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Leigh Erin Connealy, MD

The Biology of Hope and Healing

OCTOBER 2018
ISSUE #423

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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)

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

Clinical Study #4 (2016)

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

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From the Publisher

The Growing Problem of Adulteration in Chinese Medicine and Food

In July the US Food and Drug Administration recalled a variety of medications containing the drug, valsartan, commonly prescribed to treat hypertension and heart failure.[1] The products were determined to be adulterated with a carcinogen, N-nitrosodimethylamine (NDMA). The valsartan was manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd. in Linhai, China. Zhejiang supplies valsartan to generic drug manufacturers in the US and abroad for making products combining valsartan with other drugs; the company has

continued on page 8 ➤

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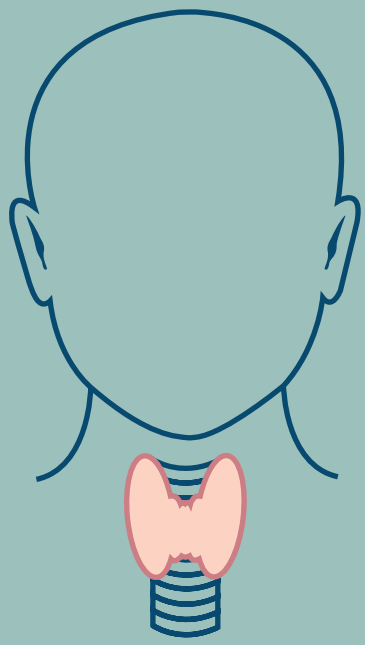

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From the Publisher

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ceased to sell and supply the pharmaceutical. China has its own Food and Drug Administration, which failed to discover the disreputable manufacturing process. One wonders how many other Chinese drugs are adulterated.

Also, in July, China announced that a drug company was producing adulterated vaccines.[2] DPT vaccines administered to infants are now considered ineffective. The same vaccine manufacturer's production of a rabies vaccine has also been deemed substandard. The Changsheng Biotechnology Co. in Jilin, China, used expired raw materials, improperly mixed vaccine batches, failed to conduct satisfactory rodent testing, falsified testing data, and destroyed production records. Local authorities discovered falsification of data last November but did not disclose this information until the rabies vaccine was determined to be adulterated in July. Chinese authorities were mum until an anonymous party posted on WeChat (similar to WhatsApp) corrupt regulators' failure to make the public aware of the improperly manufactured vaccines. Unlike the usual worry about criticizing the government, the public's anger about endangering their children with faulty vaccines has created a crisis that Xi Jinping has had difficulties controlling. The Chinese are rightly concerned that Chinese-made pharmaceuticals cannot be trusted. Jinping's clamor to transform the Chinese pharmaceutical industry by 2025 is justifiably dubious.

Adulteration is not just an issue with drug manufacturing. One recalls the imbroglio that followed the Chinese dairy industry's manufacturing of adulterated infant formula contaminated with melamine. The toxin resulted in kidney damage to hundreds of thousands of children. It is no wonder that many Chinese will only feed their children imported formula. The question that we face in integrative and naturopathic medicine is whether or not herbal and nutraceutical supplements are adulterated. One of the world's leading manufacturers of ascorbic acid is Zhonglan Industry Co. Ltd. In Shandong, China. There are no reports of adulterated Vitamin C manufacturing – but how do we know for sure? It is critical that vitamin manufacturers do quality control studies on all raw batch materials from China, and for that matter, India as well.

Cover Story – The Biology of Hope by Leigh Erin Connealy, MD

Each year there is a new book that offers the consumer (and health professionals) an overview of the world of alternative medicine cancer treatments. Last year I reviewed Leigh Erin Connealy's *The Cancer Revolution* in the August/September 2017 issue. Connealy writes our cover story in this issue on the very important concept that we, as practitioners, have the responsibility to ensure that our patients can maintain hope in their recovery. Too often we focus on the diagnostics and treatments, the lab results and the minutiae of the protocols, ignoring how the patient is really doing emotionally and mentally. We have to lift our heads from the charts and look the patient in the eyes not being falsely hopeful, nor brutally honest, but encouraging that spark of hope that fosters healing. Yes, this does take time, but it may

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From the Publisher

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make all the difference in what Bernie Siegel, MD, frames as whether the patient is living or dying day-to-day. In addition to reading Connealy's article, get her book for her insights on the best alternative approaches to treating cancer.

Outside the Box Cancer Therapies

Dr. Mark Stengler and Dr. Paul Anderson are physicians who have excelled in offering integrative naturopathic oncology care. Their approach combines not just the best of conventional care and naturopathic medicine, but they administer numerous unconventional therapies that are truly, *Outside the Box: Cancer Therapies*, their 2018 book available from Hay House. Stengler and Anderson explain better than most how alternative cancer therapies offer benefit to the patient who is engaging in conventional therapies. Contrary to the unproven claims of many oncologists, naturopathic care and intravenous therapies augment the benefit of surgery, chemotherapy, radiation, and immune modifiers. It is immensely frustrating to have patients be informed that supplemental herbals and nutrients will interfere with chemotherapy. Stengler and Anderson make the case for coordinated use of supplementation with conventional therapies detailing efficacy from the literature. Diet is very important, a point that has always been emphasized by cancer clinics for the past half century, but Stengler and Anderson sort out what aspects of dietary inclusion and restrictions are supported by the literature. Indeed, they argue that diet and supplementation must be carefully combined to offer the best enhancement of conventional and unconventional care.

The authors are strong advocates for the administration of i.v. therapies. Intravenous high-dose vitamin C is a mainstay but so are glutathione and alpha-lipoic acid. They also advocate specialized proprietary formulations in their protocols that have had demonstrated effectiveness in stage IV malignancies (you will need to read their book for this information). Stengler and Anderson examine the pros and cons of unconventional therapies including hyperbaric oxygen, hyperthermia, IPT, and vaccines. This is definitely a book you would like to have handy for the family coming in for a cancer consultation. And if you haven't read it yet, look at the August/September 2018 issue for Anderson's article and more.

