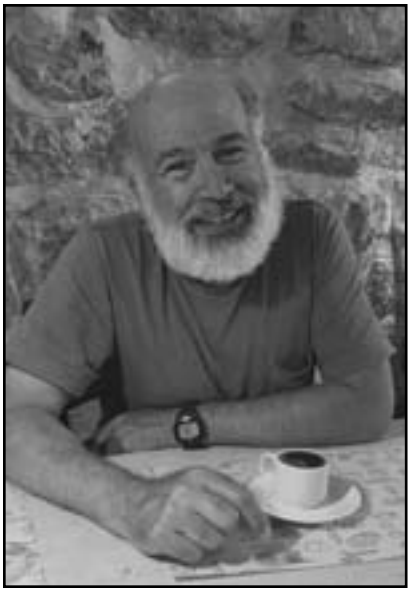

Curmudgeon's Corner

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Living in the Post-Truth World

A local medical oncologist who operates a semi-integrative practice promotes a nutritional supplement of his formulation on his website that "… combines science and nature to target cancer stem cells. [It] is designed to open the cancer genome and allow components to target and critically disrupt cancer cell survival."

That sounds like a fine thing but in truth, I have no idea what his statement means: "Open the cancer genome"? The longer I ponder this phrase the more the fact-check meter in my head drifts into the red zone. It's not long before I begin to second guess all the statements and claims made on his website. He has a good reputation among his peers in town who seem able to ignore these less than reality-based figures of speech. My reaction is still WTF is he talking about?

It is the times we live in, of course. Knowledge is increasing exponentially; and in a direct inverse relationship, truth seems to matter less and less. It's already three years since 2016 when the Oxford Dictionary declared the word of the year to be "post-truth"; but Luddite that I am, I still resist our retreat from the truth, our yielding fact to fiction, reality to lies. If anything, I've dug in deeper and find myself holding tighter to the old ways of telling the truth and expecting the same from others.

It is not just outright falsities that raise my hackles these days but lies of simple omission. I find that I want to hold my colleagues to the same standards as expected from other medical professions. I expect claims of efficacy for naturopathic interventions to be supported by literature citations. Did I, in the past, ignore dubious claims and trust what colleagues said merely by their good reputation? I can't recall what the world looked like in the pre-post-truth era: were we more trusting back then? Have I become less trusting these days? Does being able to check the *Washington Post* on any day to see the number of lies our President has reportedly told in office heighten this sensitivity (as of this writing (7-20-19), he's surpassed 10,000 false statements)?

Perhaps it's just my position as a very-part-time editor for the *Natural Medicine Journal* that's created an expectation for citations for claimed facts? It's a simple enough expectation that we ask from our writers: every statement that is not commonly known should be supported by a citation. Some would say that my minor position of power has gone to my head.

It is this habit that has me scrutinizing the websites of colleagues with the same expectations. Let me share a few pet peeves.

Naturopathic doctors in most instances are not board-certified to practice naturopathic medicine; this is a common claim made by graduates from one of our schools located somewhere between Portland and Vancouver. Naturopathic doctors or physicians are licensed in Oregon and Washington (and other regulated states) by their respective state naturopathic boards. In British Columbia, they are licensed by the College of Naturopathic Physicians. Canadians, they always do things a little different, don't they? In Colorado, we are registered, naturopathic doctors. It's illegal to call ourselves physicians. Naturopathic doctors may be certified in certain specialties; homeopathy and oncology are two such examples where naturopathic doctors might be certified by a national specialty group. My having FABNO (Fellow of the American Board of Naturopathic Oncology) after my name does not give me the right to practice naturopathic medicine. Licenses to practice naturopathic medicine are granted by respective state boards.

In our profession, it is customary to volunteer what college one graduated from, what year this graduation occurred, and in which states one is licensed. This has become routine; it sets us apart from the practitioners who do not meet the basic regulatory standards of the profession and would prefer that this fact go unnoticed. I am referring to those practitioners whose training does not meet federal accreditation standards, who 'attended' distance-learning programs or what might be referred to as 'diploma mills.' In states where naturopathic medicine is still not regulated, such practitioners often still call themselves naturopathic doctors. Transparency and providing details about

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Curmudgeon's Corner

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education and licensure aids the public in differentiating training and even aids other health professionals in doing the same. This effort at transparency should go as far as including one's license or registration numbers to further clarify status.

I'm not sure why but some doctors neglect to mention when they graduated from naturopathic medical school. Being a recent graduate should not be seen as a handicap, nor is it an excuse for not mentioning that you are new in practice. Instead, recent graduation should be considered a plus as this doctor's knowledge base is more current and up to date. It could be easily argued that those of us who were trained in the distant past are now practicing with a deficit of adequate training and up-to-date knowledge.

Claims of efficacy for certain therapies should be justified as evidence-based or not; and if the evidence is weak in support of utility, this should be acknowledged openly. I am reading the webpage of one colleague that advertises the footbath treatments her clinic offers: "The IonSpa footbath is a holistic way of approaching disease through saturation of the blood, tissues, cells and organs with ions. These naturally stimulating and relaxing 30-minute sessions are based on ionization of water and osmosis to draw toxins from the body."

I forwarded this description to our esteemed colleague Davis Lamson ND, who, decades ago, retired from a long career as a college chemistry professor. I asked his assessment of the chemistry described. His response: "I think it's bullshit. Is that simple enough?"

