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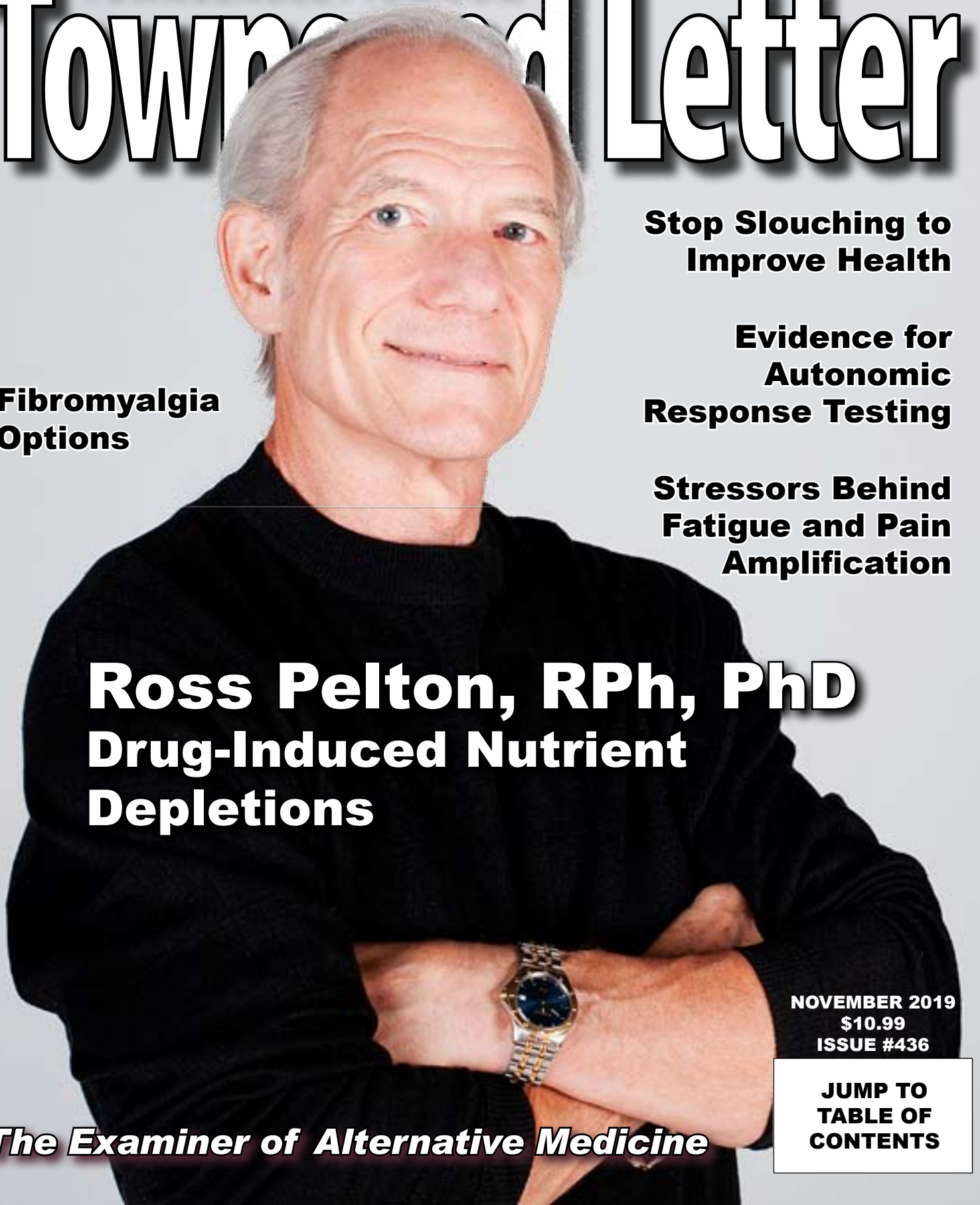

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Ross Pelton, RPh, PhD
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Antonio MAD, *et al. Journal of Infectious Diseases* 1999;180:1950–6.

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

From the Publisher

Convention Notes

The American Association of Naturopathic Physicians (AANP) held its annual conference in Portland, Oregon, in August. That was very convenient as it provided me the opportunity to hobnob with some of our writers and fellow practitioners while I could pass the evening with my daughter who lives there. She had just given birth, so we were celebrating our first grandson. I had the pleasure to meet in person our "curmudgeon" columnist, Dr. Jacob Schor, who I had become quite close to virtually through all the email correspondence regarding his writing and activities over the past few years. I also had the opportunity to chat with John Thoreson, a long-standing representative and consultant for US Biotek, Pharmax, and J.R. Carlson, ever-present at innumerable medical meetings. John had recently retired, but he was not sparing of his insightful and incisive comments about the nutritional supplement manufacturers and laboratory testing companies; both of which have ethical and not-so-ethical participants. Whether it was a harbinger of the times or the timing of having a meeting in the dog days of August, the turnout was lighter than expected, both for the practitioners as well as the exhibitors.

continued on page 6 ➤

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Letter from the Publisher

➤ *continued from page 4*

Drs. Jonathan Collin and Jacob Schor

I was happy to see that Jacob provided his observations of the conference, which appear later in these pages. He didn't comment about his lecture, which was very avidly attended and offered – like his curmudgeon column – many pearls of wisdom. In his June 2019 column, Schor discussed the archeological find of barrels of vanilla made in the Middle East. Apparently, the traders of yore appreciated the nutritional as well as healing aspects of vanilla, not a local spice.

Curcumin breaks down metabolically into vanillin. So, could we just imbibe vanilla to achieve anti-inflammatory nirvana? Not so fast. Digestion of ordinary vanilla does not offer any anti-inflammatory benefit. Schor proposes that we develop a liposomal form of vanilla to preserve the vanillin; however, such a formulation does not yet exist.

At another talk Rick Mayer, ND, proposed that less thyroid treatment is more effective for hypothyroidism. His first point of controversy was that an elevated TSH need not be treated. Mayer is not so much a fan of the old-timer, Broda Barnes, MD, who advocated for using basal body temperature as a means of making a diagnosis. Mayer prefers doing a full thyroid panel, including reverse T3 as well as thyroid antibodies. Instead of immediately treating low T3 and T4, he suggests making the patient exercise more and consider stress reduction. The fact that the TSH is markedly elevated may represent insulin resistance rather than hypothyroidism. Mayer approaches patients with insulin resistance recommending the use of nutrients such as iodine, selenium, zinc, and amino acids. His book, *The Blood Code*, offers insights on how to treat the patient without immediately rushing to hormone replacement. Do we need to reconsider our thyroid prescribing habits?

Instead of Treating Fibromyalgia, Should We Be Asking the Patient to Explore the Stressor Behind the Pain and Fatigue?

We receive quite a few unsolicited articles sent by email or snail mail, but it is unusual to be personally delivered one by the author. In this case, Rob Rennebohm, MD, a Cleveland Clinic retired rheumatologist who recently relocated to my hometown of Port Townsend, told me about an article he wrote, not for publication but for review and use in the office. When I agreed that I would be very interested in reading his work, he delivered it the next day – his home being only blocks away. I was imagining that a report from a rheumatologist would be quite technical, replete with references, presenting clinical reports and some small experimental study. No, Dr. Rennebohm's article was nothing of the sort. Instead it was his working hypothesis as to the explanation of why children

and adults experience fibromyalgia as well as chronic pain. He attributes much of the fatigue and pain as a natural physiologic reaction of the body to protect one from stressors that are not being addressed. Rob believes that our physiology generates the painful, tiring symptoms as an alarm system telling us to wake up and do something about what is bothering us, which we had been ignoring and denying.

In Dr. Rennebohm's experience the pain and fatigue of fibromyalgia, a term he dislikes and does not use, is much more severe than the symptoms experienced with active rheumatoid disease. Patients and their family members are baffled by the staggering level of fatigue and pain, and they consult with specialists expecting a definitive diagnosis. All too often the laboratories are normal with no diagnosis forthcoming, but oftentimes there is an anti-depressant or anti-seizure medication prescribed. Failure to make a diagnosis only aggravates the symptom intensity. Rennebohm argues that the first job of the physician is to explain to the patient that physiologically we react to stresses, not directly addressing them but passively stuffing them within ourselves. Realistically it takes time and deliberate explanation expressed delicately for the patient and family to hear and understand how a stressor can be the source of pain. But Rennebohm asserts in this issue that for many patients not only is this a path to getting better but, for those who honestly explore it, one capable of reversing their fatigue and pain.

Letter from the Publisher

Isn't It About Time That "Kinesiology" Evaluation and Treatment Be Given Some Respect?

Not a few of my patients employ "kinesiology" or "muscle testing" as a means to justify or verify the use of supplements. It has always been a vexing moment when I would make a recommendation to use a certain supplement after careful assessment of the case, for the patient to naysay it based on muscle-testing. Accepting the notion that energetic testing is neither bizarre nor beyond the province of acceptable medical practice, I gladly agreed to look at alternative therapeutic options. Energetic medicine or otherwise, patients are no longer wanting to be treated as though their condition is to be managed following the recipe in the medical text. Given the choice of using a drug or an herbal or a homeopathic, most alternative medicine patients opt for non-drug approaches. Hence, basing treatments solely on evidence-based medicine is no longer striking an acquiescent chord; but selecting a treatment course needs its own evidence, and for many patients and practitioners that evidence is based on some form of kinesiology.

For most MDs and NDs, kinesiology has always caused one to experience a mix of sheepishness and queasiness. The idea that one can demonstrate a change in muscle strength

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Letter from the Publisher

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while testing a supplement or diagnosing a food allergy or determining the placement of a chiropractic adjustment for a subluxation has always appeared more fitting for a carnival sideshow rather than a medical office. Criticism has been directed at the possibility that the "intent" of the tester, be it consumer or practitioner, may create biased interference with testing. George Goodheart, DC, Jr. is generally recognized as the practitioner who founded the principles of applied kinesiology. Dietrick Klinghardt, MD, PhD, modified Goodheart's technique designing a system that he called autonomic response testing (ART). Other practitioners, such as Savely Yurkovsky, MD, have created their own methodologies touting that their approach is superior in diagnostic and therapeutic capability. In this issue Patrick LaRiccia, MD, MSCI, research director at the University of Pennsylvania, examines autonomic response testing and what he broadly labels whole person system of medical care. LaRiccia and associates examined the medical literature, which not surprisingly is definitely limited. He provides case studies demonstrating the role ART can play in demarking effective diagnostic and therapeutics. Their overall assessment is that ART and related systems provide effective options not considered in standard-of-care Western medicine. LaRiccia calls for more research, especially by the naturopathic and functional medicine community.

Slouchers Are Not Going to Like This

Don't you hate it when you objected to your mother's criticism of your behavior, and it turns out that her nagging was spot-on, and your caterwauling was dead-wrong? Such is the case when we have been told "don't slouch." Erik Peper, PhD, BCB, at the Institute for Holistic Health, San Francisco State University in California and associates did research to determine how good posture compared to slouching impacts our health. Most of the benefit accrued to emotional health: confidence, happiness, productivity, positiveness, energy, appreciation, focus, and strength. However, improvement was also noted in neck, shoulder, and back pain as well as eye comfort.

Peper's study used a posture feedback device alerting subjects to whenever they would slouch. Wearing such a device enabled the individual to quickly change posture whenever they slouched. As would be expected, those wearing the device for 15 minutes daily experienced important emotional and physical health changes. Peper and associates write in this issue about identifying triggers associated with slouching, providing the opportunity for individuals to not only change their posture but behavior as well.

Cover Story: How Doctors Create Nutrient Depletion by Prescribing Medications

The pharmaceutical world has been churning out new drugs at a fast and furious pace over the past decade. Biologic response modifiers have completely upended the devastating

continued on page 10 ➤

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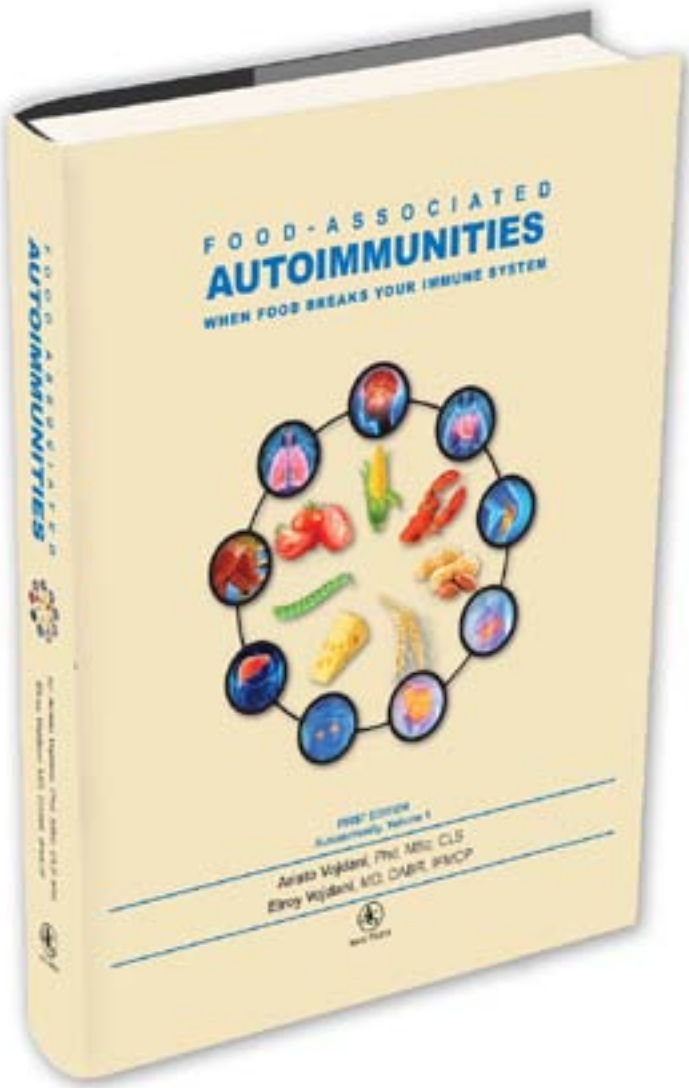

The original inventor of food IgG testing breaks decades of silence regarding the prevalence of innacurate food testing and reporting in many laboratories.

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.

Letter from the Publisher

➤ *continued from page 8*

pathology of many autoimmune diseases and related disorders – rheumatoid arthritis, lupus, scleroderma, psoriasis, vasculitis, and many more respond dramatically to these new drugs. A wide range of new drug agents offer the endocrinologist a great many options rather than dependence on insulin and metformin for managing diabetes. Multiple sclerosis now can be managed with the use of a diverse array of new drugs. Yet, nothing has changed about the risk that a drug is capable of causing significant adverse effects. No matter how beneficial a drug agent may be, it is typical that it will create at least one and generally more than one minor or major side effect. The problem for most patients is that degenerative disease and aging disorders frequently require the use of multiple drug agents. We concern ourselves with the interaction that may take place between the drugs as well as drug-food interactions and drug-nutraceutical interactions. What we don't concern ourselves with is the plain depletion of nutrients through long-term use of drug agents.

In this issue Ross Pelton, a pharmacist, nutritionist, researcher, and well-respected author, writes about drug-induced nutrient depletions. Ross became interested in this topic in 1997 when he read a book on this topic by a Cornell physician written in 1976. What Pelton discovered was the fact that a drug that can cause a deficiency in vitamin B6 or CoQ10 was not of interest to most researchers or practitioners. Of course, major nutrient depletions from drugs were concerning to doctors – the loss of potassium using a diuretic led to the clinical protocol of always prescribing a potassium agent when using furosemide. However, physicians neglect to consider that furosemide also leads to magnesium and calcium depletion as well. A great many drug agents deplete pyridoxine; but for reasons that are not entirely apparent, its reduction while using the tuberculosis drug, isoniazid, seemed to be of greater urgency than with other pharmaceuticals, such as oral contraceptives.

When Ross began to do research on drug-induced nutrient depletion, he found that it was not a topic of particular interest to the medical schools nor the drug companies. Of course, why would a pharmaceutical manufacturer want to prove that its drug caused nutrient deficiencies? So, Pelton began to dig into the literature, and thousands of hours later he put together a compilation in 1999 entitled *The Drug-Induced Nutrient Depletion Handbook*. The book is now out-of-print. But he is putting together for the readership an e-chart available to all free of charge.

Next month Ross will examine how drugs disrupt the microbiome.

Jonathan Collin, MD

Townsend Letter

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

Shorts

briefed by Jule Klotter
jule@townsendletter.com

Google Censorship

On August 26, 2019, pharmacologist Joe Graedon published an online article about recent changes in Google's search algorithm. These changes have essentially "buried" the popular website *People's Pharmacy* that he co-founded with his wife, medical anthropologist Terry Graedon, PhD. For four decades, the Graedons have provided information, using the scientific literature and anecdotal experiences from their readers, about drug side effects, drug interactions, and home remedies in a nationally syndicated newspaper column and a public radio show, heard on many NPR stations. The radio show typically consists of news about recent studies and interviews with researcher-doctors. Graedon reports that popular articles about drug side effects (eg, lisinopril and prednisone), which once elicited hundreds of comments from readers, have virtually disappeared from Google's search engine, showing up only when the article title is typed into the search. Articles about problems that occur when withdrawing from drugs, such as tramadol, duloxetine (Cymbalta), and Zyrtec, have also been hidden.

Graedon says that another website whose mission is to help people understand the risks and benefits of medicines (MedShadow.org) has "also seen its traffic drop like a rock." That website reports: "'On June 4, 2019 our site traffic dropped from 13,029 visits a day to 6,301...in one day. It has not recovered."

Joe Cohen, developer of another website devoted to the science supporting non-pharmaceutical therapies (SelfHacked.com), reports that the abrupt decline in several alternative medicine websites is not due to technical SEO (Search Engine Optimization) issues. When the web traffic for SelfHacked began to decline in the later part of 2018, he and co-workers improved site speed, user experience, content quality, and fixed SEO issues: "Those SEO changes actually helped us quite a lot with the 'dumber' search engines such as Bing and DuckDuckGo, but our Google traffic kept going down....Google is simply not ranking any sites that are not on their 'approved' list."

Cohen took the highest point of traffic in the past 1.5 years for several alternative medicine websites and standard medicine websites and compared the numbers to each site's traffic on August 22, 2019. The traffic on Mercola.com, the alternative site with the highest domain rating, showed 100% decline from its highest traffic months before. (The higher the domain number, the more "authority" a website has, and the more emphasis a search engine has given it – until now.) Dr. Andrew Weil's site had an 84% decline, Dr. Kelly Brogan's site declined 85%. Many of these sites no longer appear in a Google search unless the website name is included in the request. Meanwhile, Healthline and its affiliated site MedicalNewsToday had a 120% and 230% increase in their traffic respectively. Traffic to the websites for Cleveland Clinic, Pharmacy Times, Mayo Clinic, and Sloan-Kettering all increased by 92% or more.

Barry Brownstein, a professor emeritus of economics and leadership at the University of Baltimore, writes, "There are good reasons to be concerned that we are losing access to information with which to evaluate opposing sides of health issues." He refers to an article by Ann Marie Navar, MD, associate editor of *JAMA Cardiology,* in which she claimed patient concerns about statins' adverse effects were being caused by "'fake medical news.'" Brownstein writes: "With some doctors questioning whether to prescribe statins for everyone, there is a large financial incentive to stifle debate. Can you imagine a future government-controlled health care system, completely captured by the pharmaceutical industry, mandating statins for everyone? I can."

Kate Raines, writer for *The Vaccine Reaction*, points out that Google has a largely unrecognized conflict-of-interest. In 2015, Google's co-founders re-organized Google and its subsidiary organizations so that all come under the umbrella of a new corporation called Alphabet. In addition to Google and companies devoted to cybersecurity, artificial intelligence, investment funds, and various technologies, Alphabet includes Verily with its focus on healthcare and managing disease, and Calico, which focuses on biotech and lifespan extension. Recently, Verily has joined with GlaxoSmithKline to create Galvani Bioelectronics in order to "'enable the research, development and commercialization of bioelectronic medicines.'"

While Google is the most used search engine, it is not the only one. I have used both Ecosia and DuckDuckGo. Several others are available. If you are interested in getting a range of information, I suggest that you take time to test your options

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with requests for information about "statin side effects" or another highly debated topic and see which ones give the most diverse responses.

Brownstein B. Google Is Burying Alternative Health Sites to Protect People from 'Dangerous' Medical Advice. August 6, 2019. https://fee.org.
Cohen J. Health Websites that Have Been Crushed by Google's Censorship (and those crushing it). August 26, 2019.
Graedon J. Is Google Censoring Drug Side Effect Information? August 26, 2019.
Raines K. Google Joins the Pharmaceutical Industry. August 23, 2019.

Low-Dose Naltrexone for Chronic Pain

What objective evidence supports the use of low-dose naltrexone (LDN) for chronic pain and inflammatory conditions like fibromyalgia (FM)? Denise K. Patten and colleagues at Regis University School of Pharmacy (Denver, Colorado) looked at LDN's mechanisms of actions and available human studies to answer that question in their 2018 review article. Unlike opioid medications that induce Toll-like receptor 4 (TLR4) signaling and produce inflammatory effects, naltrexone inhibits TLR4. As a result, the production of the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) – and associated cytokines – decreases. Blocking TLR4 also inhibits the production of nitric oxide (NO), an inflammatory factor that enhances pain sensitization.

In addition to this anti-inflammatory effect, LDN (1-4.5 mg per day) temporarily blocks opioid growth factor receptors until the drug is metabolized. The oral half-life of naltrexone is four hours, and it is excreted mostly via urine. During this temporary blockade, T and B cell proliferation is reduced. Once the naltrexone has been excreted, the body compensates by increasing opioid growth factor (OGF) production and increasing the number and sensitivity of the OGF receptors on the nuclear membrane. These activities produce a rebound effect that enhances the regulation of cell growth and immune response.

The clinical studies investigating LDN use for fibromyalgia are quite small. The review authors cite a 10-week University of Alabama study involving eight women with fibromyalgia that looked at LDN's effect on serum cytokine levels and participants' pain/symptoms. The women took 4.5 mg each night at least an hour before bedtime. The Alabama researchers found that LDN inhibited pain-related cytokines, including TNF-α and IL-6. In addition, the participants, as a group, reported a 15% reduction in FM-associated pain and an 18% decrease in overall symptoms – even though the study lasted just 10 weeks. In addition to the Alabama study, another small study (n=11), in which LDN-using participants took part in mechanical, thermal, and cold pain assessments every two weeks, reported statistically significant improvement in daily pain, stress, and fatigue (Younger, MacKey. *Pain Med.* 2009;10(4); 663-72); and a double-blind crossover study with 31 participants found a significant reduction in pain with LDN, compared to baseline and to placebo (Younger et al. *Arthritis Rheum.* 2013;63(2):529-38.).

continued on page 14 ➤

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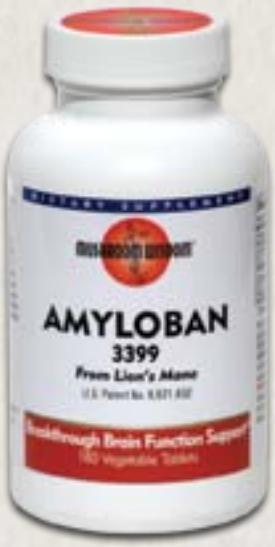

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Shorts

➤ *continued from page 12*

The review authors note that LDN may also be helpful in other chronic pain disorders, including diabetic neuropathy, chronic back pain, and complex regional pain syndrome, according to published case reports.

"Despite the fact that LDN has been demonstrated to be safe and well tolerated, the evidence showing any efficacy regarding analgesic, anti-inflammatory, and disease progression effects is still preliminary," Patten et al write. Large, double-blind, controlled clinical trials are required in order to add FM and pain-related conditions to FDA's approved list of conditions for naltrexone use; right now, it is only approved (at the oral dose of 50 mg) to treat opioid and alcohol addictions. Low-dose naltrexone is made by compounding pharmacists. Patten et al suggest that these pharmacists "could potentially contribute significantly to the literature if they were able to design a study examining the efficacy of LDN" since they have access to patients taking it.

Parkitny L, Younger J. Reduced Pro-Inflammatory Cytokines after Eight Weeks of Low-Dose Naltrexone for Fibromyalgia. *Biomedicines.* 2017;5(16).

Patten DK, Schultz BG, Berlau DJ. The Safety and Efficacy of Low-Dose Naltrexone in the Management of Chronic Pain and Inflammation in Multiple Sclerosis, Fibromyalgia, Crohn's Disease, and Other Chronic Pain Disorders. *Pharmacotherapy.* 2018.

Neural Therapy for Chronic Pain

A Swiss group investigated the effect of neural therapy on 280 patients (176 women and 104 men) with long-standing, chronic, severe pain issues that did not respond to conventional treatment. Most suffered from spine and back disorders (n=155), followed by other motor system disorders (n=41), headache (n=34), and other pain conditions (n=50). All patients were referred to neural therapy by their physicians or doctors of chiropractic.

Neural therapy (NT) uses injections of local anesthetics, such as procaine, to treat functional, inflammatory, and pain disorders: "The local anesthetic can disrupt the escalating vicious circle of nociceptor activity – sympathetic excitation – circulation disturbance – neurogenic inflammation – muscle hardening, etc. in different sites at the same time." In addition to disrupting pain perception, local anesthetics decrease neurogenic inflammation.

For this Swiss study, patient data on age, sex, duration and severity of pain, diagnosis, and outcomes of previous treatments were collected before NT began. During consultations throughout the next 12 months, the researchers documented information about NT use, change in pain, medication use, and any adverse effects or complications. The patients needed an average of 9.2 consultations during the year. At the last visit, patients were asked to evaluate their current pain level and use of pain medication.

At study's end, one of the 280 reported that his pain was worse; 60 patients reported having no change in their pain; 52 had a "slight improvement"; 126 patients had "considerable improvement"; and 41 were pain-free. Of the 193 patients taking pain medication before having NT, 50 (25.9%) reported no change in their use of medication at study's end; and 143 patients (74.1%) reported using less or no medication. "No adverse effects or complications occurred except minor, spontaneously resolving hematoma and mild dizziness lasting up to 15 minutes following treatment, which in patients with normal blood pressure was assessed as the known systemic procaine effect and simultaneous, mild vasovagal reaction."

Egli S, et al. Long-term results of therapeutic local anesthesia (neural therapy) in 280 referred refractory chronic pain patients. *BMC Complementary and Alternative Med.* 2015;15:200.

EMF and Neurological Deaths

A 2019 article in *Medical Hypotheses* posits that the rise in background electromagnetic field (EMF) radiation, interacting with petrochemicals, hormone-disrupting chemicals, agricultural chemicals and other environmental pollutants, has a major role in the rising rates of neurological diseases and associated deaths. The British authors' hypothesis was instigated by two studies: a Swedish study that analyzed national mortality data on Alzheimer's from 1948 until 2014, and a British cluster study that looked at the high incidence of motor neurone disease in an English village. The graph in the Swedish study showed that the incidence of Alzheimer's increased at a five-degree angle from 1948-1988, then shot up at a 75-degree angle from 1990-2014; the change was attributed to the increase in background EMF. Increased EMF exposure was also a factor in the cluster study; the village was near a busy airport.

To investigate a possible relationship between neurological deaths and EMF exposure, the authors used WHO global mortality categories of neurological disease deaths (NDD) and Alzheimer's and dementia deaths to calculate total neurological mortality (TNM) rates per million for people aged 55-74 and for those over-75 in 21 Western countries. The data shows "the relative sudden upsurge in neurological morbidity in the Western world" after 1989. Moreover, neurological disease deaths have increased in people age 55-74 years, which is below the life expectancy for these countries. In the United Kingdom, a new British charity, Young Dementia UK, has many clients under age 50; and the British Parkinson's Society now has set up a "Young Persons" section.

The authors report that a study out of China found evidence that resveratrol may reduce oxidative stress due to EMF exposure. The study compared 186 male workers with occupational exposure to high-voltage electricity lines and 154 male subjects (age and BMI matched) with insignificant exposure as reference control. The EMF-exposed workers, unlike the control group, had elevated urinary levels of 8-hydroxy-2-deoxy-guanosine (a biomarker for oxidative DNA damage) and F2-isoprostane (an indicator of oxidative stress associated with cancers).

Participants in both the EMF group and the control group were randomized into subgroups that received either a placebo or resveratrol (500 mg twice a day) for one year. "Compared to placebo...daily dietary intake of resveratrol was found to significantly reverse the adverse effects of ELF-EMFs on exposed workers," according to this study's authors. The authors point out their results apply to men with occupational exposure to high-voltage electricity lines; resveratrol may or may not affect damage from short-term or other types of EMF radiation.

Zhang D, et al. Resveratrol may reverse the effects of long-term occupational exposure to electromagnetic fields on workers of a power plant. *Oncotarget.* 2017;8(29):47497-47506.

Pritchard C, Silk A, Hansen L. Are rises in Electro-Magnetic Field in the human environment, interacting with multiple environmental pollutions, the tipping point for increases in neurological deaths in the Western World? *Medical Hypotheses.* 2019;127:76-83.

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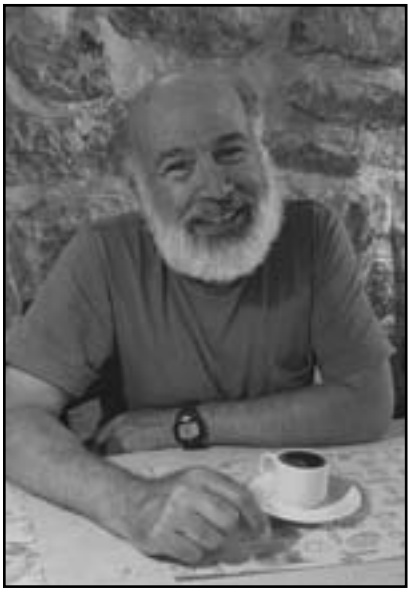

Curmudgeon's Corner

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

Strange, Rare, and Peculiar: Naturopathic Medicine at 100 Years

The annual American Association of Naturopathic Physicians (AANP) conference took place August 15-17, 2019, in Portland, Oregon, in the midst of a threatened citywide protest by the right-wing all-men white supremacist and nationalist Proud Boys and counter protests by the Rose City's own Antifa activists.

This atmosphere of conflict among people you wish would just go away permeated the city's air and at times seemed to spill over and resonate with the conference agenda itself, even if the conference had been planned well in advance. A preconference day billed as "The Closing Summit on the Future of Naturopathic Medicine" began the meeting. The conference's keynote speakers all targeted some apparent discord within the profession between vitalism and evidenced-based medicine. Apparently, there are major philosophical conflicts within the profession over these issues. Living out in the boonies of Colorado, these conflicts were news to me; and the continued narrow focus on such matters quickly bored me. In an email to one colleague who wasn't in attendance: "… the air felt like when you've been invited to dinner by a couple who have just spent the afternoon in counseling, and they are both putting on brave faces for your benefit, but the air is charged and thick with emotions that no one is talking about."

The lead-off speaker, Ian Coulter with the Rand Corporation, took on the topic of vitalism as a metaphysical belief and how it informs naturopathic medicine's worldview was an interesting start to the conference, in part because his heavy reliance on Shakespearian quotes delivered with his New Zealand accent. His lecture is worth listening to if you missed it, and I wouldn't mind hearing it again as he touched on ideas that could prove as good fodder for future rumination. Rumor has it that the AANP will post it online: www.naturopathic.org.

In general, I prefer what I call "Monday Morning" lectures, speakers whose focus is on information that will be useful in clinical practice the first Monday at the office after I get home – clinical pearls, as some would call them. I'd rather say, "new paradigms" with which to see the world. New ways to organize one's practice. I can't say that I left with very many of the later. This year it felt like the world of naturopathic medicine is all about treating SIBO and not much else. While I am fascinated by the newly published data on the human biome's impact on health, I confess to still being unsure whether SIBO is the cause of all maldigestion or just a symptom. That's probably just me; and you have to recall that the publisher of this magazine, the honorable Jonathan Collin, does publish much of my writing under the heading "Curmudgeon's Corner," apparently for good reason.

Speaking of the good Dr. Collin, he and I had the opportunity of finally meeting in person at this conference, a long overdue meeting and a great pleasure for me. We'll see if our now proper acquaintance leads to a better placement for my column or not.

The Naturopathic Medical Student Association (NMSA) held its yearly conference overlapping the AANP conference, so one could easily get confused by the schedule and hear about practicing naturopathic medicine in an unlicensed state and think "been there/done that" before trying to quietly slip out of the room. The NMSA conference was titled "Strange, Rare, and Peculiar," a title usually given to obscure homeopathic symptoms but in this context of seeing old friends, colleagues, and new doctors I hadn't met before, how could I not think it a perfect description of the members of my profession. We are a quirky bunch, a collection of rather rare and peculiar individuals drawn together for common purpose. How can we not find things to argue about given who we are; conflicting opinions and contrary attitudes are our common denominator. Rather than invest effort to resolve them, we might be better off embracing our diversity of worldviews.

The conference theme was actually about celebrating naturopathy's 100-year anniversary of the first licensing law that allowed naturopaths to practice, which was apparently passed in Washington State in 1919. There were photo displays scattered about the exhibit hall to inform attendees about this gala event. In my mind I have coalesced the two competing titles to 100-years of being strange, rare, and peculiar. How could I not?

Speaking of diverse worldviews, Mitch and Lori Stargrove did a phenomenal presentation on the "Ethics of Dying," a title which rightly gives me pause as it suggests that people may go about the process the wrong way and commit an ethical lapse as the last thing they do in life. The Stargroves pulled off this challenging topic well, and their lecture may be the one tape I'll purchase from the conference – though, of course, "tape" is an antiquated term to be sure.

There was a typo in one of the daily schedules. A written description of a lecture about LGBQT2S mistakenly described the topic as LGBQT25, and I spent an inordinate amount of time before the day's start, when I should have caught up on email, trying to Google out what the "25" stood for. After all, in my mind the conference was really about the 'strange, rare and peculiar.' To me this was a measure of just how out of the loop I've become that I didn't recognize this as the typo it was immediately. There was a plethora of lecture topics that left me feeling old and out of touch; one example was an exploration of sexual fetishes and the importance of exploring these with patients as part of being a family practitioner. ➤

Jill Ghormley, ND, Receives 2019 AANP Vis Award

Jill Ghormley recipient of the 2019 AANP Vis Award, has every appearance of being addicted to volunteering for international aid organizations and providing medical care in third world countries. This isn't that common a habit, so I asked her to tell me more about how she acquired it:

So, my journeys abroad started far earlier than my medical career. When I was 19 years old and a junior at UC Berkeley, I studied abroad for a year at Leeds University in England and then stayed in London for an additional six months before I made my way back to the US. While I was living in Leeds, I met some amazing people that have been my closest friends for the last almost 30 years! At the time, I was the youngest member of my group - I was doing a Junior year abroad while my flat mates were all working toward their master's degrees in developmental economics. My friends went on to work for the World Health Organization and United Nations. As my career developed, I have followed them around the world, learning about various protocols and policies in order to help on the health front.

Jill Ghormley, ND
Winner 2019 AANP Vis Award

I am sharing this beginning because this is the beginning that made a huge impact on me as a deaf person. While I lived and studied abroad, I didn't feel different or rather people didn't look at me as disabled. Our languages may be different but the commonality we all had at the time was a desire to learn about each of our differences no matter what. Thus, being deaf, to my friends, was one small part of the picture. They appreciated the difference. When I travel to countries where I didn't understand the language, it was my touch, my medical knowledge people wanted. My deafness was always in the background. People saw me rather than my deafness. In the US, it was the deafness first, then me. There's a much longer story here about that, but you are interested in my travels so here's the long and short of it.

When I entered Bastyr, I was already primed for the global scene and working my way through my field to find a chance to get more involved with the World Health Organization (WHO). My good friend, Dr. Sabine Thomas, and I put together a trip to her home, the Democratic Republic of Congo, in our final year of school. Dr. Thomas hadn't been to her country in 15 years, so it was a sweet homecoming. We met up with our friend, Dr. Ysu Umbalo, who went to NCNM for his training but returned home to Lubumbashi to practice our medicine. We worked in his clinic and began to understand how sustainability was difficult. Getting supplements to various clinics was difficult, and they ran out very quickly. As a naturopathic physician that set the tone for me to apply physical medicine to every global encounter I got involved with, going forward after my experience in the Congo. The following year, I went to Russia with Dr. Dean Neary to learn about balneotherapy and hydrotherapy practices.

Many of my encounters globally were all through my friends that worked at WHO and the UN. Through them, I connected with the ministry of health in each place I wanted to visit. I worked at small clinics applying my skills of physical medicine to approach healing on all fronts.

My trip this year to Nepal is through ParticipAid. This organization was founded by Dr. Erin Moore of NCNM. She invited me to lead a group in 2012 and again this year. The goal for this trip is learning sustainability in our medicine and teaching others to provide in a rural area using the resources of the region.

I know this is a long email. It's hard to condense my experience globally. I sure do love to travel and will continue to do that for as long as I can. I feel it is important to share our medicine with as many people as possible.

Jill Ghormley, ND, is the recipient of the 2019 AANP Vis Award. She received a BA in 1993 from UC Berkeley and completed her naturopathic studies at Bastyr University in 2006. She is married to Shannon L. Jones and lives in Seattle, when not traveling abroad. She practices at Naturkur Wellness Center and teaches physical medicine at Bastyr University. She is the first deaf naturopathic physician.

Curmudgeon's Corner

➤

I missed a lot of friends at this conference, particularly among long-time vendors who no longer bother to attend. Companies who used to be the anchors of the exhibit hall, Vital Nutrients, Pure Encapsulations, ITI, Great Smokies, and others were noticeable by their absence. Thorne Research happily was there, surreptitiously sharing a box of Portland's finest doughnuts beneath their booth's counter with long-time customers. Those doughnuts were perhaps the best of the "vendor give-aways" at the conference. It wasn't like the old days when I came home with a fresh supply of t-shirts, hats, and phone chargers all embossed with company logos. The 'take home' that I was most excited about this year were the toothpaste samples from Biocidin as I'm intrigued by its claimed ability to target the microfilms responsible for periodontal disease. It struck me as potentially game changing if it does what the company claims it does.

NCNM, the class of 1991 – Paul Saunders, PhD, Rena Bloom, ND, Raju Vyas, MD, ND, and Jacob Schor, ND

If the unspoken theme of the conference was "Let's all get along" probably the most awkward event was The President's Reception, a night-time boat cruise down the Willamette River. Seating was limited to 120 so you were either on the boat or off the boat, depending on your standing within the profession or who you knew and if you received an invitation or not. I thought we had all learned the same lesson in grade school; "if you have a party you invite everyone in your class, or you don't have the party." If our goal is to build and unify our profession, the tradition of having an exclusive president's reception, to which a significant percentage of conference attendees are left out, is a tradition that has outlived its purpose and has got to change.

The big Saturday night sit-down dinner, the Gala as it is called, to which everyone was invited, was better than some in past years. Most of the men wear their suits, and the women abandon all modesty and expose as much flesh as possible in a public setting. If it wasn't obvious beforehand, many of us aren't getting any younger. This year's award presentations struck me as tighter run than in past years. In part this is due to the new routine of informing award recipients ahead of time what to expect. That way they sit up front close to the stage and have a speech ready. While this makes for greater efficiency, I found myself missing the openmouthed shock displayed by award recipients who often stood speechless at the podium as they were honored. The old way had an authenticity that was precious. Apparently in the past, some people selected to be honored hadn't planned on attending and had to be roped into coming to the conference at the last moment when their absences were noticed.

Kasra Pournadeali was honored with the Physician of the Year award for a long list of contributions to the profession and the AANP in particular. I met Kasra when I served a single term on the AANP board half a decade back. The confidentiality agreements I signed as a board member are probably still in effect, so I won't provide details of that experience or any behind the scenes details. But trust me, there is no award we can give Kasra that approaches the debt we owe him. On the face of it, he also deserves an award for a notable political accomplishment that he began during his term as AANP President. He has successfully gotten the Veterans Administration to contract with NDs to pay for services rendered to veterans. In Kasra's words, "This first-of-its-kind recognition by a Federal Payor represents a sea change for our profession."

The Vis Award was given to Dr. Jill Ghormley, a doctor who I had not met but who in a matter of moments convinced me that she was more than deserving of the honor. I tend to take note of Vis Award recipients (personal reasons) and avoid belittling past winners, yet Dr. Ghormley may be the most deserving in a line of honorable recipients.

Dr. Ghormley specializes in physical medicine in particular head and neck trauma, delayed neurological development, and neurological deficits caused by trauma and brain injuries along with musculoskeletal rehabilitation, TMJ, pelvic floor, and maxillofacial rehabilitation using a long list of chiropractic, osteopathic, and naturopathic therapeutic modalities. She is a long-time instructor at Bastyr University and NUNM in Portland, a hero to students, and she also manages to volunteer internationally providing her expertise in developing countries. When she graduated from Bastyr University, she became the first licensed naturopathic physician who is deaf. Her physical presence brings with it a physical exuberance that I found more than a little addictive.

The "Champion of Naturopathic Medicine" award went to Bruce Barlean of Barlean's, the company that supplies many of our patients with flax seed oil.

Two awards were given posthumously. The Benedict Lust Award went to Gerry Farnsworth and the President's Award to Walter Crinnion. I admit that I was disappointed to see that Walter didn't share his award with Mark Gignac, another deserving physician who also died this past year. I can't imagine Walter would have minded sharing, in fact I can almost hear him saying, "What do I care? I'm dead after all."

DaVinci Laboratories received the Corporate Award, and Drs. Juliette Sweet and Diana Crumrine received the True Grit Award, which I presume is given for accomplishment in the legislative arena, though why it's named after an old John Wayne movie baffles me.