James Greenblatt, MD, on Alzheimer's Disease Prevention with Lithium

Readers of the *Townsend Letter* are familiar with Dr. Greenblatt who lectures and writes about implementing integrative medicine in treating psychiatric disorders. One of Greenblatt's favorite tools is the mineral lithium commonly prescribed in pharmaceutical doses of 1200-1800 mg for manic-depressive disorder. He uses much lower dosing of

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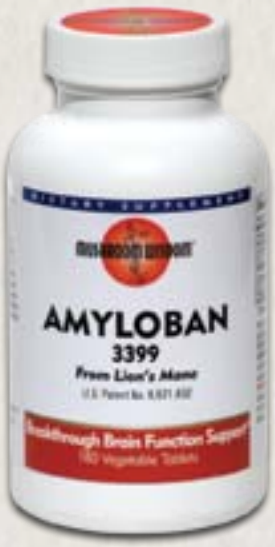

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From the Publisher

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lithium, 5-50 mg, which he refers to as "nutritional" lithium treatment. Unlike the high-dose treatment that requires monitoring and may have serious adverse effects, low-dose lithium poses no risk of side effects and offers benefit not only in treating a variety of psychiatric disorders, but also helps to preserve brain function, a key aspect in the prevention and treatment of Alzheimer's. Given the paucity of effective therapies for dementia, it would make sense to add lithium supplementation to the daily routine. Even better: supplement lithium together with Vitamin D3 and K2.

Is MSG Always a Dietary Trouble Maker? "No," says Sue Visser

Like many other medical and nutritional disciplines, there are numerous principles that we subscribe to that may or may not be true. One of the big ones is the common belief that eating meals prepared with heavy quantities of MSG, such as Chinese restaurant meals, will precipitate a variety of allergic reactions including headaches, skin rashes, and brain fog. Glutamine, an amino acid, is closely related to MSG; yet nutritionists and practitioners frequently prescribe it because of its touted benefit for a variety of medical conditions, for example, relieving side effects of chemotherapy. But glutamine and MSG are not separate entities; there is a close relationship between the two.

In this issue Visser examines that relationship between them and asks the question why and how they could have such diametrically opposite effects on the body. Visser would argue that many individuals would benefit from using MSG in their cooking and may achieve the same health benefits at much less cost than using supplemental glutamine.

David Minkoff, MD, and Julie Mayer Hunt, DC, on Craniocervical Chiropractic Care

While medicine has had a long-standing animosity to the chiropractic profession, the growing implementation of MRI technology has confirmed anatomical abnormalities diagnosed by chiropractors. In particular, the "Cranio-Vertebral Junction," involving the relationship between the occiput, atlas, axis, and adjoining ligaments, is subject to traumatic disruption. Minkoff and Hunt discuss how these disruptions will impact both blood flow and cerebral spinal fluid flow "dynamics." If the anatomic dislocations are not addressed, symptomatic problems, minor to major, will persist and not be corrected despite medical and nutritional interventions.

Minkoff opines that all patients with chronic head and brain pathologies should be assessed for craniocervical junction (CCJ) dislocation and treated accordingly.

Jonathan Collin, MD

1. Kaplan, S. Blood pressure medicine is recalled. *New York Times*. July 16, 2018.
2. Editorial: China's Vaccine Scandal. *Wall Street Journal*. July 28-29, 2018.

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Shorts

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Photobiomodulation and Brain Disorders

For decades, low-level light therapy has been used to stimulate wound healing and to reduce pain and inflammation in orthopedic conditions. Recently re-named "photobiomodulation," the use of red or near-infrared light is being investigated as a therapy to heal and protect central nervous tissue. Animal studies comprise most of the research at this point. These pre-clinical studies suggest that photobiomodulation (PBM) could be therapeutic, and possibly preventive, for a range of brain disorders, including stroke, traumatic brain injury, Alzheimer's disease, Parkinson's, and psychiatric disorders. In his 2016 review article, Michael R. Hamblin explains photobiomodulation's known mechanisms of action and summarizes key studies.

Light, depending on the wavelength and anatomical region of the skull, does penetrate into the brain, but response is not dependent on brain exposure. Hamblin reports that neurocognitive behavior in mice showed statistically significant improvement even when the animals' heads were shielded with aluminum foil and the rest of the body was exposed. Red (600-700 nm) and infra-red (760-940 nm) wavelengths are absorbed by cytochrome c oxidase (CCO), an enzyme needed by the mitochondria to make ATP. The absorbed photons cause an increase in mitochondrial membrane potential, resulting in more ATP production and triggering multiple signaling pathways that stimulate cell protection and repair mechanisms. Hamblin notes that CCO may not be the only photoacceptor since wavelengths other than red/infra-red can also produce beneficial results in some situations. Both coherent, monochromatic red laser light and non-coherent LEDs have been used in therapeutic PBM studies; it is still being debated whether one is more effective than the other.

Despite growing interest in PBM, published research on humans is limited. A small 2017 study, led by Anita E. Saltmarche, investigated the effect of PBM on five patients diagnosed with mild to moderately severe cognitive impairment or possible Alzheimer's disease. PBM treatment was applied with a headset that held four separate LED cluster heads plus one intranasal LED (810 nm wavelength) for 20 minutes during in-clinic visits (twice per week for the first 2 weeks, then once weekly for the next 10 weeks). In addition, patients were supplied with an intranasal LED device with a single diode that automatically shut off after 25 minutes to use at home on non-clinic days. Both devices were provided by Vielight Inc. (Toronto, Canada), which sponsored the study.

At baseline, the patients scored between 10-24 on the Mini-Mental State Exam (MMSE), which has a scale of 0-30 (higher indicates better cognitive function) and between 14-58 on the Alzheimer's Disease Assessment Scale (ADAS-cog), whose scale runs from 0-70 (higher indicates more impairment). Participants were re-tested at mid-way (week 6) and at the end (week 12) of treatment. Also, patients or family caregivers provided qualitative feedback during in-clinic interviews and from a daily home treatment journal. At the end of treatment, all PBM devices were withdrawn for a four-week, no-treatment period.

"After 12 weeks of PBM treatments, there were significant improvements on the MMSE (mean +2.60 points, $p<0.003$, two tailed) and the ADAS-cog (mean -6.73 points, $p<0.023$, two tailed)," report Saltmarche et al. In addition, patients and caregivers reported improved function (i.e., decreased incontinence, increased mobility), better sleep, less anxiety, fewer angry outbursts, and less wandering. Not surprisingly, caregivers reported that their own quality of life improved as their family member's behavior improved during the treatment period.

The improvement was not sustained during the no-treatment period. In fact, one patient experienced a "'precipitous cognitive and functional decline'" after only one week without treatment. "Because this was causing a high level of emotional distress for family and patient, the authors made the decision to disrupt his participation in the study," write Saltmarche et al. "The family was then given an active, intranasal-only '810' device and the [headset] device for home use, despite not completing the study. Later, the family reported anecdotally that behavioral improvements resumed."

The small number of participants and lack of a placebo-control group are limitations of this study. In addition, the authors would like future studies to include other quantitative, standardized methods for assessing changes in sleep, communication, anxiety, depression, and disruptive behaviors. They also advise that PBM therapy not be discontinued once it has been initiated in future studies because the "erosion of the positive effects...was unexpected and difficult for both the participants and the caregivers."