One need not be a chemistry professor to see this; common ions such as those of calcium, potassium, chloride, and sodium all serve crucial roles in regulating heart, nerve and homeostatic functions in the body. Disrupting the balance of any of these ions would result in potential death. Clearly, these footbaths do not "saturate the body with ions." Nobody seems to be dying from these treatments.

In contrast, my friend Ian Bier, ND, LAc, of Portsmouth, New Hampshire, who also uses similar footbaths at his clinic describes our lack of understanding about the device's mechanism of action accurately and honestly: "... For reasons that are not yet understood by science, the soles of the feet have a special relationship to the body as a whole."

We may choose to employ therapies "that are not yet understood by science" yet for which we have anecdotal and historical reasons to think are helpful. This is why what we do is referred to as 'alternative medicine.' This is why some patients come to see us. Yet our not understanding why something works does not justify our making up scientific-sounding jargon and theories that are easily recognized as metaphoric male bovine fecal material.

I admit that I believe everyone should tell the truth. I believe this is more important for those in the healing arts professions. If anything, telling the truth is even more important in naturopathic medicine as many of our colleagues are devoting their time and money to advance our profession's legislative agenda, lobbying for passage of licensing laws. While there is that argument that politicians no longer care about the truth anymore and lies don't matter, I think that when it comes to medical practice, truth does still matter; we are ethically obligated as naturopathic doctors and physicians to be honest in everything we do.

We should tell the truth to our patients, interpreting scientific and medical knowledge honestly and truthfully. We should be honest in our assessment of the evidence in support or against our recommended therapies. We should be transparent about our education, training, and experience. We should not promise positive outcomes from treatments that aren't legitimately documented.

When patients ask me questions that I don't know the answer to, but which I'm about to offer a possible hypothesis, opinion or guess, I always pause and offer a preface to what I'm about to say. I point to my undergraduate degree that is framed on my office wall and make sure they notice it is from an ivy league college. Even more importantly I make sure they see that it is a B.S. degree. Then I confirm that they are aware that what I'm about to tell them is prestigious BS and that it is unlikely true. I do make things up from time to time, but I'm honest about it. ◆

Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Lifestyle Habits That Make a Difference

Reducing Recurring Urinary Tract Infections – The Power of Water

Sometimes we get to go back to basics and simple lifestyle changes that can then make a big difference. This study in premenopausal women prone to urinary tract infections demonstrates the point.

Researchers assessed 140 premenopausal women who had at last three urinary tract infections in the previous year, and who reported a daily fluid intake of less than 1.5 liters (about 6.25 cups) of water per day.

The 70 women in the treatment group were instructed to drink an additional 1.5 liters of water each day, and the 70 in the control group were instructed not to change their typical intake.

Over the course of the one-year study, the average daily increase was 1.15 liters (about 5 cups) in the treatment group, for a daily total of 2.8 liters (12 cups). The average daily intake was 1.2 liters (5 cups) in the control group. After one year, there were 48% fewer urinary tract infections in the treatment group than in the control group. In addition to that, the number of days from the last infection to the first recurrent infection of acute uncomplicated cystitis was 55 days longer in the intervention group than in the control group (148 vs 93). The average number of days between episodes (143 vs. 85) was also better in the treatment group.

With fewer infections, this also led to 47% fewer courses of antibiotics in the intervention group than in the control group (1.8 vs 3.5).

Commentary: Approximately 60% of women will develop a urinary tract infection in their lifetime, and one in four will have a repeat infection. Urinary tract infections lead to more than 10 million doctor visits a year, and more antibiotics.

While this simple approach will not work for everyone, it is an important strategy to at least incorporate. One caution is that, for women with overactive bladder, this increased fluid intake could worsen the urgency to urinate and increase urinary incontinence.

Why does increased water intake work? What we think is that this increases frequency of flushing bacteria from the urinary tract, which means the bacteria don't have time to attach to the bladder wall and thus the overall concentration of bacteria is reduced. I would also predict that these same results would occur in postmenopausal women.

Hooten TM, et al, Women who get frequent UTIs may reduce risk by drinking plenty of water. Presentation at Infectious Disease Society of America, IDWeek 2017, San Diego, CA, October 5, 2017.

Greater Cardiovascular Fitness in Midlife Women Leads to Lower Dementia Risk Later

This study was done looking at 200 Swedish women (age 38-60) who underwent cycling testing that measured cardiovascular fitness. They were followed for an average of 29 years. Using objective assessments and repeat neuropsychiatric evaluations, 23% were diagnosed with dementia at a mean age of 80. Researchers compared women who had medium cardiovascular fitness at baseline to those who had high fitness levels and found that those with a higher fitness level had an 88% lower risk for dementia over the course of the follow-up years. Of those that were in the high-fitness category who were diagnosed with dementia, it developed about 11 years later compared to those with medium fitness.

Commentary: While fitness level cannot be asserted to be a causal effect, it is worth emphasizing the possibility that improved cardiovascular fitness in midlife could modify a woman's risk and delay or prevent dementia. There are several herbs and nutrients that have shown some suggestive influence in providing neurocognitive protection, but all research should be multifactorial in this area, given the growing numbers of individuals affected. Causation, prevention, and treatments all deserve assertive research across the spectrum of issues. Related to causation: environmental exposures, stressors, diet, brief and long-term medication exposures, and genetics. Prevention: stress, nutrition, optimal sleep habits, herbal/nutrient supplements, and medications. Treatments: natural and pharmaceutical interventions.