As always, the best take homes from the AANP conference were the little moments that had nothing to do with the rehearsed Gala speeches or the PowerPoint lectures. It was the conversations over lunch. My biggest regret is I didn't have a tape recorder running to save Davis Lamson's mutterings during and after several lectures where we sat together. Hearing how many patients one speaker crammed into his workday, Dr. Lamson's comment was something to the effect, "If you didn't try to see so damned many patients, you might have time to think about what they were saying and do a better job of taking care of them. Better to see fewer people and take better care of the ones you do see. That's your job after all."

Davis admitted to me that he is taking what seems to be obscene quantities of MSM, and more than willing to elaborate on his chemical rationale for doing so. Dr. Lamson let slip that as a onetime chemistry professor he had possessed a laboratory where one might have been able to manufacture a private supply of LSD. Too bad I lacked a tape recorder. My wife Rena Bloom led a lecture hall filled with colleagues in singing happy birthday to my friend Davis. It's not every day that one turns 85. Davis also had a few stories about Jonathan Collin, the publisher of the *Townsend Letter*. Let's see where he places this article before I decide to share them.

Eric Yarnell also stands out in my memory of the conference as he showed up wearing the "wedding vest" his wife Meredith had made for him. Obviously, it was covered with embroidered medicinal plants. Eric surprised many of us by arguing that the fancy curcumin products were not superior to plain old turmeric, a thought worth pondering at some future point.

All this aside, my lasting impression of our trip to Portland was cousin Mark pointedly asking, "Our parents and their generation had no qualms about sending off this country's treasury and a generation of young men across the Atlantic to fight fascism and here we are in Portland debating about these people…. What are we thinking?" It does seem at times with national and world events in such turmoil that our internal professional debates are embarrassingly trivial.

Next year's AANP conference is here in Denver. Well technically in Westminster, a near-in suburb, but that's still less than 30 minutes from my home. We've got two spare bedrooms.

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Jack Challem: A Nutrition "Great"

by Ralph K. Campbell, MD

Orthomolecular Medicine News Service

My childhood was spent in a fast-moving era. Vitamins had only recently been discovered and were being studied in the early 1930s. My father taught me to read at a tender age, and my mother somehow knew I would have a deep interest in how the body worked. She gave me a two-volume book entitled *Man in Structure and Function*. The first book contained an extensive section on vitamins. The topic of vitamins was the buzz word of that time. It seemed that practical knowledge of vitamins was spreading rapidly. My uncle, on a very limited income, decided to save a little money by switching from butter to cheaper, newly developed, margarine. He developed a corneal ulcer and self-diagnosed that he had a vitamin A deficiency that could be corrected by returning to butter, making it less costly, in the long run, than the margarine. I was impressed and went on to become interested in nutrition and curing disease.

I got next to zero nutrition training in medical school. I found, with my fellow pediatric interns and residents in 1954-57, that they had experienced a similar lack. It seemed a paradox to find, when I became a member of the American Academy of Pediatrics in 1966, that their journal, *Pediatrics*, was chock full of informative nutrition articles. So, I began to dig in and try to make up for lost time.

In 1996 I got on the internet and wrote an article, "Bugs That Bug Us," about the problem of bacteria becoming resistant to commonly used antibiotics. These resistant bacteria became known as "superbugs." I was dismayed about how long it took for the concept to gain attention, since more than 40 years earlier I had real personal experiences with the problem. Somehow my article must have found its way into the ether, and Jack Challem must have seen it, for out of the blue, a copy of his "Nutrition Reporter" ended up in my mailbox. What a blessing. I was amazed to see that someone could write with such clarity and thoroughness. He was a wonderful model for any writer trying to express complicated issues in simple, easily understood language. I had always felt that my pediatric patients and their parents were not overly impressed with Greek or Latin words that describe a condition; so I always tried to convert "medicalese" into simple English; "erythema multiforme circumscriptum" could just as easily be called "many red spots of different but distinct shapes." But Jack was at ease with either interpretation. If he wanted to impress a doctor, he could. If he wanted to furnish a reader with useful information, he could do that, too. His strong curiosity for wanting to know how nutrients worked seemed to be a driving force.

Jack Challem

We "talked" back and forth by e-mail. He introduced me to the concept of orthomolecular medicine. We met for the first time at the Orthomolecular Medicine Today conference in Vancouver BC, Canada, (close to home) at which he delivered a section of the program. With this being the only time we met in person, it was amazing the way our friendship developed through back-and-forth e-mail messages.

Over 200 issues of Jack Challem's *Nutrition Reporter* newsletter are now posted for free reading at http://www.doctoryourself.com/challem.html.

Jack teamed up with Hugh Riordan, MD, of the Riordan Clinic in an ambitious project to determine the optimal levels (orthomolecular levels) of individual nutrients – no easy task since nutrients work in concert, making the study of a single nutrient's effect in isolation difficult.

I recall only one instance in which the student (me) was able to teach the instructor, and this was only a reminder of what I had learned from him years earlier. He was suffering from nerve entrapment in his arm. Treatment involved administrating pyridoxine (B6), 100 mg twice a day along with a multiple B vitamin complex preparation, which includes some riboflavin, or B2, to activate the B6.

Whenever I saw someone I knew wearing the typical carpal tunnel syndrome wrist splint, I would tell them about this far-out treatment of vitamin B6 without surgery. I have often found this treatment very beneficial. If they felt this advice would seem unacceptable to their doctor, my advice is to ask him/her what objection there might be to a trial of an essential nutrient, generally free from side-effects, and proceed with its use. Even though these individuals were not officially my patients, I was comfortable giving this advice because I would do no harm.

Jack was also a very accomplished fine art photographer, but his enthusiasm for this field of endeavor made it difficult to know whether to call photography a hobby or a profession. Unfortunately for us all, Jack suffered a bout of a cancer that seemed unrelated to known causes of cancer. Nevertheless, he continued to work with his photography – and fearlessly and energetically in the nutrition field.

Ron Hunninghake, MD, of the Riordan Clinic offered a memoriam (https://riordanclinic.org/2017/08/jack-challem-memorium/) concerning Jack that expressed so well what I found in this great man. Ron praised Jack's tremendous knowledge, his curiosity, and sincere interest in people. He pointed to the fact that Jack had gained this knowledge without the benefit of having obtained a degree in any health-related subject. He too emphasized Jack's ability to make complex issues understandable, thus being of great benefit to his readers.

My feeling is that attempting to stay within the perimeters of a medical specialty can limit imaginative thinking about practical solutions to medical challenges. Jack Challem's ability to explain a wide variety of medical conditions and their solutions using nutrition in clear language prompted many of us to think "out of the medical box." In my life, Jack was an excellent mentor for an aspiring nutrition writer. His writing – over a period of several decades – continues to be of great value and inspiration for us today.

Andrew W. Saul, Editor in Chief, Orthomolecular Medicine News Service, adds this note:

> Vitamin therapy is of proven benefit to real patients with real illnesses. If your doctor, family member, or local internet troll disagrees, then they don't know Jack – Jack Challem, that is: bestselling author, and late publisher of *The Nutrition Reporter* newsletter. Jack Challem helped so many, many people. His newsletter set high standards for popular nutrition education. As an orthomolecular advocate and a just plain great guy, Jack was and will remain tops in my book. In fact, my own books first got published because Jack connected me with one of his own publishers. He graciously sent me a marvelous compilation of 19 years of his newsletters to assist me, and my daughter, in the writing of our books. I think he'd like you to be able to learn from them as much as I have. They are now posted for free reading at http://www.doctoryourself.com/challem.html. Thank you, Jack.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Probiotic During Pregnancy Prevents Allergic Disease in the Child

In a previous study, pregnant women in New Zealand who had or whose husband/partner had a history of allergic disease were randomly assigned to receive, in double-blind fashion, *Lactobacillus rhamnosus* HN001 (6 x 10^9 colony-forming units per day) or placebo. Treatment was started at 35 weeks of gestation and was continued until delivery or, if breastfeeding, until the infants were age six months. The infants were randomly assigned to receive the same probiotic or placebo from birth until two years of age. Compared with placebo, *L. rhamnosus* HN001 reduced the cumulative incidence of eczema by 49% ($p < 0.05$).[1] The present study followed these children until 11 years of age. At age 11, compared with placebo, previous probiotic use was associated with a 54% reduction in the prevalence of eczema ($p = 0.015$) and a 27% reduction in the prevalence of hay fever ($p < 0.05$).

Comment: These results demonstrate that *L. rhamnosus* HN001 can reduce the prevalence of allergic disease in young children, and that the benefit persists at least until age 11. It cannot be assumed that other probiotic strains would have a similar effect. Indeed, in the original study, a different probiotic (*Bifidobacterium animalis* subsp *lactis* strain HN019) did not significantly decrease the cumulative incidence of eczema. In another study, *L. rhamnosus* GG administered during pregnancy and early infancy did not reduce the incidence of eczema in the children and was associated with an increased rate of recurrent episodes of wheezing bronchitis.[2]

The mechanism of action of *L. rhamnosus* HN001 is not known, although it presumably works by altering the intestinal flora or certain aspects of immune function. This probiotic strain is commercially available in a number of products, either as a component of a multi-strain probiotic or as a component of a prenatal/perinatal multivitamin-multimineral.

Wickens K, et al. Effects of Lactobacillus rhamnosus HN001 in early life on the cumulative prevalence of allergic disease to 11 years. *Pediatr Allergy Immunol*. 2018;29:808-814.

Are Vitamin E Vaginal Suppositories Effective for Atrophic Vaginitis?

Fifty-two postmenopausal Iranian women (aged 40-65 years) with vaginal atrophy who had been referred to a gynecology clinic were randomly assigned to receive, in single-blind fashion, vitamin E vaginal suppositories (100 IU per suppository) or 0.625 mg of conjugated estrogens vaginal cream. The treatments were administered daily for 10 days, then twice a week for 10 weeks. Both groups demonstrated significant improvement in the Abbreviated Sexual Function Questionnaire with no significant difference between groups.

Comment: Evan Shute, along with his brother, Wilfrid Shute, was a pioneer in the clinical use of vitamin E. In a 1973 lecture, Evan Shute stated that "senile vaginitis" (another term for atrophic vaginitis) responded well to topical application of vitamin E suppositories. As far as I am aware, that clinical observation was never followed up with randomized controlled trials, until now.

In an editorial in the July issue of the *Townsend Letter*, I provided evidence to suggest that a large proportion of the nutrition research coming from Iran may be fabricated. While intravaginal vitamin E may be useful for atrophic vaginitis, it is difficult to believe it is as effective as conjugated estrogens

(which is what the present study reported). Confirmatory studies are therefore needed before vitamin E suppositories can be considered a proven treatment for atrophic vaginitis.

Golmakani N, et al. Vitamin E as alternative local treatment in genitourinary syndrome of menopause: a randomized controlled trial. *Int Urogynecol J*. 2019;30:831-837.

Vitamin D Prevents Migraines

Forty-eight patients (aged 18-65 years; mean, 44.6 years) in Denmark with migraines were randomly assigned to receive, in double-blind fashion, 4,000 IU per day of vitamin D_3 or placebo for 24 weeks. The mean serum 25-hydroxyvitamin D level at baseline was 33 ng/ml. The mean percent reduction in the number of migraine days during the last four weeks of the trial (compared with baseline) was significantly greater in the vitamin D group than in the placebo group (48% vs. 20%; $p < 0.05$). The proportion of patients who had a positive response (defined as a 50%-or-greater reduction in attack frequency) was significantly higher in the vitamin D group than in the placebo group (data not shown; $p < 0.01$). (According to a personal communication from Gazerani P, the response rate was 75% in the vitamin D group and 50% in the placebo group.) Compared with placebo, vitamin D had no effect on migraine severity.

Comment: In this randomized controlled trial, supplementation with 4,000 IU per day of vitamin D decreased the number of migraine days and the attack frequency in patients with recurrent migraines who were not vitamin D-deficient at baseline. The mechanism of action of vitamin D is not known. Other treatments that have been shown to prevent migraine recurrences include identifying and avoiding allergenic foods and supplementing with magnesium, riboflavin, or coenzyme Q10. Because the long-term safety of high-dose vitamin D (particularly in relation to the risk of kidney stones and atherosclerosis) has not been clearly demonstrated,[3] its use for migraine prophylaxis should probably be reserved for people who do not respond adequately to these other interventions. Additional research should investigate whether lower doses of vitamin D are also effective for preventing migraines.

Gazerani P, et al. A randomized, double-blinded, placebo-controlled, parallel trial of vitamin D_3 supplementation in adult patients with migraine. *Curr Med Res Opin*. 2019;35:715-723.

Non-Celiac Gluten or Wheat Sensitivity: Intestinal Inflammation as an Underlying Mechanism

Markers of immune function were examined in 78 patients with non-celiac gluten or wheat sensitivity (NCGWS; documented by double-blind wheat challenge) and in a control group of patients with self-reported NCGWS but negative results from the wheat-challenge test. Duodenal and rectal biopsies were performed after the subjects had consumed a wheat-containing diet for at least four weeks. Duodenal tissue from patients with NCGWS, as compared with duodenal tissue from controls, had significantly higher numbers of intra-epithelial CD3+ T cells, lamina propria CD45+ cells, and eosinophils. In addition, rectal mucosa from patients with NCGWS had a larger number of enlarged lymphoid follicles, intra-epithelial CD3+ T cells, lamina propria CD45+ cells, and eosinophils than rectal mucosa from controls.

Comment: Many people who do not have celiac disease believe they are sensitive to wheat or to all gluten-containing foods. While the medical community was originally skeptical about whether NCGWS is real, in recent years it has become recognized by most authorities as a true clinical entity. In the present study, patients with NCGWS showed evidence of increased inflammation in duodenal and rectal mucosa. That finding suggests that inflammation of multiple areas of the intestinal tract plays a role in the pathogenesis of NCGWS.

Carroccio A, et al. Duodenal and rectal mucosa inflammation in patients with non-celiac wheat sensitivity. *Clin Gastroenterol Hepatol*. 2019;17:682-690.e3.

Do Dietary Advanced Glycation End Products Increase Fracture Risk?

Mice were fed a standard control diet or a diet high in advanced glycation end products (AGEs), which was produced by autoclaving the standard diet at 120° C for 15 minutes. The diets were identical in energy and nutrient content. After 18 months, among female mice, the high-AGE diet, as compared with the standard diet, resulted in inferior vertebral trabecular structure, decreased bone mineral density, and decreased resistance against fractures. The results in male mice were less clear.

Comment: AGEs are formed during cooking and processing, by the interaction of a reducing sugar (i.e., glucose, fructose, or lactose) and protein, or a reducing sugar and an amine-containing lipid. AGEs present in food are absorbed intact and persist in tissues, where they increase the inflammatory response. Because inflammation is thought to play a role in the pathogenesis of osteoporosis, consumption of a high-AGE diet might increase the risk of age-related bone loss and osteoporotic fractures. That possibility is supported by the results of the present study.

The AGE content of the diet can be decreased by cooking at lower temperatures and in the presence of water, as ➤

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compared with cooking at higher temperatures and in the absence of water. Temperature and cooking method seem to be a more important factor for AGE formation than cooking time. Emphasizing boiling, poaching, and stewing over frying, broiling, and roasting may decrease daily AGE intake by up to 50%. Consuming more raw foods can further decrease AGE intake because the AGE content of raw foods is very low.

Illien-Junger S, et al. Dietary advanced glycation end products have sex- and age-dependent effects on vertebral bone microstructure and mechanical function in mice. *J Bone Miner Res*. 2018;33:437-448.

Topical Vitamin C for Senile Purpura

Eighteen patients (mean age, 88 years) with senile purpura were randomly assigned to apply, in double-blind fashion, a 5% vitamin C cream to affected areas on one limb and a placebo cream to affected areas on another limb twice a day for 12 weeks. The active treatment contained vitamin C in glycerol at pH 6.0, emulsified in a silicone base and prepared under one atmosphere of nitrogen. This product, which is available under the name Active C (La Roche Posay, France), is formulated in such a way as to minimize the oxidation of the vitamin C. Compared with placebo, active treatment was associated with a significant improvement in the overall clinical score. Improvements included a reduction of hemorrhage areas and an increase in dermal thickness and skin elasticity.

Comment: Senile purpura (also known as Bateman purpura) is a classical sign of skin aging. Manifestations include fragile skin due to atrophy of the dermis, purpuric lesions (petechiae or ecchymoses), and spontaneous stellar pseudocicatrices. These abnormalities occur primarily in sun-exposed areas. Vitamin C plays an important role in tissue integrity, including the integrity of skin tissue. Aging of the skin is associated with a decrease in the concentration of vitamin C in the dermis. Sun exposure is also known to decrease the concentration of vitamin C and other antioxidants in the skin. The results of the present study suggest that localized vitamin C deficiency plays a role in the pathogenesis of senile purpura and that topical application of vitamin C may be beneficial for this condition.

Humbert P, et al. Bateman purpura (dermatoporosis): a localized scurvy treated by topical vitamin C - double-blind randomized placebo-controlled clinical trial. *J Eur Acad Dermatol Venereol*. 2018;32:323-328.

Probiotic for Patients with Celiac Disease Who Remain Symptomatic on a Gluten-Free Diet

One hundred nine patients (mean age, 44 years) with celiac disease who had irritable bowel syndrome (IBS)-type symptoms while on a gluten-free diet were randomly assigned to receive, in double-blind fashion, a multi-strain probiotic or placebo once a day for six weeks. The probiotic contained two lactobacillus strains and three bifidobacterium strains and was manufactured by Probioresearch (Rome, Italy). The mean IBS Severity Scoring System score improved by 15.9% in the probiotic group and worsened by 8.2% in the placebo group ($p < 0.001$ for the difference in the change between groups). The mean Gastrointestinal Symptom Rating Scale score improved by 19.8% in the probiotic group and worsened by 12.9% in the placebo group ($p < 0.001$ for the difference in the change between groups). The proportion of patients who had at least a 50% improvement in the IBS Severity Scoring System score was significantly greater in the probiotic group than in the placebo group (15.3% vs. 3.8%; $p < 0.04$).

Comment: About 30% of patients with celiac disease experience (IBS)-type symptoms despite following a gluten-free diet. One possible cause of these symptoms is an imbalance of the intestinal flora. In the present study, treatment with a multi-strain probiotic improved symptoms to a modest degree in patients with celiac disease who had IBS-type symptoms while on a gluten-free diet.

Francavilla R, et al. Clinical and microbiological effect of a multispecies probiotic supplementation in celiac patients with persistent IBS-type symptoms: a randomized, double-blind, placebo-controlled, multicenter trial. *J Clin Gastroenterol*. 2019;53:e117-e125.

Mediterranean Diet Improves Pregnancy Outcomes

Six hundred ninety-seven pregnant Spanish women who did not have gestational diabetes were randomly assigned at 8-12 weeks of gestation to consume a low-fat control diet (no more than 30% of total calories as fat) or a Mediterranean diet enriched with extra-virgin olive oil (at least 40 ml per day) and pistachio nuts (25-30 g per day). The primary outcome measure was a composite of adverse maternal and fetal outcomes (emergency C-section, perineal trauma, pregnancy-induced hypertension and preeclampsia, prematurity, large-for-gestational-age, and small-for-gestational-age). Compared with the low-fat diet, the Mediterranean diet resulted in a 52% reduction in the composite endpoint ($p = 0.0001$), with a number-needed-to-treat of five. Risk of urinary tract infection, emergency C-section, perineal trauma, large-for-gestational-age, and small-for-gestational-age were each significantly reduced by the Mediterranean diet.

Comment: The Mediterranean diet refers to the diet of olive-growing regions of the Mediterranean. In addition to olive oil, the diet emphasizes salads, legumes, wheat, fruit, nuts, and garlic. In Italy a lot of pasta is consumed, whereas in Spain fish consumption is high. Fat intake is around 30-40% of total energy. Consumption of a Mediterranean diet has been reported to improve cardiovascular disease risk factors, decrease the risk of major cardiovascular events, improve nonalcoholic fatty liver disease, and decrease inflammation. The results of the present study demonstrate that a Mediterranean diet enriched with extra-virgin olive oil and pistachios, as compared with a low-fat diet, resulted in a 52% reduction in adverse pregnancy outcomes in pregnant women who did not have gestational diabetes.

Assaf-Balut C, et al. A Mediterranean diet with an enhanced consumption of extra virgin olive oil and pistachios improves pregnancy outcomes in women without gestational diabetes mellitus: a sub-analysis of the St. Carlos Gestational Diabetes Mellitus Prevention Study. *Ann Nutr Metab*. 2019;74:69-79.

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3. Gaby AR. Vitamin D. In Gaby AR. *Nutritional Medicine*, Second Edition. Concord, NH, 2017. https://doctorgaby.com, chapter 23.

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When People Are Sensitive to Everything – A Clinical Primer

by Jacob Teitelbaum, MD

So many people, especially with fibromyalgia, are incredibly sensitive to any treatments – even to herbals, nutrients, their environment, and sometimes even cell phone and other electromagnetic (EMF) frequencies. This makes it tricky to take anything to recover. Here's how they can take the needed treatments you recommend.

In this article we will discuss some of the major triggers for severe environmental and treatment sensitivities, including food and multiple chemical sensitivity (MCS). We will begin with mast cell activation and food sensitivities, as these treatments are easy, low-cost, and often highly effective.

When problems persist, that's the time to consider looking for and treating mycotoxins (mold toxins) and the Lyme co-infection Bartonella. I strongly recommend reading the book *Toxic* by my friend, Dr. Neil Nathan.

Ready to start with some simple fixes?

Mast Cell Activation

Mast cells are our body's "first responders" when making contact with things in the outside world. If they meet something in the environment that concerns them, they can pour out over 200 chemicals. The most prominent of these is histamine. This is one reason why antihistamines are a mainstay of treating allergies.

Just like our immune system in fibromyalgia can be on overdrive in general, in some people this is also occurring for their mast cells. These guardians then have an itchy trigger finger, seemingly reacting to things at random.

Random is the key word here, and this helps distinguish mast cell activation from regular allergies and sensitivities.

Easy treatments for mast cell activation and food sensitivities reduce severe environmental sensitivities.

One day people may have no reaction to something, but they react excessively to the same trigger on other days. So, no problem eating an ear of corn one day; but the next day, they may have the sudden onset of flushing, nausea, diarrhea, sweating, or palpitations.

Testing is usually not helpful for this condition. As about half of Fibro folks with sensitivities have mast cell activation and treatment is simple, it's better to simply try these and see if they help.

Treatment

I usually begin in the following order:

1. Quercetin. I start with 500 mg a day. If their main sensitivities are to foods, give it about 30 minutes before major meals so it can be in place when they eat. This simple supplement can often be very, very helpful and is low-cost. After a few days, you can increase to 500 mg (or even 1000 mg) two-to-four times daily.
2. Montelukast (Singulair), 10 mg at bedtime. This prescription asthma medication is only $0.30 a day using the Good Rx phone app.
3. Loratadine (Claritin), 10 mg in the morning. If this over-the-counter medication causes sedation, they can use it at bedtime or try cetirizine (Zyrtec). If they have any other side effects to these medications, it is likely caused by the binders or fillers rather than the medication itself. In that case, try a different brand or have it made by a compounding pharmacy without the fillers. If this medication helps, consider diphenhydramine (Benadryl) 12.5 – 50 mg bedtime.
4. Some people will get additional benefits by adding ranitidine (Zantac) 150 mg twice a day, famotidine (Pepcid) 20 mg twice a day, or even cimetidine (Tagamet) 150 – 300 mg twice daily. These acid-blocking medications are actually also antihistamines.

• Do not use the other acid-blocking medications (called PPIs). They will not help here and are quite toxic long-term, likely causing over 30,000 US deaths yearly.

• Tagamet, Pepcid, and Zantac have the additional benefit of modifying immune function quite dramatically in ways that can be beneficial, especially against Epstein-Barr virus. In fact, I have seen Tagamet knock out acute cases of Epstein-Barr (mono) in less than 24 hours. This was a tip taught to me by Dr. Jay Goldstein.

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• The downside is that they turn off stomach acid production as well, and the body needs stomach acid to digest food. The cimetidine can be the best choice of these three for long-term use in this regard. But see which one works best.

• These medications may work within days, but it may take up to two months to see the full effect

5. The supplement DAO (Umbrellex) taken 15 – 30 minutes before eating can be helpful but costs about a dollar per capsule. But worth a try. DAO contains the enzyme diamine oxidase, which helps break down histamine. Starting with one capsule taken thirty minutes before a meal, the dosage can be increased to two to three capsules before each meal.
6. Cromolyn (Rx – gastrocom) ampules (100 mg in 5 mL), one before each meal, can be quite effective for histamine reactions from food but is often not insurance covered. With the Good Rx app, they are about a $1.60 per ampule.
7. In persistent severe cases, consider a low histamine diet (these can be found online); but this is quite a nuisance, and I rarely use it.

Food Sensitivities

Many people find that they have a number of food sensitivities. They find themselves limiting their diet, and then sometimes find themselves becoming sensitive to the few foods they could eat. They find that they, over time, have painted themselves into a corner where there is nothing left to eat.

There are three main things that trigger food sensitivities:

1. Incomplete digestion of proteins because of not enough stomach acid or digestive enzymes.
2. Leaky gut from infections, especially candida, and other causes. Anti-inflammatory arthritis medications such as ibuprofen are major triggers.
3. Adrenal fatigue.

Our digestive system is one of the main borders between ourselves and the outside world. Because of this, our immune system patrols our gut pretty aggressively. When eating food, especially proteins, the border guards check to make sure that these have been broken down to their component amino acids.

Here is an analogy that may be helpful for those you treat: "You can think of proteins as being long sentences made up of letters called amino acids. The letters by themselves have no meaning but are important building blocks that the body uses to make a wide array of necessary things. But if you absorb a long string of letters (i.e. an incompletely digested protein) into your blood, your body has to treat it like an outside invader. Then you develop sensitivities to the food.

"Therefore, if your digestion does not completely break down the food, or if your border patrol is not doing its job and letting in an incompletely digested food (called "leaky gut"), your body will react. Normally, this reaction is tempered by a healthy adrenal gland. When your adrenal gland is fatigued, however, you then have the perfect triad for developing food allergies.

"When you limit your diet, you then get large amounts of just a few foods. Your digestive system is made to break down a wide array of foods; and if your diet is limited, you are more likely to have incomplete digestion of those few foods. Then you get sensitive to them as well."

Sensitivity Versus Allergy

Medically, these are two very different things. Allergy is when a specific part of your immune system is getting triggered (e.g. – IgE antibodies and histamine). Sensitivities reflect a more generic term for your body and immune system reacting adversely to something.

Most people have food sensitivities and not allergies. Sadly, most physicians are unfamiliar with food sensitivities and often believe they don't exist.

Food Allergy Testing

Most food allergy blood tests are, in my humble opinion, worse than useless. A study done at Bastyr University showed that if you have three tubes of blood drawn, and send them to the same lab (fibbing and writing different names on the three tubes), the results will come back showing the person to be allergic to about 20 to 30 foods. But each lab result will show a totally different mix of food allergies – even though all three tubes were drawn from the same person at the same time!

I would note that one lab founded by Dr. Russell Jaffe (www.elisaact.com) seems to have avoided the problems with the results being random.

If people have already had them done, I tell them to ignore the results of these tests, especially if they were Ig**G** antibody tests. The exception would be if **only** Ig**E** testing was done. This would be clearly shown on the lab report. In that case, most people have no positive results. If something shows positive, it is a true food *allergy* and that food needs to be avoided. But this test will not look for food *sensitivities*.

My preferred approach to testing? Muscle testing (see below) in the hands of somebody experienced in the technique can be very reliable.

An elimination diet is most reliable, but a nuisance. You can find a "kinder and gentler" elimination diet at www.vitality101.com (search on "Rapp Elimination Diet").

Eliminating Food Sensitivities

Although allergy shots can be very effective for inhalant allergens like pollen, they're not very effective for food sensitivities. But there is a technique that is gentle yet very powerful. This is called the Nambudripad Allergy Elimination Technique (NAET; See www.NAET.com).

NAET uses muscle testing (called applied kinesiology) to test for sensitivities. Looking at it, my first reaction as a scientist was that there was no way on earth this testing or treatment could possibly work. In fact, until my early 40s, I suffered with severe hay fever (ragweed allergy). I met an NAET practitioner who said that she could get rid of it in 20 minutes. Being an all-knowing doctor, I told her, "Leave me alone. That voodoo can't help me!"

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Clinical Primer

➤ *continued from page 28*

A few weeks later, when I was especially miserable, she said, "Stop being a nitwit and let me treat you." Twenty minutes later, my hay fever was gone, never to return.

One of my mentors, Dr. Janet Travell, used to say "first see what is going on before you need to understand it. Otherwise, you will never see anything unexpected." As a physician, however, unfortunately we are more likely to follow Winston Churchill's quote. "We often stumble over the truth. Fortunately, we get up, brush ourselves off, and quickly walk away before any real harm is done!"

Keeping both of those thoughts in mind is part of what got me into trouble as a physician. Instead of closing my eyes to what happened, and then quickly walking away, I flew to California to meet Dr. Devi Nambudripad, MD, PhD, RN, DC, LAc. Despite all the letters after her name, I found her to be brilliant, with no ego. I studied her technique and was so impressed that I went back home to Annapolis and married the woman who had used it to eliminate my hay fever!

Years later, I found that the technique often caused autism to resolve. Our foundation then funded, and I was chief investigator on, a study using NAET to treat autism. By the end of one year, 23 of the 30 autistic children were back in regular school as opposed to zero of the 30 in the control group. We published this study, and a large double-blind placebo-controlled study is currently underway. For those of you who know any autistic children, you can find information on how to enroll in the study at www.NAET.com.

NAET works brilliantly. The mechanism is not clear, but it seems to reset the immune system so that it no longer sees that food as an enemy. Kind of like hitting the "restore factory defaults" setting on your computer when it goes on the fritz.

I recommend 15 treatments to address each of the 15 major food groups. If it is not clearly helping by the end of 15 treatments, it is not likely to help. Practitioners can be found at www.NAET.com. Most practitioners are not on the website though, so do a search online for people in your area. If you find one on the website though, they are more likely to be more experienced.

I have seen NAET by itself eliminate fibromyalgia in some people with severe sensitivities.

To prevent the food sensitivities from coming back, it is important to take a good **plant-based** digestive enzyme and something to enhance stomach acid (e.g. a vinegar-based salad dressing) with larger meals; eliminate gut Candida and other infections; and address the adrenal fatigue. My favorite supplements for adrenal fatigue are Adrenaplex and Adaptra (both by EuroMedica).

Simply put, easy and rather remarkable treatments!

Molds and Mycotoxins (Mold Toxins)

When severe sensitivities persist, especially if associated with marked anxiety, consider mold toxins.

This concept was initially formulated by Dr. Ritchie Shoemaker, author of *Mold Warriors*. Ritchie is so bright as to be almost unintelligible in his complexity. His work has been synthesized and simplified by Dr. Neil Nathan, author of the exceptional book *Toxic*. If you decide to explore mold toxin treatment further, I highly recommend reading this book.

This is not a diagnosis I entertain lightly, saving it for when other treatments fail. The main problem is that if urine testing suggests high levels of the mold toxins, a very expensive Pandora box is being opened for the person being treated. My concern is that I still do not know what percent of healthy people test positive on mold urine testing, so we do not know the specificity of the test – meaning that it may be positive but not a problem. Then the person is forced into home mold remediation, which is difficult and can cost tens of thousands of dollars. Meanwhile, urine testing for mold toxins costs about $400 – $700 each time they are checked, and this is usually not insurance covered.

But when mycotoxins are the root problem, they do need to be addressed. If you are interested in a short article I have written that simplifies an approach to diagnosing and treating mold toxins, you can email me for the "Mycotoxin Article" at FatigueDoc@gmail.com.

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Jacob Teitelbaum, MD, is one of the most frequently quoted integrative medical authorities in the world. He is the author of 10 books, including the best-selling *From Fatigued to Fantastic!, The Complete Guide to Beating Sugar Addiction*, *Diabetes Is Optional* and the popular free Smart Phone app *Cures A-Z*. Dr. Teitelbaum appears often as a guest on news and talk shows nationwide including Good Morning America, The Dr. Oz Show, Oprah & Friends, CNN, and FoxNewsHealth. Learn more at Vitality101.com.

Biochemical Markers in the Urine Associated with Gastrointestinal Mold-Overgrowth Are Linked with Elevated Urinary Mycotoxins in Patients with Suspected Mold Illness

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

Abstract

Seven different mycotoxins, including aflatoxin M1, ochratoxin A, sterigmatocystin, zearalenone, roridin E, verrucarin A, and enniatin B1 that have been associated with human illness were tested by LC/MS/MS in urine samples of a control group of 89 healthy adult volunteers and 103 adult patients suspected of mold illness based on clinical symptoms assessed by their physicians and findings of mold growth in their homes or offices. In addition, markers of gastrointestinal mold and yeast colonization, mitochondrial function, and glutathione status markers were assessed in the same urine samples by GC/MS. Values for all the mycotoxins tested were significantly increased in the mold patient group compared to the control group. Markers for mold colonization of the gastrointestinal tract were all significantly more elevated in the mold-exposed group compared to the control group. Lactic acid, oxalic acid, and pyroglutamic acid were all significantly higher in the mold-exposed patient group compared to the control group. Succinic acid, a marker of mitochondrial function was also higher in the mold-exposed group but did not reach statistical significance. Elevated markers of *Fusarium* and *Aspergillus* gastrointestinal colonization in mold-exposed patients indicates a need for antifungal treatment for successful treatment of mold-exposed patients.

Introduction

Mycotoxins are physiologically active metabolites released by specific strains of filamentous fungi. Over 400 different mold metabolites have been identified, however to date only several dozen have been shown to have significant toxic potency in humans.[1] Routes of exposure include inhalation, absorption through the skin, exposure to mold from water damaged buildings, occupational exposure, ingestion of mold-contaminated food,[2,3] and mycotoxins produced by mold in the gastrointestinal tract or other organs. The mycotoxins that we evaluated in this study, including aflatoxin M1 (AFM1), ochratoxin A (OTA), sterigmatocystin (STC), zearalenone (ZEA), roridin E (ROE), verrucarin A (VER), and enniatin B (ENB), have multiple toxic properties which elicit health effects in patients. These properties include cytotoxicity, carcinogenicity, teratogenicity, hepatotoxicity, nephrotoxicity, neurotoxicity and immunosuppression.[4-6]

Mycotoxins, produced by mold in the body, inhibit mitochondria and deplete glutathione.

Exposure to mycotoxins can lead to acute as well as chronic toxic effects, which are dependent on the mycotoxin type, the amount, length of the exposure, and the health, age, and sex of the patient. Dietary deficiency, co-existing health conditions, and environmental/chemical exposure potentially create a compounding effect which can impact the severity of symptoms. Mycotoxins have been found in multiple different tissues with the highest concentrations found in liver and kidneys.[7] Other tissues that can contain significant amounts of mycotoxins include brain, muscle, fat, skin, myocardium, gastric mucosa, and bone marrow.[7] Mycotoxin exposure can lead to many different types of acute or chronic diseases.[8,9] Symptoms of mycotoxin exposure can include cough, irritation of the eyes and skin, fatigue, migraines/headaches, joint pain, and neurological illnesses such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.[10-14]

Monitoring mycotoxins and their metabolites in human samples to assess the exposure of individuals to mold is one of the first steps in determining the proper treatment for these patients. Recent advances in LC-MS/MS techniques now allow urinary biomarker assessments at environmentally relevant concentrations.[10,15-17] Studies have shown that mycotoxins are produced ➤

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by multiple species of mold, including those from *Stachybotrys, Aspergillus, Fusarium, and Penicillium*[9] genera. Some of the important mycotoxins produced by these molds include aflatoxin M_1 (AFM1) and ochratoxin A (OTA) from *Aspergillus* and *Penicillium*, zearalenone (ZEA) and enniatin B (ENB) from *Fusarium*, sterigmatocystin (STC) from *Penicillium*, roridin E (ROE) and verrucarin A (VER) from *Stachybotrys*).[15] Urine has been determined to be the preferred matrix for mycotoxin analysis because most mycotoxins are metabolized and excreted via urine.[18]

In addition to monitoring these toxins in the urine of exposed and control patients, we examined metabolic markers to assess their relevance to alterations of other biochemical functions, which could assist in determining proper treatment for mold exposure. GC/MS instrumentation was used to measure known small molecule biomarkers and to assess their correlation with mold and mycotoxin exposure. The specific urine markers that were analyzed have been shown to give insight on mold colonization of the gastrointestinal tract, yeast coinfection, mitochondrial damage, and glutathione usage.

Studies have shown that multiple species of mold can colonize different tissues in the body including the lungs, gastrointestinal tract, and sinus cavities and a recent study found *Aspergillus* and *Penicillium* species to be present in the gastrointestinal tracts of healthy volunteers.[19] Some of the most frequently diagnosed fungal pathogens come from the genera *Aspergillus* and *Candida*. To test for colonization of *Aspergillus,* we measured 5-hydroxymethyl-2-furoic and furan-2,5-dicarboxylic acids.[20-21] We measured tricarballylic to indicate the presence of *Fusarium* species.[22]

Because of the immunosuppressive abilities of mycotoxins released from *Aspergillus* and other colonizing mold species, *Candida* can frequently coinfect a patient.[23] Species of *Candida* are frequently opportunistic pathogens that may cause various infections from oral candidiasis to systemic blood stream infections.[24] There are over 200 species of invasive *Candida. Candida* albicans is the most prevalent fungal pathogen of humans, however *Candida glabrata*, *Candida krusei*, *Candida tropicalis*, and *Candida parapsilosis* can also cause human candidiasis.[25] *Candida* can colonize skin, mucosal surfaces, and the gastrointestinal tract. As a marker for *Candida* colonization, we measured citramalic acid, which has been shown to be produced by various species of yeast.[26]

Mitochondria are double membrane-bound organelles that generate the cell's energy through the production of adenosine triphosphate (ATP). The mitochondria produces other forms of energy through the citric acid cycle (TCA) in the form of NADH and FADH.[27] Previous studies have shown a role for mitochondria in mycotoxin toxicity.[28-32] OTA exposure can lead to mitochondrial transmembrane potential loss and caspase-3 activation. Multiple cellular changes occur following OTA exposure, which include decrease of Bcl-xL, survivin, (which lead to increases of apoptosis) and IL-2 and an increase of tumor necrosis factor alpha (TNF-α).[30, 32] Mycotoxins also inhibit mitochondrial efficiency by inhibiting mitochondrial translation. This repression of mitochondrial translation leads to increase in mitochondrial oxidative stress and contributes to mycotoxin sensitivity.[29] To determine if patients exposed to mycotoxins are exhibiting mitochondrial stress, we decided to measure the organic acids lactic acid and succinic acid, which have been shown to be elevated in patients exhibiting mitochondrial disease.[33-34]

Glutathione is a ubiquitous tripeptide that is present in almost all cells in high concentrations. Reduced glutathione is produced through two mechanisms in the body, *de novo* synthesis and recycling of oxidized glutathione dimers, GSSG. Its main function is to protect cells from toxic effects of oxygen-derived free radicals. There are many glutathione-dependent enzymes that perform a host of different regulatory and detoxification processes throughout the body.[35] One of these is a family of enzymes called glutathione transferases (GST). These enzymes utilize glutathione to conjugate and detoxify drugs and other xenobiotics. This pathway is one of the main pathways for the detoxification of mycotoxins. Depletion of glutathione or inhibition on the transferase enzymes can cause patients to become more susceptible to mycotoxin induced injury.[36-37] Patients that have higher utilization of glutathione have higher elimination of pyroglutamic acid in their urine.[38] Measurement of pyroglutamic acid can give us insight into the patient's utilization of glutathione.