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Non-Pharmaceutical Intervention for People with MS

In a pair of 2017 studies, Iowa researchers investigated the effects of a multimodal, home-based program on mood, cognitive function, gait, and balance in people with progressive multiple sclerosis (MS). The multimodal intervention consisted of a modified Paleolithic diet, an individualized exercise program for stretching and strengthening of the trunk and leg muscles, neuromuscular electrical stimulation (EStim) of the trunk and leg muscles, and stress management (meditation and self-massage). Medical doctor Terry L. Wahls is senior author on both studies. Dr. Wahls, herself a patient with secondary progressive MS, regained function ("scooter dependence to ability to walk without assistance") using a similar program.

The first study, led by Jennifer E. Lee, was a one-arm, open-label feasibility trial that focused on mood and cognitive function. The study enrolled 21 people with progressive multiple sclerosis (mean diagnosis length was 13.6 ± 7.5 years) who had completed a two-week "run-in" period that showed they were able to adhere to the diet and exercise aspects of the intervention. In addition to completing daily home record logs (to document food intake, exercises, ESTim use, meditation, and self-massage), the participants completed several standardized tests to assess mood and cognitive function: the Beck Anxiety Inventory, The Beck Depression Inventory, the Cognitive Stability Index and Cognitive Screening Test, the Delis-Kaplan Executive Function System, the Wechsler Adult Intelligence Scale, Expanded Disability Status Scale, and Fatigue Severity Scale. These tests were taken at baseline and every three months for the duration of the 12-month study. Also, the researchers monitored for possible adverse effects with monthly side-effects questionnaires and blood analyses (complete blood count, creatinine, calcium, magnesium, and alanine aminotransferase).

The modified Paleolithic diet excluded gluten-containing grains, dairy foods, and eggs. Green leafy vegetables, sulfur-rich vegetables, and intensely colored fruits or vegetables were recommended (ideally, 3 cups of cooked or 6 cups raw of each category per day). In addition, daily intake of omega-3 oils (2 tablespoons), animal protein (4 or more ounces), plant protein (4 or more ounces), nutritional yeast (1 tablespoon), kelp (1/4 teaspoon), algae (1/4 -1 teaspoon), and nut milks were encouraged. Dr. Wahls taught the diet to participants and supportive family members and provided recipes and menus.

Patients showed a direct correlation between their participation in the intervention and improved mood and cognitive function; the more participation, the greater the improvement from baseline to 12 months. "Mood and cognitive improvements were more closely related to a higher intake of the modified Paleolithic diet than to exercise and stress management dosage," say the authors. However, increased exercise dosage did correspond to greater improvement in anxiety and depression scores. Mood changes appeared after just a few months while cognitive improvement took longer.

In addition, fatigue decreased. "Many participants reported verbally that once they developed a daily dietary routine, the diet was not difficult to follow, and the reduction in fatigue motivated them to continue with the diet," the authors write. "Indeed, study diet intake was impressive, with participants adhering to the food guidelines 94.5 to 98% of days during the 12-month intervention."

The same cohort was used for a prospective longitudinal pilot study, led by physical therapist Babita Bisht. At baseline, 6 months, and 12 months, participants took part in a test that consisted of standing up from a chair, walking to a mark 10 feet away, turning around, walking back to the chair and sitting down. The only statistically significant finding was increased walking speed at the six-month point; neither gait nor balance showed a marked improvement in the group overall. The authors attribute the lack of significant results to the "high variability in baseline characteristics of study subjects." One participant, however, with very poor walking speed at baseline (6.1 cm/sec) consistently improved throughout the study, achieving a speed of 24.3 cm/sec at 12 months. The authors note that this person had good family support and adhered to the diet 100 percent throughout the study.

As Lee et al point out, pharmaceutical treatment for MS has undesirable effects and is extremely expensive. The

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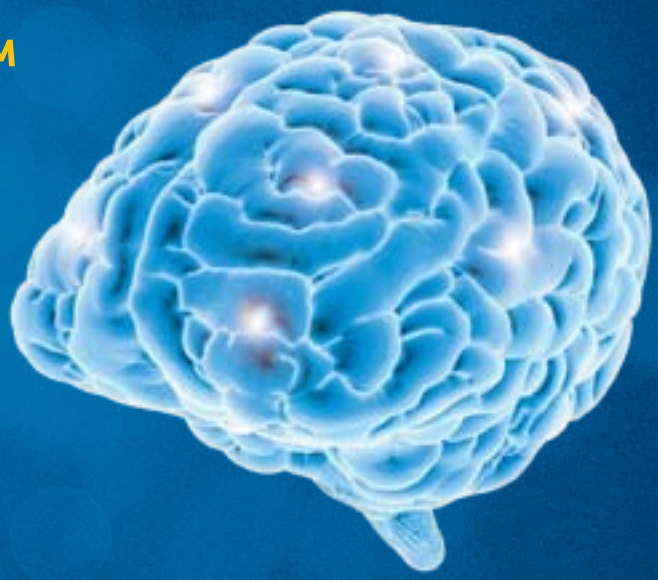

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Don't miss our next issue on Fibromyalgia, Chronic Fatigue, Chemical Sensitivity, and Pain Management

Shorts

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researchers call for randomized, controlled trials of this multimodal intervention that follow larger numbers of patients for longer periods to ensure long-term safety of the diet as well as efficacy.

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Mitochondria and Neuropsychiatric Disorders

Does mitochondrial dysfunction underlie neuropsychiatric disorders? Cellular, imaging, genetic, and post-mortem studies show that mitochondrial dysfunction contributes to bipolar disorder and schizophrenia, according to a 2018 review article by Josh Allen and colleagues. These authors believe that mitochondrial dysfunction underlies depression as well: "... recent evidence has opened the door to an expanded notion of the neurobiology of depression, such that a reduction in ATP levels, enhancement of oxidative stress, and acceleration of apoptosis are now considered to be important events...."

The brain requires about 20 times more energy, by weight, than the rest of the body. It needs ATP, produced by mitochondria, to release neurotransmitters and activate downstream signaling as well as for neuron differentiation. Dysfunctional mitochondria fail to produce the needed energy. As a consequence, oxidative stress and inflammatory responses increase, damaging cells further. In an opinion essay, Douglas C. Wallace, PhD, says, that a decrease in systemic mitochondrial production is going to affect the brain first because its needs are greater: "The milder the bioenergetic defect, the more brain-specific the symptoms, with hyperactivity or depression being likely examples." He refers to animal studies in which animals with different mitochondrial gene variations have different physiological responses to stress as well as learning and memory capacities.