Horder H, et al. Midlife cardiovascular fitness and dementia: A 44 y.r. longitudinal population study in women. *Neurology*. 2018; March 14; e-pub

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Women's Health Update

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Weight Training May Reduce Hot Flashes

There are several reasons to recommend strength training to women, including postmenopausal women: weight management, preventing decline in muscle mass, bone density, and now hot flashes!! A new clinical trial suggests that it is effective for the hot flashes of perimenopause/menopause.

When it comes to exercise, some studies suggest that exercise may help reduce hot flashes, but others show no effect. The researchers of the current study randomly assigned 58 women experiencing at least four moderate-to-severe hot flashes or night sweats daily to 15 weeks of resistance training or to a control group in which the women did not change their physical activity routine. None of the women in either group were regular exercisers or had used hormone therapy for the two months prior.

The strength training workout group had a regimen of 45 minutes sessions, three times per week, which included six exercises on resistance machines and two using body weight. Women started with lighter weights for the first three weeks, then progressively increased their weights and loads. Prior to the workout regimen, the exercise group averaged 7.5 hot flashes or night sweats a day and after 15 weeks were having an average of four to five per day. There were no changes in the control group.

Commentary: I always like to see studies on hot flashes and night sweats that offer women more lifestyle options that actually can work. If one is not already engaged in regular exercise including some kind of strength training, starting with lighter loads for the first one-to-two weeks is important in order to avoid injury. There are many non-hormonal and hormonal options to relieve hot flashes and night sweats... including dietary influences, botanicals, nutraceuticals, hormones and non-hormone prescription medications. In the case of strength training, as I said in the beginning, there are other meaningful benefits as well. Other forms of exercise are also full of benefits, including decreased incidences of heart disease, type 2 diabetes, bone loss and cancer.

Berin E, et al. Resistance training for hot flushes in postmenopausal women: A randomised controlled trial. *Maturitis*. 2019; 126:55-60.

How Many Steps It Takes to Live Longer

Most all of us are familiar with the concept that we need 10,000 steps per day to achieve health benefits. A recent study was done to investigate further the optimal number of steps daily, as well as intensity required for health benefits. This observational study was conducted in 16,700 women with a mean age of 72, who used accelerometers for at least 10 hours daily for several days at the entry into the study. Women were assessed annually over a follow-up period of 4.3 years. Lower mortality was associated with more daily steps, with a median of 5,500 steps daily. Compared with the women who were the least active, about 2,700 steps per day, women in the range of 4,400 steps daily had a 46% lower all cause mortality and women who recorded about 5,900 steps per day had a 53% lower mortality. The women in the highest step group, about 8,400 steps per day, had a 66% lower mortality. More than 7,500 steps per day had no added mortality benefit, and there was no association between mortality and speed of steps/walking.

Commentary: While I don't really want to be an advocate of lowering the amount of daily steps/exercise, I do think it is important to realized that even about half the customary 10,000 steps per day has mortality benefits; and 7,500 steps per day has optimal mortality benefits. We walk more or less on any given day, due to the demands or our lives, or the excuses we concoct; but these current results are comforting and provide a good basic guideline for how to help ourselves improve our longevity. And don't forget, walking is a therapeutic tool for depression, osteoarthritis, high blood pressure, high cholesterol, pre-diabetes, diabetes, history of cardiac disease and PMS. Plus... good for the soul, good for the planet.

Lee I-M, et al. Association of step volume and intensity with all-cause mortality in older women. *JAMA Intern Med*. 2019; May 29 (e-pub).

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2019 Metdetox Conference

The international conference on clinical toxicology (www.Metdetox.org), a meeting where academics and clinicians joined forces, was held June 10-13, 2019, in Berlin, Germany. In attendance were physicians and noted scientists from around the world, among them the eminent professors Swaran Flora from India, Boyd Haley, USA, Karolina Kot of Poland, Christopher Exley, UK, and others.

The Metdetox Conference was organized by Prof. Ulf Lindh of the Biological Education Centre of the University of Uppsala, Sweden, and Ann-Marie Lidmark of the Swedish patient dental and disability association *Tandvårdsskadeförbundet*.

Presentations and discussions focused on environmental issues, involving medical geology, metal toxicology, and clinical aspects. Acute and chronic intoxication as causes of cancer, and neurodegenerative, cardiovascular and autoimmune diseases were topics presented by scientists and physicians from Belgium, Germany, South Africa, Switzerland, and other countries.

About 70 attendees represented Bulgaria, Israel, Saudi Arabia, and other countries, exchanging knowledge and practical information on geosciences, genetic aspects, metal toxicology, and chelation. Diagnostic biomonitoring information was presented from notables such as Prof. M. Aschner of the Einstein College of Medicine (New York), Drs. Jose Centeno (FDA, USA), E. Blaurock-Busch (Germany), and Prof. Skalny of Russia.

Socio-economic costs of heavy metal exposure were discussed. Conference attendees confirmed the need for future meetings to further expedite research, including evidence-based treatment.

For more information, contact ulflindh@ibg.uu.se or lidmark@gmail.com.

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FREQUENCY SPECIFIC MICROCURRENT FOCUSING ON BRAIN HEALTH

The effects of frequency specific microcurrent on nervous system function have been documented for almost twenty years.