Table 1. Mycotoxin amounts in patients

Control Group	% Positive	Mean (ng/g creatinine)	Min-Max (ng/g creatinine)	Median (ng/g creatinine)	p value
AFM1	6.10%	0.092	0-3.1	0	NA
OTA	51.20%	1.677	0-6.31	0.263	NA
STG	10.90%	0.046	0-1.11	0	NA
ZEA	7.30%	0.008	0-3.55	0	NA
ROE	2.43%	0	0-.482	0	NA
VER	7.31%	0	0-.42	0	NA
ENB	3.65%	0.007	0-.923	0	NA
Exposed Group	**% Positive**	**Mean (ng/g creatinine)**	**Min-Max (ng/g creatinine)**	**Median (ng/g creatinine)**	**p value**
AFM1	24.30%	2.14	0-24.3	0	0.1115
OTA	85%	18.68	0-247	10.5	0.0026
STG	17.80%	1.75	0-76.5	0	0.305
ZEA	7.80%	0.44	0-13.8	0	0.1929
ROE	1.90%	0.07	0-8.01	0	0.4556
VER	1.90%	0.13	0-13.8	0	0.1329
ENB	7.80%	0.05	0-1.06	0	0.0711

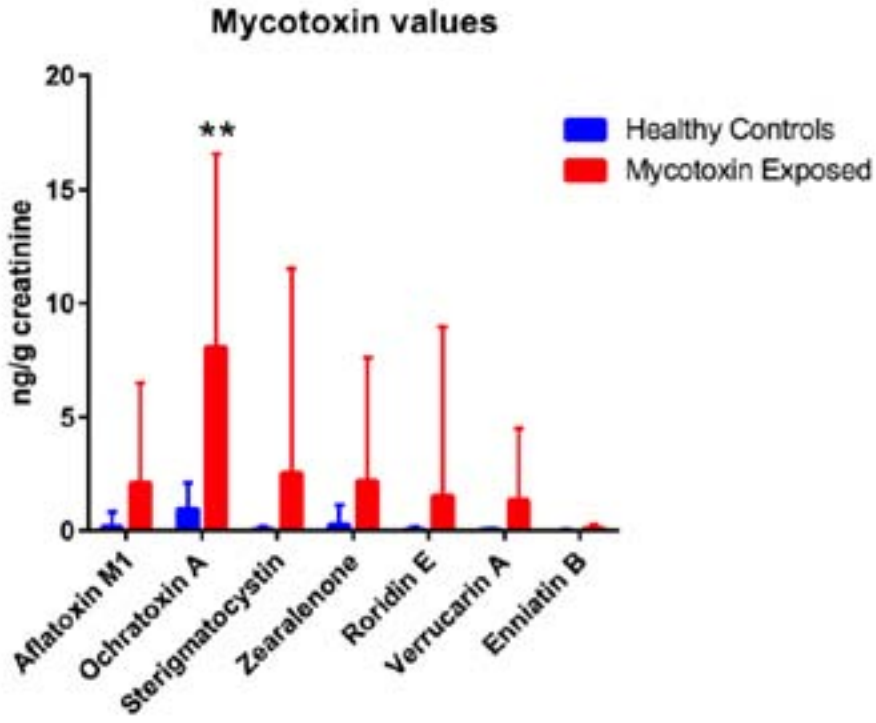
p values are based on the statistical differences between the means of exposed and control groups

Results of Mycotoxin Analysis

AFM1, OTA, STC, ZEN, ROE, VER, and ENB were analyzed by LC-MS/MS in urine for both the control group as well as the mycotoxin exposed group. For this purpose, a previously published method was used.[39] In Tables 1 and Figure 1, we detail the results from the control group and the mycotoxin exposed groups

respectively. A positive value was any detectable value above our limit of quantification, which was 1.3 ng/g creatinine for AFM1, 1.2 ng/g creatinine for OCA, 0.1 ng/g creatinine for STC, 0.5 ng/g creatinine for ZEA, 0.75 ng/g creatinine for ROE, 0.5 ng/g creatinine for VRA, and 0.09 ng/g creatinine for ENB. For AFM1, the mycotoxin was detected almost four times more often in the exposed group vs the control (24.3% vs 6.1%). The mean value for the exposed group was 23 times greater (2.14 vs 0.092 ng/g creatinine) than the control group. For OTA, the exposed group had more patients with detectable OTA than the control group. The mean for OTA was 11 times higher in the exposed group vs the control (18.68 vs 1.677 ng/g creatinine). STG was positive more often in the exposed group than the control group (17.8 vs 10.9%), and the mean value was 38 times higher in the exposed group (1.75 vs 0.046 ng/g creatinine).

Figure 1: Mycotoxin values in mold-exposed vs control populations. Each graphical plot represents the mean+ standard deviation, **designates p<0.005, comparing patient values and control values



Biochemical Markers Associated with Mycotoxin Exposure

Mycotoxin exposure can affect many different systems in the body. Measurements of these effects on patients can help in treatment. Utilizing GC/MS, we measured other markers that could be altered by exposure to mycotoxins. The markers that we were most interested in testing were related ➤

Figure 2. Biomarkers for A*spergillus* colonization. Quantified in urine using a GC/MS. Each graphical plot represents the mean±standard deviation. **designates p<0.005, comparing patient values and control values

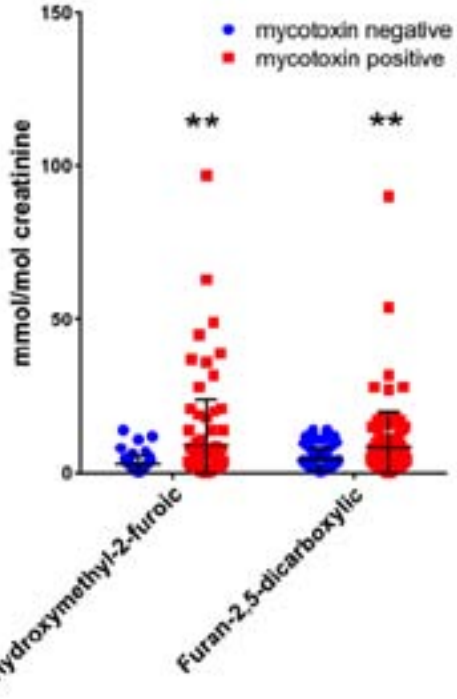
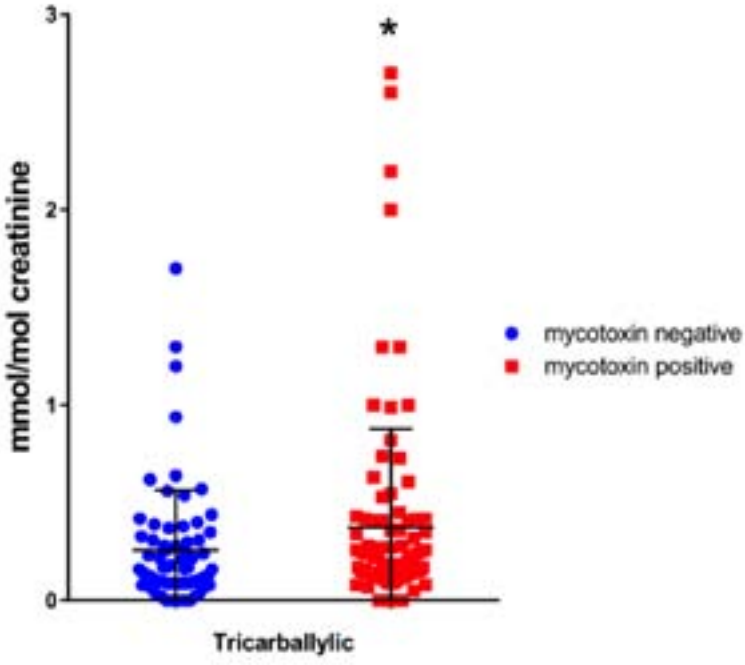


Figure 3. Biomarker for Fusarium colonization. Quantified in urine using a GC/MS. Each graphical plot represents the mean±standard deviation. *designates p<0.05, comparing patient values and control values



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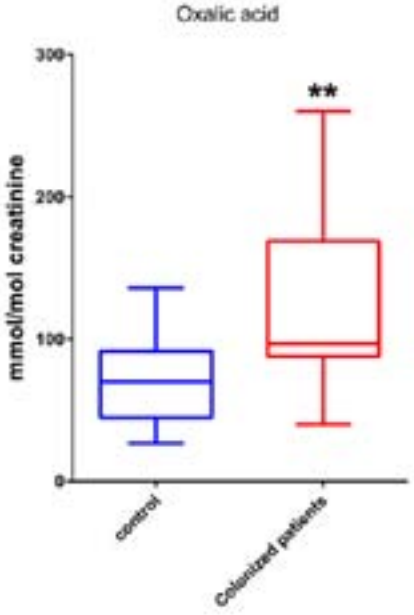
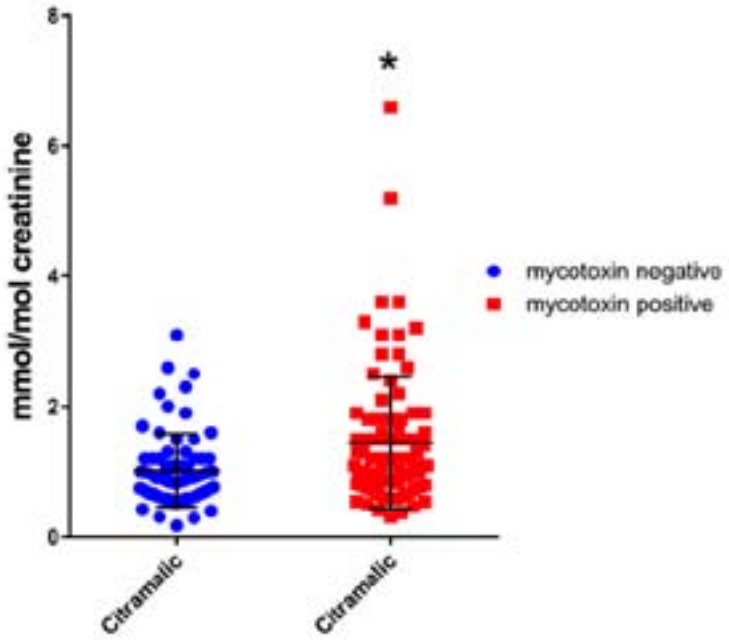
to *Aspergillus* colonization, yeast colonization, mitochondrial status, and glutathione status.

Figure 4. Biomarker for fungal colonization. Quantified in urine using a GC/MS. Each graphical plot represents the mean±standard deviation. **designates p<0.005, comparing colonized patient values and control values



To determine if markers for *Aspergillus* or *Fusarium* growth is more abundant in patients exposed to mycotoxins vs controls, we decided to measure the amounts of three different markers. Two metabolites, 5-hydroxymethyl-2-furoic and furan-2,5-dicarboxylic acids, were analyzed as markers for *Aspergillus* (Figure 2) and tricarballylic measurements were used as an indicator for *Fusarium* (Figure 3). The 5-hydroxymethyl-2-furoic acid values were higher in patients exposed to mold vs the control patients (9.11 vs 2.91 mmol/mol of creatinine) (p value= 0.00075). Furan 2,5-dicarboxylic acid was also found to be higher in patients exposed to mold. In the mold-exposed patients, furan-2,5-dicarboxylic acid was 8.23 and in the control group it was 4.32 ng/g creatinine (p value = 0.00904). The tricarballylic acid mean was found to be twice as much in the mold-exposed group versus the control group (0.46 vs 0.22 mmol/mol of creatinine) (p value = 0.0493). One additional marker that we measured was oxalic acid. Oxalic acid is a biproduct from *Aspergillus.*[40] Oxalic acid in the colonized group was significantly higher than the control group (Figure 4) (137.7 vs 72.6 mmol/mol of creatinine) (p value=0.0029).

Figure 5. Biomarkers for yeast colonization. Measured on a GC/MS. Each graphical plot represents the mean± standard deviation. *designates p<0.05, comparing patient values and control values



Candida as well as other pathogens can infect a patient that has been exposed to mycotoxins.[23] One reason for this increased risk of infection is that many mycotoxins possess immunosuppressive affects.[41] To measure the amount of *Candida* residing in a patient, we selected citramalic as a marker, which has been shown to be produced by multiple strains of yeast (Figure 5).[26] Citramalic was significantly higher in the mold-exposed group versus the control group (1.45 vs 1.02 mmol/mol of creatinine) (p value = 0.00191).

Fatigue is a common symptom of mold exposure, which can be attributed to decreased mitochondrial efficiency caused by mycotoxins.[14] To test for mitochondrial stress, lactic acid and succinic acid were measured (Figure 6). Lactic acid is produced from pyruvate by lactate dehydrogenase when additional energy production is needed. Lactic acid is then either converted back to pyruvate or converted to glucose through gluconeogenesis. Succinic acid is generated in mitochondria through the tricarboxylic acid cycle. Succinate is then converted to fumarate by succinate dehydrogenase. In patients exposed to mycotoxins, lactic acid was significantly higher in their urine than the control group (29.8 vs 18.44 mmol/mol of creatinine) (p value = 0.00229). For succinate, the observed value for the exposed group was higher than the control (9.56 vs 6.35 mmol/mol of creatinine); however, the value was not statistically significant (p value 0.12).

Glutathione conjugation is one of the primary pathways for the detoxification of mycotoxins. Mycotoxin exposure can lead to the depletion of glutathione stores, which will limit the body's ability to detoxify multiple different xenobiotics. Depletion of glutathione or inhibition on the transferase enzymes can lead patients to become more susceptible to mycotoxin induced injury.[36,37] Measuring pyroglutamic acid (5-oxoproline) in patient urine may give us insight into which patients are depleted of glutathione and are more at risk for mycotoxin inducted injury. When glutathione concentration is reduced, γ-glutatmylcysteine

formation increases and this dipeptide is converted to pyroglutamic acid in the plasma; some of the pyroglutamic acid is excreted in urine.[42] Patients exposed to mold had significantly higher amounts of pyroglutamic acid in their urine compared to controls (Figure 7) (25.69 vs 21.63 mmol/mol of creatinine, p value = 0.01461)

Conclusions

Mold and mycotoxin exposure can affect multiple systems, including detoxification, immune function, and neuronal function, among others. Mycotoxins attack multiple cell types through their interactions with mitochondria, nuclear transcription factors, as well as DNA.[27,30,32,37] We employed LC/MS/MS to quantitate mycotoxin exposure and GC/MS to measure other biomarkers that may indicate severity of effects on patients from the mycotoxins.

Ochratoxin was the most prevalent mycotoxin found in mold-exposed patients (Table 1). The mold-exposed group had detectable amounts of ochratoxin in 85% of the patients; however, the control group also had detectable amounts in over half of that population (51.2%). The mold-exposed group had over 10-fold increase in detectable ochratoxin compared to the control group (18.68 vs 1.68 ng/g creatinine). Other mycotoxins that were increased in the mold-exposed group were aflatoxin M1 and sterigmatocystin.

For biomarker analysis by GC/MS, there were several significant differences between the exposed group versus the control group (Table 2). The *Aspergillus* and *Fusarium* markers 5-hydroxymethyl-2-furioc, furan-2,5-dicarboxylic, and tricarballylic acids were all significantly elevated in patients with mold exposure. A previous study indicated that one site of mold colonization was the gastrointestinal tract that was ascertained by treatment with the antifungal drug nystatin, which is not absorbed from the gastrointestinal tract. The fact that the mold markers in that study were significantly reduced (56-63%) after 10 days of nystatin indicated that at least a substantial portion of the molds producing these markers was from the gastrointestinal tract.[43] The fact that the gastrointestinal tract was colonized with mold species also indicates that patients exposed to mold that has colonized the gastrointestinal tract might continue to have severe symptoms long after moving out of a mold-contaminated environment unless treated with antifungal agents to kill gastrointestinal molds.

Patients that were exposed to mold also had a higher instance of yeast colonization, which was measured by increased levels of the yeast metabolite citramalic. The mitochondrial marker lactic acid was significantly elevated in patients exposed to mold. Oxalic acid, a toxic metabolite of *Aspergillus*, was elevated in the patients who were colonized. Oxalic acid has been shown ➤

Table 2. Summary of biomarker data for control and exposed groups

Organic Acids	Control (mmol/mol creatinine)	Exposed (mmol/mol creatinine)	p value
Citramalic	1.02	1.45	0.0019
5-Hydroxymethyl-2-furioc	2.91	9.11	0.0007
Furan-2,5-dicarboxylic	4.32	8.24	0.0090
Tricarballylic	0.22	0.46	0.0493
Lactic	18.44	29.80	0.0023
Succinic	6.35	9.56	0.1209
Pyroglutamic	21.63	25.70	0.0146

Figure 6. Mitochondrial biomarkers in urine. Each graphical plot represents the mean ± standard deviation. **designates p<0.005, comparing colonized patient values and control values

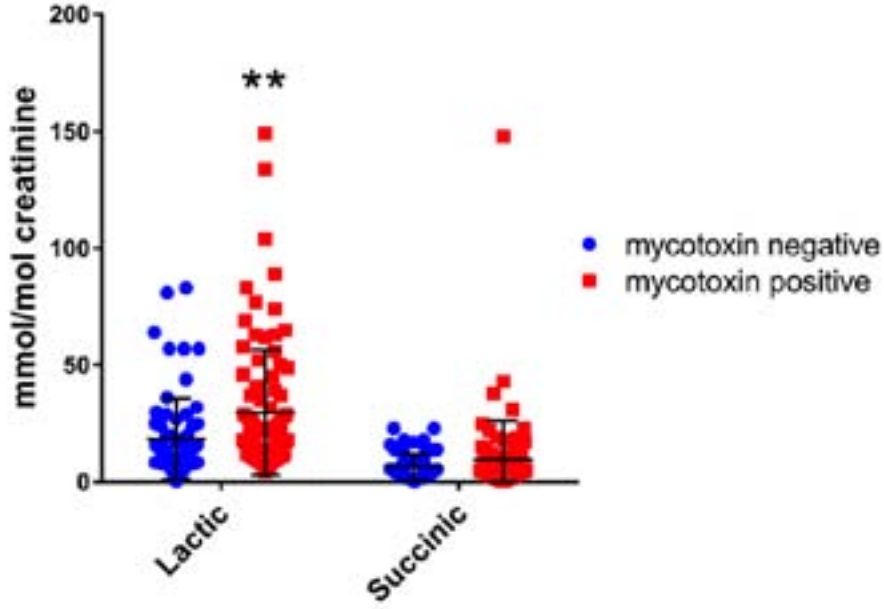
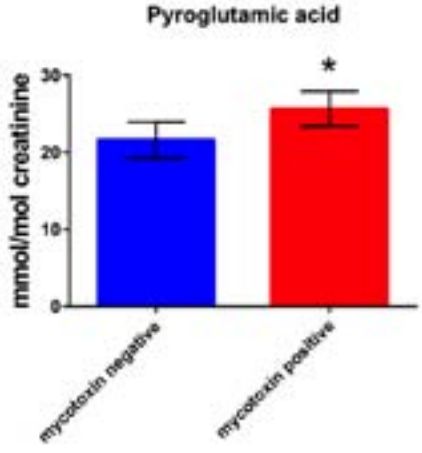


Figure 7. Biomarker for urine glutathione quantified by GC/MS. Each graphical plot represents the mean ± standard deviation. *designates p<.05, comparing patient values and control values



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to have toxic effects on virtually every organ of the human body including urinary tract, cardiovascular system, brain, muscles, thyroid gland, and eyes.[44] Lastly, pyroglutamic, a glutathione usage deficiency marker, was elevated in the patients exposed to mold versus our control samples. This was expected because glutathione is depleted in the detoxification of many mycotoxins.

This study demonstrates that patients that are exposed to mold have elevated mycotoxins in their bodies, which can be measured by urine excretion. These mycotoxins cause multiple effects in the body. We were able to measure some of these effects through different urinary biomarkers by GC/MS.

Materials and Methods

Selection of human subjects for test. This study enrolled a grand total of 185 adults, split into the self-reported mold-exposed group (n=103) and a healthy control group of adults at least 18 years old with no known mold exposure (n=82). Mold-exposed patients were reported by their medical practitioner to have symptoms that matched mold exposure.

Chemicals and reagents. Urinary organic acid standards were purchased from Sigma-Aldrich (St. Louis, MO, USA) and mycotoxin standards solutions of ZEA, OTA, STG, VER, and ROE were purchased from Romer Labs Diagnostic (Tulln, Austria). Standard solution of AFM1 was purchased from Sigma-Aldrich. Acetonitrile (ACN), ethyl acetate (EtOAc), methanol (MeOH), and chloroform (CHCl3) were purchased from Thermo-Fisher Scientific (USA). Solid standards were dissolved and combined into a multi-standard working solution for preparation of calibrants. Ultrapure water was produced by a Milli-Q system (Millipore, Bedford, MA, USA).

Equipment and conditions. Urinary organic acid analyses were performed on a gas chromatography-mass spectrometry (GC-MS) system. The GC-MS used was from Agilent (Palo Alto, CA, USA) and consisted of a 5977B mass spectrometer detector and a 7890B gas chromatograph. For GC-MS analysis, 1 µl of sample was injected onto a 10-m DB-1MS capillary column with a 0.10-mm diameter, with helium as the carrier gas. All experiments were done using electron-impact ionization with electron energy of 70 eV. The temperature program was started at 90°C, held for one minute after injection, and then increased to 280°C at a rate of 20°C/min.

A Tokyo Boeki Chemistry Analyzer was used to determine creatinine (mg/dL) using a modified Jaffe method with Pointe Scientific creatinine reagent. All results were normalized to creatinine to correct for hydration variation among participants.

Participants and urine collection. All the volunteers were informed on how to collect first morning urine samples. For analyses, 25 ml of urine was collected from each sample. The two groups of patients were healthy volunteers (82) and patients suspected to have mycotoxin exposure (103). Sample kits were mailed to participants' homes and then overnighted to the lab. The detection and quantification of urinary mycotoxin metabolites was performed using a liquid chromatography tandem mass spectrometry (LC-MS/MS) system including binary pumps, auto injector, separation column, and MS/MS detector LC-MS/MS analyses were performed on a triple quadrupole 8060 (Shimadzu, Kyoto, Japan). The method of analysis was detailed in a previous paper.[39]

Organic acid analysis. Urine organic acid analysis has historically been performed using GC/MS instrumentation. Organic acid analytes are extracted from urine and derivatized before being analyzed by GC/MS. This analysis was performed similarly as first described by Tanaka et al.[45] Urine samples were prepared for GC/MS analysis using liquid-liquid extraction technique. Samples were stored under refrigeration (-20°C) until testing. A 1 mL aliquot of each urine sample was first incubated with 200 uL ethyl hydroxylamine hydrochloride (75g/L) at 60°C for 30 minutes to convert keto-acids to their ethoxime derivatives. The samples were then acidified to pH 1 with 100 uL 6N HCl to convert organic acids to an uncharged state before being extracted with ethyl acetate and ether. Solvent extracts were evaporated to

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William Shaw, PhD, is board certified in the fields of clinical chemistry and toxicology by the American Board of Clinical Chemistry. Before he founded the Great Plains Laboratory Inc., Dr. Shaw worked for the Centers for Disease Control and Prevention (CDC), Children's Mercy Hospital, University of Missouri at Kansas City School of Medicine, and Smith Kline Laboratories. He is the author of *Biological Treatments for Autism and PDD*, originally published in 1998, and *Autism: Beyond the Basics*, published in 2009. He is also a frequent speaker at conferences worldwide.

He is the stepfather of a child with autism and has helped thousands of patients and medical practitioners to successfully improve the lives of people with autism, AD(H)D, Alzheimer's disease, arthritis, bipolar disorder, chronic fatigue, depression, fibromyalgia, immune deficiencies, multiple sclerosis, OCD, Parkinson's disease, seizure disorders, tic disorders, Tourette syndrome, and other serious conditions.

Matthew Pratt-Hyatt, PhD, received his PhD in cellular and molecular biology from the University of Michigan. He has trained under Dr. Paul Hollenberg, a prominent researcher on drug metabolism, and Dr. Curtis Klaassen, one of the world's leading toxicologists. He has over a dozen publications in well-known research journals such as the *PNAS* and *Cell Metabolism*. He is currently associate laboratory director at the Great Plains Laboratory Inc. in Lenexa, Kansas, focused on diagnosis and treatment of mitochondrial disorders, neurological diseases, chronic immune diseases, and more. He specializes in developing tools that examine factors at the interface between genetics and toxicology. His work is bringing new insight into how genes and toxicants interact and how that may lead to mental health disorders, chronic health issues, and metabolism disorders.

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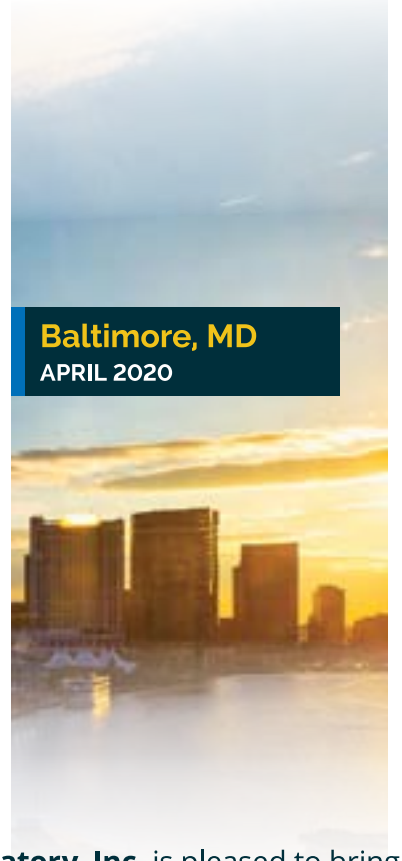

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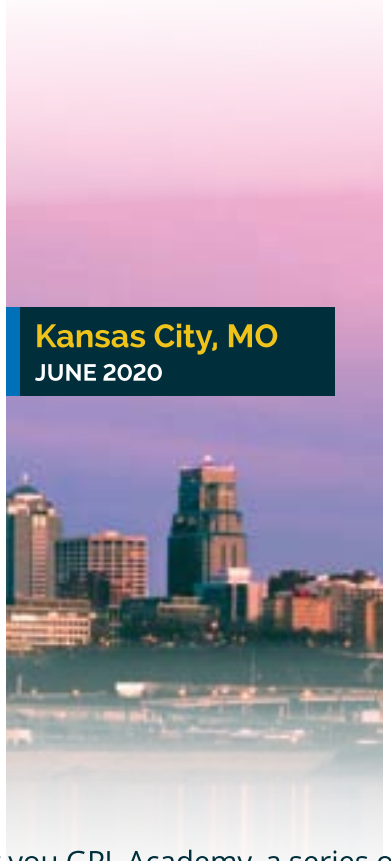

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Urinary Mycotoxins

➤ *continued from page 36*

dryness under nitrogen and reacted with BSTFA (1%TMCS) at 80°C for 10 minutes. Trimethylsilyl (TMS) derivatized samples were analyzed by GCMS with spectral confirmation against a library database. Quantitation was based on analyte specific calibrations using standards prepared at known concentrations. Low and high controls were prepared using pooled urine and standard-spiked urine, respectively.

Mycotoxin analysis. Samples were prepared as seen in De Santes et al.[39]

Statistical analyses. For the GC/MS and LC/MS/MS biomarker tests, t test with Bonferroni multiple comparisons test was performed to compare the results between the mold-exposed group and the control group. All analyses were performed with Prism version 6.07 software (GraphPad Software, La Jolla, CA, USA). A value of $p < 0.05$ was considered statistically significant.

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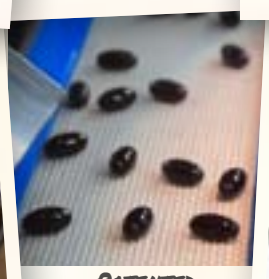

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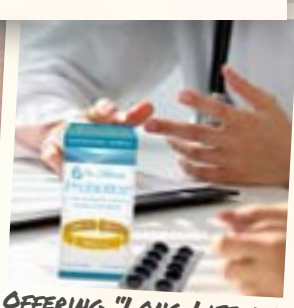

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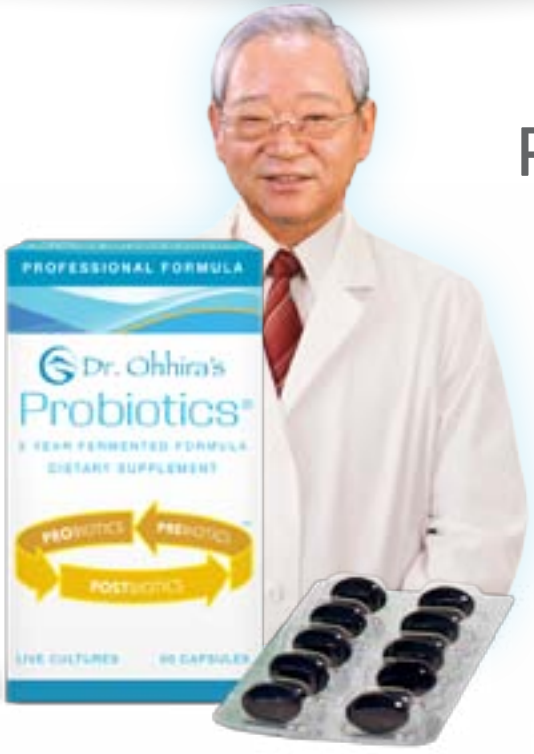

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Approaching Fibromyalgia with Regenerative Medicine

by Sangeeta Pati, MD, and John Apsley, MD(E), ND, DC

In the 1990s when I (SP) was in medical school, I had not heard of the term "fibromyalgia." As a matter of fact, this condition came directly into my consciousness only ***after*** I started to practice regenerative medicine. That's when patient after patient started coming through my door with "fibromyalgia": *fatigue and pain of unknown origin*. They were looking for a way to treat their condition that differed from conventional medical practice. Many had been placed on pharmaceutical products intended to "give them their life back." Yet these patients almost always lost much of their ability to function. In fact, many of them were on full disability. It became clear that we were not treating root causes.

Over the years, the quest for the root causes for fibromyalgia led to an understanding that they are no different from the root causes of all chronic conditions. Regenerative medicine starts with determining true causation and then restoring and rebalancing the body by tapping into the innate healing powers found in every living being. This customized approach to healing is a system that enables the body to regenerate itself. We define regeneration as unscheduled healing, that is, healing unlikely to take place with conventional approaches.

In this article, we share some insights from our Regenerative Protocols That Work™ that we have used to successfully address root causes in thousands of patients. This includes the physicians or their family members (>20%) that seek our care and learn these methods from our workshops. Chronically ill patients who adopt this regenerative model achieve a full recovery over 85% of the time. Additionally, we are even more fortunate in that when our patients consistently stick to their full program, they enjoy a much lower risk of acquiring future chronic diseases, including cancer, than the national averages.

How Joan Got Her Life Back

Joan, age 54, arrived on my doorstep in 2005 with debilitating pain. Despite a plethora of pain medications and Lyrica, she was unable to function at even a basic level and reported long-term disability. At that time, I was just getting my feet wet in the world of integrative medicine. As an Ob/Gyn, I started with bio-identical hormone therapy – some estrogen, progesterone, and testosterone. In four weeks, she returned for a follow up visit and reported, "My pain is a little better. I'm sleeping better, and I want to go all the way." It was Joan, and then hundreds of patients after her who motivated the journey and a framework that became the foundation for our five-point regenerative model. This causal approach (i.e. 5-point model system described below) has been specifically utilized to empower every patient to be "in the driver's seat for their own recovery." A key concept is the ability to wean patients off of outside influences and medications, gradually moving them towards their innate state of optimal health and homeostasis. I still see Joan today. She remains off all medications, remains pain-free, and has sustained, vibrant energy. In a phrase, Joan got her life back!

The Best Model for Regeneration

In 2017, we had the blessing of having Dr. John Apsley, author of the Regeneration Effect series, consult in our practice. With over 40 years of research, he had identified the precise means by which long-living people implement a daily regenerative lifestyle to thrive. By adding his advanced regenerative methodology to our practice, patients are more quickly enabled to become the primary driver to their own recovery. This is critical to the many patients who are long disempowered to even think recovery is possible due to chronic illnesses. A regenerative lifestyle is all about addressing the causations to how the long-living thrive. So, our clinic providers are able to manage even more difficult cases, more cost-effectively because we do not have to chase after so many of the down-stream complexities that are now so inherent to chronic cases.

For example, in the literature one finds a myriad of possible causes of fibromyalgia, including physical inactivity,[1] autoimmunity, infections,[2] parasites, toxins, heavy metals, vaccines, dysbiosis, nutritional deficits, adrenal insufficiency, mental abuse, depression[3] and chronic stress.[4] Chasing any **one** of these causes never results in a complete, sustainable cure because these are downstream from the basic factors that control the internal environment.

Here, we can learn from the long-living cultures who are regenerating in the Blue-Zones (Figure 1). Around the world there are well-studied zones, where people live long healthy lives, climbing mountains, herding goats and flourishing until they are above 100 years old.[5-7] These people experience aging biomarkers at the cell-level after an age of over 80.[8-11] In the US, although some small improvements are being seen in our young from two decades ago (e.g., metabolic syndrome), the onset of deadly chronic degenerative diseases and aging biomarkers begins in our teens. In our adult population, cancer rates, cardiovascular disease, chronic kidney disease, obesity and diabetes are soaring.[12] What is the secret of the long-living? Is it the food? Is it the water/the soil? Is it the lifestyle? Is it the purpose and joy? Only over the past decade have we begun to understand the critical components of that *Regeneration Effect*, components that can be applied in a customized fashion to reverse chronic conditions and keep us happy, healthy, and free of dis-ease.

Figure 1. The Blue-Zones

Treat the Clinical Picture, Not the Lab

At the University of Maryland in 1990, Dr. Frank Calia spoke: "Treat the patient, not the lab." The truth of that lesson only became crystal clear after I entered this field and realized that most of the patients with debilitating symptoms still had lab parameters in the "normal range." When we measure levels through the lab, we are measuring only one fraction of what actually constitutes "function." So, an active thyroid level (free T3) tells us what is circulating in the serum. The factors that affect its function, however, include the receptor-site sensitivity, co-factors like selenium and zinc, and tissue pH. This is the classic patient who has all the thyroid symptoms and are told they are normal. So, one cannot rely on the thyroid serum levels alone; we have learned that the clinical picture generally supersedes the lab.

Over time we learned that regardless of the condition, when the patient truly "feels like they're thriving," regeneration is occurring and chronic disease is reversing. Specifically, when a person experiences vibrant energy, restorative sleep, tranquility, joy, a healthy gut, and is pain-free, they are regenerating. Our experience in tens of thousands of patients is that these six clinical parameters of regeneration correlate with reversal of chronic disease. We follow and correct these parameters in every patient at every visit (Figure 2).

Figure 2. Clinical Parameters of Regeneration

Clinical Parameter	Aim (Scale of 10)
Energy AM and PM	9-10
Sleep (DNA repairs with 8 continuous hrs)	8 hours
Mood	9-10
Anxiety	0
Gastric symptoms (IBS, diarrhea, bloating, heartburn, allergies, hives, rashes)	0
Pain	0

Lab Measurement

Although, the clinical picture is primary, we follow labs for general guidance and safety. Which route and which levels?

First, we'll briefly address the conundrum of whether one looks at serum, saliva, or urine for hormones. The serum level tells us what is circulating. The salivary level tells us what is in the tissue. The urine gives us the metabolites. We started this journey in 2005 by measuring all three sources. We realized that we were basing our therapies and dosing primarily on the clinical picture as explained above; so whichever source we used, it was reasonable as long as we knew how to interpret it to address and safely coax the body back to optimal health. They provide three different pieces of information. One is not better than the other.

"Optimal" levels are different from "normal" levels. "Optimal" is defined by the upper quartile where the literature supports protective effects. We are not aiming for "normal" levels between the 5th and 95th percentile. We are aiming for the quartile in the direction of health: greater than 75th percentile for hormones and nutrients, and less than 25th percentile for sugars and cholesterols. For example, we aim for the 25-hydroxy vitamin D to be above 70 ng/mL, although the "normal" range is 30-100 ng/mL. This level is where the thyroid and metabolism function best and where maximum protection from immune failure, cancer, strokes and heart attacks lies. We are aiming for a full tank of steroid hormones (>75th percentile) in the morning, as this is where the body is optimally protected from disease. So, we aim for a DHEA-S above 200 ug/dL, whereas the "normal" range is 45-440 ug/dL. We aim for a pregnenolone above 150 ng/dL. The "normal" range is 0-237 ng/dL. Imagine waking up at a level of zero and being told that that is "normal." We aim for a free T3 above 4.5 pg/mL (normal range is 2.3-6.8 pg/mL). This is where the patient is clinically optimal. Let's see how this is applied to patients.

The Five Point Model System to Regenerative Medicine

There are five basic, foundational areas that need to be **optimized** in order to produce a regeneration effect at the DNA level that will reverse any condition, including fibromyalgia. Together, they comprise our Regenerative Protocols That Work™. These areas are 1) mind/heart,[13-15] 2) body,[16-18] 3) hormones,[19-21] 4) nutrition,[22-24] and 5) detoxification[25-27] (Figure 3).

When these five basic, foundation areas are optimized and coordinated, it replicates the factors causing the people of the Blue-Zones to thrive. For illustration, the long-living folks in the Blue-Zones connect themselves to everyone and everything around them through 1) joy, 2) oxygen, 3) sunlight, 4) earth/soil, and 5) structured water (Figure 3). When practiced all together and concomitantly, our Regenerative

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Protocols That Work™ are created, which in turn facilitate each patient to enter "the driver's seat to their recovery" and feel their life is thriving.

Figure 3: The 5-Point Model System for Regenerative Protocols That Work™

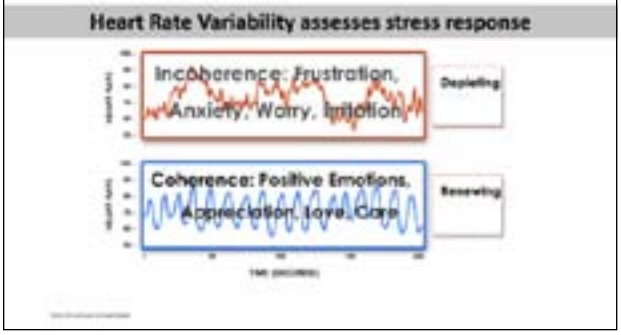
So, what is this basic framework utilized to empower every patient to be "in the driver's seat for their own recovery?" First, it is critical that patients have a Regenerative Health Coach for 90 days who works with them closely to master the protocols that comprise the five-point model system:

Mind/Heart stress is the base of all chronic disease. The easiest way to gauge this is to assess whether JOY is present or not. If joy and purpose are not present, the body has no reason to stick around. One can think of mind stress as those stressors that are in our consciousness like relationships, finance, health, and hope. These account for about 10% of what affects our body. Then there is the heart stress or emotional stressors, which can account for approximately 90% and can often be in our subconscious, so we need to address both.

It is not necessarily the occurrence of stressful events and emotions in life that creates dis-ease. It is the way in which we respond to these events. We cannot change a hurricane; we can alter the way in which we respond to the hurricane and the impact it has on our physical body. When the response is sustained, we are in an *inflammatory chronic stress response*.[28-30] Here, the "fuel tank" of hormones and nutrients is depleted. Here, the message to the body is not one of hope. There is not one patient with "fibromyalgia" who does not have the chronic stress response as a major contributor. The ability to address this major contributor, with simple tools, has truly become one of the necessary tenets of our program. A few main components of optimizing this area include the following:

- We start by teaching tools to help people become aware of their life activities (thoughts, words and actions) and to prioritize, reduce draining activities, laugh, play, and simplify life.
- Once we discovered that the heart signals control the brain signals 9 to 1; we started to use heart-focused meditation, which can convert the nervous system in 30 seconds. We ask every patient to utilize Heart-Math Institute's heart rate variability (HRV) application (i.e. InnerBalance App) and aim for a "coherent heart rhythm" for five minutes twice a day, through creating a feeling of joy.[31,32] The effects lasts for hours (Figure 4).
- In a "coherent state", the patient must state their affirmation to fully recover with vibrant energy and a pain-free life. Often the subconscious program or belief in chronically ill patients is a major source of continued illness. As we know the heart to be the strongest electromagnetic field in the body, the vibration created by HRV helps to program the water structure in the body and around the DNA, either with a full recovery or with incoherence and continued dis-ease.

Figure 4. Heart Rate Variability (HRV)



Note that as we have become aware that the gut impacts 70% of the nervous system,[33-35] we have correlated incoherent heart rate variabilities with gastric inflammation, which is a component in every chronic disease including fibromyalgia. Gut imbalances present in a variety of ways including IBS, colitis, autoimmunity, bloating, and leaky gut syndrome.

Body stress is ultimately related to the level of oxygenation in the small vessels. The physical body stressors are gauged by the level of pain and the level of physical activity. When pain and physical activity are high, the "fuel tank" of hormones and nutrients is being depleted and oxygenation to organs is low. By mass, oxygen accounts for about 65% of the human body,[36] so improving oxygenation to the cell level is an essential part of every program. A few main components of optimizing this area include the following:

- Reducing physical activity where heart rate is above 120 beats per minute. Replacing that with oxygenating restorative exercise, such as yoga, tai chi, qi gong, stretching, gentle walks.
- Using techniques of conscious breathing such as pranayama and alternate nostril breathing.
- Using oxygen concentrators to deliver 98% oxygen during exercise (as opposed to lesser percentages, i.e., 30% to 70%, of inspired oxygen).[37] High-Intensity Interval Training or HIIT with hyperoxia (e.g., Exercise With Oxygen Therapy – EWOT)[38] is significantly superior than HIIT without hyperoxia.[39-44]
- Epsom salt baths with six to eight pounds of Epsom salts or one to two pounds of magnesium chloride flakes. This helps with magnesium, which is a mainstay.
- Aggressively reducing pain with anti-inflammatory agents such as liposomal curcumin,

continued on page 44 ➤

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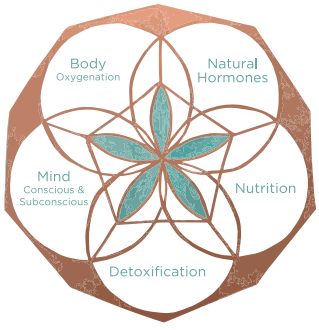

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palmitoylethanolamide (PEA) and cannabinol derivatives (CBD). Reducing pain also occurs with the aggressive correction of cortisol pathway depletions (such as progesterone, DHEA, testosterone and cortisol) and nutritional deficiencies (such as high dose fish oil, lipid-soluble magnesium). The pain has got to go along with the medications used to control pain.

brain fog, depression, weight gain, constipation, skin dryness, and even pain.

Most patients eventually dial back their doses and even discontinue many hormones once they master optimizing their lifestyle. As they lower the "speed of the engine," such as mental and physical stressors, they need less fuel.

Nutritional imbalances always accompany hormonal imbalances. When the "speed of the engine" is high over a prolonged period, the fuel tank gets depleted and nutritional levels fall below the 75th percentile, as we have learned through thousands of Spectracell™ micronutrient tests. A few main components of optimizing this area follow:

- The mainstay of the program is to optimize *dietary food* intake. We recommend organic food in a balanced plate ratio of 50% vegetables, 25% lean protein, and 25% complex carbohydrates.
- Eliminate all inflammatory foods like dairy and sometimes meat and fish.
- When using supplements, we aim for the least number of vegetarian capsules with no dyes, preservatives, fillers, or magnesium stearate.
- In addition to correcting measured deficiencies, there are four core supplements that these patients must have including magnesium (acetyl-taurinate) up to 1000 mg (depending on bowel tolerance), high dose fish oil (enteric coated), essential minerals and vitamins (for the adrenal/ thyroid axis), and probiotics.