From another perspective, George B. Stefano and colleagues hypothesize that antibiotics that cause abnormal psychological symptoms and behaviors in some patients do so because of their effects on mitochondria. Minocycline, for example, inhibits ATP synthesis and calcium retention in the mitochondria in brain cells. "The commonality of these antibiotic-induced side-effects lead physicians to create a term for this phenomenon called antimicrobial-induced mania, or antibiomania, since it can occur in neural tissues due to higher metabolic rates," they state.

Orthomolecular practitioners who treat mental disorders will not be surprised by the mitochondrial hypothesis. Nutrients that have shown benefits for their patients, nutrients such as niacin, pantothenic acid, and other B vitamins, are essential for healthy mitochondrial function.

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Digital Addiction

Do you go through "withdrawal" if you can't use the internet or your smartphone? Or is it a welcome relief?

As a recent article in *The Guardian* explained, the tech industry has deliberately designed smartphones to be addictive; and even the designers themselves are struggling to curtail their use of Snapchat, Twitter, Facebook, and Reddit. Erik Peper and Richard Harvey, at San Francisco State University, explain that "the visual and auditory notifications activate neurological pathways that are powerful and similar to what would have been triggered by a surprise, or even...a danger signal in our environment...causing us to momentarily 'freeze' and orient to the source." The inconsistency of "reward" when we respond to the notification (sometimes the waiting message really *is* interesting) strengthens the urge to re-fresh the page or check automatically for other notifications in the hope of finding another bit of information to excite the neurons. Peper and Harvey say that "the behavioral addiction of smartphone use begins forming neurological connections in the brain in ways similar to how opioid addiction is experienced by people taking Oxycontin for pain relief – gradually."

Being tied to smartphone use has consequences. First, the divided attention and multitude of interruptions that accompany smartphone/internet addiction foster distractibility and limit the ability to truly focus. Internet/smartphone addiction has also been associated with fewer social connections and higher levels of loneliness, depression, and anxiety. Perhaps most importantly, constant stimulation from this digital technology stresses the nervous system. Peper and Harvey say we need unprogrammed time for reflection, for silence, and for rest that permits regeneration: "Our nervous system, just like our muscular system, grows when there is enough time to regenerate after being stressed. Ongoing stress or stimulation without time to regenerate leads to illness and neural death."

Peper and Harvey offer several suggestions for reducing smartphone dependence. First, turn off app notifications when you need to focus on work. Tech executive Justin Rosenstein took it a step further. He told *The Guardian* that he asked his assistant to put a parental-control feature on his new iPhone that prevents any apps from being downloaded. Peper and Harvey also suggest checking email and social media only at specific times and letting friends and colleagues know that you respond only at those hours – instead of being 'on-call' throughout the day and evening. Peper and Harvey also urge making time for silence, for time without stimulation, to allow for self-reflection and regeneration.

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Methylation 2018 Summit Highlights

Understanding how methylation plays a role in chronic disease was the focus of the Methylation 2018 Summit in Chicago, Illinois (July 13-15, 2018). The conference was jointly organized by Dr. Carolyn Ledowsky, a naturopath from Australia whose practice focuses on methylation, and Researched Nutritionals. Her clinic, MTHFR Support Australia, focuses entirely on methylation. The methylation cycle turns genes on and off by transferring a methyl group between proteins. This transfer of methyl groups is also involved with a range of critical metabolic issues including detoxification, processing hormones, forming phospholipids to repair cell membranes, and supporting neurotransmitter levels.

Dr. Carolyn Ledowsky

Dr. Ledowsky presented multiple lectures throughout the conference. She began with some basics about genetic SNPs (single nucleotide polymorphisms) including methylation, the folate cycle, and the sulfur cycle. Throughout her lectures she used a pathway planner that detailed the biochemistry of these cycles, including the nutritional cofactors involved in each reaction along with environmental factors that would positively or negatively impact a specific genetic SNP. Her focus throughout the conference emphasized how our environment impacts the biochemical cycle of methylation through epigenetics.

After Dr. Carolyn Ledowsky's introduction on epigenetics, Dr. Nicole Bijlsma gave two presentations on the impact of environmental chemicals on our genetics. In Australia, she is an expert on the impact a home or office building has on health. She described in detail how mold can infect a house and cause chronic insidious symptoms in people from recurrent miscarriage to tinnitus. Mold overgrowth is a problem in many more homes than people realize. Because of genetic susceptibility and poor ability to detoxify, some people will have much more serious issues from mold than others. Dr. Bijlsma, along with several other presenters stressed the importance of supporting your ability to detoxify with glutathione for mold and other environmental toxins, such as organophosphate pesticides and heavy metals.

Dr. Andrew Rostenberg and Dr. Carrie Jones each discussed specific genetic SNPs that impact targeted health issues. Dr. Rostenberg elaborated on genetic SNPs that are critical for mood and behavioral issues such as COMT and MAO. If a person has different forms of the enzyme COMT based on different genetic SNPs, they may have either low or high dopamine and catecholamines. Elevated levels of dopamine are associated with high motivation but also anxiety and perfectionism. On the other hand, low dopamine is associated with difficulty waking up in the morning, low motivation, and addiction issues. Luckily, there are nutritional supplements that may help increase or decrease dopamine depending on COMT status and symptoms. Critical information for all of us to know to help our patients.

Dr. Nicole Bijlsma

The enzyme COMT is also involved in estrogen and other hormone metabolism, which was the focus of Dr. Jones's lecture. Depending on COMT status, estrogen can be broken down by different pathways. Some metabolites of estrogen may be beneficial while other metabolites may increase breast and other hormonal cancer risks. Urine testing can show the multiple breakdown products of estrogen and their ratios to understand the biochemistry of each individual woman. By understanding these ratios, specific supplements such as DIM may be helpful. Learning when to use DIM versus other supplements such as sulforaphane was a good clarification for practitioners.

The last few lectures at the conference went through case studies, providing examples of how to successfully implement protocols based on genetic and environmental susceptibility. Dr. Ledowsky was full of clinical pearls about different genetic SNPs and supplements that impact them. Overall the conference was very informative about how to include genetic and environmental susceptibility into clinical practice protocols to maximize patient outcome. ◆

International College of Integrative Medicine 2018 Conference Highlights

ICIM gathered together in the iconic city of Cincinnati, Ohio, for another excellent conference from April 18-22. Attendees came from all over the country and even internationally to hear experts discuss "What Works in Clinical Medicine." A diverse array of topics was covered, including ozone therapy, stem cells, clinical endocrinology, hair tissue mineral analysis, manual medicine, alternative pain management, medical marijuana, vitamin E, hemp oil, gut flora analysis, and an opioid symposium. It provided a solid foundation of topics in integrative medicine for newcomers and significant detail to challenge and further equip those already in the field. With the practical theme of the conference in view, a fascinating process of understanding biochemical mechanisms ascended into clinical application.