2000: blood samples analyzed at NIH showed log-rate reductions in all of the inflammatory cytokines by factors of 10 - 20 times in response to only one frequency combination. Only frequencies targeting the medulla and nervous system increased serotonin levels.

2003: Only one frequency combination (40/116) reduced lipoxygenase (LOX) mediated inflammation by 62% in four minutes in blinded animal research. COX mediated inflammation declined by 30% in four minutes. No other frequencies reduced inflammation.

2010: PTSD protocol reduced symptoms and scores after only four treatments in four weeks in 3-5-year chronic combat-induced PTSD. No improvement is expected when PTSD is more than two years chronic.

2013: significant and dramatic EEG changes were documented in TBI and autism patients treated with a combination of FSM and speech therapy.

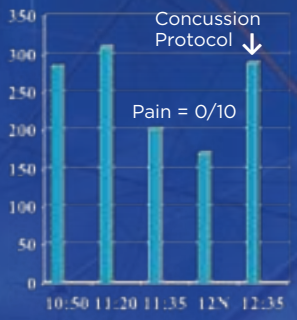
2013: only specific frequencies targeting the sympathetic and parasympathetic nervous systems changed autonomic function and heart rate variability dramatically and quickly.

The data suggests that combining FSM rapid effects with nutrition makes treating the brain more effective, more efficient and less expensive.

ONLY ONE FREQUENCY SEQUENCE INCREASED SEROTONIN

#1 Serotonin = 285.6
#2 Serotonin = 309.2
#3 Serotonin = 202.1
#4 Serotonin = 169.5
#5 Serotonin = 289.6

Serotonin
normal=100-300 ng/ml



- Serotonin dropped during pain treatment (40/10) as endorphins rose.
- Pain was 0/10 at 12N
- Only one protocol increased serotonin levels by as much as double in 35 minutes in every patient
- Serotonin was the only parameter that changed direction with that protocol

TREATING PTSD WITH FREQUENCIES ALONE

Case #1 Combat exposure score 28 (high)

4 years chronic (2006)
5 Treatments

	6/24/10	7/24/10
BDI	43	13
GAD 7	21/21	2/21
PTSD-M	77/85	60/85
PTSD-C	79/85	58/85

Case #2 Combat exposure score 35 (Heavy Exposure)

3 years chronic (2007)
4 Treatments

	3/17/10	3/30/10
BDI	47	32
GAD 7	19/21	2/21
PTSD-M	78/85	60/85
PTSD-C	79/85	61/85

Case #3 Combat exposure score 27 (high)

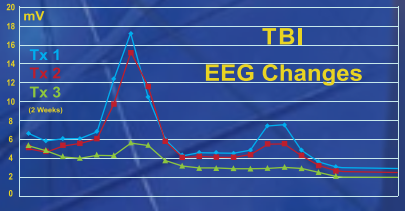
DOI 2005, Dx 2007
4 Treatments

	4/2/10	4/27/10
BDI	29	not done
GAD 7	8/21	4/21
PTSD-M	43/85	22/85
PTSD-C	44/85	22/85

THE PERFECT COMBINATION

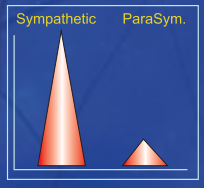
- **Specific frequencies change cell signaling to reduce inflammation**
- **Frequencies change neurotransmitters quickly and safely**
- **Specific frequencies change the brain**
- **Support those changes with nutrition and lifestyle**

Frequencies Change The Brain

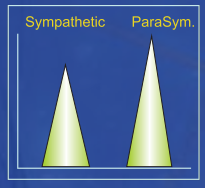


Change Autonomic Balance

Pre-Treatment

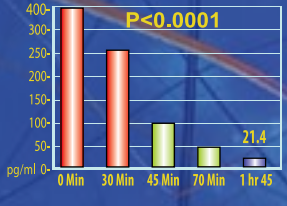


Post-Treatment

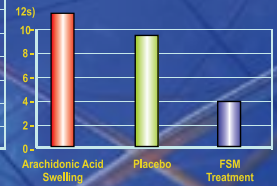


Reduce Inflammation

Reduce IL-1



Reduce LOX 62%



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Frequency Specific Microcurrent and the Nervous System

by Carolyn McMakin, MA, DC

The brain is a neuro-chemical, neuro-endocrine, neuro-electrical network that regulates cognition, emotion, and physiology. Every body process depends on neuro-endocrine regulation and all neurological processes depend on supplies of nutritional elements and neuroendocrine feedback that comes from the body. The system is a completely interdependent neuro-chemical-immune-electrical network.

The effects of frequency specific microcurrent (FSM) signaling on nervous system function have been documented for almost twenty years. The data needs much more research to flesh out mechanisms and confirm the results, but at this point the very specific effects of specific frequencies on the nervous system cannot be ignored or dismissed.

FSM and Inflammation

In 2000, blood sample data was analyzed by the premier micro-immuno-chemist at NIH, Terry Phillips, PhD, who documented log-rate reductions in all of the inflammatory cytokines by factors of 10 and 20 times in response to one and only one frequency combination, 40 hertz to reduce inflammation and 10 hertz to target the spinal cord. These changes happened only in patients with fibromyalgia from spine trauma, and their pain decreased from 7.4/10 to 1.4/10 in 60 minutes. While the cytokines dropped and endorphins increased at log rates, serotonin dropped. When the pain was zero, the frequencies were changed to target the medulla and balance the nervous system. In every case, serotonin reduction stopped, and the levels of serotonin increased only in response to this protocol. In one case, the level more than doubled in 30 minutes. No nutritional intervention was used.