We use nutritional intravenous therapies in the first two months as needed to accelerate results.

Detoxification aims at correcting water intake and pH. We have learned that identifying and addressing specific toxins through measurement is to be done only after the patient feels better because chasing toxins when a patient is feeling ill usually leads to further deterioration. Still we always start with detoxification basics, which address over 75% of toxins. A few main components of optimizing this area include the following:

- Drinking clean, structured water at least 100 ounces per day with pink salt and lemon. Water molecules comprise over 98% of all other molecules in human cells.[45] Studies in the 1800s actually show reversal of chronic disease with adequate water intake.
- Monitor AM urine pH. Aim for >6.7. With proper hydration and alkaline pH, the toxic acids and xenobiotics stored in the body fat are automatically eliminated, often returning optimal immune functions.[46-48]
- Addressing the lining of the gastrointestinal system is critical in these patients. If there are gastric symptoms, we use a protocol with broad spectrum probiotics and enzymes. Sometimes we add glutamine and aloe, if we have evidence of significant gastric inflammation. Turns out most patients do have this.
- Once the patient is feeling better, usually after the first 90 days, we address kidneys, liver, gallbladder, skin, and lymphatics.

Lastly and critically, it has become clear that every chronic condition is associated with a degree of immune compromise and insidious chronic infection, including chronic periodontal disease and chronically infected root canal teeth. So, we have had to perfect identifying and treating these through various diagnostics including muscle testing and combinations of hydrosol silver, ozone, and anti-infectives.

Chronic illnesses reverse as patients begin to thrive and experience joy.

Hormonal imbalances are centered around insufficiency in adrenal and thyroid function. As discussed, every fibromyalgia patient has a *chronic stress response* that depletes the "fuel tank" of hormones and nutrients. While we are addressing the chronic stress response, we must "optimize" the fuel tank, including the adrenal and thyroid levels. We use serum levels as they are covered by insurance, defensible as the medical standard, correlate with published protective levels, and are convenient for the patient. Most importantly, we have learned how to interpret the levels properly in order to get the maximum results. Hormone imbalances are quite straightforward to correct when one uses a natural order of correcting the adrenal imbalances and then the thyroid. Only bioidentical hormones are used. A few main components of optimizing this area include the following:

- Whether male or female, we start with oral progesterone to calm down the nervous system and the HRV. We titrate this until the patient is sleeping for a solid, restorative eight hours without interruption.
- We optimize (>75th percentile) DHEA-S, testosterone, and pregnenolone. Often, we use a short course (less than 6 months) of up to 40 mg of oral cortisol to break the cycle.
- We optimize thyroid until symptoms are resolved. These include fatigue,

Conclusion

It is very encouraging to realize that *all* chronic conditions are treatable by addressing underlying root causes that also control our self-healing gene expression. When faced with a chronic condition like fibromyalgia, one must empower the patient's self-healing mechanisms to take the driver's seat for a complete cure. Our role as doctors is

to provide awareness, hope, and tools that work. The effectiveness of tools and protocols is dependent on their simplicity aiming at the least steps and fewest capsules, so that the patient is not overwhelmed. When we can accomplish this, it is common to get tangible results within 90 days. Over time we have learned that regardless of the condition, when the patient truly begins to thrive, regeneration has been optimized, and their dis-ease is reversing. The defining elements to thriving are when a person experiences 1) vibrant energy, 2) restorative sleep, 3) tranquility, 4) joy, 5) a healthy gut, and 6) becomes pain-free (Figure 2).

Consider the five areas in the five-point model (Figure 3) as the "environment" or milieu that controls our genes (epigenetics). The most important component of this is the vibration of JOY that structures the water surrounding our DNA. This instantly initiates the receding of our inflammatory state. We would not be exaggerating if we expanded the message of the Beatles "All You Need Is Love" and concluded that "All You Need Is Joy."

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Healing with Homeopathy

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

Healing Through Community

Back Home

This is the time of year when Bob and I are halfway through our stay in the northern hemisphere, enjoying the glorious Puget Sound summer – harvesting first our snow peas, then strawberries, raspberries, kale, and chard. The Yukon gold and red fingerling potatoes practically self-seed. The garlic grows like crazy. And my favorite beets, cylindrical, went wild this year (6 quarts of beets pickled with ginger, star anise, maple syrup, and apple cider vinegar). Wish I had planted more! The carrots are always touch and go, even though we extra rabbit-proofed the garden this year.

Coming back from spring, summer, then early fall in Chile to another of the same in the NW is glorious! Long days, grey whales, soaring bald eagles, awkward and squawky blue herons. Simply magical. But, above all, what I most look forward to greeting is our remarkable community – various, amazing rich layers of community with decades of history.

Studies show that one of the most essential keys to a long, happy life is interacting regularly with others. Interestingly enough, it doesn't necessarily need to be family or even your tribe. It is said that just smiling at the familiar postal clerk or the cheery (not always) checkout person when you buy your groceries is often enough to carry you into a fulfilling longevity. Add singing and, especially, dancing, and you are a prime candidate to be a happy camper well into your 70s, 80s, or 90s. And don't underestimate the joyous effect of gardening!

Best Friends Sheila and Stephen Merritt

Living in a small town (Langley, Whidbey Island, Washington) has been a godsend, especially the wealth of caring, supportive friends just minutes away. But you can find community just about anywhere. Well into our 60s and 70s (and my most senior role model who is still hiking internationally at 94), we are now supporting each other not only to live life fully but, like the apropos title of Ram Dass' latest book, *Walking Each Other Home* (which I will soon discuss with a group of close women friends), at celebrations of life just before and after our passing. The completely unexpected death of one of the most vital and loving members of our Langley community, at 59, three months after receiving a diagnosis of glioblastoma, shook all of us to our roots. Laurie's passing, and her remarkable grace in the process, brought us all together in the most incredible way. A poignant reminder of the transitory nature of our lives, and how dear we all are to each other – and of how crucial a tight, loving community is during times like these. And thank you, *Caring Bridge*.

Maintaining Close Ties with Friends in Need

I began drafting this article in the car on the way up to Bellingham to spend a few hours with some very precious friends. I almost married him, but our lives led us to different partners and very different lives. But the four of us have always kept in very close touch, especially during rough times. He has had more than one close brush with death over the years, and she recently fractured a cervical vertebra. Bob and I have traveled far and wide; and they, until recently, mainly stayed put on their rural organic farm. This year has brought them a

wealth of rich blessings in the form of the marriages of both of their children, on two continents, and their first grandchild – a cause of great celebration that we could, thankfully, share with them. Though we only see them a couple of times a year, there is a deep, abiding love between us that we do not at all take for granted. At our age, one never knows if, or when, we will actually see each other again. Holding the preciousness of each moment quite dearly, rather than taking another meeting for granted, is a poignant reminder that we truly only have this moment. And another. And another. Until we don't.

In the Spirit of a Moving Community

We love to travel far and wide. One of the most remarkable and vibrant experiences of community that we have ever experienced is that of the pilgrims on the *Caminos de Santiago de Compostela.* Some of our veteran *Townsend Letter* readers likely followed our 35-day walking journey on the *Camino Francés* three years ago, and our 12 days on the *Camino Portugués* this past May. Imagine sincere and determined individuals of all ages (we met an 82-year-old Dutch woman this time who was hiking the *Camino* for the eighth or so time), each with his or her own purpose, story, and baggage (literally and figuratively). These folks from around the world, ever so briefly, joined together in an ambulatory, transient, intersection pilgrimage. I write this while driving back from Vancouver, British Columbia (BC), where Bob and I just spent three rich and wonderful days hanging out with two Canadian

Expat Christmas Celebration Pucón, Chile

friends with whom we hiked for three days in Spain in 2016. It is the first time we've reunited since then, despite much wishful thinking previously. Our mutual love of hiking, international travels, great food, and simply an incessant curiosity about life and the world made for a memorable weekend and the inspiration for two trips in the future: part of the *Camino Norte* in Spain, from which they just returned, and, finally, to Africa.

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No sooner had we arrived at their home in BC when they invited us to a neighborhood bluegrass concert across the street, and turned us on to another neighbor who invented a song about their very street. They've lived 20+ years and raised their two kids in that same house, built over 100 years ago, which they rent out, now and then, to Canadian TV or movie crews, to film for a week or so. (Flexibility is a useful and necessary trait for anyone who would consider hiking a *Camino*.) Their neighbor across the street had just bought an old camper van and invited them to use it for spill-over guests if they ever need it. Now that's a friendly neighborhood!

We live in the charming, bunny, deer, and human-friendly village of Langley on Whidbey Island. How to solve the controversy, a couple of years ago, about the 4-H escapee bunnies that were wreaking havoc with the gardens downtown? Bring in raptors, suggested some. Neuter the bunnies (??)! Transport them. Cook them up in a stew. The solution in a tourist-hungry, pacifist town? Make a splash in the national media to attract tourists and invent yet another holiday: Bunny Daze. The neighbor dressed up in his version of Peter Rabbit and everybody (except the downtown gardeners), especially the floppy-eared residents, were pleased as punch. In Langley, like many other counterparts worldwide, most of the time you are pretty sure to meet friends, or at least acquaintances or friendly faces, in the local grocery store. And most of those folks are smiling because they're just plain happy to be in such a cute, sane, charming little slice of America. Actually, the island dwellers here call the island "the rock" and refer to ferrying over to the mainland as, "Going to America." It is sweet little towns like this that epitomize those qualities below, which I believe to be integral to health and well-being.

The Healing Components of Community

Connection. This means knowing people well enough to recognize, greet, and strike up a conversation with them when you see them. It helps to have shared, experiences, and activities. You may or may not have anything in common regarding education, values, or opinions. We have belonged to an athletic club on our island for nearly 20 years. A number of us have Zumba'd, Boby Pumped, and done yoga with each other for that long. It is primarily a senior's, use-it-or-lose-it gym. Nothing to prove to each other. Just trying to preserve the body, have fun, and stay healthy. The majority of us are 65+, are quite faithful to our routines, and appear to change remarkably little over the years. No doubt there will be a time 10-15 years ahead where familiar faces begin to disappear, but in the meantime we're happy to meet and greet each other and give each other as much encouragement as we can. Running into friends and acquaintances on a regular basis

can be a life-saving (or, at least, life-enhancing) antidote to anonymity, loneliness, isolation, and despair.

Caring Support. Most *TL* readers are likely quite familiar with *Caring Bridge*, an online site, paid by donation, for folks with serious, life-threatening illness. The person who is ill, or a spokesperson, shares updates, both medical and transformative personal stories, so those efforts do not need to be duplicated. It is a place to express needs, offer heartfelt tributes and sharing, and to request specific assistance. Not so much to commiserate as to share the miracle of life, love, healing, and transitioning to the end of life. Community reminds us that, whether or not we still have family around to assist us (Bob and I do not except for his brother who lives far away), we are there for each other in an authentic, seat-of-the-pants way – whether it is offering to cook meals, to clean house, to take a walk, to sing your heart out, to offer advice (if invited), or to be a silent listener.

Witnessing Each Other's Lives. Community is about sharing joys, sorrows, ups, and downs. Just being present. A friend from Oregon recently shared that her beloved 28-year-old son had died very suddenly in a boating accident off Vashon Island. Though bereft beyond belief, they were overwhelmed by the comfort of friends and neighbors attending the funeral (500 guests), and their sharing the most wonderful stories about her son. Though filled with the deepest of grief, she and her husband will never forget the difference that it made to have their grief shared in such a poignant and genuine way.

Celebration. I had a most joyous celebration of my 65th in Chile, complete with an in-home, live music concert, a delicious spread of libations, and a circle of open-hearted sharing. And a smaller version on my 70th. Many of us are now finding deep meaning in "life celebrations" either prior to or after one's passing. These events can be unforgettable, life-affirming for spouse, partner, family, and provide an ever-deeper bonding among community members. Singing and dancing, whether alone or with others, is one of the most life-affirming and longevity-encouraging activities!

A Soundboard. How important it is to have someone you can call anytime and anyplace to lend an ear! It may be a family member. In my case, it's several, long-time friends (besides Bob). We can call each other on our stuff, be brutally honest or deeply nurturing. Someone to follow the thread of our lives and simply be there. I know that I do that very thing for some of my patients that I have seen for 25-35 years. I am their doctor, homeopath, mirror, cheerleader, and counselor. And if it's been a while since we've communicated, a little bell goes off in my head and I contact them. Sure enough, they tell me they were just thinking about calling me. And they are profusely grateful that I am there for them. And I am, even more, so grateful to be able to do something I so love that helps so many heal.

Sharing Common History Helps. New friends can be just great, but there is much to be said for those who have known us for decades, been there for our ups and downs, and shared what we've gone through. It is not to say you can't move to a new place and find a wonderful community, but I so treasure the many folks in my/our immediate circle who have known me for 20-40 years. It is they who have seen me at my best and worst and who recognize my resilience as well as my vulnerability. We have another far-flung community in Southern Chile, some of whom have known us over 15 years, from the time we first embarked on our lives there. Even during that time, we've shared births, deaths, comings, goings, and significant life changes. And had enough time together to be real rather than superficial.

Eating Together: I happen to love creating special and wonderful meals, harvesting life-filled, organic fruits and veggies, and sharing them all in a beautiful setting – and to gift the delicious produce that I lovingly preserve to folks that I know will be thrilled to receive them. When we travel near and far, it gives me great joy to buy that unique Spanish olive oil or Slovenian pumpkin oil or chocolate-cherry liqueur, to bring back for my friends – and to break bread together, perhaps share a bottle of wine, and (more than satisfying the taste buds) warm the heart. We just celebrated our annual Bastille Day dinner at the home of a close friend…for about the twentieth time. These foodie, garrulous, play-pretentious, wine-punctuated meals have sometimes left us stuffed to the gills and quite tipsy. A week ago, the atmosphere was much more intimate, fabulously delicious, but much more heartfelt and genuine. Talking about tough, real-life, mind-boggling issues. There were only seven of us instead of 20, but it was a much deeper and more satisfying evening for all of us. I even had a chance to, informally, turn them on to some very useful medical information, and we were able to open up to each other in a more profound and poignant way.

No matter where we live, what language we speak, whether or not we have living family members, we can join together to form community. In this crazy world with millions of refugee families with tents to call home, healing can still occur in the most unlikely, uncomfortable, and challenging of circumstances. Lifelong friendships, healing bonds can happen anywhere at any time. The richness and depth of sharing life with others is deeply healing, nurturing, and a balm to the soul.

Judyth Reichenberg-Ullman is a licensed naturopathic physician, board certified in homeopathy and has a background in psychiatric social work. Along with her husband, Robert Ullman, she has written eight books on homeopathy as well as *Mystics, Masters, Saints and Sages – Stories of Enlightenment*. They also have an app: Natural Travel Doctor. Apple version: https://tinyurl.com/l7song8 and Android: https://tinyurl.com/m7cnexh**.** She practices in Edmonds, Washington, and by Skype. Her practice is international, and she is fluent in Spanish and French. The Edmonds office address has changed, as you will see on the website below. They live on Whidbey Island, Washington, and in Pucón, Chile. Visit www.healthyhomeopathy.com and Facebook at Healthy Homeopathy. Call 425-774-5599 or email drreichenberg@gmail.com .

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On the cover

Drug-Induced Nutrient Depletions

by Ross Pelton, RPh, PhD

This is Part 1 in a two-part series on drug-induced nutrient depletions. In Part 1, I will discuss the history and importance of the topic and summarize the nutrients that are depleted by several classes of commonly prescribed drugs. In Part 2, I will discuss microbiome-disrupting drugs, which is a new category I developed in recognition of the overwhelming importance the microbiome plays in regulating all aspects of health.

These articles will introduce readers to drug-induced nutrient depletions, but I cannot cover this entire topic in one or two articles. Instead, in Part 1, I will discuss several classes of drugs that enable me to explain factors related to the cause, frequency, and potential seriousness of drug-induced nutrient depletions (I sometimes use the acronym DIND to refer to drug-induced nutrient depletions). In Part 2, I will explain how specific classes of drugs disrupt the microbiome and offer suggestions on how to correct or minimize the problem.

My overall goal for these two articles is to increase your awareness and knowledge of this topic, and I hope you will be better able to offer advice to your patients. At the end of this article, I will provide directions on how you can obtain a complete drug-induced nutrient-depletions chart.

My "journey" into the topic of drug-induced nutrient depletions began in 1997, when I found a book titled *Drug-Induced Nutritional Deficiencies*, written by Daphne Roe, MD, who was a professor in the department of nutritional sciences at Cornell University.[1] I was immediately attracted to this topic because in addition to being a pharmacist, I am also a certified clinical nutritionist (CCN) with extensive knowledge in nutritional biochemistry.[2] Dr. Roe's book, which was published in 1976, only addresses four classes of drugs. I quickly realized that this topic needed to be expanded and updated.

When I began my research, I discovered that most classes of drugs deplete nutrients and that drug-induced nutrient depletions probably cause or contribute to many health problems. I also began to realize that even though hundreds of studies on drug-induced nutrient depletions exist in the medical literature, this information was not being publicized to healthcare professionals or the general public. Consequently, I made a commitment to update this topic. This project took me two years and thousands of hours of research. In 1999, *The Drug-Induced Nutrient Depletion Handbook* was finally published,[3] which is a reference book for pharmacists, physicians, and other healthcare professionals.

One year later, my business partner, Jim LaValle, and I wrote *The Nutritional Cost of Drugs*,[4] which presents drug-induced nutrient depletions to the general public. These books have now been out-of-print for a number of years, so I am happy to have the opportunity to present this material to healthcare professionals who subscribe to and/or read the *Townsend Letter*.

I hope that one day, government authorities and/or politicians will recognize the importance and seriousness of this topic and mandate that part of the FDA's new drug approval (NDA) process would require/demand that drug companies research and report on the drug-induced nutrient depletions that their drug causes. However, due to the well-known cozy relationship between drug companies and the FDA, I doubt that this will happen in my lifetime.

I want to begin by addressing some questions I am frequently asked when I give presentations on drug-induced nutrient depletions.

"Why doesn't my doctor know about this?" or "Why didn't my doctor tell me about this?" I have located over 500 studies reporting drug-induced nutrient depletions, which have been published in nearly one hundred different medical journals over the past 50 years. Although these studies get published, they seldom get publicized to physicians; and most physicians don't have the time to dig through the scientific literature to locate these studies. Also, although I organized all this information into one central reference book, most physicians do not have a copy of the *Drug-Induced Nutrient Depletion Handbook* and many are not aware, or only minimally aware of this body of knowledge.

"Many of the studies you cite are really old, aren't there any newer studies?" Some of the studies I cite were published in the 1970s, 80s and 90s. However, this doesn't negate the value of these older studies. Studies on DINDs are difficult to get funded. Pharmaceutical companies have enormous financial resources, but they are not interested in spending their money to fund a study that will announce to the world that their new drug is causing nutrient depletions.

What frequently happens is that an alert physician becomes aware of the fact that a number of patients who are taking a specific drug are experiencing the same side effect. Subsequently, they run blood tests on a number of these patients and compare the results to a number of patients who are not on the drug in question. If, for example, they find that the patients taking the drug have lower levels of one or several nutrients compared to age-matched controls who are not taking the drug, they submit this result to a journal for publication. These small observational studies usually do not get published in the big prestigious medical journals, but the information is still important.

"Why isn't there any information about drug-induced nutrient depletions on the drug I'm taking?" Drugs are often on the market for a number of years before side effects, especially those caused by drug-induced nutrient depletions, begin to surface and get reported. Hence, there is frequently a time lag before DIND side effects begin to develop. Also, as mentioned previously, drug companies are not motivated to fund studies that tell you and me that their drug is responsible for nutrient depletion-related side effects. Consequently, many drugs on the market have not been studied for DINDs.

What is the mechanism of drug-induced nutrient depletions? There are numerous possible causes. For example, a drug can inhibit absorption, synthesis, storage, metabolism, or excretion of a nutrient. In some cases, drugs bind with receptor sites, transport proteins, or enzymes. However, many studies reporting DINDs are observational studies, in which a clinician reports that people taking a specific drug have lower levels of a certain nutrients compared to non-users; but the mechanism of how or why the depletion occurs is not researched or reported.

"How will I know if I am developing a drug-induced nutrient depletion?" When a person develops a side effect from a new drug, the problem is easy to identify because nausea, vomiting, a headache, itching or a rash usually develops within the first 24-48 hours. Side effects due to drug-induced nutrient depletions are more difficult to identify because they develop gradually over time.

Consider the following scenario: a woman who has been taking oral contraceptives for eight years, seemingly without any problems. However, over the past six months, she has been increasingly complaining to her husband that she is tired all the time. She has trouble getting up in the morning, or by mid-afternoon, she feels so exhausted, she can hardly function. Oral contraceptives deplete folic acid, vitamin B12, coenzyme Q10, and magnesium. Each of these nutrients is critically important for energy production. A depletion of any one of these nutrients can cause tiredness, weakness, lethargy and/or anemia over time. However, this woman probably doesn't realize that the medication she has been taking for years has been causing nutrient depletions that are now causing health problems.

I think similar scenarios happen all too often. People take a medication and gradually a nutrient depletion develops, which begins to cause a problem. People then go to their doctor reporting a symptom(s)…and they are given another prescription drug rather than realizing that appropriate nutritional supplements could prevent or correct these symptoms.

What dose do I need to take to correct a drug-induced nutrient depletion? This is difficult to answer because there are so many variables related to genetics, diet, nutritional status, personal health, etc. However, I think dosage levels should usually be greater than the government-recommended RDA. The RDAs were originally developed to provide an adequate amount of a nutrient that ensures that most people would not develop an outright nutritional deficiency disease. For example, the RDA for vitamin C is 65 mg/day, which is sufficient to prevent scurvy in most people. The RDAs were set decades ago. Nutrient content in foods has continued to decline, environmental pollution levels have escalated, reliance on nutrient-deficient processed foods and fast foods has increased, and people are taking more medications than ever. The RDAs were never intended to provide optimal levels of nutrition. I think clinicians need to assess the health and nutritional status of patients on an individual basis and make appropriate recommendations.

The following study illustrates this point: "Therapy of side effects of oral contraceptive agents with vitamin B6."[5] The author states that oral contraceptives deplete vitamin B6, which results in lower levels of tryptophan. When these OC-users develop low tryptophan, symptoms that develop include depression, anxiety, decreased libido, and impaired glucose tolerance. When 40 mg of vitamin B6/day was administered (RDA is 1.2 to 1.3 mg/day), biochemical values were restored, and clinical symptoms were relieved. Hence, doses above RDA levels may be appropriate and/or required. ➤

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In addition to individual pharmaceutical drugs, other factors contributing to nutrient depletions include the following:

Factory Farming: Numerous studies document the fact that there has been a continual decline in the nutritional content of the commercially available food supply in the United States over the past 70 years. There are multiple contributing factors. During the 1950s, farmers began switching from organic manure to nitrogen-based chemical fertilizers; mono-cropping replaced crop rotation; hybrid seeds were developed which increased yields, but weakened the immune system of the plants; and chemical companies convinced farmers that they needed to use pesticides, insecticides, and herbicides that ultimately kill soil bacteria, which decrease the uptake of nutrients into plants.

Fast Foods/Processed Foods: Many people regularly consume highly processed foods, fast-foods, and "junk" foods that are calorie dense but nutritionally deficient.

Environmental Toxins: Biochemical detoxification processes in the body utilize nutrients. Increased exposure to toxins depletes specific nutrients that are utilized in detoxification processes, especially in the liver; and of course, the environment is more toxic now than at any time in history. According to the EPA, over 85,000 chemicals are approved for use in the United States, and the vast majority have not been tested for toxicity.[6]

Polypharmacy: A study just released in April 2019 titled "Medication Overload: America's Other Drug Problem" reported that over 40% of older adults take five or more medications. When OTC (over-the-counter) drugs are included, nearly 20% of older people take 10 or more drugs and it is not unusual for some older people to be taking more than two dozen different medications.[7] I find that *many people are taking two, three, or more drugs that deplete the same nutrient.* This substantially increases the likelihood that drug-induced nutrient depletion health problems will develop.

Common Drug-Induced Nutrient Depletions

Virtually all major classes of drugs, which include both prescription medications and OTC drugs, cause nutrient depletions. It is beyond the scope of this article to present or list the nutrients that are depleted by all medications, since there are nearly 1,500 FDA-approved drugs on the market in the US.[8] In this article, I will present several examples that will express the extent and potential health risks associated with DINDs. I will discuss several classes of medications that cause serious health problems due to their DINDs, and I will also discuss a couple nutrients that are depleted by multiple classes of drugs to show how polypharmacy can multiply the seriousness of drug-induced nutrient depletions.

Oral Contraceptives: When I wrote *The Drug-Induced Nutrient Depletion Handbook*, I was astounded to learn that oral contraceptives deplete more nutrients than any other class of medications. This alarmed me so much that I wrote a book titled *The Pill Problem*, which teaches women how to avoid the side effects from birth control pills.[9] Results of a survey (2011-2013) reported that 25.9% or 9.7 million women between ages 15-44 use "the pill," which makes oral contraceptives the most commonly used form of contraception.[10]

Studies document the fact that more women than men suffer from health problems such as depression and insomnia. For example, a survey conducted by the National Sleep Foundation reported more women than men (63% vs 54%) suffer from insomnia several nights weekly.[11]

A literature review from 1966-1999 reported that women experience depression twice as often as men.[12] Another study, sponsored by the World Health Organization (WHO), reported that depressive disorders occur from 1.5 to 3 times more frequently in women than men.[13] Furthermore, a meta-analysis of 9 clinical trials reported that rates of depression ranged from 16-56% in women using oral contraceptives.[14]

I am convinced that oral contraceptive-induced nutrient depletions help explain why women have higher rates of depression and sleep problems than men. This is due to the fact that OCs deplete vitamin B6[15] and tyrosine, which are precursors for the synthesis of the key neurotransmitters serotonin, dopamine, and norepinephrine. Thus, OCs deplete nutrients that cause neurotransmitter imbalances, which increase the likelihood of developing depression.

I previously mentioned a study of oral contraceptive users developing B6 deficiency, which resulted in women having increased incidence of depression, anxiety, decreased libido, and impaired glucose tolerance. The clinician then prescribed 40 mg of vitamin B6 daily and reported that this dosage restored the biochemical values and relieved the clinical symptoms in these women.[5] I want to emphasize that the B6 RDA for women is from 1.2 to 1.3 mg/day. A dose of 40.0 mg/day is substantially higher than the RDA. This highlights that fact that people who have developed drug-induced nutrient depletions may require doses of nutrients that are higher than the RDA to correct the nutrient depletion-associated problems.

Here is a complete list of the nutrients depleted by oral contraceptives: Vitamins B1, B2, B3, B6, B12, folic acid, vitamin C, vitamin E, magnesium, selenium, zinc, tyrosine, DHEA, and coenzyme Q10.[16] Fourteen nutrients depleted by a class of drugs that is taken by millions of women. Throughout this article, I will not discuss the health problems associated with specific nutrient depletions. In addition to not having the space, I also assume that most readers of the *Townsend Letter* are knowledgeable about the health problems associated with deficiencies of essential nutrients.

Acid-Suppressing Medications. It is a well-established fact that level of acidity in the stomach and throughout the intestinal tract is a critical factor that regulates digestion of food and absorption of nutrients. Acid-suppressing drugs

such as PPIs, H-2 blockers, and OTC antacids all either suppress or neutralize acid. This creates a more alkaline pH, which hinders the normal processes of digestion and nutrient absorption. H-2 blockers such as cimetidine, ranitidine, and others have been shown to deplete vitamins B12, D, folate, and the minerals calcium, iron, and zinc.[16] There are fewer nutrient depletions recorded for PPIs and antacids, but this is probably due to the fact that no studies have been conducted on these other nutrients with these drugs.

Multiple Drugs Depleting the Same Nutrient

Coenzyme Q10. Now I want to approach things from a different angle. Instead of listing all of the nutrients that are depleted by a drug, or a class of drugs, I want to list all of the classes of drugs that deplete a specific nutrient, coenzyme Q10. This will highlight the fact that many people are taking multiple drugs that deplete the same nutrient, which increases the likelihood that a depletion of the nutrient will develop into one or more health problems.

Drugs that deplete coenzyme Q10 include the following: oral contraceptives, hormone replacement therapy (HRT), biguanides (metformin), sulfonylureas, hydralazine (a vasodilator), thiazide diuretics, alpha-2 adrenergic receptor agonists (clonidine & others), beta-blockers, statins, gemfibrozil, tricyclic antidepressants, and major tranquilizers (such as Thorazine & Mellaril). Fourteen different drugs or classes of drugs can deplete coenzyme Q10!

Many people are probably taking two or three drugs that deplete CoQ10. I'm especially concerned about the widespread use of statins, which I think is one of the most successful and immoral marketing jobs in the history of the world. CoQ10 is essential for mitochondrial function and protection of mitochondrial DNA (mDNA). The mitochondrial theory of aging tells us that mitochondrial dysfunction is at the core of the aging process. Statins and other drugs that cause CoQ10 depletion will accelerate free radical mDNA damage and mitochondrial dysfunction in cells throughout the body. In ten years, I expect to see studies reporting that people taking statins have accelerated aging. In general, low CoQ10 levels are associated with increased risk for atherosclerosis, elevated blood pressure, low energy, kidney dysfunction, neurological problems, sore muscles, and weak heart.

Folate is another important nutrient that is depleted by numerous drugs. The list of folate-depleting drugs includes oral contraceptives, antibiotics, anti-convulsant meds, biguanides (metformin), potassium-sparing diuretics, many chemotherapy drugs, corticosteroids, NSAIDs, bile acid sequestrants, and H-2 acid blockers. So again, you can see that many people could be taking two or more drugs that deplete folate. Folate deficiency increases risks of birth defects, low energy, anemia, and elevated homocysteine. I wonder how many women who give birth to an infant who is born with birth defects were taking two or three medications that deplete folate.

Conclusion

As I mentioned previously, time and space limitations do not permit me to discuss all of the drugs that deplete nutrients and list the multiple nutrients that are depleted by these drugs.

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Moldy Buildings, CIRS, Sick People, and Damaged Brains: 25 Years of Research Brought Us to the Cure Word, Part 4

by Ritchie C. Shoemaker, MD

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Editor's Note: Exposure to mold in water-damaged buildings (WDBs) 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 Parts 2 and 3 (August/September 2019; October 2019), the authors explained how to maintain the building envelope and CIRS diagnosis procedures.

The Treatment Steps

Removal from exposure is the first step in treatment. This is followed by use of bile acid sequestrants, including cholestyramine or Welchol. Removal of biofilm-forming MARCoNS (multiple antibiotic-resistant coagulase negative staphylococci) is our third step.

(4) Correction of antigliadin antibody positivity in non-celiac patients is key, with removal of dietary gluten indicated for those with the antigliadin antibodies. The role of MSH (alpha melanocyte stimulating hormone) deficiency is paramount in antigliadin antibody positivity and gluten sensitivity.

(5) Antidiuretic hormone (ADH) dysregulation of osmolality is shown routinely in over 80% of CIRS patients. Dysregulation can mean absolute high or low ADH; absolute high or low osmolality; or too little ADH for a given osmolality; or too much ADH for a given osmolality. These findings are paralleled by those that we see as abnormal for ACTH and cortisol. By looking at these two pairs of labs, we look at disruption of normal feedback relationships in MSH deficient patients.

(6) Androgen deficiency can be due to hypothalamic dysregulation of gonadotrophins, especially when MSH is low. A second mechanism for "Low T" is increased activity of *aromatase*. This enzyme converts androgens to estrone and then to estradiol. Don't simply prescribe androgens!

(7) We must correct MMP-9, an indicator of pro-inflammatory cytokine effect on endothelial cells.

(8) We must also correct low (or high!) levels of VEGF. Interestingly, the effective use of omega-3s for correction of MMP-9 and VEGF has been a welcome addition to treatment.

(9) When C3a is elevated, there is presence of a bacterial membrane in blood. The membrane will serve as a source of attachment of the fragment of complement activation called C4bC2a that then provides a mechanism for attachment of C3 that will then lead to attachment of C5, 6, 7, 8 and 9. Complement puts a hole in bacterial cell, lysing the cell.

(10) C4a is probably the most important proinflammatory marker we have as part of the complement cascade. There is an enzyme, mannose binding protein associated serine protease-2 (MASP2), that can autoactivate. If that occurs, C4a will be produced even when *no stimulation* of MASP2 by antigen is occurring. This unique finding suggests "sicker quicker."

(11) Reduction of TGF beta-1 is mandatory, not just for its role as a pro-inflammatory cytokine but also for its role activating a whole series of metabolic pathways involved with T-regulatory cell function in tissue and reduction of autoimmunity.

The last step is use of vasoactive intestinal polypeptide (VIP). See below.

SAIIE

An adaptation of the treatment protocol permits use of a diagnostic, prospective re-exposure trial. Called "Sequential Activation of Innate Immune Effects (SAIIE)," this protocol is used when we must show causation. As opposed to a case/control study, one that lets us conclude an association of exposure with symptoms, visual contrast sensitivity (VCS) deficits, proteomics or transcriptomic abnormalities, a prospective study design can confirm the presence of the epidemiologic concept of risk and therefore, causation.

We take a known case, a patient who meets the GAO case definition, use the Shoemaker Protocol to correct symptoms, VCS, and proteomics. Before starting, we know that the building suspected to be making the patient ill is contaminated. We will also know that the building where the patient is staying is safe (using ERMI or HERTSMI-2).

The first step, after informed consent is obtained, is after RX 1 (AC1, usually beginning on Friday). Symptoms, VCS and selected labs (C4a, MMP9, leptin, VEGF and von Willebrand's profile) are recorded. All CIRS meds are stopped; the patient is kept away from the suspect building for three days, after having been exposed to "the ubiquitous fungi of the world." On Monday morning, having completed the prospective trial of no-known exposure to a water-damaged building (WDB), symptoms, VCS, and labs are repeated. This step, called Home Off Meds (HOC), ends when blood is drawn on Monday.

The patient then enters the suspect building each day for three days, with study measures done daily. On Tuesday AM, symptoms, VCS and labs are performed, showing us what happened on day 1 of re-exposure (BOC-1, Tuesday). The patient re-enters the building. Symptoms, VCS and labs are performed on Wednesday, telling us what happened on day 2 of exposure (BOC-2). The patient returns to the WDB a third time, with symptoms, VCS and labs done on Thursday (BOC-3) showing us what happened on Wednesday, day 3. If the building is causative, by BOC-3 VCS will fall, symptoms will increase to approximately 95% of initial levels; labs will show distinctive profiles sorted by day of trial. Because the lab changes are stereotyped, according to known physiology, a scoring system can be applied to not only quantitate recrudescence of symptoms, but recrudescence of objective parameters as well.

As an aside, this protocol readily shows absence of validity to alternative hypotheses regarding causation, such as presence of mycotoxins in urine[1] reflecting fungal infection, for example.

Perspective on Medical Rx

In the course of 23 years working on CIRS, there have been relatively few novel therapies that have stood the test of time. The Shoemaker Protocol is one of those therapies; it is marked by one intervention at a time for 30 days in sequence, with monitoring of diagnostic biomarkers before and after any given intervention. This methodical approach lets us identify what is working with treatment and what is not.

The Shoemaker Protocol is a methodical approach to treating chronic inflammatory response syndrome.

Initially, when symptoms persisted beyond (a) removal from exposure and then (b) use of binders, it was almost a trial and error approach to patient-centered research that brought the protocol to its current status. The protocol is fluid in the sense that there are new approaches to treatment that are evolving as the disease itself evolves. A simple example is the emergence of multiple unusual bacterial resistances in MARCoNS, initially in users of anti-fungal medications. A previously effective nasal spray, used safely and effectively from 2002-2015, became useless in a span of weeks. Sharing plasmids for bacterial resistance, likely due to horizontal gene transfer, is what the promiscuous MARCoNS do! What happened? The organisms changed; our treatments changed to continue to be effective.

Perspective on Treatment of WDB

The treatment protocol begins with one step that has been called the hardest of all: removal from exposure. Removal from exposure can mean either literally moving away from a school, workplace or residence; or removing particulates from the air and elimination of reservoirs of potential particulates found inside WDBs. Remediation of a building can be expensive; alternatively, correction of particulate reservoirs can be agonizingly obsessive, especially when remediation isn't completed. The advantage of clearing the air and reservoirs of particulates is that we are not talking about burning a house down or leaving all possessions, walking out with the clothes you have on. What we are talking about is correction of the source of inhalation of particulates, understanding we may not have eliminated all potential sources of contamination.

Remediation is a subject for many thousands of words on another day. A few concepts will be shared here. Follow the ABCs: **A**bate the water intrusion. **B**uilding materials that are contaminated must be removed (or be encapsulated if structurally irreplaceable). **C**lean reservoirs on possessions; **c**lean reservoirs in air; and **c**lean reservoirs on walls, floors and ceilings. Every room must be cleaned in a given building if air from one room could get into another. Even though many individuals aren't going to be affected by CIRS; cleaning must be performed assuming that all who enter the rooms in the future are CIRS patients. Finally, if you are talking with a remediator who doesn't use HERTSMI-2 to clear a building as cleaned, you can't assume the building is safe for a CIRS patient to re-occupy.

By taking another look at the section on definition of WDB, we can look at our check list for what has been found to be present and what is not present; stated another way, what is not safe about the house and what is safe about the house, for example. We know that there is no such thing as a safe basement even though people do all they can to make such structures safe. In treatment, there will be a dedicated air sanitation device running 24/7 in the basement. We look for maintenance of ambient humidity to be less than 55%. Sometimes that will require use of a dehumidifier with a transport mechanism combined with the dehumidifier to convey moisture removed from the air safely outside.

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For prevention of exposure I often will use "three machines" approach. This approach will use an air sanitizer as the "heavy lifter." I have no conflicts of interest to disclose in this regard, but I do use Air Oasis devices liberally, with a recent paper presented in January 2019, showing use of an Air Oasis device, the iAdaptAir, alone corrected transcriptomic abnormalities in a CIRS case,[2] without causing adverse changes in a control.

The second machine is a HEPA filter. HEPA means high efficiency particulate air but it involves passing air in an indoor environment through a filter that is 0.3 microns in diameter when it starts, understanding that there will be reduction of pore size over time as particles can clog the filter (NB: clean filters regularly) with use of HEPA filters. In my cynical moments, I sometimes think that there is only one manufacturer of HEPA devices in the world, with a stack of different machine labels to be put on similar HEPA devices and shipped to the US. It seems that the less expensive devices perform equally as well as expensive devices if there is the 0.3-micron pore size filter. HEPA filters are often used one to a floor in a building, with one in the crawl space or the basement. Moving the HEPA units every twelve hours or so (but not between the basement and main house) helps deal with the boundary layer problem. Finally, with an Air Oasis sanitizer in use which will remove particulates from the air by essentially making them so heavy that they will precipitate on the floor, we must have a mechanism to vacuum these particulates up and remove them from the indoor space. So, the three machines are an air sanitizer, HEPA filter, and a vacuum cleaner (HEPA is better).

I do not feel that we need to use expensive machines, we just need to use inexpensive machines regularly, moving them from spot to spot and room to room (twice a day each!) to disrupt boundary layers of air, keeping airborne particulates in circulation and available for removal.

Selected Aspects of Treatment

Once we have begun the process of removal from exposure then we need to verify that the case definition has been met. As the case definition is satisfied, use of bile acid sequestrants begins. The oldest and least well tolerated of these compounds is **cholestyramine** (CSM). CSM has a positively charged nitrogen side chain built into a polystyrene chain. This long molecule is not absorbed so that when it is swallowed there will be a location of binding action beyond the stomach, in the duodenum and jejunum where CSM will bind to bile acids and biotoxins. CSM has been used for years to bind hydrocarbons such as DDT and DDE as well as PCBs but also will bind unusual compounds such as the M protein of Arava, a rheumatoid arthritis drug, as well as dioxin. CSM is organic glue! Once glued, down the tubes!

A less gastrointestinal troublemaker is **Welchol** (colesevelam), which is another bile acid sequestrant. CSM is taken one scoop (4 grams of active ingredient) four times a day on an empty stomach, waiting 30 minutes before eating or taking medication. Welchol on the other hand, is taken with food already in the stomach to prevent mild symptoms of reflux. The dose of Welchol is 625 mg, two tablets taken three times a day with food.

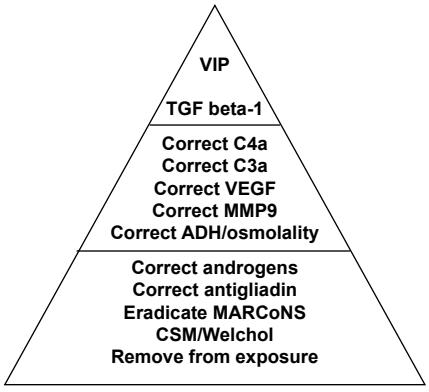
Many people will want the better efficacy of CSM, which does have 25% more binding sites compared to Welchol. I often suggest a "combo program," taking CSM first thing in the morning and at bedtime, with Welchol taken with lunch and supper. The combo causes far less disruption of daily activities.

Unfortunately, despite our concerted efforts, we could never show salutary changes in objective biomarkers after we used "natural" binders like clay (bentonite), charcoal, pectin, chitin or chitosan, chlorella and more. Added to the "confirmation of no-benefit" list was absence of improvement in VCS scores.