This learning process was enhanced further through pre-conference readings, rich Q&A panel discussions, and case presentations by ICIM members. It was incredible to have so many experts gathered in a single place, with such a diversity of expertise and experience to offer. As a result, each clinical topic was thoroughly explored from multiple vantage points. This learning environment afforded attendees a plethora of clinical pearls to take back to their practices and utilize on Monday morning. In addition, valuable lectures were given on upcoming changes in office compounding regulations and informed consent from a legal perspective. Attendees could claim up to 20 CME credits for the conference.

This meeting was not only educational but also engaging. The atmosphere was light-hearted as local comedian John Bromels handled the announcements and introductions. Attendees also dined on exceptional food – a difficult feat to pull off for a group of very health-conscious people! In the evenings, events were planned that allowed members to socialize and enjoy activities together. It was clear from the outset that ICIM truly values and emphasizes fellowship. Old friends caught up and first-timers were warmly welcomed into this special community. Connections were made, advice was offered, and ideas were exchanged between practitioners. In some ways it was reminiscent of a family reunion rather than just an academic meeting.

It was another dynamic conference by ICIM, and they will be back at it again in Minneapolis, Minnesota, for "An Orthomolecular Approach to Cancer" on October 18-22, 2018. ◆

In Memoriam: Dr. Edward Wolff McDonagh

Dr. Edward Wolff McDonagh passed away peacefully July 8, 2018, surrounded by family in Scottsdale, Arizona, at the age of 86.

He was born in Pittsburgh, Pennsylvania, in 1932, to James and Catherine (Wolff) McDonagh. Edward attended pre-medical school at LaSalle College and Temple University in Philadelphia. He entered the Army in 1955 and served in the 21st Infantry in Korea and Japan. He then attended Kansas City College of Osteopathic Medicine. Dr. McDonagh established McDonagh Medical Center in Gladstone, Missouri. Along with being an accomplished author and lecturer in alternative health, he was a pioneer in chelation therapy. Dr. McDonagh retired at the age of 80 in 2012 and moved to Arizona.

He was married to Norma Jean (Enderson) McDonagh from October 1964 until her death. He was also preceded in death by his brothers, James Edward and Ronald McDonagh, and his parents, James and Catherine (Wolff) McDonagh.

Dr. McDonagh is survived by his wife, Mary L (Beason) McDonagh, whom he married in September 2006; two daughters, Jamie Sue (Brian) Gross and Jodi Ann (Rodney) Oathout; two stepchildren; six grandchildren; and five step-grandchildren.

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Coffee and Brain Health

by Steven M. Helschien, DC

"Coffee and Brain Health" is one in a series of articles, written to educate the healthcare community about the science behind the healthy benefits of coffee.

Introduction

Caffeine wasn't discovered until 1821, but the origin of coffee plants dates back to the 4th century, A.D., in Ethiopia. The earliest evidence of coffee drinking is from the 15th century, in the Sufi monasteries of Yemen. By the 16th century it had reached other parts of the world.

Only in recent years has the scientific community studied coffee in depth, and found premium coffee to be a superfood, rich in antioxidants and beneficial for health, performance, and longevity.

Due to the polyphenols found in coffee, the potential health benefits include protecting against cardiovascular disease, type 2 diabetes, cancers, and more. It has also been found to enhance brain function and efficiency. It reduces the risk of Alzheimer's, Parkinson's, dementia, and MS. It helps fight depression and enhances mood, increases energy, and improves mental performance. Coffee improves focus, concentration, cognitive function, and working memory. Research shows that coffee consumption increases attention span, the ability to reason logically, and dramatically improves reaction time.

Depression

Unfortunately, depression is prevalent in modern society and it reduces the quality of life significantly. It affects almost 7% of Americans. A Harvard Study, following 50,739 women from the Nurses' Health Study, suggested that women who drank at least four cups of coffee every day reduced their risk of depression by up to 20%.[1]

Studies have also shown that drinking coffee daily can reduce the risk of suicide by 53%, in both men and women.[2] Researchers found that caffeine not only stimulates the central nervous system but may act as a mild antidepressant by boosting production of neurotransmitters in the brain, such as serotonin, dopamine, and noradrenaline.

Mood

Your emotional state plays an important role in your focus and energy levels. Consumption of coffee raises brain chemicals that promote a sense of wellbeing, allowing you to perform in a state of emotional efficiency; feeling less stressed, depressed and anxious. The reason isn't only related to caffeine, but also the antioxidants found in coffee.[3]

Scientists have known for many years that coffee stimulates the release of dopamine, a neurotransmitter in the brain. Dopamine produces the euphoric and pleasant feelings that people often associate with coffee. Many drugs release dopamine and produce euphoria, including cocaine and amphetamines. This helps explain why caffeine is the most widely consumed psychoactive substance in the world.

Increases Energy and Enhances Physical Performance

Coffee can provide increased energy and potentially improve physical and mental performance by increasing the release of catecholamines (such as

adrenaline) via the sympathetic nervous system, which among other things can make your heart beat faster, sending more blood and increasing oxygen to your muscles and brain. It also signals your liver to release sugar into the bloodstream for energy.

There are so many metabolic effects of caffeine that it's hard to sort out which are responsible for the increase in physical and mental energy. Caffeine can help muscles contract by encouraging the sarcoplasmic reticulum in muscle fibers to release calcium ions and reduces the percentage of maximum exertion that a given exercise requires. Increased circulation and intracellular substrate availability, or fuel for the muscles, occurs in response to changes brought on by caffeine, and may help to explain the perception of reduced exertion during exercise.[4]

Reduces Stress

Stress is a normal response that is helpful when faced with challenges. However, it begins to affect many bodily processes when continued over an extended period of time. Too much stress has been linked to high blood

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pressure, heart disease, insomnia, obesity, and mental health disorders. According to the American Psychological Association, 33% of Americans never discuss ways to manage stress with a health care provider.*

Researchers discovered that mice given caffeine were better able to handle stress than mice subjected to stressful situations sans caffeine. The reason: While caffeine usually blocks adenosine receptors from activating sleep processes, it also prevents the receptors from reacting to, and causing a stress response, including a bad mood, memory problems, and an enhanced susceptibility to depression, the researchers found.[5]

Improves Focus, Concentration, and Cognitive Function

Anyone studying for an exam or preparing for an important presentation knows they are able to focus better after they've had a cup of coffee. This is because caffeine helps your brain function more efficiently. It also increases your attention span, your ability to reason logically, and dramatically improves your reaction time. Once you drink that morning cup of Joe, your bloodstream absorbs the caffeine and carries it to the brain where it blocks adenosine, an inhibitory neurotransmitter, which increases dopamine levels, firing neurons, and boosting your mood, focus, and concentration.