In 2003, blinded animal research showed that only one frequency combination (40/116) reduced lipoxygenase (LOX) mediated inflammation by 62% in four minutes in every animal tested. This is a time dependent response in a well-established animal model of inflammation. In the same research, 40 hertz combined with 116 hertz reduced COX mediated inflammation by 30% in four minutes, which was equivalent to injectable Toridol when it was tested in the same animal model. No other frequencies reduced inflammation.

FSM and PTSD

In 2005, the two-hour frequency protocol for treatment of PTSD was developed. The frequencies aim to reduce the activity of midbrain stress centers, reduce inflammation in the forebrain, and quiet the sympathetics. The protocol has been used by thousands of FSM practitioners for 14 years. There have been no failures to date and no negative side effects as long as medication is reduced when symptoms improve. In 2010, data collected on three-to-five-year chronic, combat-induced PTSD showed dramatic and rapid reduction in PTSD symptoms and scores after only four treatments in four weeks. No improvement is expected in PTSD when it has persisted for longer than two years. The recommended treatment calls for eight sessions in seven weeks. The data show significant improvement after only half the recommended treatment. No nutritional or medication interventions were used.

FSM and Brain Injury

The treatment protocols for traumatic brain injury, stroke, and concussion have been in use since 1997. In 2013, Alicia Thomas, EdD, documented significant and dramatic EEG changes in TBI and autism patients treated with a combination of frequency specific microcurrent and speech therapy processes. Experience has shown that when these protocols are combined with nutritional support and brain exercises, the effects are even more dramatic and positive.

FSM and Autonomic Function

In 2013, Roger Billica, MD, documented rapid dramatic changes in autonomic function and heart rate variability in response to only very specific frequencies targeting the sympathetic and parasympathetic nervous system. The frequency to "increase secretions" of the sympathetic nervous system was applied for 60 seconds and dramatically increased sympathetic tone and reduced parasympathetic tone as demonstrated by HRV readings. That effect was reversed when the frequency to "increase secretions" in the parasympathetic system was applied for 60 seconds and tested after a two-minute wait. Clinical responses consistently reproduce these effects. For this testing no nutritional intervention was used. In clinical settings, nutritional and dietary support are always recommended.

Conclusion

Nutritional approaches to brain health are clearly effective, but they take too long and, in general, work too slowly to optimize patient compliance. The data and common sense suggest that combining the rapid response to frequency specific microcurrent therapy with nutritional approaches that maintain those immediate changes would make treatment more effective, more efficient, and less expensive.

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Pediatric Pearls

by Michelle Perro, MD

Brain Health in Children

ADHD – Are US Children Ritalin® Deficient?

To understand what's happening to children in the US, a visit to any primary school may shed some light. The Centers for Disease Control (CDC) estimates that up to 11% of children are diagnosed with attention deficit hyperactivity disorder (ADHD) and approximately 6% of children between the ages of 4-17 take pharmaceutical medication for this issue. ADHD is broken down into three subtypes: combined-type, predominantly inattentive-type, and predominantly hyperactive-impulsive type. Kids with ADHD often begin to show up diagnostically between the second and third grades when the demands of sitting in their seat, paying attention as well as exhibiting non-disruptive behavior begin. Teachers are often the ones to point out these behaviors since family life can be more accommodating of ranges of behavior unlike the school setting.

The psychostimulant methylphenidate (Ritalin®) was first approved by the FDA in 1955 and began to be prescribed heavily in 1987. It still leads the way in prescription drugs in the treatment of ADHD.

Like other neurocognitive disorders facing our children such as autism spectrum disorder (ASD), the rise in numbers of children with this disorder was initially attributed to "better diagnosing" and/or "over-diagnosing" by practitioners. This theory has not panned out, and the rise is real (as well as the fact most grandmas can diagnose a child with ADHD). Boys lead in the diagnosis of ADHD with a 2:1 predominance.

So, do our children have a Ritalin® deficiency?

Management of a Boy With ADHD

JS is a fifth grader in a suburban Californian primary school, diagnosed in second grade with ADHD and placed on Ritalin® by his pediatrician with improved behavior, focus, and attention in school. His mother came to see me when JS was in fourth grade due to the fact that he hadn't gained any weight while on the pharmaceutical (anorexia is an effect of amphetamine-derived drugs), and she was uncomfortable maintaining him on medication long term.

The patient was placed on a high-protein, low-carb/sugar-free organic diet. JS showed slight improvement with dietary changes. Whether it is the actual reduction in sugar or the fact that sugary foods are nutrient deficient is not clear according to a literature search on the topic. Children with ADHD eat no more sugar than average. My concern is the role of high-fructose corn syrup (HFCS), which, if not organic, is GMO/pesticide-enriched (as well as mercury containing[1]), and its subsequent effect on children's health. Although diet and behavior in childhood are linked,[2] however, it should be noted that changing the diet does not always result in improvements in all kids, attesting again to the need for individual holistic care assessments. There does seem to be links not only to sugar/HFCS and ADHD but also to food colorants, which have been published since the 1970s,[3] as well as food sensitivities (particularly gluten and dairy[4]).