A word on reduction of **TGF beta-1**. This step is vital for adequate performance of the treatment protocol. TGF beta-1 is a cytokine that has both pro- and anti-inflammatory responses. The difference between the two is due to tissue receptors including retinoic acid orphan receptor (ROR). In order to determine the role of TGF beta-1 in the complex issues of abnormalities in regulation of gene transcription, use of the test "Genomic Expression: Inflammation Explained" (GENIE) is recommended.

Treatment of elevated TGF beta-1 is accomplished by use of losartan (sold as Cozaar) a mild anti-hypertensive in the ARB class. If systolic blood pressure is less than 120, we can't use losartan due to the risk of hypotensive episodes. Patients are recommended to measure blood pressures at least twice a day for at least two weeks at home with a reliable blood pressure measuring device to know whether there is blood pressure present over 120 that would sustain use of losartan. If blood pressures stay at, say 130/90, then losartan can be initiated in adults. The adult dose is 12.5 mg at bed, increasing to 25 mg as tolerated. Losartan is the only ARB that has the breakdown product, named EXP 3179, that lowers TGF beta-1. The rights to use of this molecule belong to Merck. One would hope that sometime in the future we would see a pure anti-TGF beta-1 medication made available to the public.

Figure 2. The Treatment Pyramid



VIP: The last step is step #12, that being use of vasoactive intestinal polypeptide (VIP) to (i) correct residual proteomic abnormalities; (ii) correct transcriptomic abnormalities; (iii) correct grey matter nuclear atrophy. Simply stated, VIP is a remarkably safe regulatory neuropeptide that has been used in humans as a nasal spray in the US since 2008. It has a much longer prior history of use in Europe. VIP is currently available as a compounded medication; two groups are actively working with the FDA to create an IND.

VIP, 50 mcg/0.1ml, is most often used one spray taken four times a day independent of fasting. It has shown the ability to reduce pulmonary hypertension and markedly improve exercise tolerance. Higher doses are used for correction of transcriptomic abnormalities and gray matter nuclear atrophy. Please review the module on use of VIP before prescribing it. The module is found on www.survivingmold.com.

VIP in MCS: Some patients who are markedly intolerant of foods, medications and organic substances will have difficulty using cholestyramine or Welchol. For these patients, "mini-dose" VIP has been used with excellent results. By dosing VIP at 1/100 dilution with a steadily increasing number of doses used per day ("ramping up"), up to six doses a day, can then lead to 1/10 dilution following the same increasing dose schedule. Once 1/100 and then 1/10 are tolerated, then full-strength VIP can be initiated for approximately three weeks at which time VIP can be stopped. At that time, medications can usually be taken without adverse effects.

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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.

Self-calibrated position for sitting upright

UpRight Go vibratory feedback reminding me that I am collapsing

Corrected position while working

"Don't Slouch!" Improve Health with Posture Feedback[1]

by Erik Peper, PhD, BCB[2,3]; Richard Harvey, PhD; and Lauren Mason

Institute for Holistic Health, San Francisco State University

"Although I knew I slouched and often corrected myself, I never realized how often and how long I slouched until the vibratory posture feedback from the UpRight Go 2™ cued me to sit up (see Figure 1)."

– Erik Peper

For thousands of years we sat and stood erect. In those earlier times, we looked down to identify specific plants or animal track and then looked up and around to search for possible food sources, identify friends, and avoid predators. The upright, not slouched posture body posture, is innate and optimizes body movement as illustrated in Figure 2 (for more information, see Gokhale, 2013).

1. The article was adapted from the blog, "Don't slouch!" Improve health with posture feedback, www.peperperspective.com.
2. Correspondence should be addressed to: Erik Peper, PhD, Institute for Holistic Healing Studies, San Francisco State University, 1600 Holloway Avenue, San Francisco, CA 94132. Tel: 510-681-6301; Email: epeper@sfsu.edu; web: www.biofeedbackhealth.org; blog: www.peperperspective.com
3. The article is based upon the collaborative research with Richard Harvey, Lauren Mason, I-Mei Lin, Monica Joy, Annette Booiman, and Shane Colombo.

Figure 1 (above). Wearing an UpRight Go 2™ to increase awareness of slouching and as a reminder to change position.

Being tall and erect allows the head to rotate freely. Head rotation is reduced when we look down at our cell phones, tablets or laptops (Harvey, et al. 2018). Our digital world captures us as illustrated in Figure 3.

Looking down and focusing on the screen for long periods of time is the opposite of what supported us to survive and thrive when we lived as hunters and gatherers. When we look down, we become more oblivious to our surroundings and unaware of the possible predators that would have been hunting us for food.

This slouched position increases back, neck, head and eye tension as well as affecting respiration and digestion (Devi, et al, 2018; Peper, Lin, & Harvey, 2017). After looking at the screens for a long time, we may feel tired or exhausted and lack initiative to do something else. Our mood may turn more negative since it is easier to evoke hopeless, helpless and powerless thoughts and memories when looking down than when looking up (Wilson, & Peper, 2004; Peper, Lin, et al, 2017). In the down position, our brain has to work harder to evoke positive thoughts and memories or perform cognitive tasks as compared to when the head is erect (Tsai, Peper, & Lin, 2016; Peper, Harvey, et al, 2018). By looking down and focusing at the screen, our eyes may begin to strain. To be able to see objects near us, the extraocular muscles of the eyes contract to converge the eyes and the cilia muscles around the lens contract to increase the curvature of the lens so that the reading material is in focus.

Eye Strain

Become aware how nearby vision increases eye strain**.** Hold your arm straight ahead of you at eye level with your thumb up. While focusing on your thumb, slowly bring your thumb closer and closer to your nose. Observe the increase in eyestrain as you bring your thumb closer to your nose.

Eyestrain tends to develop when we do not relax the eyes by periodically looking away from the screen. When we look at the horizon or trees in the

far distance the ciliary muscles and the extraocular muscles relax (Schneider, 2016).

Neck and Back Tension

Head forward posture increases neck and back tension. When we look down and concentrate, our head moves significantly forward. The neck and back muscles have to work much harder to hold the head up when the neck is in this flexed position. As Dr. Kenneth Hansraj, chief of spine surgery, New York Spine Surgery & Rehabilitation Medicine, reported: *"The weight seen by the spine dramatically increases when flexing the head forward at varying degrees. An adult head weighs 10-12 pounds in the neutral position. As the head tilts forward the forces seen by the neck surges to 27 pounds at 15 degrees, 40 pounds at 30 degrees, 49 pounds at 45 degrees and 60 pounds at 60 degrees"* (Hansraj, 2014). The head tends to tilt down when we look at the text, videos, emails, photos, or games and stay in this position for long time periods. We are captured by the digital display and are unaware of our tight overused neck and back muscles. Straightening up so that the back of the head is repositioned over the spine and looking into the distance may help relax those muscles.

To reduce discomfort caused by slouching, we need to reintegrate our prehistoric life style pattern of alternating between looking down to being tall and looking at the distant scenery or across the room. The first step is awareness of knowing when slouching begins. Yet, we tend to be unaware until we experience discomfort or are reminded by others (e.g, "Don't slouch! Sit up straight!"). If we could have immediate posture feedback when we begin to slouch, our awareness would increase and remind us to change our posture.

Posture Feedback with UpRight Go

A simple posture feedback device such as an UpRight Go 2 can provide vibratory feedback each time slouching starts as the neck and head go forward. The wearable feedback device consists of a small sensor that is attached to the back of the neck or back (see Figure 1). After being paired with a cellphone and calibrated for the upright position, the software algorithm detects changes in tilt and provides vibratory feedback each time the neck/back tilts forward.

In our initial exploration, employees, students, and clients used the UpRight feedback devices at work, at school, at home, while driving, walking, and other activities to identify situations that caused them to slouch. The most common triggers were the following:

1. Ergonomic-caused movement such as bringing the head closer to the screen or looking down at their cell phone (for suggestions to improve ergonomics see recommendations at the end of the article);
2. Tiredness;
3. Negative self-critical/depressive thoughts;

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Figure 2. The normal aligned spine of a toddler and the aligned posture of a man carrying a heavy load.

Figure 3. Captured by the screen with a head forward positions.

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4. Crossing the legs protectively, shallow breathing, and other factors.

After having identified some of the factors that were associated with slouching, we compared the health outcome of students who used the device for a minimum of 15 minutes a day for four weeks as compared to a control group who did not use the device. The students who received the UpRight feedback were also encouraged to use the feedback to change their posture and behavior and implemented some of the following strategies.

- Head down when looking at their laptop, tablet, or cellphone.
  - Change the ergonomics such as using a laptop stand and an external keyboard so that they could be upright while looking at the screen.
  - Take many movement breaks to interrupt the static tension.
- Feeling tired.
  - Take a break or nap to regenerate.
  - Do fun physical activity, especially activities where you look upward to re-energize.
- Negative self-critical, powerless, and depressive thoughts and feelings.
  - Reframe internal language to empowering thoughts.
  - Change posture by wiggling and looking up to have a different point of view.
- Crossing the legs.
  - Sit in power position and breathe diaphragmatically.
  - Get up and do a few movements such as shoulder rolls, skipping, or arm swings.
- Other causes.
  - Identify the trigger and explore strategies so that you can sit erect without effort.
  - Wiggle, move and get up to interrupt static muscle tension.
  - Stand up and look out of the window and the far distance while breathing slowly.

Posture Feedback Improves Health

After four weeks of using the feedback device and changing behavior, the treatment group reported significant improvements in physical and mental health as shown in Figure 4 and 5.

Summary

Slouched posture and head forward and down position usually occur without awareness and often result in long-term discomfort. We recommend that practitioners integrate wearable biofeedback devices to facilitate home practice especially for people with neck, shoulder, back and eye discomfort as well as for those with low energy and depression (Mason et al., 2018). Wearable devices that monitor spinal posture are very promising since they are capable of assessing spinal posture with

Figure 4. Using the posture feedback significantly improved the Physical Health and Mental Health Composite Scores for the treatment group as compared to the control group (reproduced from Mason, L., Joy, Peper, & Harvey, 2018).

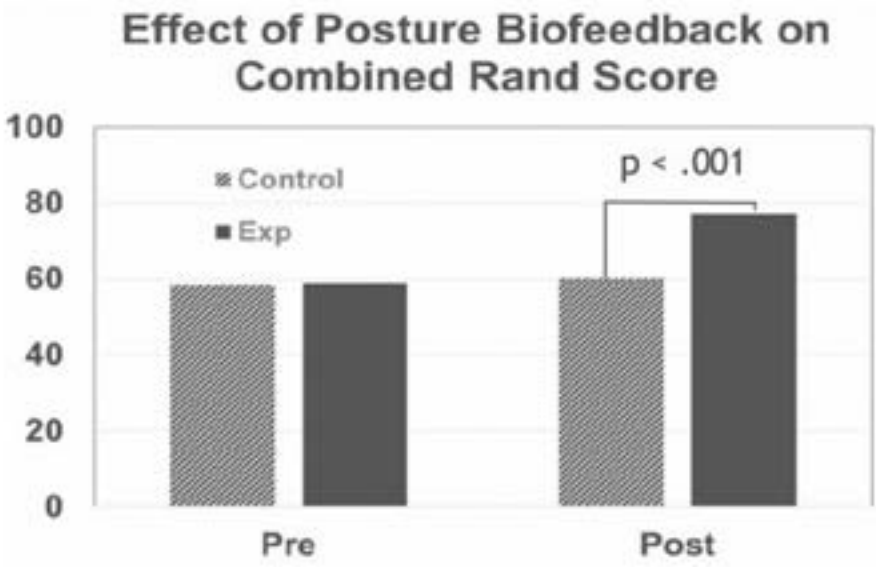
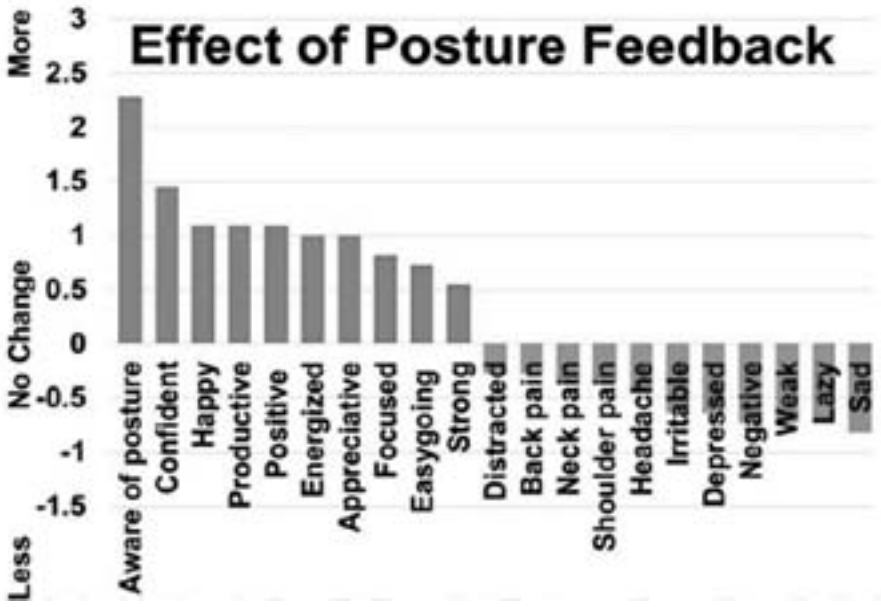


Figure 5. Pre to post changes after using posture feedback (reproduced from Colombo, Joy, Mason, L., Peper, Harvey, & Booiman, 2017).



good accuracy and can be used clinically (Simpson, et al, 2019). We observed that a small wearable posture feedback device helped participants improve posture and decreased symptoms**.** The vibratory posture feedback provided the person with the opportunity to identify the triggers associated with slouching and the option to change their posture, behavior, and environment.

As one participant reported,

> I have been using the Upright device for a few weeks now. I mostly use the device while studying at my desk and during class. I have found that it helps me stay focused at my desk for longer time. Knowing there is something monitoring my posture helps to keep me sitting longer because I want to see how long I can keep an upright posture. While studying, I have found whenever I become frustrated, tired, or when my mind begins to wander I slouch. The Upright then vibrates and I become aware of these feelings and thoughts, and can quickly correct them. This device has improved my posture, created awareness, and increased my overall study time.

Resources to Reduce Slouching and Improve Ergonomics

How to arrange your computer and laptop: https://peperperspective.com/2014/09/30/cartoon-ergonomics-for-working-at-the-computer-and-laptop/

Relieve neck and shoulder stiffness: https://peperperspective.com/2019/05/21/relieve-and-prevent-neck-stiffness-and-pain/

Cellphone health: https://peperperspective.com/2014/11/20/cellphone-harm-cervical-spine-stress-and-increase-risk-of-brain-cancer/

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Improved posture brings significant physical and mental health benefits.

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Narrative Review: Autonomic Response Testing as a Whole Person System of Health Care

by Patrick J. LaRiccia, MD, MSCE; Tracy L. Brobyn, MD, FAAFP; Jonathan Curzon, DC, DIBCN, FIAMA; Mark McClure, DDS, FAGD; and Myung Kyu Chung, MD

Abstract
Autonomic Response Testing is a whole person system of medical care. Herein is presented a concise descriptive overview of the system, including a review of published outcome reports of patients assessed within the autonomic response testing framework, limitations of the published research, and possible future research perspectives.

Introduction

The United States has been known to spend more on health care than other high-income countries and have poorer health outcomes.[1] Chronic illness is a contributor to health care costs. Whole person systems of medical care may hold promise for improving the health outcomes related to chronic illness. We present a review of one of them: autonomic response testing (ART).

Whole person systems of medical care are multi-faceted. They are challenging to thoroughly describe and to evaluate.[2,3] A detailed description of Ayurvedic medicine, traditional Chinese medicine (TCM), or chiropractic cannot be done in a review article format. Though ART is a modern form of a whole person system of health care, it draws on all forms of health care both traditional and modern. Thus, we present an informative overview rather than a detailed description. ART provides an assessment tool that can fit within other forms of medical care, informing the assessments made within other systems and informing the selection of interventions and the ongoing use of interventions. ART is a whole person system that enhances assessment and treatment planning. Herein is presented a concise description of ART, an overview of publications of clinical outcomes related to ART assessment, limitations of the evidence to date, and future research perspectives.

ART Basic Principles

ART postulates five levels of healing which are from lowest to highest: physical, energetic, mental, intuitive, and spiritual.[4] ART identifies seven categories of factors that initiate, maintain, or aggravate disease conditions: 1. Toxins 2. Biochemical 3. Structural 4. Energetic 5. Food 6. Psychological and 7. Geographic.[4] (See Table 1.)

Toxins include heavy metals, pesticides, bio-toxins from microorganisms in clinical and subclinical infections, etc. In ART a toxin reduces the optimum performance of a person. Thus, it is better to think of the toxic burden presented by a substance rather than a standard level of toxin, which is considered pathological, such as a lead level equal to or greater than 5 micrograms per deciliter. Sensitivity to levels lower than 5 micrograms per deciliter will vary across individuals. According to the US Agency for Toxic Substances and Disease Registry, no blood lead level above zero is free of all risk.[5] **Biochemical** imbalances include hormonal problems, genetic disturbances of metabolism, and nutritional problems. Examples of **structural** problems are malocclusion and vertebral subluxations. **Energetic**

Table 1. Seven factors that can initiate, aggravate or maintain disease.

1. Toxins	includes heavy metals, pesticides, bio-toxins from microorganisms in clinical and subclinical infections, etc.
2. Biochemical	imbalances include hormonal problems, genetic disturbances of metabolism and nutritional problems.
3. Structural	Examples are problems of malocclusion and vertebral subluxations.
4. Energetic	disturbances include phenomena associated with acupuncture points and meridians; chakras; interference fields such as scars and focal infections; nervous system problems; and emotions.
5. Food	factors include both intolerances and allergies.
6. Psychological	Includes psychological conflict and trauma.
7. Geographical	factors pertain to a person's habitual location and the influence of light, electromagnetic smog, underground water streams, and other geophysical influences on patients.

disturbances include phenomena associated with acupuncture points and meridians; chakras; interference fields such as scars and focal infections; nervous system problems; and emotions. **Food** factors include both intolerances and allergies. **Geographical** factors pertain to a person's habitual location and the influence of light, electromagnetic smog, underground water streams, and other geophysical influences on patients. Finally, but not least, are the influence of **psychological** factors such as psychological conflict and trauma.[4]

The ART assessment method aims to identify the presence of the above factors and which areas of the body and mind are being affected. The ART examination assesses all parts of the body. The ART assessment procedure also helps predict ameliorating and aggravating factors such as medications, homeopathic remedies, nutrients, herbs, etc.

ART Assessment Method

ART is a version of applied kinesiology. Applied kinesiology was originally developed by George Goodheart, Jr, DC.[6] Today, many forms of applied kinesiology are used clinically. Different originators of applied kinesiology methods believe that their method is an improvement compared to other versions.[7-11] Many chiropractors and integrative physicians use some form of applied kinesiology. The version practiced in our centers, known as ART, was originated by Dietrich Klinghardt, MD, PhD, and Louisa Williams, DC, ND,[12] and further extended by Klinghardt.[4] Different forms of applied kinesiology can give results that conflict with the results obtained with other forms. Klinghardt demonstrated this situation in a video on his website.[13]

In manual muscle testing an assessment of muscle function is made and recorded. Applied kinesiology expands manual muscle testing assessment to a second muscle function assessment that occurs in the presence of a stimulus such as a food, toxin, allergen, etc. The two assessments are compared, determining whether the response to the added stimulus was weakening, no change, or strengthening of the muscle function. The interpretation of the muscular response informs the assessment of the patient and makes a prediction of positive, negative, or neutral responses to therapies. Different forms of applied kinesiology vary in the muscles tested, the interpretation of a weak muscle response, the type and number of preparatory steps, and the manner of presentation of specific stimuli. Thus, different forms of applied kinesiology can give different results.[13] A systematic review by Hall et al[14] of applied kinesiology across different forms of applied kinesiology was unable to draw clear conclusions and recommended studying applied kinesiology using a pragmatic study design. No ART studies were included in that systematic review.

Autonomic response testing can be used with any type of medical care.

Schwartz et al[15] published a negative experimental study; however, no distinction was made regarding the various forms of applied kinesiology. No designation was given as to which form of applied kinesiology was being tested. It was implied that the form studied generalized to all versions of applied kinesiology. The article did state that the utilized protocol was not the approved Goodheart version[6] of applied kinesiology. The concluding statement appeared to lump all versions of applied kinesiology together. It is clear that neither ART[12,13] nor the official Goodheart protocol[6] was tested in the Schwartz et al[15] study. Just as antibiotics and diagnostic tests can differ one from another, so can different forms of applied kinesiology differ one from another.

We published a pilot study (14 patients) on the validity of ART for predicting the results of an Immunoglobulin E blood test for allergy identification.[16] Our results were positive: Sensitivity, specificity, positive predictive value, negative predictive value, overall accuracy, phi coefficient, and Cohen's kappa were all in the desired direction. As the correlation was good, it was not perfect. The results of ART assessments are to be interpreted in the context of standard medical assessment methods. No other study evaluating the validity of ART assessment has been published to date per our literature search of PubMed (which includes MEDLINE), EMBASE, AMED, and CINAHL. We hope this review of ART will prompt serious attention from the research community toward ART. Our clinical experience with ART as an assessment tool to help identify contributing disease factors and helping to guide the choice of interventions has resulted in positive clinical outcomes in patients who have failed standard medical therapy. [17-23]

ART Therapeutics

ART draws on all available therapeutics. Therapeutic interventions can be drawn from Chinese medicine, Ayurvedic medicine, homeopathy, osteopathic medicine, allopathic medicine, chiropractic medicine, dentistry, etc. Therapeutic options are in continual evolution. The crux of ART is the assessment procedure, which informs the identification of contributing factors and the choice of intervention.

One of the therapeutics that is often drawn on in our centers is neural therapy (NT),[24] which frequently involves injecting ART-indicated scars with procaine. In NT, scars and dental foci can act as interference fields. The interference field can have an influence at a distance e.g., the scars from tongue piercings influencing abdominal pain and nausea.[22-23] The proposed mechanism is chronic stimulation of autonomic afferent nerves, which feed back into autonomic nervous system with resultant effector reflex activity such as nausea, vomiting and pain.[25]

Clinical Outcomes Associated with ART

We searched the previously mentioned literature databases for outcome studies involving ART. We ➤

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searched specifically for ART as opposed to any version of applied kinesiology. No published studies were found other than those published by the authors of this paper.

In each published report, ART assessment was used to identify the contributing/maintaining disease factors and predict positive result-producing interventions. Common to the reports is that the patients had failed to obtain satisfactory improvement from standard medical assessment and treatment; some of the patients had already visited other complementary/alternative medicine practitioners. The reports come from a practice located near the major medical centers of Philadelphia and Camden, New Jersey. The patients had multiple opportunities to experience a placebo response due to contact with providers, medical tests, and interventions before participating in the multi-modal approach described herein. These patients also had stable baselines of the intensity of their chief complaints. Their improvements were beyond the best points of their pretreatment baselines thus arguing against regression to the mean.

In a seven-year-old male with obsessive compulsive disorder, ART assessment identified gluten as a food factor, burdensome levels of lead and mercury, subclinical infection, and energetic disturbances on ear acupuncture points.[17] (See Table 2.) All factors were addressed in a multi-modal approach. The patient did exceptionally well. Based on our clinical experience, it was felt that gluten sensitivity was the dominant factor; however, as with all multi-modal approaches, we cannot be certain of the dominance of any one factor nor of a specific combination or specific sequence of factors. These are questions for further research.

In a 33-year-old male disabled metal worker with chronic lower leg edema and recurrent cellulitis, ART identified the contributing factors of subclinical infection, scar interference fields, burdensome levels of lead and mercury, gluten sensitivity and sub-optimal mineral levels.[18] (See Table 2.) All of these ART findings were addressed in a multi-modal fashion. The patient did well and was able to return to work.

We (MKC, PJL) reported a case series of three women with chronic neck and back pain, one of whom failed two surgical procedures which included implantation of a spinal cord stimulator.[19] All three patients had treatment by other complementary/alternative medicine practitioners, which included acupuncture for two of the patients. ART identified energetic disturbances related to surgical breast scars; body, ear, and scalp acupuncture sites; and a tooth interference field. Also identified were structural factors related to the vertebrae. (See Table 2.) All three had an excellent response to a multi-modal approach guided by ART.

In a 10-year-old girl ART helped identify a psychological trauma that occurred before birth as a result of the therapeutic abortion of one of her sibling triplets.[20] (See Table 2.) Bringing this event into awareness helped the child to overcome her severe emotional lability problem with further treatment.

ART identified the correct ear acupuncture point related to a scar energetic interference field in an NFL football player presenting with hip flexor weakness.[21] After placing an acupuncture needle at this point, there was a sudden increase in the strength of the player's hip flexors for which he was seeking help. (See Table 2.)

In the next two reports[22, 23] the treatment arms of the case reports were the main focus; thus ART was not described although it was performed. In two young women with chronic abdominal pain,[22] treatment of the ART-identified energetic factors from scars due to tongue rings appeared to be dominant factors in their dramatic recoveries. (See Table 2.) In a young woman with chronic nausea and vomiting,[23] a tongue ring scar and tattoo scar with energetic disturbances were involved in the multimodal treatment approach. One single office visit resulted in full lasting recovery.

Table 2. Contributing factors identified with ART in seven different chronic clinical presentations

Contributing Factor(s)	Obsessive Compulsive Disorder[17]	Chronic Cellulitis Edema[18]	Chronic Neck/Back Pain[19]	Emotional Lability[20]	Hip Flexor Weakness[21]	Chronic Abdominal Pain[22]	Chronic Nausea[23]
Energetic: body acupuncture system		X	X			X	X
Energetic: ear acupuncture system	X		X		X	X	X
Energetic: scalp acupuncture system			X				
Energetic: scar interference field		X	X		X	X	X
Energetic: tooth interference field			X				
Food sensitivity	X	X					
Biochemical (nutritional): sub-optimal minerals		X					
Psychological trauma				X			
Structural: musculoskeletal problems			X				
Toxin: Burdensome level of heavy metals	X	X					
Toxin: Sub-clinical infection	X	X					

Discussion

ART is a whole person system approach to health care. The main conceptual tenets of ART are the five levels of healing and the seven disease factors. ART provides a specific assessment method used to help identify the seven disease factors. A pilot evaluation of the ART assessment method indicated good correlation with the results of blood immunoglobulin E levels for allergy assessment. A review of seven published reports in which ART was utilized in the medical care of patients who had failed standard medical care indicated excellent clinical outcomes.

Outcome studies consisted of retrospective case studies and two very small retrospective case series. Case studies/series sit at the bottom of the evidence hierarchy; however, case studies are often the starting point for new discoveries. Our hope is that this review will energize the research community to examine ART with an open mind and with larger more rigorous studies.

Among confounding factors in case reports are placebo response, regression to the mean, and spontaneous remission. In the context of stable baseline disease activity, it is unlikely that spontaneous remission would coincide so closely with the advent of the ART-guided treatment program in all these cases. In regard to regression to the mean, again in the context of stable baseline disease activity, the treatment effect was larger than at any previous period of time for all the patients. In regard to placebo effect all patients had multiple opportunities for placebo response elicitation by interaction with mainstream health care personnel, mainstream diagnostic tests, and mainstream interventions. Some also had treatment by other complementary/alternative medicine practitioners. Yet none of the patients had a prior placebo response. Publication bias is another possible limitation. Three of the authors (PJL, MKC, MM) have over 90 years combined experience in complementary/alternative medicine (CAM) modalities and have been in leadership positions within different local CAM organizations in major metropolitan areas. Two of us (PJL, MKC) have had combined continuous academic affiliations of over 60 years. We are unaware of any **negative** outcome studies of ART that were rejected for publication. We are unaware of anyone even attempting to perform either an outcome study or diagnostic study related specifically to ART. Practitioners do not have funding and time to conduct or report studies. We have found conducting and reporting studies an expensive, time-consuming process. In addition, we have perceived resistance by both main stream and complementary/alternative medicine journals.

The above is clear preliminary evidence that justifies further research

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activity specifically on ART. How does one go about studying a complicated set of procedures as described above? Weeks has proposed "studying the way we practice."[2] Kliger and Weeks[26] have recommended the aggregation of case studies that have followed the CARE guidelines[27] and the use of mixed methods research designs (designs which combine quantitative and qualitative methods). Kligler and Weeks also call for openness and honesty regarding what we actually know with certainty and the unavoidable need for clinical judgement in which experience and intuition cannot be dispensed with.[27]

We are in full agreement. With ongoing incoming data, models forecasting effectiveness and safety can be developed, evaluated, and adjusted just as is done for models to forecast the weather.[28] We project that such an approach will be more beneficial than searching solely for the magic bullet and/or waiting to determine the underlying mechanism for each and every existing integrative modality or combinations of modalities before informing the public and giving chronically ill people the opportunity to try.

The research community currently has the capability of tracking multiple variables, outcomes, and adverse events along with the capability of constructing models and evaluating those models in the context of natural occurrences, e.g. weather forecasting, which has not depended on randomized controlled trials yet has produced steadily improved forecasts over the years. In addition to forecasting if a treatment approach can be effective, we must use the incoming data also to model who the responders and non-responders will be along with those at risk for adverse events. Simultaneously, the traditional methods of biomedical research can be employed such as cohort studies, pragmatic studies, comparative effectiveness studies, and randomized controlled studies where feasible.

Another method of research is the use of site visit studies such as that carried out by Lisi et al, [29] in which nine medical practices, which had integrated chiropractic clinics on site, were qualitatively assessed for outcomes and perceived value by everyone involved. Multi-modal medical practices could have site visits incorporating chart reviews, clinician interviews, and patient interviews focusing on types of problems treated, types of patients treated, outcomes, identification of predictors of responders and non-responders, adverse events, and cost. The site visits can be recurring and incorporate quantitative assessments. Site visit evaluations should include established private practices in addition to university-affiliated integrative medicine practices. Information from site visit studies, along with standardized case reports, and the results of our frequently used current types of research studies can flow into the health care "big data" pool from which predictive models for effectiveness and the risk of adverse events can be developed and adjusted. Thus, actionable information can be provided to healthcare providers, patients, and policy makers while waiting for the conclusion of explanatory studies.

Conclusion

Preliminary evidence has been presented for the utility of ART in the context of chronic disease to be considered for further research. We hope this narrative will stimulate further research. We are willing to advise and collaborate.

Conflicts of Interest: All of the authors report no conflict of interests.

Patrick J. LaRiccia, MD, is board-certified in internal medicine and a licensed acupuncturist. He has served as president of the Acupuncture Society of Pennsylvania and president of the New York Society of Acupuncture for Physicians and Dentists. He received an award for his contribution to acupuncture from the Acupuncture Society of Pennsylvania besides sharing a research prize in acupuncture from the Medical Acupuncture Research Foundation. Dr. LaRiccia is an adjunct scholar at the Center for Clinical Epidemiology and Biostatistics at University of Pennsylvania School of Medicine.

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by James Greenblatt, MD

Adapted from his book *Integrative Medicine for Depression: A Breakthrough Treatment Plan that Eliminates Depression Naturally*

Depression is a disabling illness that can profoundly impact physical and psychological well-being, trapping those who struggle with it in a quagmire of sadness and despair. It is as prevalent as it is all-encompassing, currently ranked by the WHO as the leading cause of global disability and estimated to impact over 300,000,000 people worldwide – a number representing an increase of more than 18% from 2005 to 2015.[1,2] In the United States, major depressive disorder encumbers the national economy to the tune of approximately $210.5 billion per annum, has a lifetime prevalence rate of approximately 19.2% and, in apparent lockstep with global trends, is on the rise.[3] Epidemiologic studies have lately tracked increases in rates of depressive illness in the US, most notably in adolescent populations. Between the years 2017 and 2018, rates of adolescent depression increased at least 60%, with the largest increases noted amongst teen and pre-teen girls.[4]

These are daunting numbers, indicative of an increasing global disease burden, yet in a way these statistics are of less concern than those associated with depression treatment success. Mainstream psychiatry has long since established a therapeutic model for depressive illness – a medicalized model in which symptom suppression is the primary goal and go-to treatments tend to be pharmaceutical; yet despite the widespread implementation of this model throughout the United States and beyond, depression incidence rates continue to rise and treatment success rates remain, at best, mediocre. Standard antidepressant treatments effect complete symptom elimination in only about one-third of patients; of these, the majority eventually relapse and are associated with a disturbing array of side-effects from weight gain and sexual dysfunction to addiction and suicidality.[5-8]

Most of us need neither statistics nor incidence tracking data to know how serious depression is, how widespread it is, or how difficult it can be to resolve. Those who have battled depression can attest to its devastating impact on body, mind, and spirit; those with friends or family members with depression have likely witnessed this devastation firsthand.

I have treated patients with depression for over thirty years, have listened to them, learned from them. It is apparent to me that our current treatment offerings – and, at large, our reigning therapeutic paradigms for the treatment of depressive illness – are not enough. People all around the world are struggling, yet the main lifeline that the medical and psychiatric communities have to throw them is falling short.

A Typical Psychiatric Evaluation

Let us consider what happens when a patient struggling with depression visits a psychiatrist. In fact, let's imagine that you are stepping into the office. Perhaps you have sought out help on your own, perhaps you have been referred to the psychiatrist by your primary care physician, or maybe this visit comes at the behest of concerned friends and family members…regardless, you've made the brave decision to seek professional treatment.

Upon entering the psychiatrist's office, you are immediately struck by the degree to which it does *not* bear resemblance to what you consider a 'normal' medical office. There are no stethoscopes, blood pressure cuffs, scales, or other instruments that doctors utilize to evaluate and quantify various parameters of physical health. Instead, there are chairs, or perhaps a comfortable couch, and a box of tissues.

Seeing this, you realize that this visit is not going to involve a standard medical exam, even though psychiatrists are doctors who complete four years of medical school after college followed by at least four more years of specialized training in clinical psychiatry.

The psychiatrist enters the room, sits down, greets you, and then begins the consultation: "What brings you here today?"

Despite, perhaps, not knowing where to begin, you forge ahead and describe how you've been feeling over the last weeks/months/maybe years. As you talk, the psychiatrist takes detailed notes on a medical pad or a computer, occasionally asking more detailed questions to gather the information he or she needs to make a diagnosis.

As you continue your talk, which quickly becomes more of an interview than a conversation, you begin to wonder how the trained medical professional in front of you can make a diagnosis based purely on…talking, without running any tests or conducting any sort of physical exam. Yet that's the way it's done and has always been done, so you go along with the program, hoping for the best.

At a certain point, after the line of questioning has run its course, the psychiatrist turns to a thick book sitting behind him or her on a bookshelf. This is the DSM, the *Diagnostic and Statistical Manual of Mental Disorders*, an authoritative treatise published by the American Psychiatric Association that offers common language and standardized criteria for the classification of mental illnesses.[9] By matching the information that you have provided about your symptoms to the DSM classifications, your psychiatrist is seeking to establish a diagnosis and formulate an approach to your treatment.

A Note on the DSM Categories of Depression

As psychiatry evolved into a distinct field of medicine, the development of clear diagnostic categories became necessary such that professionals could discuss, reference, and research mental health phenomena. The goal was to create precise classifications that would facilitate the most accurate diagnoses possible. A question, however, that has beleaguered this endeavor from the beginning, and which merits our close attention now is: just how precise is the *science* behind these classifications?

The very first edition of the DSM, published in 1952, described a total of 107 mental illnesses.[10] Members of the authoring entity – the American Psychiatric Association, or APA – voted on the list of disorders to be included in the volume, and about 10% of the total membership was asked to approve the initial draft of the work. Somewhat less than half of those (or about 5% of members) voted to formally adopt the DSM, greenlighting the book's publication and paving the way for its eventual establishment as the go-to authority on the classification of mental illness for doctors, researchers, insurance companies, pharmaceutical companies, and government entities.

The current DSM – the DSM-V – was released in 2013 after a decade's worth of editing, revision, and reorganization of the previous edition, an accomplishment reflective of the APA's intent to better represent elements and diagnostic criteria that were lacking in the DSM-IV.[11]

These changes, and more, were made to the DSM with the intention of improving diagnostic criteria for patients with mental disorders such as depression. But was this effort successful? Is the current edition of the DSM 'better' than the old one, and did these changes affect any measurable, meaningful improvements in the treatment of patients with depression?

The answer is, simply, no.

What's Missing

Going back to our hypothetical scenario, in which you are a patient seeking professional help for depression and visiting a psychiatrist for the first time, let us consider what *wasn't* included in your evaluation.

The psychiatrist in this scenario never asked you about your medical history – significant illnesses you may have had in the past, current diagnoses for non-psychiatric conditions, medications you are taking, or major life events like a surgery or an accident – or the medical histories of your close relatives. Traditional psychiatrists rarely explore medical histories that are not directly related to a patient's immediate symptomatic presentations and almost never ask questions about family medical history.

Do you recall how much medical equipment wasn't in the office of your [hypothetical] psychiatrist? This image is an accurate one; rarely would a traditional psychiatrist listen to your heart, take your blood pressure or pulse, examine your eyes or your skin, or otherwise try to determine if there are any physical symptoms that might be related to your depression.

Integrative psychiatry recognizes that the body's biochemistry and nutritional needs affect mental health.

Your imaginary evaluation did not include any discussion of diet – what you typically eat in a day, your food preferences, etc. – or the cosmetic products you might be using (which may or may not be a source of exposure to harmful chemicals). Nor was laboratory work ordered to check your nutritional status, hormone levels, inflammatory markers, or to detect the presence of any environmental toxins that may have accumulated in your body.

In addition, no attempt was made to discover whether allergies that you may or may not be aware of could possibly be affecting your physical status and, accordingly, your mood.

These omissions demonstrate in no uncertain terms that mainstream psychiatry operates on the principle that the brain is the brain, the body is the body, and that brain and body are two distinct, entirely separate things.

Unfortunately, this separation of brain and body often prevents physicians and mental health professionals from identifying the causes of depressive illness – not the symptoms, but the pathologic states or processes that are *creating* the symptoms. And doctors can only treat what they identify to be present.

It is an incomplete paradigm, one which leaves patients suffering as a result.

A Shot in the Dark

Let's return once again to your hypothetical psychiatric evaluation. The clinical interview is over, and the DSM

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has been consulted. Now it's time to choose a treatment strategy which, in traditional psychiatry, is often hit-or-miss. As we have discussed, standard psychiatric intake evaluations do not consider etiology, do not involve objective measurement, and operate from the philosophic and methodologic view that brain and body are separate. The underlying causes of mental disorders, therefore, frequently remain unidentified even after evaluation, meaning that treatments are prescribed without a precise understanding of causality.

Put simply, many psychiatrists prescribe treatments – which are often medications – without comprehending the root causes of the disorders they seek to treat. So they are, in essence, guessing.

Look at it this way. Medical doctors, such as internists, primary care physicians, cardiologists, gastroenterologists, and others offer patients specific treatments that are designed to address a specific underlying biologic problem. In the case of a bacterial infection, for example, a physician will prescribe an antibiotic, and frequently only after performing a culture to identify what kind of bacteria is causing the issue. The treatment (the antibiotic) is thus carefully matched to cause (the specific bacterial strain), ensuring the highest possible rate of treatment success and recovery.

Many traditional psychiatrists, in contrast, make treatment decisions and recommendations based on guesses, prescribing one medication after another and hoping that one – or some combination – will work. Patients usually take multiple psychiatric medications over time and may even be prescribed two or more antidepressants to take simultaneously… in addition to, perhaps, a drug to help with sleep… and maybe also another pill for anxiety. A study published in the *Archives of General Psychiatry* confirmed this trend, finding that 59.8% of visits to office-based psychiatrists resulted in the prescription of two-plus psychiatric medications.[12] One-third of office visits resulted in three-plus prescriptions. And if the first prescription(s) didn't solve the problem, new ones were offered.

A traditional psychiatrist may therefore try one medication after another to see what works. Sometimes, a 'symptom suppression jackpot' is hit, but it is far, far more likely that the first medication either won't work outright or won't provide relief. And so patients are given a second, third, fourth, and even a fifth medication to add to this pharmaceutical battery. It is not uncommon for some doctors to keep prescribing medications *without stopping the old ones*. This rapidly expanding trend – called polypharmacy – is, sadly, the rule rather than the exception when it comes to mainstream approaches for the treatment of depressive illness.

The Way It Could Be

I began this article by asking you to imagine that you had taken a brave first step in seeking help for depression and had gone to see a psychiatrist. As you recall, during the imaginary psychiatric examination, you were asked only about how you felt, and your answers became the sole basis of your diagnosis of depression and any treatments or medications that you received.

Rewind, if you will, and imagine instead that this psychiatrist asks you, in detail, about your diet, the medications and supplements you take, the health of your relatives and what you do every day, trying to identify any situations or substances that may be causing your depression.

Next, this psychiatrist orders lab tests to look for physical problems that might cause or worsen depression, such as the following:

- Vitamin deficiencies,
- Toxic metals,
- Hormonal imbalances,
- Low levels of certain vitamins,
- Amino acid and fatty acid imbalances,
- Low or high levels of certain minerals,
- Celiac disease and other food sensitivities,

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- Imbalanced levels of digestive enzymes,
- Dysbiosis ("bad" bacteria, yeast, or other flora in your intestines), and
- Parasites.

After these tests are completed, the psychiatrist does not automatically give you a prescription because he or she wants to see the results *before* making a treatment decision. After all, your depression may be rooted in a food sensitivity, nutrient imbalance, or something else that can be corrected without the use of psychiatric medications.