Coffee Enhances Working Memory

Think of your computer's RAM as the processing power of your brain. By increasing your working memory, you are less prone to distraction, and this allows your brain to work more efficiently.

We've known for a while that caffeine has cognitive-enhancing effects, affecting short-term memory; but studies from Johns Hopkins University now show its positive effects on strengthening memories, making them resistant to, or reducing forgetting for over 24 hours.[6]

Protects Against Alzheimer's, Parkinson's, Dementia, and MS

Alzheimer's is the most common form of dementia, and it generally affects those over 65 years of age. There is no cure currently; however, there are plenty of preventive steps you can take. In addition to exercising and eating healthy, drinking coffee can also be effective.

Researchers from the University of South Florida and the University of Miami tested the blood levels of caffeine in older adults with mild cognitive impairment, or the first sign of serious forgetfulness, and then re-evaluated them two to four years later. Participants who had little or no caffeine circulating in their bloodstreams were far more likely to have progressed to full-blown Alzheimer's than those whose blood indicated they'd had about three cups' worth of caffeine.[7] Those who drink coffee on a daily basis have a 65% less chance of developing Alzheimer's or other dementia as they age.

The second most common degenerative disease, Parkinson's, is caused by the death of neurons that generate dopamine inside the brain. Studies published in *The Journal of the American Medical Association* have shown that coffee drinkers are up to 60% less likely to develop Parkinson's due to the caffeine content.[8] Drinking decaf coffee will not lower the risk of Parkinson's.

Studies also show that drinking at least four cups of coffee every day can reduce the risk of multiple sclerosis. The belief is that it prevents the inflammation that leads to the development of the disease.[9]

Choose Quality Coffee for the Greatest Health Benefits

The best quality coffee yields the greatest potential health benefits. The way coffee is grown, handled, and roasted has a direct effect on its quality. Independent tests have shown that out of 100 organic coffee brands tested, Purity coffee had the highest levels of antioxidants with no mold or mycotoxins.[10]

Brain Booster Supplements

There are three products, that when used with coffee, are healthful brain boosters: L-theanine, Percepta, and Teavigo.

L-theanine is an amino acid found almost exclusively in teas from the plant, *Camellia sinensis*, (containing green tea catechins and caffeine). It is used to promote brain health; most notably relaxation, without sedation, and rejuvenation. It has been shown to be effective at reducing stress.

Percepta is a unique, proprietary plant-based nootropic nutraceutical, designed to target the accumulation of "plaques and tangles" in the brain that directly contribute to memory loss. Starting in early adulthood, our brains begin a slow, deliberate decline, as they begin to accumulate "plaques and tangles." Percepta is the first dietary supplement to target the real reason we lose memory as we age – brain "plaques and tangles." Studies have shown that Percepta halted, reduced, or dissolved plaques and tangles in the brain. Percepta is backed by over 15 years of scientific studies and has over 50 issued patents.[11]

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

Teavigo is caffeine-free green tea extract with EGCG. EGCG is a powerful green tea catechin that has many health benefits, including improving brain function.

Conclusion

Many studies have shown that coffee not only protects against cardiovascular disease, type 2 diabetes, cancers, and other diseases and conditions, but it has important benefits for the brain.

Currently, 5.7 million Americans have Alzheimer's. Depression affects 15 million Americans each year, and anxiety disorders are affecting 40 million Americans a year. Suicide rates are at a 30-year high. Patients need their healthcare providers to care for their brains and mental health, along with the rest of their body. Due to the research on the benefits of coffee, healthcare providers can help their patients by recommending quality coffee for their brain and mental health.

* To receive a copy of Dr. Helschiens's monograph, "When Stress Becomes Distress," please email: Doc@Level1Diagnostics.com.

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FCT®, Brain, Patients, Researchers and Doctors

by Savely Yurkovsky, MD

The Problem

As the media and politicians keep us occupied with the threat to America from the far lands of Russia and Middle East, the ominous medical statistics point to one of internal and urgent nature – the skyrocketing epidemics of chronic diseases, with the brain being the leader.

From the young children with autism, ADHD, and learning disabilities, to starting Alzheimer's earlier in life, and in-between, they all keep growing. The 'in-between' consists of countless millions of people suffering from depression, anxiety, insomnia, poor memory, brain fog, substance abuse, bi-polar, OCD, concussions, brain tumors, and electromagnetic hypersensitivity creating a zombie-like state. All of these and their causes remain a mystery to our brain scientists. Over 100 million chronic pain sufferers, from brain to toe, neither they nor the neurologists and pain specialists have a clue. The only thing that they know about pain for sure is to prescribe more opiates, which kill 60 thousand people a year. As our political leaders keep the public pacified by generously supplying NIH with new stacks of billions of dollars to generate 'more research' and its related hope, the reality behind both is that the billions just keep feeding a bonfire since, as with all chronic diseases, nothing really comes out from this research that works. As unbelievable as this statement may sound, it is a simple truth that our 'scientific medicine', like any hyped inept endeavor just keeps replaying the script of a Russian saying: "While doing business we were having fun but when opened a register we started crying."

Here is what is really in the register of our hyped neuroscience research, after billions of dollars have been turned into the ashes: "…although researchers worldwide are publishing tens of thousands of neuroscience studies every year, neither our understanding of basic brain functions nor our ability to treat brain disorders seemed to be progressing much." This statement belongs to the world-renowned Israeli brain researcher, Professor Henry Markram, MD, the head of the just failed 1.3 billion-dollar brain project in the European Union. The register of other specialties is just as empty. "Even papers in immunology or cell biology mystify me – and so do some papers in my own field, neurobiology. Every day my expertise seems to get narrower. So, scientists have had to fall back on another strategy for coping with the mountain of information: we largely ignore it…." This was recently said by Columbia University professor Stuart Firestein, PhD. The quotes of cancer scientists are just as hopeless. What does our medical think tank, NIH, says about this total failure and its bonfire? While remaining inept, they finally started waking up years back and suspected a big rat in their 'research' projects which cannot solve anything. As a result, and to their credit, they quietly came out with Translational Research Initiative, in 2005, to somehow translate medical research findings (bench) and spent dollars on something that would finally work in medical practice (bedside). They even invited other sciences to come to the rescue, but why they keep failing they still don't know.