On IgG food antibody testing, JS was noted to be highly reactive to gluten, dairy, eggs, and soy. This finding is not usual in children since these are the major foods consumed by American kids. (Just check out the kid's menu in restaurants, interestingly, not to be found in food-forward France!) Removal of the offending antigenic foods improved his focus, and the teacher also noted lessening of his distracting classroom behavior.

In my practice, when I note significant levels of food antibodies across the board to different food groups, suspicion of intestinal permeability arises. In addition to dietary changes, JS was treated with Intestinal Restore (Desbio®), containing L-glutamine, colostrum, digestive enzymes and several gut-healing herbs; and the patient responded well (and actually liked the taste – which can be a rate-limiting factor). Whenever possible, I try to minimize the number of supplements and combination products. Parents will appreciate not battling with their children over iffy-tasting supplements. Often, I may not know exactly what improved a patient's gut health, but I am treating a child and not conducting a science experiment.

Nutrient deficiencies are commonplace in childhood behavioral disorders, and brain function/cellular function is dependent on the child's nutritional status. Although a family may be eating organic, non-processed foods, the nutritional content of even organic food has dropped precipitously in the US over the past 40 years. Testing in JS included red blood cell magnesium and zinc levels, serum ferritin and urinary organic acids. Some of the most consistent laboratory findings in kids with ADHD are low magnesium and zinc levels. Additionally, they may have a mineral toxic load consisting of lead, aluminum, cadmium, and manganese. JS was noted to be

continued on page 94 ➤

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Lyme Disease - Zev Myerowitz, DC, Dipl Ac (NCCAOM), LAc, FICC, DABCA, BCIM
Complex Biotoxin Infections - Roger Billica, MD
ACES: The Lifelong Impact of Adverse Childhood Experiences - Michelle Perro, MD, DHom
For Better or Worse: Managing HerX Reactions - Lisa Holt, DACM, L.Ac., NCCA OM
Leaky Gut: The Gateway to Health & Disease - Gil Kajiki, CFMP, DC
Environmentally Unstable: Environmental Toxins -Jeff Thomas, ND
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Pediatric Pearls

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low in magnesium, zinc, iron, vitamin B6, and showed high levels of hair mercury and aluminum. His organic acids tests showed evidence of dysbiosis.

We know that zinc is a co-factor in converting essential fatty acids to prostaglandins, so in addition to treating JS with a vitamin and mineral supplement (https://www.brainchildnutritionals.com/adhd), omega 3 fatty acids (fermented cod liver oil) were added. Boys are known to have higher need for EFAs than girls. The literature and clinical correlation show that essential fatty acids may be deficient in kids with ADHD in both sexes as well as other neurocognitive disorders. Some of the issues with gluten and dairy can also be explained by the fact that they can give rise to exorphins in the gut, which can also block the conversion of EFAs to prostaglandins (PGE1).

Increments in improvement in health were continued to be noted over approximately six months, and JS was able to come off Ritalin® and maintain his behavioral gains. JS also jumped in his height and weight from below the 3rd percentile to the 25th percentile. Also added in his regime was a plant-based iron supplement (http://www.floradix.net) since the patient was not a big fan of red meat or dark green veggies.

As with many children as they improve, JS slowly dropped off my patient panel, but showed up a year later with an exacerbation of his previous symptoms with the added features of insomnia, migraine headaches, and "buzzing" in his body. His regular pediatrician placed him back on Ritalin®, which exacerbated most of his symptoms.

Change in diet? No. School? No. Home upsets? No. Bullying? No. (Always ask about school and bullying!) At this juncture I wanted to do a heavy metal challenge test, but mom was hesitant about using chelators from her own research. So, considering EMF exposure and toxicity because of his new symptomatology, I took a map view of his school and home and saw a 5G antenna newly placed in the neighborhood of his school. JS went to spend the next three months with grandma in Oregon (who didn't have wifi at her home) and all of his symptoms dissipated. (Another important topic for a future *Townsend Letter*!)

Our work with JS is not done and amino acids, heavy metals as well as dysbiosis are to be addressed as I continue to work with JS and his family. However, the "Ritalin® deficiency" resolved.

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Michelle Perro, MD, is a veteran pediatrician with nearly four decades of experience in acute and integrative medicine. More than fifteen years ago, Dr. Perro transformed her clinical practice to include pesticide and health advocacy. She has both directed and worked as attending physician from New York's Metropolitan Hospital to UCSF Benioff Children's Hospital Oakland. Dr. Perro has managed her own business, Down to Earth Pediatrics. She is currently lecturing and consulting as well as working with Gordon Medical Associates, an integrative health center in Northern California. She has co-authored *What's Making Our Children Sick?* with Vincanne Adams, PhD, and is executive director for the prominent science and health-based website, www.gmoscience.org.