When the results have come in and the psychiatrist sees you for a second visit, he or she may recommend a medication and nutritional support. But the medication will be carefully selected and targeted, and thus much more likely to work. It won't be a "try-it-and-see-if-it-works" prescription based on studies of hundreds of people who are nothing like you; it will be an individualized, targeted treatment based on your specific, matchless, and wholly unique biologic markers. In other words, it will be just for you.

This is integrative psychiatry, a way of looking at an individual as a whole person with unique biochemistry and nutritional needs that, when balanced, allow health and vitality.

By focusing on the individual as a whole, integrative psychiatry often produces improvement and encourages healing where traditional, symptom-based treatments have failed.

The Future

The statistics, the plot lines, and the percentages derived from epidemiologic studies confirm what to so many of us seems glaringly, tragically obvious: the reigning therapeutic paradigm for the treatment of depression is insufficient, inadequate, and leaving far too many patients still suffering. And yet, in the face of this inadequacy, psychiatry as a field has taken to blaming patients for its own failures. We see this in the terminology that doctors so frequently use, saying that, for example, a patient has "failed treatment" or is "treatment-resistant."

Yet I ask: if the patient is taking medication prescribed by his doctors and hasn't recovered…who has failed?

We – psychiatry, the mental health community, the research community, and the healthcare system at large – can do better, much better, if we take advantage of the decades' worth of scientific research that shows depression is not "all in your head." The mind and body are one; what happens in the body affects the mind and the mind affects the body. Nutritional deficiencies, hormone imbalances, allergies, and other physiologic ailments have been proven to be key factors in the pathogenesis of depressive illness and, accordingly, must be incorporated into its assessment, evaluation, and treatment.

I have been recommending these therapies for more than thirty years and have seen thousands of patients improve and recover from depression. And yet I remain impatient, frustrated by mainstream psychiatry's continued and widespread adherence to outdated, ineffectual treatment paradigms that, as we have explored, leave far too many patients still struggling, still suffering, still in pain.

But it does not have to be this way. The science is available, right now: scientifically informed integrative medicine models that reach beyond consequence to identify causality, and evidence-based interventions that target the biologic imbalances that research has shown to precipitate neurologic, cognitive, and behavioral dysfunction. The understanding – and the ability to act upon it to affect lasting, positive change in the lives of patients with depression – is here.

This is integrative psychiatry, and it is a beacon of hope shining out against the darkness of depression.

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Cannabidiol's Potential Role in ADHD and Autism

by Chris D. Meletis, ND

Attention-deficit hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and impulsiveness that interfere with a person's ability to socialize or perform well academically or at work. According to the American Psychiatric Association, 5% of children have ADHD.[1] The Centers for Disease Control and Prevention estimates 6.1 million children and adolescents suffer from the disorder.[2] An estimated 29.3% of children with ADHD remain diagnosed with the condition into adulthood.[3]

Attention deficit disorder (ADD) is a subtype of ADHD that does not involve excessive hyperactivity and restlessness. ADD is considered the predominantly inattentive type of ADHD.

ADHD can also occur as a comorbidity of autism spectrum disorder (ASD).[4]

The Role of the Endocannabinoid System in ADHD and Autism

Impaired dopamine transmission in the striatum is involved in the development of attention-deficit hyperactivity disorder.[5] Dopamine transmission in the striatum also influences the endocannabinoid system (ECS) through acting on CB_1 receptors.[5] Dysfunctions in dopamine's modulation of this system can lead to hyperactivity.[5] Furthermore, the endocannabinoid system is frequently impacted in ASD patients with seizures, anxiety, cognitive problems, and impaired sleep.[6] Compared with healthy controls, lower plasma levels of the endocannabinoid anandamide have been found in children with ASD; and children with ASD were more likely to have low anandamide, implicating dysfunctional anandamide signaling in the etiology of ASD.[7] This impaired anandamide signaling is thought to play a role in the social dysfunction that occurs in ASD, further linking the endocannabinoid system with this disorder.[8]

CBD Use for ADHD

Formal research on CBD's effect on ADHD is in its infancy. Clinically CBD is a powerful tool in dampening many of the presentations of ADD/ADHD. Studies investigating the use of CBD are often on symptoms that are similar to those suffered by ADHD patients and suggest probable benefit in ADHD patients as well. For example, CBD was found to improve sleep in Parkinson's patients.[9] In another study, CBD had a calming effect on patients suffering from anxiety.[10] Its relaxation effects in people with social anxiety disorder appear to be due to its influence on the limbic and paralimbic brain areas.[11] In one study of adults with ADHD using an oral spray containing both CBD and the psychoactive component of marijuana THC, cognitive performance did not improve; but there were marked improvements noted in hyperactivity, impulsivity, and inhibition measures.[12]

CBD and Autism

CBD has been found to improve many symptoms that are common to autism and other disorders. In addition to its calming effects as noted above and its ability to improve sleep, also addressed earlier in this article, CBD may improve social functioning. In two rat models of schizophrenia, it inhibited social withdrawal and reduced deficits in social interaction and cognition.[13,14] Furthermore, in a mouse model of Dravet syndrome, CBD reduced seizures and autism-like behaviors.[15]

Conclusion

Though there are limited human studies investigating the effects of CBD on ADHD and autism, there is scientific justification explaining why CBD may be supportive in these disorders. The association between the endocannabinoid system, ADHD, and autism is one factor pointing to the possibility that CBD may have a part to play and that employing strategies that impact the endocannabinoid system may lead to significant improvements. There is also growing evidence that the endocannabinoidome that describes the interplay between the human microbiome and the endocannabinoid system will undoubtingly further increase the clinical applications of CBD relative to modulation of the gut-brain axis.

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The End of Addiction?

by K. Paul Stoller, MD, FACHM

Alcoholism affects more than 27 million Americans. In a world where less than 10% of those with alcohol addiction are getting treatment, one of the conditions most satisfying to treat is alcohol use disorder (AUD).

Suboxone

Addiction medicine hasn't changed for a long time with the exception of the introduction of Suboxone – an opioid buprenorphine in combination with naloxone. Naloxone, frequently referred to as Narcan, is an opioid receptor antagonist that effectively occupies the human opioid receptors but blocks any action. Suboxone is one of the primary pharmaceuticals used today in medication-assisted therapy (MAT) for opiate addiction.

Suboxone obviously helps with neurotransmitter aspects of an opioid addiction because it is an opioid that provides a short-term fix that makes it easier to adapt to long-term treatment. If one is choosing between Suboxone and doing nothing, then Suboxone is a better choice. But it is not real addiction treatment for opioid addiction, let alone any other kind of addiction.

The process of addiction – and the underlying disorder that addiction mitigates – is the actual problem. Opioids, nicotine, cocaine, or alcohol are ultimately a form of self-medication – just the means to an end.

Naltrexone and the Sinclair Method

Naltrexone is a treatment option that was introduced in the 1960s and is used in the Sinclair method as a stand-alone drug for alcohol addiction treatment. The medication reduces opioid effects by competing for opiate receptors and displacing opioid drugs from these receptors, reversing their effects. The metabolite of naltrexone, 6β-naltrexol, is also an active agonist. Consequently, the effects of naltrexone arise from both the parent drug and its major metabolite and last about a day. It is capable of antagonizing all four types of opiate receptors.

AUD patients prescribed naltrexone take the medication orally about an hour (and only then) before drinking, blocking the positive-reinforcement effects of alcohol, which allows the person to stop or reduce drinking (the Sinclair method). This occurs because for an alcohol addict, drinking causes massive release of dopamine and endorphins, the source of intense craving for alcohol – even years after being sober. Alcohol also increases the activity of GABA (γ-aminobutyric acid), a major inhibitory neurotransmitter in the brain that suppresses activity of the central nervous system with accompanying calmative effects.

This opioid blocker is intended to reduce and eventually erase habit-forming behaviors, diminishing a person's craving for alcohol to its pre-addiction state. This assumes that the primary underlying dynamics in alcohol addiction are habit and conditioned response. However, the limited success of naltrexone alone makes it clear that more complex neurochemical and genetic factors are involved.

Naltrexone and naloxone differ in their utility in addiction treatment. Naloxone is effective in opioid overdose rescues, acting within minutes to reduce opioid levels, which lasts for about an hour because of rapid metabolism. The different half-life of naltrexone and naloxone explains why the two drugs have different purposes. Naltrexone is used to block cravings for both opioids and alcohol, but naloxone is not; naloxone can treat overdoses but naltrexone cannot. Both drugs block the analgesic action of both exogenous opioids and the pleasure response of endogenous endorphins, but naloxone acts quickly enough to treat an overdose while naltrexone does not. For these same reasons, naltrexone cannot be used to rescue someone from an overdose but can be used to help people who are addicted to opioids have less craving for them.

However, I have never used naltrexone to treat addictions. Rather, I use the bio-identical hormone oxytocin to achieve the same effect because it also sits on the body's opioid receptors, is capable of putting opioid addicts into withdrawal, and has agonist action comparable to naltrexone.

Oxytocin

No one, as far as I know, has compared oxytocin to naltrexone; but naltrexone is considered only modestly successful at treating AUD, and oxytocin by itself has had only modest success in my clinical experience. Consequently, I do not use oxytocin alone for AUD

because it does not get the job done. Modest success is not satisfactory.

Initially, I started using oxytocin because it helped my brain-injured patients deal with the PTSD that comes along for free when one has a stroke, TBI, or some other form of brain injury. As the brain heals and one becomes more aware of how messed up life is, that can cause a great of anger and anxiety; the oxytocin blocks inappropriate fear and panic from engaging the limbic area of the brain. It even seems to help the brain process more effectively. When I learned that one of the effects of drinking alcohol is to increase oxytocin levels, I thought it was worth a trial to use it in alcohol cessation. However, while oxytocin may be a secondary gain from drinking alcohol, oxytocin-seeking is not the driving mechanism of the addiction.

Rather, I believe that the ultimate hook in alcoholism is the endorphin explosion that those prone to addiction experience. Without this endorphin explosion in individuals with the wrong constitution or genetics, there would be no craving and no addiction.

Baclofen

This brings us to the classic drug baclofen. Without getting too technical, the mesocorticolimbic (MCL) dopamine (DA) system plays a critical role in mediating the positive reinforcing effects of a variety of abused drugs, including cocaine, amphetamine, nicotine, and opiates.[1-3] This anatomical pathway originates from the ventral tegmental area (VTA) in the midbrain and projects to several forebrain regions, including the nucleus accumbens (NAcc) and medial prefrontal cortex (mPFC).[3,4]

Since opiate receptor activation generally inhibits individual neurons, opiate-induced DA release was initially hypothesized to be mediated by a disinhibitory mechanism, i.e. opiates inhibit VTA GABAergic interneurons to decrease GABA release, which subsequently disinhibits VTA DA neurons, leading to an increase in NAcc DA release.[5] The mesolimbic DA system may be the substrate upon which opiates act to produce their reinforcing effects.[6] One could then postulate that if GABA is provided in therapeutic amounts, the VTA DA neurons will not become disinhibited.

Baclofen has already distinguished itself in the medical literature for utility in treating AUD (when the dose is allowed to be titrated up to whatever level a patient needs to obtain control). This point bears repeating because the medical literature is replete with randomized trials showing that baclofen does not work; but when you consider the dose used in the trials, it was inadequate. It is only when the patient is allowed to slowly titrate the dose up without limit that one sees the desired effect.[7] Be that as it may, the mixed results from studies with suboptimal doses have stifled baclofen's utilization for treating addictions, specifically in AUD. A double-blind RCT using baclofen for cigarette cessation published in 2015 was successful at 20 mg four times a day.[8] Still, that dose is usually far too low for AUD. The logistical issue is that there are very few physicians who will give an AUD patient the opportunity to try baclofen because they have no training in using it for AUD, let alone using it with potentially high-dose titration. It is noteworthy that not all AUD patients need high dose levels, but many do. This all makes sense if you understand that as a GABA agonist, baclofen seems to prevent the disinhibition of the VTA DA neurons (i.e. inhibiting dopamine production), so there is no reinforcement for the addictive behavior.

CBD

This brings us to CBD. Discrete disturbances of AMPA GluR1 and cannabinoid type-1 receptor expression, observed in the NAcc, associated with stimulus cue-induced heroin-seeking, were normalized by CBD treatment.[9] CBDs can be initiated at full dose out of the starting gate – there is no need to wait to bring up the baclofen dose to therapeutic levels (however long that takes). Between baclofen and CBD, the VTA DA neurons remain inhibited and oxytocin is just icing on the cake – the endorphin cake – by inhibiting a release that would only serve to reinforce the addictive behavior and by supporting a sense of wellbeing.

When used in combination, Baclofen, CBD, and oxytocin, can address underlying addiction mechanisms.

Protocol

These three relatively benign medications in tandem support an affordable, effective intervention in which the mechanisms for eliminating addiction reinforcement are relatively well understood and well-documented.

- **Baclofen.** I start patients off at a very low dosage of baclofen because some people are very sensitive, so we begin at 5 mg twice a day. I have them slowly increase their dose to 20 mg QID. This is the dosage that was used in the cigarette trial. One has to increase the dose slowly while the patient acclimates to the somnambulistic quality of baclofen. However, as pointed out, that dose is usually inadequate for AUD.

  Caution in weaning. It is also important to wean off the baclofen slowly. This is absolutely not a drug that can be quit cold turkey. Reported potential side effects of abrupt weaning include hallucinations and seizures.[10]
- **CBD.** The required dose of CBD is 40 mg QID.

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- **Oxytocin.** The oxytocin cannot be used until the patient is sober because that will put people with opioid addiction into withdrawal. Once they are sober, sublingual troches of 25 mg of oxytocin, used up to four times a day, complete the protocol.
- **Contraindications.** Note that oxytocin cannot be given to pregnant women. Patients with brain injuries, stealth brain infections such as Lyme or cytomegalovirus, or severe dementia may not be good candidates for this protocol.

Nothing works 100% of the time on 100% of people. For the majority of patients, this protocol has great potential and is relatively inexpensive. Oxytocin 25 mg troches can be purchased (via compounding pharmacies) for less than a dollar/day in most cases, so perhaps $3/day at maximum dosage. CBD can vary widely in price, but a fair price is $60 for an ounce tincture in which one drop is 1 mg, so at maximum dose, the cost is $120 per week. Baclofen is sold for pennies a tablet. The cost is about $500 per month for this protocol. How long anyone stays on the protocol is between him or her and their physician.

Addiction management is ultimately very individualized. If the patient needs a high dose of baclofen, it can take a couple of months to ramp up the dose to a helpful level. While I let folks wean themselves off baclofen when they no longer need it, I encourage them to take the CBD and oxytocin ongoing. These are benign calmatives. Additionally, the patient can always reintroduce the baclofen if they need it.

Discussion

While naltrexone, used in the Sinclair method, is only $50 a month if insurance is covering the medication, in my experience it does not work for everyone. While the naltrexone prevents the endorphin explosion after drinking, it does not help brain processes that are mitigated by oxytocin.

Naltrexone also does not deal with the ongoing cravings (psychological) that many experience for a lifetime afterward, even after years of sobriety. The naltrexone only blocks secondary gain (dopamine and endorphin release) at the moment of imbibing. Additionally, naltrexone is not effective for addiction to cigarettes, cocaine, or other substances. Those prone to addiction get addicted to all sorts of things. Ultimately it is the underlying addiction chemistry itself that we need to address.

Addiction treatment using Suboxone can take two years, serving as a bridge while one is doing other things in their life to cope with the addiction. The medication often only works when it is taken consistently. It doesn't really move the gauge, just keeps the gauge from going into the red zone.

To date, no one has published on the clinical use of baclofen and CBD in combination with oxytocin for addiction mitigation. Nevertheless, I do not expect that what I just revealed will change the face of addiction medicine. In fact, it is not a problem limited to addiction medicine; it is ubiquitous through the entire medical paradigm. If a medication or an intervention is not going to make a profit for a corporation that can adequately promote, market, and educate the medical community, no one is going to hear about it, let alone use it.

My problem is that pharmaceutical companies will sit on useful medical knowledge they could share, but do not share, because they either will not profit from it or because that knowledge will interfere with the marketing of something they want sold. The corporate control of medicine is so endemic, most physicians have no idea their clinical choices are controlled and truncated by corporations, not science. It is a regrettable situation when so many are needlessly suffering, and there are potential solutions for them.

K. Paul Stoller, MD, is a fellow of the American College of Hyperbaric Medicine and has an integrative medical practice in Santa Rosa, California. A pediatrician, he has documented the effectiveness of hyperbaric oxygen in reversing fetal alcohol syndrome in children (*Pediatrics,* 2005). He began working with patients of all ages with brain disorders in the late 1990s, including traumatic brain injury, stroke, cerebral palsy, multiple sclerosis, chemo-brain, autism, and Lyme. He is author of the book, *Incurable Me: Why the best medical research never makes it into clinical practice* (New York, Skyhorse, 2016).

Dr. Stoller is available remotely for medical consultations, including consults on addiction medicine. Website: www.hbotsf.org

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The Natural Pain Reliever They Don't Want You to Know About

by Owen Fonorow ©2019

The number of people who experience chronic pain in their daily lives increases as the population ages. This pain equals profit for the drug industry, which sells an astounding number of pain-relieving drugs such as Tylenol® or the nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin. What most people don't know is that most of this pain and suffering is caused because our bodies are making a reduced amount of a natural hormone. This hormone is essential; without it humans can only live a day or two.

Many people, and most doctors, do not know that a simple and natural bioidentical hormone replacement would relieve the pain in millions of people who experience symptoms ranging from chronic fatigue syndrome (CFS), fibromyalgia, multiple sclerosis, rheumatoid arthritis, lupus, asthma, polymyalgia rheumatica (PMR), and other conditions mislabeled as "autoimmune" diseases. This kind of hormone replacement would relieve the pain from any disorder with symptoms caused by inflammation.

Small so-called physiological dosages of this natural hormone have been clinically effective in treating other conditions such as chronic allergies, various autoimmune disorders, ovarian dysfunction and infertility, gonadal dysfunction, allergic rhinitis, hyperthyroidism and diffuse goiter, chronic thyroiditis and diabetes mellitus, functional hypoglycemia, hirsutism, acne, and chronic cystic mastitis.

Taking this hormone is surprisingly safe, despite the fact that most medical doctors will tell you it is the most dangerous drug that they can prescribe. Unlike Tylenol®, which sends thousands to emergency rooms with liver failure caused by glutathione depletion every year, or aspirin, which damages tissues in the stomach causing ulcer-like lesions, there are no adverse side effects at safe physiological dosages of this natural adrenal-produced pain-relieving hormone.

There is a deliberate campaign to steer doctors away from prescribing the hormone. Like vitamin C, this essential hormone is inexpensive and threatens the profits of the drug industry. This hormone is one of several produced in every human body by the adrenal glands. Its discovery in 1949 garnered a Nobel Prize in physiology or medicine for the Mayo Clinic in 1950. The hormone? Cortisol, the natural steroidal anti-inflammatory.

Author's Experience with Addison's Disease

During the summer of 2012, about one year after my brother and business partner Mike Till, Sr. died, I developed a pain in my back and a shortness of breath that persisted. When I finally saw a doctor, the physician suggested that I go to the emergency room. I was admitted for very low blood pressure. From an ultrasound, they determined that I had fluid in the pericardium, a sac that surrounds the heart. This fluid made it harder for my heart to beat. After an immediate surgical procedure to drain the fluid, I remained in intensive care for ten days. A team of specialists tried to determine what was wrong. These experts suspected that I had a serious infection, but they could not culture any organism.

Before this episode, I had waited too long before seeing the doctor. I tolerated the pain in my back and shortness of breath. Next, around thirty days after I was discharged from the hospital, the same symptoms appeared again and this time I immediately went to the ER. I was put into intensive care while another team of five specialists tried to figure out what was wrong, again suspecting that I had an infection. No infection was cultured; and because I had no idea what was wrong with me, I began documenting this experience at the Vitamin C Foundation's online forum.

After the second ten-day stint in intensive care during the span of two months, with no infection cultured or real diagnosis, one of the more brilliant specialists recommended high-powered IV steroids. Completely ignorant of steroids and cortisol, I resisted and asked my primary care doctor for intravenous vitamin C (IV/C) instead. Without apparent options, she ordered the IV/C at the hospital. However, as Dr. Levy points out in his book *Primal Panacea*, no hospital in the United States at that time used intravenous vitamin C. In my case, the pharmacy wasn't equipped to supply IV/C, so I never received the vitamin C intravenously at the hospital. I did receive the IV/steroids and was discharged.*

My then primary care doctor prescribed a methyl-prednisolone steroid pack after the second hospitalization. She hoped that these steroids might help keep me out of the hospital for a third time. Like everybody else, I was afraid to take steroids and set them aside in favor of IV/C.

Outside the hospital, I began a series of intravenous vitamin C infusions that may have reached 200 grams per session.

*Dr. Levy had warned me of the possibility of retribution if I asked the hospital for IV/C. And in fact, my primary care doctor, the one who ordered the IV/C, was let go from her practice about two months later.

I hoped and believed that these infusions could cure whatever was ailing me; however, vitamin C could not cure my inability to make a necessary hormone. My ailment, general, body-wide pain, and malaise resembling rheumatoid arthritis was not caused by an infection after all. Later I learned that the *hormone that I wasn't making enough of is the steroidal anti-inflammatory cortisol.*

Part of the fear of this hormone is that like cholesterol, vitamin D, and other similar substances formed out of cholesterol, this adrenal hormone happens to have a specific chemical configuration that makes it a steroid.

The intravenous vitamin C provided temporary (several hours of relief) but was not a cure. Desperate, with ever-increasing pain all over my body, I began taking the methyl-prednisolone prescription that my primary care physician had given me. These tiny pills worked quickly. I started taking 8 mg of methyl-prednisolone (that I now realize is a concentrated form of cortisol, a drug on the order of prednisone) and felt cured; at least for 24 hours, so long as I continued the daily pills.

I began reading about cortisol after realizing that my extended hospital stays were the result of my body's failure to make cortisol and that steroid pills quickly cured what was wrong with me. Many authors characterize cortisol as the "stress" hormone, which it is because under stress we need and produce more, but usually "health" books depict cortisol as generally bad for us. Most books on cortisol detail the "scary" effects of stress or taking too much.

Eventually, I read *Safe Uses of Cortisol* (3rd edition) by William McK. Jefferies, MD, and the proverbial light bulb went on. Not only did I need cortisol, the right bio-identical form, but it was far from harmful at the correct dosages. My cortisol deficiency is something like an insulin deficiency in the diabetic. I learned that the 8 mg of the methylprednisolone that I was prescribed was almost a total replacement dosage, as if my adrenal function had completely shut down.

Jefferies' book begins, "*Cortisol is the only essential hormone.*" We humans can live without every other hormone for long periods. However, if we are completely deprived of cortisol, even for a single day, we suffer and then die a painful death. The only ways to die faster are from trauma, heart attack, or suffocation (lack of oxygen). We can live as long as seven to 10 days without water, perhaps two to four weeks without food. Without vitamin C we would die of scurvy in about a month.

This means that all of us are making some cortisol. (Or like me, we are supplementing it daily.) Production of cortisol varies and blood levels are higher after we wake up and during the day and begin to lower during the afternoon with the lowest levels during sleep. However, if our adrenal glands are not able to make a sufficient supply, the result is pain. Ever-increasing pain occurs in the tissues that are deprived of our natural steroidal anti-inflammatory.

"That cortisone and cortisol are normal hormones of the adrenal cortex implies that in physiologic dosages they must be safe," wrote Dr. Jefferies. In his book, he focuses the discussion on the bio-identical version of cortisol, i.e., hydrocortisone. (The dosage of hydrocortisone is different from its drug counterparts. The bioidentical hydrocortisone replacement dosage is something like 4 to 5 times the 8 mg methyl-prednisolone, or 35 to 40 mg.) Most doctors are unfamiliar with hydrocortisone and are more familiar with the more toxic steroids, such as prednisone and methyl-prednisolone. Fortunately, hydrocortisone is what the endocrinologist who finally diagnosed my adrenal insufficiency prescribes.

I also learned that today's doctors are misinformed. They are taught and firmly believe that cortisol analogs, the so-called glucocorticoids (e.g., cortisol, hydrocortisone, prednisone, and methyl-prednisolone) are the most dangerous drugs in their medicinal arsenal. This may be true for the drug analogs, the prednisone; in my opinion, this fear is completely unfounded when prescribing the correct dosages of hydrocortisone. Every cell in the body expects and relies on cortisol. Yet, before my correct diagnosis, it was almost impossible to get a long-term prescription for a natural hormone that kept me out of a wheelchair and that as an Addison's patient, I attribute to saving my life.

My mother spent most of her life in pain after she was diagnosed with rheumatoid arthritis. Her search for pain relief led her to Linus Pauling's book on vitamin C. The adrenal glands also have among the highest concentrations of vitamin C of any tissues in the human body. Sometimes vitamin C can wake up the adrenals, and thus persons supplementing vitamin C experience pain relief simply by taking high-dose vitamin C. (One theory as to why vitamin C may have such a profound effect on the common cold is that higher dosages allow the adrenals to make more cortisol.) For my mother, vitamin C was the only substance that helped mitigate her pain, except for one cortisone shot she received at the Mayo Clinic *circa* 1974. Had my mother known what I now know, her life would have been pain free, and I would probably know nothing about vitamin C.

From these experiences, I began to understand that most of the chronic pain suffered by humanity is because of too low levels of cortisol in the blood caused by an adrenal or brain malfunction.

Does Cortisol Harm or Enhance Immunity?

"We now know that the influenza virus attacks the human body by impairing the production of adrenocorticotropic hormone (ACTH), which, in turn, impairs the production of cortisol, the only hormone that is absolutely essential for life," William McK. Jefferies, MD, *Safe Uses of Cortisol.*

Medical doctors are taught to be cautious of prescribing cortisol-like steroids because of their negative effect on immunity. This wrong interpretation of the literature is yet another illustration of how medical doctors are steered away from a lower-cost alternative to newer, more expensive prescription drugs. World-expert endocrinologist William McK. Jefferies, MD, wrote:

> Concern regarding the occurrence of respiratory illness in such patients was enhanced by the knowledge that large doses of glucocorticoids (prednisone, hydrocortisone, etc.) could impair resistance to infection while masking the symptoms.
>
> It was, therefore, a finding of some surprise and considerable relief that years passed with patients consistently reporting that they had either no common cold or only very mild attacks. Most of these patients had no symptoms even suggestive of such disorders; but

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when symptoms did occur, a prompt increase in the replacement dosage of glucocorticoid was often followed by a disappearance of the symptoms with recurrence when the dosage was returned to maintenance levels. During this time, other members of the patient's families seemed to have the usual quota of respiratory illnesses, so the absence of such illness in the patients could not be attributed to lack of exposure to the viruses.

An additional reassuring observation was that when patients with adrenal insufficiency developed respiratory infections, the increase in dosage of replacement glucocorticoid did not cause an increase in complicating bacterial infections such as sinusitis or bronchitis, and unless a bacterial complication developed, antibiotic therapy was not necessary. (Jefferies 2004, p. 127-128)

The possibility that cortisol might enhance resistance to infection was so contrary to the well-known effect of its impairment that it was initially considered with skepticism. Yet, Jefferies' review of the medical literature revealed an impressive amount of evidence that physiological amounts of glucocorticoid (e.g., cortisol) can have a protective effect against infection.

What Cured My GERD?

Postulate: Gastroesophageal reflux disease (GERD), commonly known as heartburn, is caused or magnified by low cortisol levels in the blood and tissues.

Recently, I missed a couple of my hydrocortisone dosages and woke up unable to walk or hardly move. I suffered a massive lung "infection" that resulted in my again investigating a major hospital from the inside. Diagnosed with sepsis, kidney failure, and low blood pressure, this time (March 2017) the doctors knew exactly what to do. They gave me lots of IV steroids. I was only in intensive care one night.

The next day, after they switched me to a regular room, the cortisol was accidentally dropped from my chart. The first symptom I experienced was heartburn; meaning that my GERD had returned. Later, with generalized pain, I started to question whether I was getting the cortisol. It turned out that I wasn't. This experience reinforced my theories and educated me on how it feels when I am not getting enough of this hormone. It is not a pleasant feeling, but it is one experienced daily by millions of older Americans.

I have had similar experiences after lowering my cortisol dose for one reason or another. One time, pain started in the fingers, with typical rheumatoid arthritis-like pain, all because I missed 3 mg of the methylprednisolone I was then taking. It took seven days of normal dosing for the pain and inflammation to subside. I should also point out that this delayed response issue doesn't seem to be a problem for the bio-identical hydrocortisone, which works in 30 minutes, and remains in the blood for six hours. A brother-in-law has had chronic heartburn or GERD for years. We were discussing it over dinner. *It was then that I realized that my own esophagus had recently healed, and I no longer had chronic GERD pain.* It causes me anger to think of all the people (including my late mother) who had no idea that medical science had discovered exactly what causes and how to stop the chronic pain: simple, natural hormone replacement. With this angst off my chest, the following is a copy of the letter that I sent my brother-in-law. I include it in hopes others suffering heartburn and GERD might find it helpful.

Dear brother-in-law,

I could tell that you are still suffering from "heartburn"/GERD, and I know from experience it is torture. Let's review how I cured mine. I hadn't even thought about the fact that I now sleep through the night without any heartburn.

There are two valves or sphincters in the stomach, one to the connection to the intestines, where digested food is supposed to go, and the other at the top of the stomach, connected to the throat/esophagus.

It is the upper sphincter on top of the stomach that causes the problem. It is supposed to keep the acid contents of the stomach, in the stomach.

The stomach is designed for high acid, but the throat/esophagus is not. If stomach contents back up from the stomach through the open sphincter into the esophagus, it will burn and damage the throat. This is the cause of the pain. And "they" are right in the commercials, in that this must be allowed to heal.

The book entitled *Why Stomach Acid Is Good for You* by Jonathan Wright and Lane Lenard explains why, surprisingly, *low* stomach acid often causes GERD because of poor digestion. The fix, if this is the case, is to take stomach acid (betaine HCL) with meals. Not intuitive, so read the book. Taking antacids interferes with digestion and turns the problem into a chronic condition.

What seems to happen when the stomach acid is low, is that the upper sphincter muscle relaxes. (This may be why the vinegar fix seems to work; the acid causes the sphincter to tighten. The only problem is, if the throat is already raw and inflamed, this will cause even more pain. A slice of cheese is a good substitute for the vinegar.)

The other thing I learned is that the stomach completely empties six hours after a meal, and when it empties, as the lower sphincter relaxes and opens, the upper sphincter may open too, especially if you are lying down. (You'll note the maximum pain and discomfort, like clockwork, is six hours after your last meal at night).

One idea that is not always easy is to eat more than six hours before going to bed and lying down so that you are upright when the stomach empties into the intestines. Barring that, don't lie flat six hours after the night meal. When I felt the pain at night, I would immediately sit up for a while; or if I lied down, I used enough pillows so I was at a 45-degree angle. This

Owen graduated from the United States Air Force Academy in 1976. In 1996, after his career as a member of the technical staff at AT&T Bell Laboratories, Owen founded the nonprofit Vitamin C Foundation, along with his brother Michael S. Till, Sr. Owen has since written more than thirty articles, and these papers have been published in assorted alternative medical journals including the *Townsend Letter, Nexus, Life Extension Foundation Magazine, American Naturopathic Medical Association's Monitor, Florida ECO Report*, the *International Council for Health Freedom newsletter*, and *Media By-Pass.* Many of the themes in these articles have been incorporated in his book, *Vitamin C Cures* (Formerly *Practicing Medicine Without A License? The Story of the Linus Pauling Therapy for Heart Disease*).

allowed gravity to help drain the stomach from the bottom sphincter.

I know that the throat/esophagus can heal, because mine has, and I now get through the night without any pain; especially if we eat early. But it can take some time, and while it is healing, you have to avoid spicy/acid foods. In fact, instead of taking ascorbic acid vitamin C (a mild acid) I switched to sodium ascorbate vitamin C, which is non-acidic.

Try avoiding acid/irritants going down, and the stomach contents from coming up. You do this by keeping the sphincter tight, and proper acid in the stomach seems to be key to keeping the sphincter tight, unless there is something else going on. (If you remember our friend C., she had a huge hiatal hernia, which was surgically repaired, and now she feels great.)

One other factor in the healing may be due to the low dose prednisone (cortisol replacement) I have been taking (ever since I figured out that low cortisol production by my adrenals caused all those hospitalizations a few years back). It turns out that if you aren't making any cortisol, you die in 24-48 hours, so everyone has to be making some. It is not widely recognized, especially by medical doctors, that as we age, like other hormones, we can make less cortisol, leading to inflammation and pain.

Cortisol is the steroidal anti-inflammatory (where aspirin is a nonsteroidal anti-inflammatory: NSAID). Cortisol stops and controls inflammation. Since the GERD pain is from inflammation of the esophagus, the reason mine cleared up may have something to do with restoring my cortisol levels to normal. It is something you could mention to your doctor, because a short course of prednisone during the attempt to heal the throat may make it go faster and easier.

Saliva Testing

Cortisol levels in the blood vary throughout the day, rising from a low in the early morning to the highest level in mid-afternoon. Blood tests can be used to monitor the varying levels, but having blood drawn throughout the day is challenging outside of a hospital setting. In my experience, all-day saliva testing is as accurate as blood testing (*although most medical doctors are taught the opposite – that hormone testing from saliva is unreliable.*) A "ZRT" day-long series of saliva samples showed my endogenous cortisol levels to be 20% below the "low" on their assay. This lab result explained the replacement hydrocortisone dose that I required at that time to move my blood cortisol into the middle of the normal range. These tests are available online and do not require a prescription from a doctor. If you suspect that your pain is due to low levels of endogenous cortisol, you can easily find out. If your own cortisol is inadequate, the problem will then become finding a medical doctor who will be willing to act on your lab result.

A Final Thought

There would be much less pain and suffering in the world if medical doctors read William McK. Jefferies, MD's book, *Safe Uses of Cortisol* (3rd edition; 2004), now available electronically online.

Vitamin C is a threat to the profitability of medicine. It is available without prescription, so medical doctors are deliberately made ignorant. They are not informed about any of the existing research or made aware of this essential substance's medical potential.

Cortisol is different only because obtaining it requires a prescription. It is also essential and poses a threat to the profitability of the drug industry, particularly the over-the-counter pain reliever industry. Even though cortisol (as hydrocortisone) is a natural, bioidentical hormone, it is only available through medical doctors. (The FDA does allow hydrocortisone topically as a 1% [to 2%] cream.) In my opinion, medical doctors have been deliberately misinformed about the supposed dangers of steroids because a lack of cortisol in the human body creates a huge number of doctor visits. ◆

Arnifenac Cream: A Blend of Arnica, DMSO, and Diclofenac

by Dr. Douglas Lobay, BSc, ND

When the German homeopathic company Heel, abruptly exited the United States and Canada at the end of 2014, I felt like I lost a friend. I was particularly fond of the herbal analgesic and anti-inflammatory cream called Traumeel. It seemed to work well, and patients seemed to like it, and it appeared to have minimal side effects. Afterwards, I tried a variety of generic alternatives available in the marketplace but ended up disappointed with the clinical results. And so, began my quest for a suitable alternative topical cream for pain and inflammation.

After several months of experimentation, I came up with a blend of arnica, dimethyl sulfoxide, and diclofenac, mixed in a plain hypo-allergenic cream base. I called the cream Arnifenac and used it topically for pain and inflammation in muscles, joints, and other connective tissues. I custom compound the cream in my office and sell it only to clients of my clinic. Patients seem to like it, and it seems to work well.

Being curious I asked myself the question, why is arnica considered a good natural analgesic and anti-inflammatory? I began to research the pharmacology and clinical efficacy of arnica on medical databases including PubMed and Medline. I re-read some papers from naturopathic school days on the chemistry and pharmacognosy of arnica.

I learned that *Arnica montana* is a perennial herb of the Compositae or Asteraceae family that grows to approximately 0.6 meters in height. It is native to the mountainous regions Europe and North America and has been introduced into Asia. The plant is composed of bright and distinctive yellow flowers that are characteristic of the daisy or sunflower family. [1,2]

The chemical composition of arnica includes volatile oils, resins, aromatic constituents, including terpenes, thymol and thymol esters, tannins, flavanone glycosides, and carotenoids, including lutein. The concentration of the volatile oils varies up to 1% the weight with 0.3% being the average. Several bitter sesquiterpene lactones also known as pseudo-guaianolides have been isolated from the flowering head and leaves. The lactones are chemically cyclic esters of carboxylic acid. Their concentration varies from 0.2 to 0.8%. The main lactone is called helenalin. Helenalin and its related lactones are considered to be the ingredient responsible for the analgesic and anti-inflammatory effects of this plant. Helenalin is also considered to be the chemical responsible for the toxicity of this plant.[1-3]

Helenalin, dihydro-helenalin, and other allied lactones have several targets that inhibit inflammation. The lactones' main action is to inhibit NF-kB activation. NF-kB also known as nuclear factor kappa beta and is a protein complex that controls cell growth, division, transcription, immune response, cytokine production, and cell adhesion. The lactones methylate the p65 subunit of NF-kB and inactivate it. This reduces pro-inflammatory cytokine production and decreases cyclooxgenase-2 (cox-2) activity, which decreases inflammation. The lactones can also inhibit platelet adhesion, prostaglandin synthesis, nitric oxide, and lipoxygenase activity.[4,5]

Arnica has been used for over a hundred years in natural medicine as an herbal anti-inflammatory and pain killer. Despite its historical use, there have been few good quality scientific studies that have validated its effectiveness.

In a 2016 paper, the effectiveness and safety of *Arnica montana* in post-surgical pain and inflammation was studied. The researchers concluded, "Arnica is more effective than placebo when used for the treatment of several conditions including post-traumatic and post-operative pain, edema and ecchymosis. They further stated that "cumulative evidence suggests that *Arnica montana* may represent a valid alternative to non-steroidal anti-inflammatory drugs, at least when treating some specific conditions." They also cautioned that "dosages and preparations have produced substantial differences in clinical outcome."[6]

One 2014 systematic review of the efficacy of topical *Arnica montana* for

the treatment of pain, swelling and bruises evaluated controlled trials from reputable medical databases. A total of 11 controlled trials were found and met the criteria for evaluation. The researchers concluded that "the efficacy of arnica at doses of 10% and below is not supported by the available evidence. More research is needed to determine if higher doses would be effective and remain safe." Moreover, the researchers said that the included studies were usually of small sample size and had a high risk of bias.[7]

A 2007 randomized double-blind study of 204 patients with inter-phalangeal joint pain in the hands evaluated the effectiveness of arnica gel versus the 5% non-steroidal anti-inflammatory ibuprofen. The researchers found no difference between the two groups in levels of pain and hand function improvement. Adverse events were 6.1% in the ibuprofen group and 4.8% in the arnica group. It is important to note that the researchers used an arnica preparation that contained 50 grams of a 1:10 tincture per 100 grams of gel. This gave a DER or drug extract ratio of 1:20 meaning that they used a 5% weight to weight preparation of arnica.[8]

The Cochrane database concluded in 2013, "Arnica gel probably improves symptoms as effectively as a gel containing anti-inflammatory drugs, but with no better and even possibly worse adverse events profile."[9]

I also did an informal review of Amazon and iherb websites on the reviews of arnica cream and gel. In my survey about 50 to 70% of respondents posted 4- and 5-star favorable reviews about the efficacy of arnica on their symptoms. Only about 5% to 8% posted unfavorable reviews of 1 and 2 stars, which invariably stated that the medication did not work.

And so, I tried to make an effective arnica cream. I have used arnica powder, arnica oil and arnica tincture. I also added DMSO, and diclofenac. DMSO or dimethyl sulfoxide is generally considered to be one of the best universal solvents and absorbers available. It also has demonstrated anti-inflammatory activity. Diclofenac is a widely used prescription and OTC non-steroidal anti-inflammatory. It is available in 1% cream and gel over the counter in pharmacies.

In my Arnifenac cream formula, I use 5% to 10% weight to weight ratio of arnica to cream, mixed with 1% to 3% diclofenac and 3% to 5% DMSO. I have also experimented with the addition of other anti-inflammatory co-factors including magnesium, menthol, capsicum, calendula, chamomile, comfrey, echinacea and Saint John's wort. I use the cream for muscle and joint pain and arthritic inflammation. Patients are advised to apply the cream moderately one-to-two times per day as needed. The patient feedback has been favorable, and the cream seems to work better than just plain arnica alone. Patients are advised to discontinue the cream if redness or rash occurs and generally not to apply to open skin or wounds.

The therapeutic natural database posted a review of arnica, based on the current scientific evidence and made some important points about its safety and side effects. Arnica is not safe for oral consumption and is considered toxic. This would include the raw herb, powder, and tinctures. Oral consumption can cause gastro-intestinal irritation including nausea and vomiting, liver and kidney damage, and hypertension and tachy-arrhythmias. However, it is important to mention that this does not include dilute homeopathic remedies, which have been used and are generally considered safe. Arnica can cause skin irritation and rash and should be discontinued or at least at a decreased dose if this occurs. It is not recommended to be used, or only for a short duration, on open, broken skin. Arnica should be avoided during pregnancy and lactation.[10]

Arnifenac cream is a synergistic blend of *Arnica montana*, DMSO, and diclofenac. It is an effective topical preparation for musculoskeletal and arthritic pain and inflammation.

Arnica montana has a long history as an herbal anti-inflammatory and pain killer.

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Protective Physiologic Reactions: A Hypothesis Regarding Chronic Fatigue and Pain Amplification

by Rob Rennebohm, MD

This document is intended to help patients and families better understand how musculoskeletal pain (even extreme pain), or chronic fatigue (even profound disabling fatigue), or both pain and fatigue, might sometimes be due, at least in part, to "protective physiologic reactions." It represents just one way of understanding chronic fatigue and musculoskeletal pain. Please understand that the concepts presented represent a hypothesis, rather than proven fact.