The general cue to the very heart of the problem, of both the research and its based treatments, was offered by a distinguished neuroscientist who specializes in brain and peripheral nervous system related to pain. "We cannot fix the problem of chronic pain because its main underlying problem – medical model – has been completely wrong," said Professor Sean Mackey, MD, of Stanford University. The implications are that a model of disease represents how disease is actually viewed and ought to be researched, investigated, and treated; and once this model is "completely wrong," the outcome can only be apples to treat oranges. In this case apples are drugs, based on some generic disease labels, to treat the mismatched oranges – individual patients with their own individual causes behind their diseases.

Instead of determining what really makes people sick, the completely wrong model researches only the myriads of their symptoms whether high blood sugar or cholesterol, blood pressure or inflammation, and a thousand other things. In brain disorders the model was stuffed with symptoms related to neurotransmitters – dopamine, serotonin, GABA, and others – and their corresponding receptors. These then are matched with drugs to only make symptoms less abnormal while the underlying real disease keeps destroying the body and more diseases emerge. On a whole, Harvard scientists have called the current model of disease as grossly outdated, dating back to the end of 19th century when proposed by Sir William Ossler, MD. The question why is it outdated and what exactly is missing?

By the admission of conventional academicians themselves, which you won't find on CDC and NIH websites or CNN, the main missing pieces to the puzzle are exact causes of diseases, which we can liken to bullets lodged in the internal organs

and producing hundreds of abnormal findings and diseases. But not only are these inaccessible to laboratory and imaging tests, these causes also act in gangs of interacting layers that make the investigative mission of the mainstream molecular research and labs beyond impossible. The next missing pieces are individualized, systemic treatments, coined as system biology – instead of treating just isolated organs and tissues, as tagged by outdated generic disease labels. However, while the hope for individualized systemic treatments mainly lies with more drugs pertaining to genes, the effective diagnosis and treatment of disease-causes (which cause multi-systemic and gene malfunctions too) can automatically provide individualized systemic treatments, also. Many toxicological, infectious, and other morbid agents cause multi-systemic morbidities; and their combinations and a person's vulnerability is always individual. Getting to the causes hiding inside the internal organs can only be done through one of the salvation sciences that NIH is still looking for, physics, and its related diagnostic and therapeutic energetic methods – bio-resonance testing and a novel way to practice homeopathy, respectively. Nobel laureate in medicine, Professor Albert Szent-Györgyi, even in the middle of the 20th century, already commented that without the concept of energy of physics, molecular research might, just as well, study a dead meat.

Bio-Resonance Testing, Advantages, Limits and Treachery

Many years ago, after getting frustrated with the alternative twin of this model in alternative medicine, I was lucky to come across an article by the former chairman of the materials science department at Stanford University, Professor Emeritus William A. Tiller, PhD: "Future Medicine will be Based on Controlled Energy Fields." Among the modalities considered were bio-resonance and homeopathy, based on the fundamental energetic level of our bodies. Thousands of other scientific references from throughout the world in support of this type of medicine still remain ignored. After years spent on evolving a different model by deepening and making more specific cause-related diagnostic and therapeutic abilities of bio-resonance testing and homeopathy, this prophecy has proven correct, based on the reversals of numerous cases of severe chronic diseases, through FCT. Among these are many brain disorders.

However, I wish to draw the attention of medical practitioners to the key word in professor Tiller's prophecy, which is not energy or fields, because failures and even side effects in energy medicine are common too, but the word "controlled." Controlled means precise, meaningful, reliable, safe, which are the hallmark of true science, in relation to a problem at hand. As much as all of us need our cars to have a gas pedal, not too many want it uncontrolled and full of surprises. Many FCT practitioners have found that "controlled" is what sets Field Control Therapy apart from other treatments that seemingly use 'similar' bio-resonance testing or homeopathics. And this is where the concept of a right or wrong model ➤

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"A cause is something without which a disease would not exist." - *Prof. Colin Alexander, MD.*
"After practicing for 15 years and assembling a lot of technology, I feel that my concept of 'underlying causes' requires a shift into a different level." - *ND.*

Students' comments…

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"Getting to the root cause of illness!"
"Deep insights into causes of illness." "World class practitioner allowing us to all benefit from his system."
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does not let go either as it always, like a shadow, follows any action in medicine or science. The facts are that, besides the majority of bio-resonance testing methods failing to meet the necessary outlined above requirements to be successful, many practitioners are not aware of the numerous technical blocks in these methods either. Among these, conducting the testing in the area where powerful ambient EMF block readings. Here, skillful bio-resonance testing is indispensable, again, in sorting out just 'EMF protective' devices from those that really deliver, such as an excellent German Memon technology. But, besides this and other mechanical blocks that obscure the important findings, there is, even, a quantum treachery in action, too.

Many FCT practitioners have found that "controlled" is what sets Field Control Therapy apart from other treatments that seemingly use 'similar' bio-resonance testing or homeopathics.

It is related to the phenomenon of quantum weirdness having to do with the brain-to-brain non-local energetic entanglement, known as Einstein-Podolsky-Rosen paradox. In our case, this takes place between the brains of a patient and a practitioner conducting the test. This treachery misleads a practitioner into assuming that the treatments that the patient is being tested for, whether through muscle or computerized testing, and accepting as seemingly beneficial for his/her condition, are necessarily so. However, what really is the case is that a patient is rather involuntarily consenting to the treatment rather than genuinely accepting it, because of 'scanning' the practitioner's brain through entanglement. Following this, he/she realizes that the choices are, often, limited. From there, if better options do not exist a patient tests as accepting the treatment that may carry only a minor or no benefit, at all, and, even, risking side effects. Certainly, the entanglement may also include the practitioners imposing their will on a patient to accept the tested treatment. A concrete and benign example of consenting to 'beneficial', yet mediocre treatment took place at one of my seminars. An alternative practitioner, a biological dentist, had determined through conducting bio-resonance testing that a patient had a beneficial muscle response to the products usually used by biological dentists and alternative practitioners for mercury detoxification. In order to avoid any element of subjectivity on my part, by testing the patient myself for FCT homeopathic mercury detoxification regimen, I offered him to test it on his own on that patient.

Following this, the practitioner stated that the patient's reaction was positive to these remedies, too. I asked him, then, to re-test his initially 'beneficial' mercury detox products which, to his surprise, the patient immediately rejected once his body recognized a better, FCT option. This equally concerns EAV-computerized testing devices.

As a bad example of this 'acceptance', one patient who was referred to me by a practitioner whose treatment, based on his 'special' muscle testing, produced severe detrimental outcome shared with me that she afterwards questioned the doctor of the validity of his test. To this he gave an honest answer, "I don't know what to say." Recently, I saw a chiropractor with severe memory and many other health problems, who had undergone many treatments in alternative medicine, for 20 years, including those based on a bio-resonance testing. His conclusion: "I've been having some health issues that no one has really gotten to the bottom of."