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Calendar

Please visit TownsendLetter.com for the complete calendar

OCTOBER 3-5: IVC ACADEMY @ Riordin Clinic in Wichita, Kansas. Learn the fundamentals of using intravenous vitamin C for cancer and chronic illnesses. CMEs available. CONTACT: https://riordanclinic.org/events-archive/ivc-chronic-illness-symposium/

OCTOBER 4-6: LABORATORY, ENDOCRINE, AND NEUROTRANSMITTER SYMPOSIUM (LENS) in Portland, Oregon. Practical and applicable advanced neuroendocrine training for your integrative practice. Earn up to 14.5 CMEs. CONTACT: http://www.fx-ed.com

OCTOBER 4-6: DESBIO COMPLEX CLINICAL SCENARIOS SYMPOSIUM in Providence, Rhode Island. CONTACT: 800-827-9529; https://desbio.com/events-calendar/3-day-event-providence-ri/

OCTOBER 6: NEW YORK ASSOCIATION OF NATUROPATHIC PHYSICIANS ANNUAL CONFERENCE in New York City, New York or online. CONTACT: http://www.nyanp.org/

OCTOBER 10-13: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE FALL CONFERENCE – Fatigue: A Complex Diagnosis and Treatment Dilemma in Louisville, Kentucky. CMEs available. CONTACT: http://www.aaemconference.com/fall/

OCTOBER 11-13: KOREN SPECIFIC TECHNIQUE (KST) in Philadelphia, Pennsylvania. Locate and release physical and emotional stresses. Also, **NOVEMBER 22-24** in Seattle, Washington. CONTACT: www.korenspecifictechnique.com; phone 267-498-0071.

OCTOBER 11-13: AMERICAN INSTITUTE OF HOMEOPATHY CONFERENCE – Mapping the Cancer Journey with Dr. Farokh Master in Charlottesville, Virginia. https://homeopathyusa.org/education/2019-conference.html

OCTOBER 12-14: FIELD CONTROL THERAPY® (FCT) INTENSIVE TRAINING with Savely Yurkovsky, MD, in White Plains, New York. CONTACT: 914-861-9161; http://www.yurkovsky.com

OCTOBER 18: GastroANP PreCON in Portland, Oregon. Gastroenterology Pre-Conference, hands-on learning sessions, complex case review, 5 CE, $40 members/$50 non-members. CONTACT: https://www.gastroanp.org/precon-registration-page/

OCTOBER 18-19: GREAT PLAINS LABORATORY, INC. presents GPL ACADEMY PRACTITIONER WORKSHOPS in Costa Mesa, California. A special engagement with The Autism Community in Action (TACA) annual conference. Organic acids testing, toxic chemical testing, mycotoxin testing, and more. CONTACT: http://www.gplworkshops.com/

OCTOBER 18-20: THE AUTISM COMMUNITY IN ACTION (TACA) NATIONAL CONFERENCE in Costa Mesa, California. CONTACT: https://tacanow.org/conference/west-coast/

OCTOBER 23-27: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE (ICIM) – Healthy Parents, Healthy Children in Toronto, Ontario. CONTACT: https://icimed.com/

OCTOBER 25-26: ANNUAL MICROCURRENT CONFERENCE in Scottsdale, Arizona. CONTACT: http://microcurrentconference.org/

OCTOBER 25-27: ADVANCED APPLICATIONS IN MEDICAL PRACTICE (AAMP) FALL EVENT – Integrated Oncology at the Next Level in Seattle, Washington. CONTACT: 954-540-1896; https://aampconferences.com/

NOVEMBER 1-2: SCIENCE, SPIRIT & CLINICAL PEARLS, NHAND 19TH ANNUAL CONFERENCE in Nashua, New Hampshire. CONTACT: https://www.nhand.org/call-for-abstracts/; conference@nhand.org

NOVEMBER 2-3: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION and PsychANP JOINT CONFERENCE in Scottsdale, Arizona. CONTACT: https://www.aznma.org/

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Classified Ads

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opinion of a group of people that another group of people consider to be experts). Since expert opinion is by definition not based on strong evidence, we should at the very least expect the "experts" to be free of conflicts of interest. Unfortunately, that is not the case.

Practice Guidelines Tainted by Conflicts of Interest

A review of several recent studies reveals that conflicts of interest are widespread among physicians who develop clinical practice guidelines. Of 49 physicians who were involved in writing American Academy of Dermatology guidelines (published from 2013 to 2016), 40 (82%) received payments from industry (primarily pharmaceutical companies). Among those who received payments, the mean total amount was $192,542 over a three-year period. Fifty-five percent of the authors who received payments did not accurately disclose industry relationships. In some cases, authors received payments from companies that were marketing products directly related to the guideline topic.[5]

In another study, of the 16 members of the committee that developed the ACC/AHA cholesterol management guidelines, seven (44%) had financial conflicts of interest. That same study found that, of the 29 members of the committee that wrote the 2014 American Association for the Study of Liver Diseases and Infectious Diseases Society of America hepatitis C virus management guidelines, 72% had financial conflicts of interest.[6] Among 125 authors of the National Comprehensive Cancer Network practice guidelines, 86% were found to have financial conflicts of interest. These authors received an average of $10,011 in general payments (such as consulting, meals, and lodging) and an average of $236,066 in payments related to research.[7]

Conclusion

To summarize, practice guidelines in conventional medicine are often based on weak evidence and are written by "experts" who are frequently tainted by financial conflicts of interest. And then they tell us that the type of medicine we practice is not evidence-based. There is a Yiddish word for that: chutzpah.

Alan R. Gaby, MD

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Clinical Practice Guidelines Are Based on Weak Evidence and Fraught with Conflicts of Interest

One of the claims made frequently by conventional doctors who do not believe in so-called alternative, integrative, holistic, natural, or naturopathic medicine is that this type of medicine is not evidence-based. In contrast, they claim that conventional medicine is solidly grounded in evidence. But are both of those claims actually true?