Many people, including children, experience what I prefer to call a "chronic fatigue/pain and sensory amplification" disorder – a disorder that, I hypothesize, represents a complex set of protective physiologic reactions to chronic physical tension, emotional tension, or both. This set of reactions is intended to get our attention, get us properly attended to, and encourage us to reduce the unhealthy tensions that our physiology has sensed. It is an example of a way in which our "body speaks to us."

Normally, our human physiology hums along silently, as it takes care of our body's needs. It silently maintains and regulates our blood pressure, heart rate, body temperature, digestion, and our autonomic nervous system, etc. It also lets us know when we have been physically injured – by sending appropriate pain messages to our consciousness.

Our human physiology is very protective, sensitive, and wise. It is beautifully designed to be that way, and we should be thankful for this.

Our human physiology cares about us. It senses when we are tense – physically, emotionally, or both. It senses when we are physically bracing ourselves to meet the usual challenges of everyday life, as well as unusual challenges. It senses our emotions – when we are unsettled, uncomfortable, un-relaxed, ill-at-ease, worried, fearful, confused, frustrated, tense, overly intense, anxious, stressed, overwhelmed, resentful, demoralized, dispirited, disheartened, feeling helpless, feeling hopeless, or feeling as if we are "not measuring up" (to our own expectations, to the expectations of others, or to both), or feeling bad about ourselves. It becomes particularly concerned when it notices that such physical and/or emotional tension is chronically present. It does not want us to go through life, chronically, carrying such tension. It does not like to see physical or emotional unrest (which often go hand-in-hand). It prefers to sense that we are emotionally and physically relaxed, at ease. It wants us to feel good about ourselves. *It wants us to be at peace* – with ourselves and our surroundings.

In addition to sensing emotional and physical tension, our human physiology senses and reacts to whether we are getting enough exercise and whether we are sleeping well. It does not like to see us not using all our muscles and the full range of motion of our joints. It worries when it senses we are not invigorating our hearts. It knows when we are not descending into sufficiently deep and restorative sleep. When it senses these disturbances, it assumes that something might be wrong and might need attention, including medical attention.

Our human physiology is pretty smart. It is constantly monitoring us, for our own good. It is very sensitive and not easily fooled. It senses disturbance before we may be conscious of it. Just as we, as human beings, tend to worry, our human physiology tends to worry and is programmed to react to perceived disturbance.

It is important to realize that there is a spectrum, regarding how sensitive, reactive, caring, and smart peoples' human physiologies are. Some people have very sensitive and/or very reactive physiologies; others have quite insensitive and/or unreactive physiologies. Everyone is different in this regard. (More on this later.)

Our human physiology wants to protect us and is programmed to do so. When it senses chronic emotional or physical tension, it wants to let us know of its concern. It wants to get our attention, in hopes that its signals to us will lead to remedy of whatever is causing the tension. It wants to force change for the better. It feels the need to change the status quo. It does not want to simply provide symptomatic relief, by pouring out endorphins or other substances that would make us feel good. That would be too easy, would cover up the problem, would not

encourage us to address the root causes of our tension, and would violate our free will.

Our human physiology has limited but very good ways to signal its concern, safely get our attention, and force corrective action. Kindly, it does not want to get our attention in ways that could cause bodily harm. Two good ways to safely get our attention are to *create fatigue* and to *amplify pain* (and/or sensation). If our human physiology makes us feel profoundly tired, it becomes difficult for us to keep going through life the same way we have been. If our physiology amplifies pain so that we are suffering from musculoskeletal misery or chronic headaches or frequent abdominal pain, that pain makes it difficult for us to keep doing what we have been doing. (Pain amplification occurs within the brain itself. Please see the section entitled MSK-PAP for a more detailed explanation of how "pain amplification" might occur.)

The profound chronic fatigue (often totally exhausting), or the pain amplification, or both, force us to take stock and take some sort of corrective action. At the very least, these symptoms force us to realize that something is wrong and to ask "what's wrong." Usually, these symptoms prompt (sooner or later) a visit to a physician, who then, ideally, helps us to accurately figure out "what is wrong."

A good physician will consider all plausible explanations for "what is wrong," including combinations of causes. The list of plausible explanations includes all of the diseases that can cause chronic fatigue (and/or pain) but also includes the possibility that the fatigue or pain could, at least in part, represent a protective reaction on the part of our human physiology. Subsequent investigation is designed to clarify "what's wrong." Is it one of the plausible diseases? Or, at least in part, is the person experiencing a protective physiologic reaction(s) that is causing profound, very real, even disabling, fatigue and/or pain?

Ideally, if the fatigue (or pain) is, at least in part, due to a protective physiologic reaction, the physician will recognize such and will effectively explain this phenomenon to the patient. Misdiagnosis, either way, does no good. If the fatigue is largely or completely due to a protective physiologic reaction, it is counter-therapeutic to erroneously or unconvincingly attribute the fatigue to a specified or unspecified disease process. Misattribution just causes more mystery, confusion, worry, fear, frustration, resentment, unrest, and tension – the very kinds of emotions that, in fact, prompt and fuel our human physiology's concern and protective reactions. Likewise, it obviously does no good to attribute the fatigue to a protective physiologic reaction if, in fact, it is due to a specific disease process, such as an autoimmune disease.

Fatigue and pain/sensory amplification are two ways that the body signals the need to address unhealthy physical and emotional tensions.

Also, good is limited if, after thorough investigation for plausible diseases, the physician declares that he/she could find "nothing wrong" and ends the patient-physician encounter on that only half-reassuring, half-helpful, and only half-correct note. Even worse would be an incomplete investigation, followed by the expressed or implied insinuation that the problem is "all in your head," followed by no further effort to explain matters or help the patient, who is now left bewildered and alone, to fend for herself/himself. Even if the physician correctly determines that the "what's wrong" is a protective physiologic reaction, good is limited if the physician does not fully explain this phenomenon to the patient and does not discuss how to reverse the reaction.

How does one reverse protective physiologic reactions? The short answer is to eliminate or, more realistically, diminish or cope better with the very tensions (physical and/or emotional) that one's human physiology is appropriately reacting to in the first place. The protective reaction will decrease or cease only when our human physiology senses that unhealthy tensions are trending in the right direction, such that there is less for our physiology to be concerned about. The protective reaction diminishes only when our human physiology becomes convinced that unhealthy tensions are being adequately addressed, such that it can consider its job (of protecting us) to be done. If it sees no progress, it will continue to express its concern (through persistent creation of fatigue, pain amplification, or both). Our human physiology is not easily convinced that its job has been done. It cares too much and is too smart to allow itself to be falsely reassured. It needs lots of convincing. The longer answer includes the following.

The first step is an educational, intellectual one. The patient needs and deserves to fully understand the concept of "protective reactions on the part of our human physiology." Knowledge empowers, inspires, and frees. Without this understanding, the patient is left confused, sceptical, unempowered, and ill-equipped to do what is necessary.

The above education is of limited value, however, if the patient does not believe the concept being explained, is not convinced that the concept applies to his/her situation (assuming it does), or is still worried that some disease process is being missed.

So, the education needs to be both understood and trusted – but only if it deserves trust, of course.

Often, successful education goes a long way in helping the patient to

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***To Patients and Clinicians*: To help us determine the value of the concepts presented in this article, please consider sending us a brief comment regarding the extent to which you found this article to be clinically helpful and effective, or not. You may send comments to: editorial@townsendletter.com**

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reverse the fatigue/pain amplification reaction and the vicious cycles that often accompany it. The emotional relief that this clarifying education provides can help turn things around, sometimes greatly so. The new understanding can largely reduce, even eradicate, the fears, mystification, confusion, worry, frustration, and resentment that build when it is unclear "what is wrong." Education is freeing.

The next step is to create a list of the life situations or life thoughts that seem to create the most physical and/or emotional tension. The patient needs to identify those things or feelings going on in their lives that make them the most uncomfortable, un-relaxed, stressed out, tense. Sometimes, the number one "stressor" is the just mentioned confusion, mystification, fear, frustration, and resentment associated with having symptoms and not knowing "what's wrong" and not receiving effective help in fully determining and understanding "what's wrong." Often there are other underlying stressors. Creating a list requires honesty, courage, and objectivity. Sometimes patients, by themselves, can figure out what belongs at the top of the list. Sometimes parents or friends need to help. Sometimes the help of an objective and skilled psychologist/counsellor is needed.

Once these top stressors are identified, the next step is to determine how best to either eliminate, diminish, or better cope with these stressors, starting with the biggest culprit. Some ways of coping are unhealthy; other ways are much healthier.

The next step is to break into and disassemble the various vicious cycles that tend to evolve during the development of a chronic fatigue/pain amplification disorder – as in the following examples.

Exercise: When a person is chronically tired or chronically achy or both, they tend to not feel up to exercising. We rely on a certain amount of gently invigorating physical exercise to generate natural energizers and natural pain killers to help us through an ordinary day. It is a disadvantage to go through each day with suboptimal levels of natural energizers and natural pain killers. These low levels increase our fatigue and pain, thereby contributing to the vicious cycle. We can break into that vicious cycle by gradually getting more exercise, in moderation, in the best way our circumstances permit.

Sleep: During good quality sleep, natural energizers and natural pain killers are generated to help us get through the next day. If we are not getting good quality sleep, we go through the next day with suboptimal levels of natural energizers and natural pain killers – which may already be low because of lack of invigorating exercise. This makes us even more tired and achy – thereby contributing to a vicious cycle.

Furthermore, without adequate exercise, we are not as pleasantly tired and relaxed at bedtime; so, we do not sleep as well. And, without good quality sleep, we do not feel up to exercising the next day. This is how vicious cycles develop, which make the chronic fatigue/pain amplification even worse. By breaking into these vicious cycles, the chronic fatigue/pain amplification can be decreased in intensity. The way to break in is to develop a gently invigorating exercise program that avoids the extremes of no exercise and exercise that is too much, too soon. The other component of breaking into these vicious cycles is to work on sleep hygiene.

Emotional stress can also accelerate these vicious cycles, in part by interfering with sleep. So, again, it is often important to identify and effectively address emotional issues.

Nutrition: Good nutrition can also help to break into vicious cycles and restore balance.

Successful treatment of a chronic fatigue/pain amplification disorder, therefore, requires a comprehensive approach – paying attention to all of the concepts mentioned above. In addition, there is sometimes a role for temporary use of various medications, such as gabapentin, Lyrica, anti-depressants, or sleep aids. These medications can provide temporary symptomatic relief, while the patient works on the underlying root causes of their physical and emotional tension. Such medications are simply options and are often not necessary.

The good things about a "chronic fatigue/pain and sensory amplification disorder" are that it is completely reversible, causes no bodily harm while it is present, and makes you a better person afterwards (once you have recognized it for what it is and have successfully made the needed healthy changes). In that sense, it is a kind, wise, protective, caring set of physiological reactions, designed to help you.

As stated earlier, it is important to realize that some people have human physiologies that are very sensitive, very reactive, and very "worrywart-ish," while other people have human physiologies that are not very sensitive or very reactive. Sociopaths, for example, have quite insensitive and unreactive physiologies. That is why sociopaths can pass a lie detector test, even when they have just lied. There is a spectrum, regarding how sensitive, reactive, caring, and smart peoples' human physiologies are. That is why one person, who is dealing with only an average or below average amount of tension, might develop a chronic fatigue/pain and sensory amplification disorder, while another person, who is dealing with extraordinarily great stress, does not develop a chronic fatigue/pain and sensory amplification disorder. It is people with particularly sensitive and reactive physiologies who are most likely to develop a chronic fatigue/pain and sensory amplification disorder. So, it is not so much the level of tension/stress that determines whether a chronic fatigue/pain and sensory amplification disorder develops; it is the level of physiologic sensitivity and reactivity that is the determining factor.

It is also important to realize that adolescence is a particularly stressful time for virtually all adolescents. It is a difficult time of life for most people, including people who seem to have everything going for them (like high intelligence and lots of school success).

If I were to describe the typical personality traits of the adolescents who develop protective physiologic reactions, here is how I would describe them: They are emotionally sensitive, very responsible kids. They care deeply about others. They take life seriously, including their obligations to be the best they can be. They put lots of pressure on themselves to perform well in school and to be liked by their peers. They worry about whether they are measuring up – not so much to the expectations of others, but to their own (usually very high) expectations of themselves. They drive themselves hard. They work hard and are high achievers. They worry very much about others and aim to please and care about pleasing. They are pretty hard on themselves – probably too hard on themselves. They often feel as though they are not adequately measuring up – and often carry this worry secretly and chronically. Lazy, insensitive, uncaring kids don't develop a chronic fatigue/pain and sensory amplification disorder.

Musculo-Skeletal Pain Amplification Phenomenon (MSK-PAP)

What follows is a hypothesis regarding pain amplification. A musculoskeletal pain amplification phenomenon (MSK-PAP) represents a *protective physiologic reaction* in which that part of the person's physiology that is responsible for sensing, processing, interpreting, and reporting pain to our consciousness (in short, our "*pain-reporting apparatus*") goes into a state of overdrive – *all in an effort to protect us*, to let us know that it is concerned about us.

This pain-reporting apparatus consists, roughly, of our peripheral nerves, spinal cord, the "central pain processing center" within the brain, and the neurons (within the brain) that relay the central pain processing center's ultimate message to our consciousness. In a pain amplification situation, most of the pain amplification is probably occurring within the central pain processing center. In a pain amplification situation, the central pain processing center becomes very active (hyped up), neurophysiologically – such that it sends very loud messages of pain to our consciousness. A person is at the mercy of what their "pain-reporting apparatus" ultimately reports to their consciousness. If that report/message is one of loud, screaming pain, then, that is what the person actually feels.

Why is the central pain processing center amplifying its pain message? It is doing so in an effort to protect us. As explained earlier, this represents a protective physiologic reaction. Our human physiology is not being mean and trying to hurt us; it is trying to help us. It is important to "listen to what our body (our human physiology) is saying."

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Protective Physiologic Reactions

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Patients, or their parents, are often skeptical or surprised that a chronic fatigue/musculoskeletal pain amplification phenomenon can cause such severe pain, or such severe fatigue (or both). They often think, "How can my child be having so much pain or so much fatigue (or both) without there being a worrisome disease process responsible?" My response to this question is as follows.

If I were to line up all of the patients we see in our rheumatology clinic – all of those with rheumatoid arthritis, all with lupus, all with other rheumatic diseases, and all with a chronic fatigue/musculoskeletal pain amplification disorder – and line them up according to the severity of the pain or fatigue they are having, it is kids with a chronic fatigue/musculoskeletal pain amplification phenomenon who are having the most severe pain and the most profound fatigue. Kids with a chronic fatigue/musculoskeletal pain amplification disorder often have pain and fatigue that is far greater than the pain and fatigue experienced by kids with the worst cases of arthritis or lupus. Not all kids with a chronic fatigue/musculoskeletal pain amplification disorder have that much pain or fatigue, but some certainly do. Some can be severely disabled by their pain and fatigue. So, I am never surprised by how severe the pain, fatigue, and disability can sometimes be with a chronic fatigue/musculoskeletal pain amplification disorder. And, it is very real pain, fatigue, and disability – nothing is being exaggerated. In fact, the sheer magnitude of the pain and/or fatigue is a good clue that the patient is suffering from a chronic fatigue/pain amplification disorder – especially when appropriately complete lab testing is normal and the patient looks healthy to the casual observer.

Summary

Physiologic chronic fatigue and pain amplification represent normal protective reactions on the part of our human physiology. Though such reactions wreak havoc with the quality of life, they do not involve processes that are capable of causing any bodily harm, and the reactions are totally reversible. Although these protective reactions make life miserable (temporarily) for us, our human physiology is not punishing us; it is kindly helping us. Our job is to recognize what our human physiology is signalling to us and to then help ourselves.

I once had a 13-year-old adolescent female patient with chronic fatigue, who, after listening intently to the above explanation about "protective physiologic reactions," wisely said: "You mean my 'human physiology' is kind of like my inner Mommy? Like, my 'inner Mommy' worries about me and wants to let me know when it senses that something is wrong, including being stressed out? And, it keeps worrying about me (and signalling its worry) until I start dealing better with that stress?"

I replied that that is exactly what I meant. Our human physiology is very much like an "inner Mommy" who cares very deeply about how we are going through life and kindly gives us signals (fatigue, pain amplification, or both) that alert us to the need to take action and find remedy. Like a good mother, our "inner Mommy" will not stop sending those signals until it is convinced that the problem(s) has been accurately identified and is being effectively addressed.

Definitions

What is "fibromyalgia" and how is it related to a chronic fatigue/pain and sensory amplification disorder? "Fibromyalgia" represents a chronic fatigue/musculoskeletal pain amplification disorder. Fibromyalgia = chronic fatigue + musculoskeletal pain amplification. Usually, the musculoskeletal pain is widespread throughout the musculoskeleton, symmetrical. Throughout this article, I have avoided using the term "fibromyalgia," because the term is so greatly misunderstood by so many people (including some physicians) and, therefore, has become largely unhelpful. The terms "fibromyalgia" and "chronic fatigue/musculoskeletal pain amplification disorder" can be used interchangeably. I prefer not to use the term fibromyalgia.

What is "chronic fatigue syndrome" and how does it relate to a chronic fatigue/pain and sensory amplification disorder? Chronic fatigue syndrome represents a chronic fatigue/pain and sensory amplification disorder without the pain and sensory amplification component. In other words, in a "chronic fatigue syndrome" the primary protective physiologic reaction that is occurring is the reaction that causes fatigue; and little or no pain and sensory amplification is occurring.

Incidentally, the physiological reaction that is responsible for the

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fatigue (in a chronic fatigue syndrome) is probably a reaction that is the opposite of an endorphin reaction. You have probably heard of a "runner's high," which refers to the burst of considerable energy that is triggered by vigorous physical exercise. This exercise-induced burst of energy is due to the release of endorphins, which both energize the body and decrease pain. In the chronic fatigue syndrome, something opposite of endorphin release is probably occurring; perhaps, normal endorphin levels are not being released, or perhaps something that we might tentatively call "fatigueins" are being released. I hasten to add, however, that no such fatiguing physiological substances have, so far, been identified. Endorphins have been identified, but we do not know whether "fatigueins" exist.

Some patients have pain and sensory amplification but no chronic fatigue. In other words, the primary protective physiologic reaction that is occurring is pain and sensory amplification, and no fatigue-causing reaction is occurring. An appropriate label for that situation would be a *pain and sensory amplification disorder*. Sometimes, the pain amplification is widespread, involving much of the musculoskeleton, symmetrically – *a musculoskeletal pain amplification disorder* – as is the case in in fibromyalgia. Other times, the pain amplification is regional – i.e., affecting only one extremity, e.g. (like a foot). This would represent a "*regional pain amplification disorder*." An ordinary tension headache represents a pain amplification disorder occurring in the head region.

Irritable bowel syndrome (IBS) represents a pain and sensory amplification disorder that is primarily occurring in the abdomen – causing, for example, abdominal discomfort, loose bowel movements (often alternating with constipation), and a sensation of bloating.

Some people experience several of the above-mentioned protective physiologic reactions to tension, sometimes all at the same time – chronic fatigue, musculoskeletal pain amplification, headaches, IBS, other sensory amplification.

Protective Physiologic Reactions

Bear in mind, too, that pain from a disease process, like rheumatoid arthritis, can be heightened when, in addition, the patient develops an emotions-related pain amplification disorder. In such an instance the patient's pain is partly due to the painful rheumatoid arthritis process but also due to pain amplification. Both can contribute to the pain – equally or asymmetrically. So, when a patient with definite rheumatoid arthritis complains of severe pain (with or without fatigue), it should not automatically be assumed that all of their pain (and/or fatigue) is due to the rheumatoid arthritis.

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Complete article and references can be accessed at www.TownsendLetter.com

Defining Naturopathy

by Jacob Schor, ND, FABNO

The College of Naturopathic Doctors of Alberta (CNDA) asked me to lecture at their June 2018 conference and dictated my topic would be "Back to Basics." This sounded easy enough when first suggested, nearly a year before, as in theory I wouldn't have to read and learn new information. I could just stick with basic stuff that we already all know. It would be preaching to the choir, I thought, a piece of cake, as they say. Yet preparing this lecture turned out to be more challenging than I thought it would be and likely more controversial than I really want it to be. Mind you, I do not shy away from controversial ideas, curmudgeon that I am, but even I worry that colleagues may stop talking to me.

To speak about basic naturopathy, it was apparent that I needed a clear definition of what naturopathy is. To point my audience backwards in the direction of basic naturopathy necessitates accurately defining what naturopathy is. As I began to think about this and plan the lecture in my mind, it became apparent that the definitions we rely on are inadequate, not just for my purpose but for a range of other things such as legislation, public relations, and education.

A good definition describes the meaning of a word so that it expresses the essential nature of the thing; a good definition gives a clear outline of the subject in question, marking its border so it stands out and is distinguishable from other similar things. A definition defines; it draws a line around the thing.

My usual first step to understanding the meaning of a term is usually to look at the root words it derives from. So "naturo," is probably from the Latin word *natura*, to which the Greek suffix "-pathy" is tagged on. The suffix "-pathy" derives from *pathos*, meaning "suffering or disease." The same suffix is used in loads of terms such as myopathy (muscle disease), neuropathy (nerve disease), or even sympathy (suffering together).[1]

Thus, naturopathy might have two possible meanings. First it might mean, "nature-disease" or "suffering nature." If so, then climate change or drought might be examples of naturopathy. Or perhaps naturopathy could mean "suffering caused by nature," perhaps an example would be frostbite. My lecture audience is, after all, going to be Canadians. The roots of the word "naturopathy" seem insufficient to define naturopathic medicine.

Many websites tell us that Dr. John Scheel patented the term "naturopathy" in 1895, and that Lust purchased the rights from him. My search through the patent records has so far failed to locate this patent. I had hoped Scheel might have described what he meant by the term in his patent application.

The definition of naturopathy that is often quoted in the legislative arena to carve out a scope of practice is originally from the federal *Dictionary of Occupational Titles* published in 1931:

> Doctor, Naturopathic (medical services) 079.101-014 A Naturopathic physician, diagnoses, treats and cares for patients, using a system of practice which bases treatment of physiological functions and abnormal conditions on **natural laws governing the human body**: utilizes physiological, psychological and mechanical methods, such as air, water, light, heat, earth, phototherapy, food and herb therapy, psychotherapy, electrotherapy, physiotherapy, minor and orificial surgery, mechano-therapy, natural processed foods and herbs and nature's remedies. Excludes major surgery, therapeutic use of x-ray and radium and use of drugs, except those assimilable substances containing elements or compounds which are components of body tissues and are physiologically compatible to body processes for maintenance and life.[2]*

During the process of winning licensure, naturopathic medicine was defined by the individual state licensing statutes, but these definitions were legal scope-of-practice definitions, often conflicting with each other, reflecting different standards of practice in different places; they just told us the limits of what we could do legally, not what we were doing. In 1965, the US Department of Labor's *Dictionary of Occupational Titles* became the formal and widespread definition because it was federal and superseded state definitions. The definition was controversial as it primarily reflected a nature cure perspective:

> Diagnoses, treats and cares for patients using a system of practice that bases treatment of physiological function and abnormal conditions on natural laws governing the human body. Utilizes physiological, psychological and mechanical methods such as air, water, light, heat, earth, phytotherapy, food and herbs therapy, psychotherapy, electrotherapy, physiotherapy, minor and orificial therapy, mechanotherapy, naturopathic corrections and manipulations, and natural methods or modalities together with natural medicines, natural processed food and herbs and natural remedies. Excludes major surgery, therapeutic use of x-ray and radium, and the use of drugs, except those assimilable substances containing elements or compounds which are components of body tissues and physiologically compatible to body processes for the maintenance of life.

We rarely use this definition when describing who we are and what we do in public. I cannot name any "natural laws governing the human body" aside from gravity.

*Why radioactive materials were excluded is something of a mystery as during this period many radium cures were in popular use. Radioactive water dispensers were selling by the thousands and radioactive toothpaste and beverages were widely sold.

The current definition the American Association of Naturopathic Physicians (AANP) uses is as follows:

> Naturopathic medicine is a distinct primary health care profession, emphasizing prevention, treatment, and optimal health through the use of therapeutic methods and substances that encourage individuals' inherent self-healing process. The practice of naturopathic medicine includes modern and traditional, scientific, and empirical methods.[3]

This implies a single self-healing process shared by all individuals. That feels rather vague to this reader. So does the word distinct. A good definition should distinguish between primary health care professions and tell us how naturopathic medicine is distinct.

The Canadian Association of Naturopathic Doctors (CAND) definition reads as follows:

> Naturopathic medicine is a distinct primary health care system that blends modern scientific knowledge with traditional and natural forms of medicine. The naturopathic philosophy is to stimulate the healing power of the body and treat the underlying cause of disease. Symptoms of disease are seen as warning signals of improper functioning of the body, and unfavourable lifestyle habits. Naturopathic medicine emphasizes disease as a process rather than as an entity.

Process? Entity? I admit I don't think I've ever thought about this. I'll have to ask those Canadians about this. That lecture in Calgary I am committed to giving is only a few weeks off as I write this.

Benedict Lust's 1905 definition also attempted to distinguish the profession by claiming it is distinct but then claims ownership of osteopathy and chiropractic under the heading naturopathy:

> Naturopathy is a distinct school of healing, employing the beneficent agency of Nature's forces of water, air, sunlight, earth power, electricity, magnetism, exercise, rest, proper diet, various kinds of mechanical treatment such as massage, Osteopathy and chiropractic, and mental and moral science." [4]

If you want to read more of these definitions, the white paper Iva Lloyd, ND, wrote for the World Naturopathic Federation lists over a dozen different definitions of naturopathy.[5]

We don't pay much attention to these definitions anymore as our profession backed away from striving for a clear definition of naturopathy about 30 years back and instead substitutes a list of principles that supposedly underlie naturopathic medicine. Here is the short version copied from Bastyr University's website, though most naturopathic doctors know them by heart:

- The Healing Power of Nature (*Vis Medicatrix Naturae):* Naturopathic medicine recognizes the body's inherent ability to heal itself...
- Identify and Treat the Causes (*Tolle Causam*) ...
- First Do No Harm (*Primum Non Nocere*) ...
- Doctor as Teacher (*Docere*) ...
- Treat the Whole Person…
- Prevention…
- Wellness…. [6]

How did we come to these principles? The credit goes to Drs. Pam Snider and Jared Zeff. Actually, some of the credit for this switch in focus from definition to principles should be shared with Roger Fisher and William Ury. These two guys wrote a book called *Getting to Yes* that was published in 1981.

For those of you too young to remember, there was an optimistic period in the 1980s when conflicts were considered resolvable by a "getting to yes" idea, promoted in that book. The premise was that when negotiating, rather than focusing on points of disagreement, instead to focus on common goals or points of agreement.[7] This simple idea changed the dynamics of many an argument and gave us hope that other conflicts could be resolved. (I recall one of our lobbyists forcing me to read it before taking the Colorado ND Association on as a client.) These 'getting to yes' tactics were so popular that one did not need to have read the book to ask, "Let's find what we can agree on to move forward and each get what we need instead of arguing."

Naturopathy aims to trigger adaptive responses that lead to healing.

This is in essence what the AANP did in the late 1980s.[8] Jared Zeff described the challenges back then:

> In 1985 or so, when the AANP began, we knew we needed to accomplish 5 things to reestablish our profession. We needed a national professional organization, we needed our schools accredited, we needed a national standard/national licensing examination, we needed a peer-reviewed journal, and we needed a useful definition for legal, educational, and other purposes. The extant definition was the US Department of Labor, Dictionary of Occupational titles definition, which was strictly a modality-based definition: "Naturopaths treat the sick with diet, earth, air, water, etc." This was not useful to us legislatively, and we would tend to argue about whether it should include or exclude this or that. I was given the job of developing a useful definition, along with Pamela [Snider].
>
> We were to lead an open session at the Alderbrook Convention in 1986, our second AANP conference, to begin the process of developing the definition. We knew what would happen and had a secret plan to implement. We had a room full of naturopaths: older, younger, men, women, students, US and Canadians. Any time this had been done in the past, the argument broke out about what should be included. And that is how this meeting began, with arguments about modalities. After a while of the arguments, I posed a question; 'Is there anything about which we do agree?' I knew the answer in advance. It was that we all agreed that there was a philosophy that underlay the medicine. Once the room acknowledged that we agreed that there was a naturopathic philosophy, then we proposed that we determine what that was. What were the tenets of that philosophy? Certainly, *Vis Medicatrix Naturae*, Do No Harm, and what else? … the process we went through to answer that question, … took three years, and resulted in the definition we now use. We built into the process a review every 5 years to make sure we did not leave something out, etc. It has gone through 2 reviews since the initial unanimous adoption, and has not yet been changed.
>
> …The first time there was a proposal for the consideration of 3 new tenets to add to the 6-tenet definition. They were: Least Force, Ease Suffering, and one other that escapes me. These were written, proposed to the House [of Delegates, AANP], debated, and defeated.[9]

Dr. Pam Snider remembers a similar process: "The Committee wrote the first draft and presented it at Alderbrook. There was an open mike, more revising over the weekend, the first draft was ➤

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published for the profession to comment on, and Jonathan Wright had also solicited a lot of input from old and new docs, students etc. in a booklet he pulled it all together in and sent to me and Jared. A 1988 bound report to AANP has a lot of input reported in it…this went on for 3 more years."[10]

This method helped our profession resolve what could have been an impossibly contentious process given how opinionated and set in their beliefs some of my colleagues may at times be. However, it was a temporary fix, meant to further our ability to pass legislation legalizing our profession. It was meant to evolve over time. The results no longer serve as an adequate definition. This is because they do not demarcate what naturopathy is and how it differs from other schools of medicine.

If we were to turn these principles into a Venn diagram, they define the category, the group, we might best label "physicians."

When I asked about the origin of the principles, Pam Snider wrote me that, "Scraps of these ideas are in the nature literature from way back but not as a coherent set of principles within a definition of naturopathic medicine, scope, modalities etc. You can see [them] in old nature and nature doctor writings. Lust's journals mention many of these concepts, so they certainly derive from a naturopathic medicine lineage."

My attempts to convince myself that this is true did not met with success. These principles originated with medical doctors and do not specifically describe naturopathic medicine. The fact that the 1986 conference attendees found a consensus about these ideas is more a measure of our desire as second-class practitioners to emulate physicians; we do not own them. Recall at that time we were still naturopaths who practiced naturopathy. Laying claim to them was like our wearing white coats and carrying stethoscopes. It was our saying, "We are physicians too."

Take the phrases *Tolle causam* or *Vis medicatrix Naturae*: these are concepts to which all of us gladly pledge our allegiance and that have a history in medicine that long predates the nature cure movement. Samuel Hahnemann apparently took rather strong exception to both ideas in *The Organon*.[11] In Hahnemann's thinking, finding the cause of disease was a ludicrous pursuit, "… as it is not perceptible and not discoverable. For as far the greatest number of diseases are of dynamic (spiritual) origin and dynamic (spiritual) nature, their cause is therefore not perceptible to the senses…"[12]

Keep in mind that microbes were still unknown at the time of his writing and the cure for scurvy was still being debated. In fact when the term *Tolle causam* came into use, it was not an exhortation to identify the etiology or mechanism of a disease process (or is it entity?), rather it was a reminder to employ a belief system that explained the disease in order to prescribe what was thought appropriate treatment. Does one purge the patient or bleed the patient? That was probably the question.

Hahnemann also took strong opposition to the notion that there was a healing intelligence within the body that would direct a cure. "In Hahnemann's sense … the healing endeavors of nature (living power) are considered as completely insufficient and inappropriate, this reproach signifying nothing else than that the therapy of the 'allopaths' is partly worthless and partly highly disastrous."[13] Hahnemann lists a range of tasks that any physician might do to aid a patient from setting a bone to lancing a boil, that the healing power of the *Vis* is incapable of performing.

That our homeopathic-focused colleagues did not take Hahnemann's side and pursue debate on these principles is perhaps more a measure of the lulling effect of the "getting to yes" process that encourages agreement, rather than a measure of their unfamiliarity with Hahnemann's actual beliefs. Clearly these precepts are contrary to a homeopathic worldview. Both were terms widely used by allopathic medical doctors.

"*Tolle causam*" could today serve as a motto for a number of medical and scientific specialties; a list might include epidemiologists and geneticists and could easily be used as a slogan for the Center for Disease Control (CDC). Using it cannot distinguish our school of medicine from others.

We might also extend some forgiveness to our colleagues who in their youthful enthusiasm for our profession laid claim to the term "*primum non nocere"* as being our own, a concept they thought sounded naturopathic in origin.

I recall being chastised by a member of the Colorado House of Representatives back in 1992 during a late evening legislative hearing. The representative was a nurse, married to a medical doctor. In the middle of my testimony describing naturopathic medicine, just as I mentioned *primum non nocere*, she could no longer contain herself and interrupted me with an angry tirade that began, "What gives you the right to appropriate a term that our medical professions have been using since the time of Hippocrates….?"

All modern medical practitioners, including naturopathic doctors, strive to adhere to this Hippocratic injunction; we are not unique. Except that this *primum* thing is not a Hippocratic injunction. The representative's alluding to *primum non nocere* as a Hippocratic injunction was not exactly accurate. While the Hippocratic oath, or some version of it, goes back millennia (the earliest version found dates to third century Egypt[14]), the oath has gradually evolved and changed over time.[15]

The actual term "*primum non nocere*" is a rather recent addition to the oath, amended into the British and American versions by either Worthington Hooker in 1847, or Thomas Syndeham in 1860. A French doctor named Auguste Chomel (April 1788 in Paris – April 1858) came up with the *primum* phrase a few years earlier.[16,17] I did not point this out to the already irate Representative during the hearing. (She voted to 'postpone indefinitely,' that is kill our ND legislation, as did the majority of that committee, so ending the first, but not the last, legislative attempt to regulate naturopathic medicine in Colorado.)

Nor can we claim "*docere*" as a uniquely naturopathic precept; not only is the term in the Hippocratic oath that all physicians use, but we have to remember that people trained in the healing arts have been referred to as doctors for a long, long time. The Hippocratic oath requires doctors to be teachers and pass on their art.[18] We translate it as meaning we are supposed to teach our patients. In recent years, the *docere* concept has been expanded, at least in allopathic medicine, to include 'truth telling' or informed consent.[19] We could claim that we place greater or different emphasis on these principles, but neither of these phrases, *tolle causam, primum non-nocere,* nor *docere* defines naturopathy as distinct from other schools of medicine. All doctors lay claim to these ideas, and these other schools of medicine have longer held claims to these principles.

Defining Naturopathy

What we are doing is kind of like defining "hummus" as a smooth, creamy, edible suspension, but not telling how it differs from pudding, mayonnaise, or ketchup.

At some point I had to admit that our guiding principles do not define naturopathic medicine as clearly as I needed for my lecture. The principles did not provide the compass bearing that would allow me to do a 180-degree about face that would lead us back to the origins of naturopathy, back to basics. The principles were a temporary compromise that allowed our profession to move forward during a period of need; they provided a necessary requirement, a point of agreement, but they are not the solution.

Actually, I should write, they were a brilliant maneuver by Zeff and Snider, a group of ideas all of us could more or less say yes to; a composite agreed upon by our diverse congress of practitioners is not easily come by. This was about getting to yes and it worked.

That was then, this is now. If I am going to talk about the basics of naturopathy, I need to come up with a definition that I feel comfortable with. While time is short, there is no pressure. These were Canadians I was going to speak to and for them, "It's a 'process' not an 'entity." Perhaps that is what I will say about my definition?

But how would I define naturopathy?

Our family subscribes to the print version of the *Denver Post*. My habit is to unlock our front door at 5:00 am every morning to retrieve the paper. Half awake I never bother to put on shoes.

This past February, with five inches of fresh snow on our front sidewalk and the temperature hovering at -4 degrees F (-20 C), I followed this routine (my wife reported that she heard me whimpering when I got back inside). A few hours later when she shoveled the sidewalk, my bare footprints were still visible where the snow had melted beneath my hot feet and refrozen to the concrete. Those iced impressions remained for days.

"Why didn't you put your shoes on?" she asked over breakfast tea.

"Because I'm a naturopath."

There's a famous line attributed to US Supreme Court Justice Potter Stewart. In a court opinion he wrote in 1964, in a case that attempted to define "hard-core" pornography, Justice Stewart wrote, "… I know it when I see it…"[20]

Naturopathy, thus, is in a way like pornography: 'We know it when we see it.'

Let us wipe the slate clean of all of these principles and old definitions and attempt to start afresh and actually define what it is we believe and do in a way that sets our profession of naturopathic medicine apart from other schools of medical practice. We are looking for a definition that can serve as a yardstick with which we can take a measure of any given therapy and ask ourselves if this is naturopathy or not.

In my thinking, any definition should ideally define my walking barefoot in snow as naturopathy.

Give me a little space here because I am exploring territory where we do not wander often. This is a process. There are a few basic ideas that I think must be included.

Jacob Schor, ND, addressing AANP conference in August 2019.
(This article is based on the lecture Dr. Schor made to the Canadian Naturopathic Doctors of Alberta in June 2018.)

The first is that we naturopathic physicians put great value on nature; we value exposure to nature and the essence of nature that resides in the elements that come from nature. We place high value on the unadulterated, natural world, and we assume mere exposure to it has a healing action, that exposure to water, air, sunlight, and the other aspects of nature, is essential to health and restoration of health. I would go so far to claim that nature nourishes our souls. Or at least the opposite; in environments deprived of exposure to nature, our souls suffer a deficiency, that they starve for something essential.

We have evidence of these deficiency effects in the modern scientific literature. (Kurt Beil, ND, has written extensively and beautifully on this topic in his numerous pieces in the *Natural Medicine Journal*.) By extension we believe that our living environment, the water we drink, and the food we eat should be 'natural' as opposed to processed and synthetic. Yet this belief in itself does not demarcate us from all other schools of medicine. There is little doubt that we put greater value on a natural hot spring than a hot tub, a pristine lake than a swimming pool, a fresh wind than a blow dryer. Or at least my generation of doctors did, and I assume younger doctors still do. How do we put this into words? We put great emphasis on the healing elements that we borrow from nature?

Elements of a definition:

1. Nature and natural elements have a healing effect.

My second assumption is that our therapies all have something in common; they attempt to trigger a reaction in which the body fixes the problem. We give the body or the organism a shove, a stimulus, and this triggers a healing response, a healing crisis if the shove is hard enough. Our therapies serve more as catalysts for change rather than controlling forces. We catalyze healing rather than force change. I recall the late Wade Boyle, ND, speaking how naturopathic herbs tonify or strengthen their target organs and that this is how we differed from the allopaths; they prescribed an herb (or drug) to control their targets to either suppress or turn on action.

Elements of a definition:

1. Nature and natural elements have a healing effect.
2. Naturopathic therapies act as catalysts to trigger healing response.

Our profession evolved from the European Nature Cure Movement of the 1800s to which some decidedly American and Canadian elements have been added over the last century. Clearly, Vincenz Priessnitz was a major influence on our early thinking, and his influence lingers.

We naturopaths all know the story how, as a child, Vincent witnessed an injured deer immerse itself in a cold mountain

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stream after being injured, seemingly with the intent to heal itself. Vincent imitated this behavior later in his own life when he was himself injured and had apparent success. He imitated this process with many 'patients' over the years.[21] There were several aspects to these treatments. Priessnitz employed natural elements, in particular, cold water and exercise, rougher versions of clothing, and simpler coarser foods than people might choose of their own volition. The patients were made uncomfortable. Patients were also removed from their 'modern environment,' a lifestyle that had become increasingly toxic. We still carry reservations about modern lifestyles and have an underlying faith that living simpler lives closer to nature is associated with better health.

So third, we have a lasting belief that harmful substances either in the environment or in our bodies are to blame for much of modern illness. (We might now include endotoxins generated within the body in this list.)

Elements of a definition:

1. Nature and natural elements have a healing effect. Exposure to harsher elements is beneficial.
2. Naturopathic therapies act as catalysts to trigger healing response.
3. Toxic exposure causes many illnesses.

We have to remember that while we complain about environmental pollution today, toxic exposures in 19th century Europe could be far worse. One example was the wallpaper craze of the midcentury. In the early 1800s, chemists had invented green pigments from a combination of arsenic and verdigris.[22] Variations of these chemicals also produced yellow, green, and blue pigments, and these new colors inspired a wallpaper craze that lasted nearly a century. If you lived in a Victorian home in England, Europe, or even the United States in the 19th century, you wall papered. William Morris who started the British Arts and Crafts movement became the foremost wallpaper designer and seller of the era, and the owner of England's largest arsenic mine. Beautiful as these wallpapers were, they released arsenic as a gas, enough to poison a house's occupants over time. By 1874, Britain produced 32,000,000 rolls of arsenic impregnated wallpaper per year and apparently a significant portion of their population was afflicted by what was called 'witch fever.'[23] Getting out of the house for some fresh air, and getting outside into nature had a salubrious effect to a degree that is hard for us to imagine today.

Granted this is a historic detour, but let's put this into context with our nature cure movement. Getting outside from Victorian wallpapered houses was associated with a reduction in a wide range of symptoms. The benefits were so clear that the theory that being outdoors improved health did not require randomized controlled trials. Getting outside for fresh air back then was profound and became foundational to nature cure and by inheritance, to naturopathy.