Most critics of alternative medicine are unaware that there have been thousands of randomized controlled trials demonstrating the effectiveness of modalities such as nutritional therapy, herbal medicine, and acupuncture. It is true, however, that much of what we do in alternative medicine is based only on uncontrolled trials, anecdotes, or tradition. But is that necessarily a problem? Some of what we all know to be true – such as drinking water prevents dehydration, or wearing a parachute when jumping out of airplanes saves lives – is based on nothing more than anecdotal evidence. In many cases, the most appropriate treatment choice may not be the one that is supported by the highest level of evidence. For example, if anecdotal evidence suggests that a safe and inexpensive natural remedy is beneficial for a particular condition, one might reasonably try it first, before trying the toxic and expensive drug that has been shown to be effective in multiple randomized controlled trials. But let's put that point aside, and examine whether conventional medicine really is based on the highest levels of evidence.

A Brief History: Conventional Medicine Often Based on Weak Evidence

In a 1978 report, the Office of Technology Assessment (an office established by the US Congress) estimated that only 10-20% of all procedures currently used in medical practice have been shown to be effective by controlled trials.[1] A 1993 editorial in the *Journal of the American Medical Association* (*JAMA*) stated that much, if not most, of contemporary medical practice lacks a scientific foundation. The editorial further pointed out that some treatments, such as episiotomies and routine electronic fetal monitoring, continued to be in widespread use even after randomized controlled trials found them to be of no value and (in the case of electronic fetal monitoring) potentially harmful.[2] In 1997, a researcher asked a group of physicians to determine the scientific basis of 21 practice guidelines issued by different medical specialty societies. For 17 guidelines, physicians rated the available evidence as "poor" or "none." In three cases, the guidelines were based on sound evidence, but contradicted current clinical practice.[3]

Since that time, a number of studies have concluded that clinical practice guidelines created by specialty organizations are often based on weak evidence. One of the more recent studies, published on March 19, 2019 in *JAMA* examined the level of evidence supporting clinical guidelines established by the American College of Cardiology/ American Heart Association (ACC/AHA).[4] Level A (the highest level) was defined as supported by multiple randomized controlled trials (RCTs) or a single large RCT. Level B (the middle level) was defined as supported by observational studies or a single RCT. Level C (the lowest level) was defined as supported by expert opinion only. Among 26 current ACC/AHA guidelines, which included a total of 2,930 recommendations, 248 recommendations (8.5%) were classified as Level A, 1,465 (50.0%) as Level B, and 1,217 (41.5%) as Level C.

Since 2015, ACC/AHA guidelines have indicated whether recommendations with Level B evidence were based on observational studies or an RCT. In the eight guidelines documents published since 2015, there were a total of 543 recommendations with Level B evidence; of those, 73.5% were based only on observational studies. If the data from these eight documents can be extrapolated to the entire data set, then about 78% of ACC/AHA guidelines are based on nothing more than observational studies (which are among the weakest types of evidence) or "expert" opinion (which is just the

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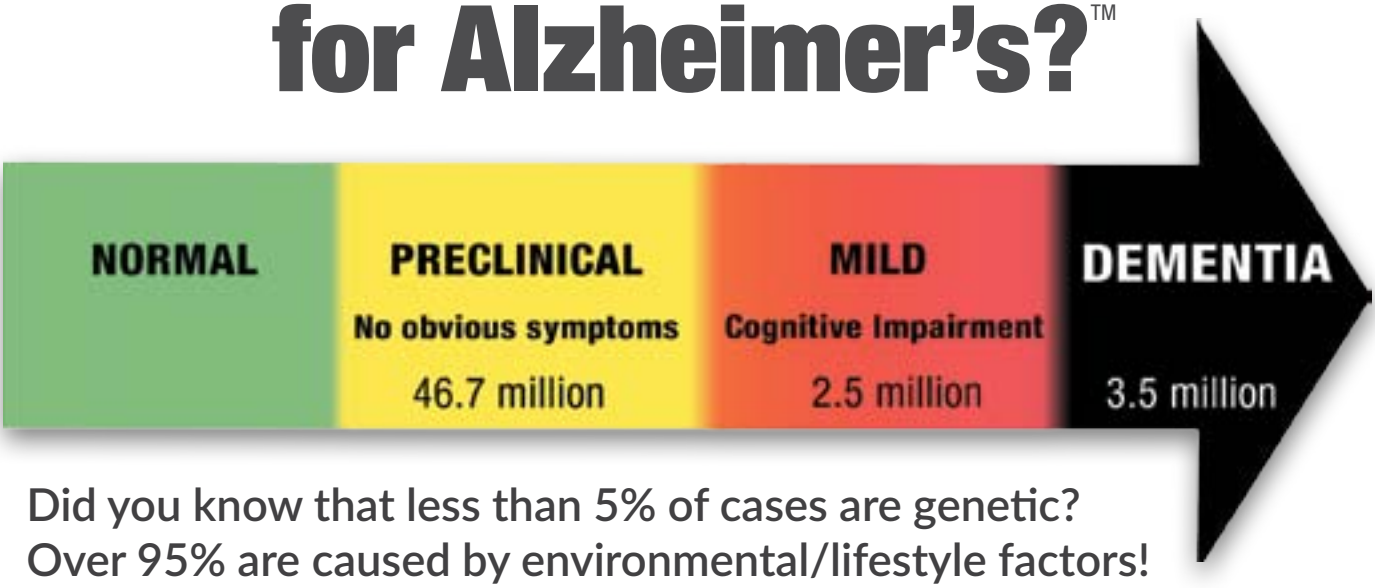

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