Is there an innate self-repair mechanism hardwired within the body that Priessnitz was able to trigger with his mix of cold-water exposure and other therapies? Our assumption is yes. This could be the "inherent self-healing process" talked about in the AANP definition? Is this the same self-healing intelligence that Samuel Hahnemann so doubted because it wasn't capable of lancing a boil or setting a fracture?

Elements of a definition:

1. Nature and natural elements have a healing effect.
2. Naturopathic therapies act as catalysts to trigger healing response.
3. Toxic exposures cause many illnesses, and reducing toxic burden improves health.

Adaptive Responses

Two concepts that this writer considers fundamental to defining naturopathic medicine are the ideas of homeostasis and adaptive response. What we now call homeostasis, that there is some sort of harmonic equilibrium "…among bodily humors dates back to the pre-Hellenic thinkers and was converted into medical suggestions by the Hippocratic school. This concept was handed down to posterity by the several schools of Medicine before being resumed by the great naturalist Jean-Baptiste Lamarck in purely physical terms." Walther Cannon is given credit for formulating the rules that transformed this general concept into a paradigm in the 1920s.[24]

What nature cure and most of naturopathic medicine does, when successful, is to restore a body to homeostasis, a state that we might equate to as health. These 'therapies' do so in a manner that may define our medicine. Naturopathic therapies initially push the organism further away from homeostasis, and this triggers an adaptive response that restores function closer to the homeostatic normal. Reliance on this sort of adaptive response may distinguish what we do from allopathic medicine. Reading this over, what I've written doesn't sound quite correct. The very nature of our biology is to seek to restore this equilibrium; naturopathy may give it a nudge, but it is nature that 'heals.'

Elements of a definition:

1. Nature and natural elements have a healing effect.
2. Naturopathic therapies, **by pushing the organism away from homeostasis, trigger adaptive responses** that act as catalysts to trigger healing response.
3. Toxic exposures cause many illnesses, and reducing toxic burden improves health.

Hormesis

Triggering adaptive responses might be better defined as employing hormetic responses, from the term "hormesis." Hormesis describes dose effects, specifically the idea that the effects on biological systems may shift with dose size. In fact, the effect may vary as doses increase from good to bad, bad to good, or positive to negative, or visa versa. The simplest dose response, of course, would be a straight line. Effects of a drug often simply increase with dose.

An example of a straight-line dose response is the change in forced expiratory volume in asthmatics based on increasing amounts of albuterol given. In a hormetic response, increasing doses increase response initially but then at higher doses the response decreases, and actually shifts to negative.

Anyone who has graphed biological data will recognize these u-shaped curves, but this concept has been controversial and until recently ignored. What we are seeing in hormetic responses are over-compensatory adaptive responses. Let me back up and cover some history.

Although Rudolph Virchow is technically credited with writing the first published description of a hormetic response, the actual concept of hormesis is generally credited to Hugo Schulz, a German pharmacologist, who in the mid-1880s came up with the concept through his experiments using disinfectants to kill yeast: "…. Schulz observed an unexpected biphasic dose–response

in which high doses were toxic and suppressed metabolism, while the opposite seemed to occur at low doses."[25] Low doses stimulated growth.

This was an era when scientists were hunting for 'laws' to describe the universe, and Schultz teamed up with Rudolf Arndt and together, in 1888, they proposed a 'law' to be used in toxicology: "For every substance, small doses stimulate, moderate doses inhibit, large doses kill." While this 'law' was an interesting idea at the time, a forward-thinking progressive idea, it was ignored. Not only ignored, but the very idea was actively campaigned against by the scientific establishment. This is because Arndt and Schulz tried to use it to justify homeopathy. But that's another story.

About 20 years ago Edward Calabrese, a professor of toxicology, risk assessment, and environmental health at the University of Massachusetts, Amherst, became interested in this concept of hormesis and began researching and writing about it. He has since almost single handedly revived and advanced this concept. There are few modern papers related to hormesis that don't have his name on them as an author. He has successfully pushed hormesis into a scientifically valid and accepted phenomenon:

> Hormesis is an adaptive response characterized by biphasic dose response of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced or **the result of compensatory biological processes following an initial disruption in homeostasis**.[26]

The ill reputation of the Arndt-Schulz law and its association with homeopathy forced many researchers to call hormesis by other names. PubMed articles on hormesis are often camouflaged under euphemistic terms, including beneficial effects of low doses, intermediate disturbance hypothesis, and subsidy-stress gradient; and dose responses get described as U-shaped, J-shaped, biphasic, stimulatory-inhibitory, facilitation-inhibition, reverse, bidirectional, dual, bell-shaped, compensatory, and as paradoxical, usually without mention of the term hormesis.

Using these search terms, we realize that a wide range of supplements we use in naturopathic practice, probably most of them, exhibit these sorts of U-shaped dose responses characteristic of hormetic responses.

An appealing example is chocolate.[27] Steinhaus et al suggested in 2017 that eating chocolate regularly is associated with a decreased incidence of heart failure (HF) (n= 31,917). Compared with guys who never eat any chocolate, eating just one-to-three servings of chocolate per month lowers risk by about 12% and eating one-to-two servings per week lowers risk even more, 17%. The greatest reduction in risk, 18% below the guys who never ate chocolate, was for men eating three-to-six servings a week. Eating any more chocolate than this backfires; with one or more servings of chocolate per day, risk of heart failure increased to 10% higher than for those who never ate chocolate.[28]

Similar patterns of dose response have been seen in studies on coffee and risk of stroke,[29] or cognitive decline,[30] and depression.[31] The benefits of vitamin D also display a hormetic response including against cardiovascular disease,[32] fracture risk,[33] and prostate cancer (in which the ideal dose was reported to be between 18-28 ng/ml),[34] and overall mortality risk.[35]

Consumption of fish or fish oil shows a similar pattern. The right dose helps depression but too much worsens it.[36] Risk of psychosis decreases with the addition of some fish oil and then increases with higher doses.[37] The right dose of curcumin helps wound healing, too much hinders it.[38]

This hormetic dose-response that results from apparent compensatory biologic processes is so common to naturopathic therapies that I cannot help but wonder if this reliance on hormetic responses does not in part define our profession?

While we may not think about it, we often choose therapies that disrupt homeostasis; and it is the adaptation by the patient's body that compensates to this disruption that restores or at least nudges us closer to a homeostatic balance. Curcumin, berberine, and resveratrol are neurotoxins, at least to insects and mild neurotoxins in humans. Exposure to them triggers neuroprotective pathways in humans. That's why they are helpful to protect cognition.

Exercise causes oxidative damage to muscle. We don't just adapt to handle the damage, we overcompensate and become better at neutralizing oxidative damage. Over-adaptation to stressors is perhaps the common denominator of naturopathic medicine and rare in allopathic medicine. Exercise, fasting, saunas are all examples of this over-adaption response triggered by more physical stressors.

The benefits of walking barefoot in snow might fit into this realm.

Thus, perhaps a fourth aspect of a possible definition of naturopathy is the triggering of hormetic over-adaptation responses, using stimuli and triggers typically from natural elements or natural agents, to restore homeostasis and increase resilience. These triggers selected are often close to a natural state: exposure to water, heat, and light, and ingestion of foods, plants, botanical extracts, and mineral elements.

Elements of a definition:

1. Nature and natural elements have a healing effect.
2. Naturopathic therapies, **by pushing the organism away from homeostasis, trigger adaptive responses** that act as catalysts to trigger healing response. These are often hormetic responses; the triggering of hormetic over-adaptation responses using stimuli and triggers typically from natural elements or natural agents to restore homeostasis and increase resilience. These triggers selected are often close to a natural state: exposure to water, heat, and light, and ingestion of foods, plants, botanical extracts and mineral elements.
3. Toxic exposures cause many illnesses, and reducing toxic burden improves health.

If this is what nature cure is, I would say a possible definition of naturopathic medicine could be "nature cure in the age of evidence-based medicine."

Is this list adequate to demarcate naturopathy from other medical treatments? Maybe, maybe not.

Naturopathy's heyday was in the first half of the 1900s, an era in which identifying essential nutrients and curing diseases caused by deficiency reached a zenith; and we maintain an optimism that more vital nutrients and deficiency diseases exist that might be cured with the correct extract. I do not know that this is a distinguishing characteristic of our profession, but perhaps our continuing belief still in part defines us?

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Defining Naturopathy

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Here is another thought: A number of cancer chemotherapy agents apparently act by causing damage to the gut lining that in turn allows bacterial translocation into the lymph system, which in turn triggers an immune hyperreaction that kills cancer cells. Could we claim chemotherapy as a naturopathic therapy? If it triggers an adaptive response….? Most of us will object to this adamantly, so a definition must retain the notion that we emphasize safety or low toxicity.

Another problem with the idea of using natural substances to stimulate a response, in particular an immune response, are the adjuvant chemicals added to vaccines. These are the small doses of fairly objectionable chemicals added to immunizations to provoke an immune response to the vaccine antigens and that increase the likelihood the patient will develop immunity. This is why mercury, formaldehyde, and other undesirable substances are added. A definition that includes chemotherapy and vaccines may not be acceptable.

In my own thinking, I find that I am often trying to envision ourselves in an evolutionary context and how we might inform our thinking based on what our bodies were 'designed' for or evolved to tolerate. Such thinking informs our belief that we need more vitamin D and longer melatonin production at night, that we should get more exercise, relax more, eat more fiber, and so on.

But for the moment let's look at what I've listed:

1. Nature and natural elements have a healing effect.
2. Naturopathic therapies, **by pushing the organism away from homeostasis, trigger adaptive responses** that act as catalysts to trigger healing response. These are often hormetic responses.
3. Toxic exposure causes many illnesses and reducing toxic burden improves health.
4. Safety of therapy. Green preference.

There are three descriptors of our school of medicine that I think need inclusion: emerging, evolving, and rational. Emerging means we are still new in the medical field and going through developmental stages. Evolving means we are still changing and adjusting to our place in medicine. Rational is a term that goes back to the Hippocratic era. Hippocrates is credited with turning away from divine notions of medicine and using observation of the body as a basis for medical knowledge. Prayers and sacrifices to the gods did not hold a central place in his theories, but changes in diet, beneficial drugs, and keeping the body "in balance" were the key.[39] We might call it 'fact-based medicine.' This was termed "rational medicine," and most of us would rather be thought of as rational than its opposite, irrational. These days it may be called evidence-based medicine. Rational, though, is a more Hippocratic term.

Naturopathy is an emerging and evolving school of rational medicine, that encourages use of natural substances, and or exposure to nature and its elements, as catalysts to restore homeostasis through triggering adaptive or hormetic responses. Other strategies employed for improving health include lowering toxic burden, providing nourishment in cases of deficiency, or stimulating a healing response. Therapies are viewed as existing on a spectrum of force or potential for harm and are selected conservatively, referentially selecting the least invasive, safest options. Knowledge and discoveries from modern science are translated into 'greener' approaches to treatment.

Thus, this is where I am at the moment. But as our medicine is evolving, so should the definition.

I invite suggestions and comments on these thoughts. ◆

CALENDAR

Please visit TownsendLetter.com for the complete calendar

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/

NOVEMBER 7-10: 21st CENTURY HORMONE ADVANCEMENTS: The Practitioner's Comprehensive Guide to Bioidentical Hormones Through Menopause & Andropause in Irvine, California. CONTACT: https://www.womenshormonenetwork.org/upcoming_events/7

NOVEMBER 8-10: GREAT PLAINS LABORATORY presents ENVIRONMENTAL TOXIN SUMMIT in Nashville, Tennessee. CMEs available. CONTACT: 913-341-8949; https://www.gplworkshops.com/

NOVEMBER 12-13: 13th INTERNATIONAL CONFERENCE ON AUTOIMMUNITY in Brisbane, Australia. CONTACT: https://autoimmunity.global-summit.com/

NOVEMBER 13-15: AMERICAN COLLEGE OF NUTRITION 60th ANNUAL CONFERENCE – Personalized Nutrition 2019: Regenerate Health in Our Toxic Environment in San Diego, California. CONTACT: http://americancollegeofnutrition.org/conference

NOVEMBER 13-16: ACADEMY OF COMPREHENSIVE INTEGRATIVE MEDICINE presents FAVORITE INTEGRATIVE TOOLS CONFERENCE & PRE-CONFERENCE in Orlando, Florida. CONTACT: http://www.acimconnect.com

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

DECEMBER 13-15: 27th A4M / MMI ANNUAL WORLD CONGRESS in Las Vegas, Nevada. CONTACT: 888-997-0112; https://www.a4m.com/world-congress-2019/home.html

FEBRUARY 1-2, 2020: CHELATION WORKSHOP in Kuala Lampur. Malaysia. CONTACT: drmaung@hotmail.com

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

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MARCH 3-7: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE SPRING MEETING – The Roots of Toxicity in Dallas, Texas. CONTACT: http://aaemconference.com/

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

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

APRIL 3-5: ENVIRONMENTAL HEALTH SYMPOSIUM 2020 -Immunotoxicity: The Intersection Between Toxic Exposure, Infectious Disease, and Autoimmunity in Scottsdale, Arizona. CONTACT: https://environmentalhealthsymposium.com/ ◆

Classified Ads

The Fulfillment of Hope from GENIE Continues

Beginning with the storage of frozen PAXgene tubes in 2008, "for use when the science caught up to what we learned from CIRS [chronic inflammatory response syndrome]," followed by whole transcriptome sequencing that showed rich veins of new information, to the current targeted findings of GENIE, the new transcriptomics test, especially hypometabolism and the CIRS curve, we now are seeing exponential leaps of new insight regarding inflammation and disease.

Just imagine attending a lecture series about CIRS or Lyme or CFS from just three years ago. Would we have learned about correction of (i) hypometabolism; (ii) defective apoptosis; and (iii) the pro-thrombotic basis for cerebral neuronal loss? Not a chance. And yet, those same topics are unveiled by the research that led to GENIE to be crucial to understanding the pathophysiology of chronic fatiguing illnesses. There is much more data contributing to new therapies.

If the physician and the patient don't know what GENIE can show, we have to help them learn.

Granted, we didn't know how common defective apoptosis was, particularly necroptosis. How could we? There was no way to know about cell death causing endogenous inflammatory illness without GENIE. We didn't know how important exposure to actinomycetes (a large group of bacteria that are commonly found inside water-damaged buildings (WDB)) and endotoxins was, even though sparse literature was showing us that *inflammation followed gene response* to actinos and endotoxin, not just exposure alone. And now, we are seeing the salutary benefit of correction of prothrombotic coagulation genes for those with concerns about brain atrophy, particularly in grey matter nuclei.

One clinical focus for GENIE is dementia, an area recognized by the relationship of neuronal loss to exposure to WDB. We have shown (unpublished) that correction of the unregulated over-expression of coagulation genes accompanies clinical benefit seen in small, but ever-growing numbers of patients. Now, every time I talk with family members of younger-aged Alzheimer's patients whose illness coincided with exposure to the interior environment of WDB, and improvement coincides with correction of coagulation genes, I have to remind myself that watching five or ten people get better isn't regarded as earthshaking. Small numbers won't sway a seasoned scientist. For those patients and their families, however, N=1 isn't just a study; it is a life returned.

The challenges of GENIE are many. Do we use GENIE to follow up on promising advances in the transcriptomics of chronic fatigue syndrome (CFS)? Do we simply re-define CFS as hypometabolism? Numerous researchers have spent their careers trying to define the illness at a cost of (likely) billions of dollars and lack of vitality of countless patients. Our answers to the inflammatory basis of CFS were published years ago. GENIE now puts inflammation, cytokines and coagulation together in a tight package.

Do we open our work to the Lyme community, one that has been mired in argument for years over "antibiotics forever" versus an opposing stance of "antibiotics for never?" Or do we simply recognize that the insights brought by GENIE will spread in the CIRS, CFS, and Lyme communities? Those who might be a naysayer now may decide to wait to learn more until the published GENIE literature is more robust. One thing is certain, the train of new information won't wait for anyone.

We have known for years that CIRS patients will have the prothrombotic abnormalities in transcriptomics, first published in ciguatera,[1] and seen in RNA Seq.[2] Thanks in large part to the published work of a number of researchers, especially those from Rockefeller University (notably Sidney Strickland's lab[3-13]), the strength of the vascular hypothesis of Alzheimer's makes additional clinical sense in CIRS patients. All those patients we saw with unexplained elevations of d-dimer, PAI-1 and von Willebrand's factors, not to mention those Lyme patients with clotted PICC lines and CFS patients with pulmonary emboli, were telling us that a systemic coagulation problem was ongoing. Involvement of the brain ends up being no surprise, but only now we have a literature that tells us our observations on inflammation, cytokines, and coagulation are robust.

The vascular hypothesis of neuronal injury and Alzheimer's (AD) has evolved from observations in 2010 that beta amyloid (AB) bound to fibrinogen, enhances thrombosis and reduces fibrinolysis in the CNS, and (possibly) contributes to neuronal loss.[7] Prior research (cited in reference 7) confirmed that AB bound to other mediators of inflammation and coagulation creates a prothrombotic state affecting CNS structures like the hippocampus, but also promotes systemic inflammation. Sounds like CIRS! Noting AD increases after systemic infection, Strickland, et al state, "Activation and/or modulation of the delicately balanced coagulation and inflammatory systems by AB could lead… to chronic and pathological occlusion and inflammation, both of which could contribute to the neuronal death observed in AD."[7]

Data supports this idea, including AB interaction with fibrinogen, thereby leading to deposition of fibrin in cerebral blood vessels, inducing microinfarcts (and cerebral microbleeds) and loosening of the blood brain barrier. Since AB also activates Factor XII and XIII, the propensity for fibrin deposition is increased through the intrinsic coagulation system, inhibiting plasmin-fibrin interaction, and by activating bradykinin.

Additional data, from biopsy specimens, as well as involving AB with Factor V, Factor XIII and integrins, demonstrates the role of AB binding to products of coagulation genes is related to cognitive deficits. Further, hypoxia promoted tau hyperphosphorylation.[3] Tauopathies are a group of dementias that have in common the formation of intracellular filamentous deposits seeded by the microtubule-associated protein tau, in abnormally hyperphosphorylated form(s). Tau inclusions are common among all of these tauopathies leading to diverse phenotypic manifestations, brain dysfunction, and degeneration.

All these coagulation products are evaluated by GENIE, with resolution of upregulation of gene activity correlating with clinical improvement.

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Guest Editorial

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The coagulation problems shown by GENIE are not just prothrombotic: risk of *hypo*-coagulation and bleeding after exposure to WDB is also shown by coagulation gene *suppression*. In one isolated trial, correction of excessive abundance of actinomycetes by a room-sanitizing device (iAdaptAir; Mold Congress, Fort Lauderdale, Florida, 1/2019) as the only therapy, reversed coagulation gene suppression and stopped intractable epistaxis. In a study in a single practice (RS) looking at von Willebrand's profile in CIRS patients, over 1300 results showed that 66% of patients had abnormal findings, with 60% being predisposed to clotting and 40% to bleeding. Control patients had less than 5% each predisposed to clotting and bleeding. GENIE tells who is at risk for clots or hemorrhage.

Before anyone begins preventive treatment for AD with aspirin, warfarin or the newer oral anticoagulants, please remember that such ideas were prevalent for years in attempts to prevent repeat myocardial infarction, only to find out that anticoagulation had significant risks. There is a complexity of the role of gene activation that underlies failure of confirmation of benefit from widely used therapies. Genes are not gene products! Taking a treatment does not necessarily feedback to downregulate gene activity.

This fundamental separation of gene and gene product demonstrates why widely used CFS therapies from the early 2000s, including heparin and treatment using "coagulation panels" never showed group benefit. The same failure can likely be said for the current association of histamine with "mast cell activation syndrome," as the genes that control histamine production (shown by GENIE) are present in *all nucleated cells*, not just mast cells.

In the near future we will be reporting data to illustrate how the benefit of using transcriptomics to assist in diagnosis and monitoring response to treatment of CIRS is multifactorial. GENIE touches many elements of DNA responses to environmental cues simultaneously.

In addition to showing us what a patient has, GENIE will often show what a patient *doesn't have*. GENIE may also show reasons for lack of response to therapies, or even some adverse effects of well-intentioned, but wrong-headed therapies. When independent-thinking physicians decide on a treatment for a complex fatiguing illness, the patient needs to know that transcriptomics show data and not opinion. Therapy, we feel, must be grounded in reliable science and not conjecture, trial and error, or anecdote.

Similarly, use of VIP, the "miracle" compound that corrects proteomics, transcriptomics and grey matter nuclear atrophy in CIRS when used according to a strict published protocol, has been misused by some providers who skip the mandatory controls for safe use of VIP. Let GENIE guide you! Don't skip necessary steps!

For the future, we will keep insisting on integrity in medicine and science. We "keep our head down, but with eyes wide open," letting evidence-based medicine be our guide. We know we are on the cusp of extending the principles of hypometabolism to a series of illnesses beyond CIRS, but each new step must be rigorous, validated, and repeated to confirm findings. We feel that there are valid grounds to investigate other common illnesses affected by CIRS, other than dementia, including diabetes, obesity and atherosclerosis using the principles that underlie GENIE. We don't have the answers yet; but when our findings are solid, we will let you know.

Ritchie C. Shoemaker, MD
Andrew Heyman, MD

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Gastra Girl

Vital Information to save your Colon and your Health!

Why Infrared Saunas are an absolute necessity !

Rebecca Harder has one of the nicest looking, pristine Hydrotherapy clinics in Portland Oregon, which includes hyperbaric oxygen chambers, ozone therapy, massage, etc. She gives this extremely resourceful resource guide (GASTRA GIRL, Saving America One Colon at a time!) to many of her clients, which includes about 40 articles on environmental toxicity and natural solutions, written by some of the most famous individuals in the industry.

One of the articles is entitled, "Why Infrared Saunas are an absolute necessity for Everyone," (Rebecca had been promoting wooden far infrared saunas for 10 + years. She now recommends Relax Sauna.)

"Now I know the Relax Infrared Sauna does not look impressive making it hard to believe that the best Sauna is not necessarily the most expensive and nicest looking one. Especially when you compare the Relax Sauna to the beautiful wooden saunas ... I Understand your GUT REACTION! For the last 10 years, I have turned my nose up at the Relax Sauna every time I saw them at the health conferences until this last year when I tried one. I was sold on the Relax Sauna within the first 3 minutes! Right away I could feel the difference. No preheating like with wood saunas I experienced Instant Relaxation."

Home heat stress training & Review of the Relax Sauna

"I made a post giving my thoughts on a more systematic way to evaluate saunas for home use and quantify heat stress training, citing some existing research."

I also noted that Both the $250 and $500 Amazon saunas I ordered were dismal failures. After my intense disappointment I started to research the more expensive but seemingly reputable brands in this category. I went with the Relax Sauna.

I was still skeptical of the Relax Sauna but as you'll see below, the results exceeded my expectations greatly. At 25 minutes my temp rose to 101.1F. Second, my heart rate went from 90bpm to 133bpm.

I'm thoroughly impressed with this unit and even more amazed as I write this up and am comparing my numbers to those in the studies on the benefits of Far Infrared Saunas.

I would recommend sauna training and The Relax sauna in particular to anyone (especially paired with cold showers). It seems to have such wide ranging benefits.

The Relax Sauna is probably the best and only realistic option to do hyperthermic heat stress training at home that can replicate (or actually exceed based on my results) the benefits found in studies (on the benefits of Far Infrared Saunas.) ... Do not waste your time with sub $500 units on Amazon.

see: www.relaxsaunas.com/reddit
for the complete Relax Sauna Review.

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Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

Fibromyalgia and Fluoroquinolone Toxicity – A Case of Antibiotic-Induced Fibromyalgia

Introduction

In October 2018, a 48-year-old woman came to see me for severe muscle and joint pain that affected her sleep, moods, energy levels, and overall quality of life. Her symptoms began suddenly five months prior while she was taking ciprofloxacin (Cipro) for a urinary tract infection. She had been a previously healthy woman who worked in health care at a large hospital. She had never taken Cipro in the past nor did she get frequent UTIs. The dose was standard for an uncomplicated UTI, 500 mg ER once a day for three days, prescribed by her primary care physician for confirmed UTI. A day after completing the course of treatment, she developed abdominal pain, cramping, and loose yellow stool with muscle and joint pain. The muscle pain gradually worsened and moved around her body including arms, legs, and abdomen. It continued to worsen and on May 31, 2018, she went to the emergency room and had an abdominal/pelvic CT scan, urinalysis, and basic blood work. She was sent home because everything came back normal. By the time she came to my office five months later, she had already seen her primary care doctor, a gastroenterologist, a cardiologist, two neurologists, a rheumatologist, urologist and two other naturopathic doctors.

Her symptoms since taking ciprofloxacin were muscle pain, joint pain, green stool with undigested food, thirst, frequent urination, and anxiety causing a 10-pound weight loss. She had a colonoscopy, EGD, cystoscopy, brain MRI, cervical and thoracic MRI, pelvic MRI, and numerous blood and stool tests for bacteria and yeast. All labs and imaging where normal. Lyme disease, viruses, valley fever and autoimmune conditions were ruled out. She was also screened for hormone imbalance and heavy metals all which were normal. The only abnormal lab was a blood cortisol of 24, which was most likely due to the muscle pain and the stress and anxiety; but she went to an endocrinologist for further work-up anyway, and all other endocrine tests came back normal.

She had already tried two courses of prednisone, a non-fluoroquinolone antibiotic for possible gastroenteritis despite normal stool tests, anti-fungal medication, PPI, gabapentin, and valium. The gabapentin and valium helped the most, and she was on these when she came to my office for a consult. She was diagnosed with fibromyalgia by the rheumatologist, which eased her mind somewhat to have a diagnosis.

Every doctor she had seen since May 31, 2018, told her the symptoms were induced by the course of ciprofloxacin and that it would take time to resolve. Symptom management was what was offered. She researched her condition online and discovered numerous reports of people having similar side effects from ciprofloxacin and other fluoroquinolones, (FQs) and that a new term has emerged called 'floxed.' She came to me seeking treatment for fibromyalgia induced by a fluoroquinolone antibiotic.

Fluoroquinolones and the FDA

Oral fluoroquinolones (FQs) are one of the most prescribed classes of antibiotics in the world. The fluoroquinolone antibiotics include ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), and ofloxacin (Floxin). They are used to treat or prevent numerous bacterial infections. For years there have been reports of severe side effects prompting the FDA to issue warnings about fluoroquinolones, yet the class of drug remains on the market. Side effects range from ruptured tendons, and muscles, to pain in the joints and muscles, and effects on the nerves and central nervous system.

The FDA first added a boxed warning to fluoroquinolones in July 2008 for the increased risk of tendinitis and tendon rupture. In February 2011, the risk of worsening symptoms for those with myasthenia gravis was added to the warning. In August 2013, the FDA required updates to fluoroquinolone labeling to disclose the potential for irreversible peripheral neuropathy from fluoroquinolones. In 2016, an FDA safety review showed that systemic fluoroquinolone use is associated with permanent and disabling adverse effects involving the musculoskeletal and nervous systems. The FDA stated then that the negative side effects associated with fluoroquinolone drugs outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections and that other treatments should be considered.[1] In July 2018, the FDA issued warnings about the risks of mental health side effects and serious blood sugar disturbances with fluoroquinolones.[2] Most recently in December 2018, the FDA issued a warning about fluoroquinolones and increased risk of ruptures or tears in the aorta blood vessel.

In November 2015, an FDA review coined the phrase "Fluoroquinolone-Associated Disability, FQAD" to track FQ adverse

effects in patients being treated for UTIs, sinusitis, and bronchitis. It states a patient must have adverse events from two or more of the following body systems: musculoskeletal, neuropsychiatric, peripheral nervous system, skin, cardiovascular, and senses (vision, hearing, etc), that last 30 days or longer after stopping the fluoroquinolone. A summary can be viewed at https://www.fda.gov/media/104060/download. Despite thousands of disability reports from hundreds of cases, fluoroquinolones remain on the market.

Fluoroquinolones and Fibromyalgia

The American College of Rheumatology (ACR) updated its fibromyalgia diagnostic criteria in 2016 and acknowledges that the widespread pain syndrome most likely stems from the central nervous system. It described fibromyalgia as a "central pain amplification disorder" that has some triggering event – something sets off the symptoms of fibromyalgia. FDA warnings and published case studies point to fluoroquinolones as a possible trigger. Many doctors managing patients with fibromyalgia may not be making the connection to past use of antibiotics.

A 2018 meta-analysis aimed to compare the adverse effects of fluoroquinolones to other commonly prescribed antibiotics in primary care. It concluded that the occurrence of gastrointestinal-related and central nervous symptom-related adverse events were higher with fluoroquinolones compared to any other antimicrobials such as macrolides or cephalosporins.[3]

However, in 2019, the *British Journal of Clinical Pharmacology* published a large case-controlled study with a different conclusion. It looked at patients diagnosed by a rheumatologist with fibromyalgia and controls. It found the risk of fibromyalgia with fluoroquinolones is similar to that with amoxicillin and azithromycin. The risk of fibromyalgia was higher for use of any antibiotic versus none.[4] This study had numerous limitations but did hypothesize that the fibromyalgia symptoms were not triggered by the antibiotic but triggered by the infectious process for which the drug was prescribed. There are indeed numerous studies aligning viral and bacterial infection to fibromyalgia risk. It also hypothesized that the antibiotics changed the gut microflora, which has been linked to fibromyalgia.[4]

As early as 2012, there have been published reports of fluoroquinolone-induced musculoskeletal conditions such as fibromyalgia. Often these patients seek help via chiropractic manipulation and massage therapy, which may or may not help. Depending on when the patient presents with symptoms or diagnosis of fibromyalgia, the doctor may overlook the link to the use of FQs. Fluoroquinolone-induced muscle pain seems to be caused by several factors, including inhibition of cell proliferation in tendons, inhibition of tenocyte migration, and increased matrix metalloproteinase expression, which induces collagen degradation.[5] A researcher at the University of California-San Diego believes FQs are damaging mitochondria. This kind of harm can affect every cell in the body, explaining why a wide range of symptoms can appear and get worse over time. Current studies are taking place to prove this theory.[6]

The FDA isn't the only agency issuing warnings about fluoroquinolone antibiotic. The European Medicines Agency (EMA) has also issued warnings on disabling and potentially permanent

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side effects of fluoroquinolones. However, neither agency has pulled the medications from the market; instead, they advise doctors that FQs should not be used in situations where other options are available or where the use of antibiotics is questionable.

Treatment for Fluoroquinolone Side Effects

Despite FDA black box warnings and published reports of FQ toxicity, there is very little published research on how doctors should manage patients experiencing acute or chronic symptoms. Numerous integrative medicine clinics offer treatment information on their websites for patients who have been 'floxed.' Treatments range from minerals, vitamins, amino acids, antioxidants (both oral and intravenous), detoxification protocols, ozone therapy, hyperbaric oxygen, and many others. Blogs and forums have emerged on the internet offering treatment advice as well. Yet there is very little published research on these treatments being effective for fluoroquinolone adverse effects.

In 2012, a case report of fibromyalgia induced by fluoroquinolones outlined a four-month treatment program consisting of intravenous glutathione, glutamine, d-ribose and n-acetyl cysteine, an oral probiotic and gluten-free/soy-free diet. Over the course of treatment, the patient did improve.[5]

A 2017 published article looked at possible areas of treatment to focus on including reduction of oxidative stress, restoring reduced mitochondrion potential, supplementation of cations that are chelated by FQs, stimulating the mitochondrial proliferation, removing FQs permanently accumulated in the cells, and regulating the disturbed gene expression and enzyme activity.[7] Options for achieving this include N-acetyl cysteine, vitamin C, vitamin E, resveratrol, selenium, minerals, and CoQ10.[7] These treatments are based on the proposed mechanism of how fluoroquinolone adversely affect the body.

Most practitioners will at some point have patients with symptoms induced by fluoroquinolone antibiotics. The symptoms may be acute or chronic, and health providers need to take a thorough history asking about antibiotic use in the ten years prior to onset of symptoms. Treatments should be individualized, focused on symptom management, and directed at the mechanism of fluoroquinolones' toxic effects in the body.

Case Report

The patient who came to see me in 2018 was having muscle pain, joint pain, and green-colored stool for five months post a three-day course of a fluoroquinolone antibiotic for urinary tract infection. She previously had been healthy, and these symptoms, tests, doctors' appointments, and failed treatments were creating stress and anxiety and weight loss. As a reminder, all labs, tests, and imaging were normal except mildly elevated cortisol. The only diagnosis she had been given was fibromyalgia. She was currently on gabapentin and valium, no supplements, and still symptomatic.

I began by working on stress management with meditation and deep breathing instruction and encouraged counseling. I placed her on vitamin D3 (4,000 iu a day), magnesium (250 mg twice a day), N-acetyl cysteine (600 mg twice a day), herbs to lower the cortisol, CBD oil, and a very high dose probiotic. The probiotic is key because people with fibromyalgia have an altered gut microbiome, and one of the proposed mechanisms of fluoroquinolone toxicity is an alteration of the gut microflora.[4,8] The patient wanted off gabapentin due to side effects; and the magnesium, vitamin D, and CBD oil were to assist in managing the muscle pain. Later low-dose naltrexone (3 mg) was added as well to help ween off gabapentin. LDN has great published research on its benefit for fibromyalgia.[9, 10]

I recommended infrared sauna therapy designed to increase blood flow to the organs of elimination and perspiration. She was asked to spend 10 minutes in the hot sauna, then do a 60-second cold shower rinse and repeat these five times ending with the cold rinse. This equaled one hour of time, and it was recommended she do this one or two times a week. The research on using sauna therapy, hydrotherapy for fibromyalgia, and elimination of toxins is outstanding.[11-13]

Initially the patient was non-compliant and continued to seek advice from other doctors, friends, family, co-workers, and the internet. Eventually she returned and stuck to the plan, and her symptoms have slowly improved.

Summary

Fluoroquinolones are one of the most prescribed classes of antibiotics in this country. The fluoroquinolone antibiotics include ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), and ofloxacin (Floxin). For years the FDA has issued warnings about severe and debilitating side effects, including fibromyalgia-type symptoms. Instead of removing these drugs from the market, the FDA urges physicians to only prescribe them when absolutely necessary. Fibromyalgia affects about 4 million adults in the US, causing widespread muscle pain and often taking years to diagnose. There is typically some triggering event for the condition, and fluoroquinolone use is emerging as a common trigger. Doctors are encouraged to take a thorough history looking for past use of antibiotics in patients with fibromyalgia. Since there is very little published research on how to manage fluoroquinolone-induced fibromyalgia, most physicians are left managing the symptoms and known mechanisms of FQ-adverse effects on the body.

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= 9). After 12 weeks, the mean total score improved by 77% (from 5.8 to 1.4) in the niacinamide group and by 11% (from 5.5 to 4.9) in the placebo group ($p < 0.05$ for the difference in the change between groups). Mean improvements in erythema, scaling, and infiltration were each significantly greater in the niacinamide group than in the placebo group. Two patients receiving niacinamide reported a mild burning sensation and pruritus, whereas no side effects were reported in the placebo group.

Melasma

Twenty-seven Mexican women with melasma (a common condition that causes hyperpigmentation) were randomly assigned to apply, in double-blind fashion, 4% niacinamide cream to one side of the face and 4% hydroquinone (a skin-bleaching agent) to the other side for eight weeks.[7] It was not specified how many times per day the creams were applied. The mean improvement in the Melasma Area and Severity Index was 62% with niacinamide and 70% with hydroquinone (difference not significant). Niacinamide reduced the amount of mast cell infiltration and improved solar elastosis in melasma-affected skin. Niacinamide is believed to improve melasma by reducing inflammation and by decreasing the transfer of melanosomes.

Photoaging

Fifty women (aged 35-60 years) with signs of facial photoaging (fine lines and wrinkles, poor skin texture, and hyperpigmented spots) were randomly assigned to apply, in double-blind fashion, 5% niacinamide in an oil-and-water vehicle to half of the face and the vehicle alone to the other half twice a day for 12 weeks. Compared with vehicle alone, niacinamide significantly improved fine lines and wrinkles, hyperpigmented spots, red blotchiness, skin sallowness (yellowing), and skin elasticity.[8]

Where to Obtain Niacinamide for Topical Use

Niacinamide 4% cream is available under the brand name Niafourmin (Ecological Formulas, Concord, California) in 3.5-ounce tubes.

Alan R. Gaby, MD

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Topical Niacinamide for Dermatological Conditions

Niacinamide is one of the two forms of vitamin B_3 (the other being niacin). Niacinamide as an oral supplement has been used successfully by practitioners of nutritional medicine to treat osteoarthritis, schizophrenia, and anxiety, and to prevent actinic keratoses and non-melanoma skin cancer. Studies in mice suggest that niacinamide may also be effective for preventing and treating glaucoma. I reviewed these uses of niacinamide in the August/September 2017 issue of the *Townsend Letter*.

It is less well known that topical application of niacinamide has been reported to relieve certain skin conditions. Topical niacinamide has anti-inflammatory activity[1] and also reduces skin dryness by improving stratum corneum barrier function.[2] According to the studies described below, topical niacinamide is beneficial in the treatment of acne vulgaris, seborrheic dermatitis, and melasma. Topical niacinamide has also been found to reverse some of the signs of photo-aging. In clinical trials, topical niacinamide was generally well tolerated with only occasional mild local side effects being reported.

Acne Vulgaris

Three double-blind trials have demonstrated that topically applied niacinamide is as effective as topical clindamycin, an antibiotic approved by the FDA to treat acne. The mechanism of action of niacinamide appears to be related, at least in part, to its anti-inflammatory effect.

Seventy-six patients with inflammatory acne were randomly assigned to receive, in double-blind fashion, a gel containing 4% niacinamide or 1% clindamycin. The gel was applied to the face twice a day for eight weeks. The proportion of patients who improved was 82% in the niacinamide group and 69% in the clindamycin group. The only adverse effect was mild stinging or burning at the application site, which appeared to be due to the gel vehicle, rather than to the niacinamide.[3]

Eighty patients (mean age, 24 years) with moderately severe inflammatory facial acne were randomly assigned to apply, in double-blind fashion, topical 4% niacinamide or 1% clindamycin gel twice a day for eight weeks. Mean acne severity (as determined by the Cook's acne grade) decreased by 65% in the niacinamide group and by 64% in the clindamycin group. Among patients receiving niacinamide, 100% of those with oily skin, but only 21% of those with non-oily skin, had a favorable response to treatment. In contrast, clindamycin was more effective in patients with non-oily skin than in those with oily skin. It was not stated how many patients had oily and non-oily skin.[4]

Sixty female patients (mean age, 21 years) with mild or moderate acne were randomly assigned to apply, in double-blind fashion, 5% niacinamide gel or 2% clindamycin gel to the affected areas twice a day for eight weeks. The mean score on the acne severity index improved significantly ($p < 0.0001$) compared with baseline in both groups, and the degree of improvement was similar in the two groups.[5]

Seborrheic Dermatitis

Thirty-nine patients (aged 20-50 years) with seborrheic dermatitis of moderate severity were randomly assigned to apply 4% niacinamide cream or placebo once a day for 12 weeks.[6] Erythema, scaling, and infiltration were each graded on a 4-point scale, with 0 indicating none and 3 indicating severe. The scores for each of these parameters were added to obtain a total score (maximum possible score

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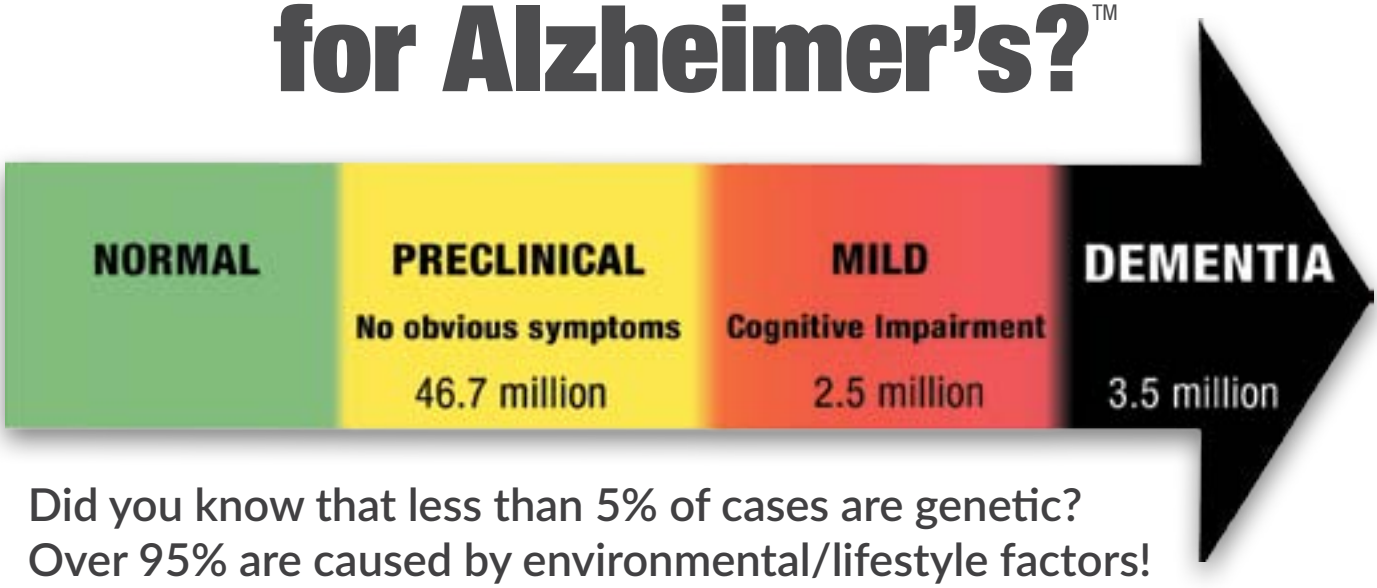

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