Obviously, there are thousands of questions and treatments which the involved models of this test and treatments offer, that is why I often receive these types of frustrated feedback such as this from an integrative MD; after spending tens of thousands of dollars and just as many hours on different bio-resonance testing techniques, including our god, computer-related, none worked. His conclusion was the same, because these failed to get to "the root cause" of diseases. The end result was exactly reminiscent of mine in the past, "I've wasted a lot of time and money on muscle testing and other machines that have not panned out."

Speaking of god and brain, I had a demo in my office of computerized testing equipment, by the company technician, on actual patients. Among the total 90% in inaccurate readings, the computer missed brain and the rest of the nervous system pathology in a patient with multiple sclerosis and diagnosed a happy patient as being depressed. In order not to ruin all of the patient's high expectations of god's prescriptions, I refrained from expressing my pessimism concerning these. The end result, none has reported any improvement, and the happy patient treated for 'depression' ended up with the bad headache and stopped the treatment. Another email from a patient reported a case of long-lasting aggravation, following the 'god's' treatment, that a practitioner could not resolve. Perhaps it would be useful for us to know what real scientists, such as MIT leading computer scientist, Professor Marvin Minsky, PhD, said of computers: "No computer has ever been designed that is ever aware of what it's doing; but most of the time, we aren't either." My acquaintance, retired physics professor at MIT, George E. Pugh, PhD, shared with me how his computer software, designed for the Pentagon to conduct strategic operations during the Cold War, kept failing until he made the generals aware that computers have limits. As to the quantum treachery, none can avoid it, as far as I know. However, whether the potentially better treatment options exist or not, if consistent reversals of severe diseases is the case, this Achille's heel of the testing is not critical.

Treating Root Causes of Brain Disorders with FCT

In addition to overcoming many blocks in testing and navigating deep penetrating power of homeopathic energetics, based on modern, not 250-year-old outdated medical knowledge, the FCT has also taught me other good lessons. As valuable as some common knowledge in alternative medicine is concerning morbidity of mercury and other toxic metals, infections such as candidiasis, parasites, Lyme or molds, and many other things, including noxious EMF, none of these is generic but is strictly individual. There is only individual mercury toxicity, Lyme disease, mold, and 100 other problems. It is because all of these affect each person due to his/her individual set of malfunctioned organs, genetics, lifestyle, environment,

and loads and degree of intensity and interplay of these agents in the body. From here for a treatment to be truly successful, it must be individualized, systemic, and based on the hierarchy of importance and sequence in treating the causes of each patient's illness. The following successful patient cases were based on this individualized, systemic approach, even though seemingly the same generic causes were treated.

One of the interesting returns on the individualized systemic FCT 'investment' were many elderly patients whose common complaints of poor memory, retention, insomnia, tinnitus and others are all enthusiastically 'reassured' by their doctors as "due to old age." Yet, patients in their seventies and eighties often reported that, strangely for their age, their memory, word search, insomnia, eye sight and hearing problems were all improved and, even, dramatically, in some cases. A woman, near eighty, who was cured from depression also reported that she was able to write better poetry, felt wiser, and able to analyze events and make decisions better.

A woman, near 60, cured from brain fog, extreme EMF sensitivity, severe systemic Lyme disease which infected her brain too, reported that she suddenly found, that after 30 years of use, her contact lenses became unnecessary. A note to the doubters concerning a possible placebo effect, years preceding this while undertaking far more impressive, on the surface, massive treatments for Lyme from 'Lyme literate' and other integrative doctors produced zero progress.

A 90-year-old woman, who seemed to have gone out of her mind with severe paranoia due to her old age, was cured from it after bio-resonance test diagnosed her and homeopathic energetics cleared her brain Lyme infection.

However, the problems with memory, concentration and retaining of information have become endemic not only among the young adults but even teens and children. A young 20-year-old college student was virtually cured from these in just one treatment.

A few more concrete brain disease cases include the following:

- A man in his 40s on Klonopen for 15 years for severe anxiety and depression was cured following treatment for Lyme and worm infections, toxic metals, and EMF all acting as a gang in his brain. Off Klonopen for eight months.
- A boy with PANDAS with hundreds of face tics, headaches, irrational fears, inability to concentrate cured.
- A man with bi-polar disorder, anxiety, depression cured.
- A girl with tandrums, OCD, hyperactivity cured.
- A boy with autism spectrum disorder pronounced by his pediatric neurologist cured.
- A young man with suicidal depression, anxiety for 10 years and with many psychotropic drugs cured. All drugs stopped years back.
- A very interesting case, like some that present a challenge in not readily resolving, required detective work. As usually the case, these involve re-poisonings – often with supplements, foods or the most 'pristine' waters on Earth. In this case, this was indeed 'pristine' and 'natural' Himalayan salt, which a search on the internet did confirm as containing very toxic ingredients:

  "This treatment was incredible, it's awesome. I have so much more energy and being more active. I feel like I am 25 (she's 52). Actually I feel better than when I was 25. I have an increase in muscle mass and tone. Much smaller waistline. Tinnitus disappeared. I never felt so good for so long. I am not craving sugar or anything. Just for a few days after I took Himalayan salt remedy I craved sea salt before it stopped."

Don't be surprised that some 'holistic educators', like Dr. Mercola, peddle it too, among the other useless products which, often, contain toxins. Speaking of 'pure' waters, until one tests these and other 'pure' organic things with skillful bio-resonance testing they are to be assumed as 'pure' as regular city tap water. In quite a few cases, severe memory problems and migraines could be cleared only after the patients both stopped consuming these and took a remedy prepared from the corresponding waters. Needless to say, no treatment can possibly work when a continuous re-poisoning takes place.

The conclusion is obvious; getting to root cause of diseases is the only model that works, and we must keep getting better at it. ◆

Savely Yurkovsky, MD, is internationally known as an author and teacher with an extensive background in the thorough study of scientific principles behind the numerous alternative and conventional approaches. Having realized that the primary source of health and disease, according to physics, stems from the corresponding cellular energy fields, he adopted a revolutionary new medical model, one that interfaces the theories of biology and physics established by his mentor, Professor Emeritus William A. Tiller, Ph.D. of Stanford University.

Having evolved a unique bio-energetic medical system that integrates a great deal of pertinent but, until now, underused knowledge from medical and non-medical sciences, Dr. Yurkovsky's system has been able to transform the often vague nature of medical specialties from "hit and miss" paradigms into a far more effective, exact and predictable science. Dr. Yurkovsky has founded a teaching organization, "*SYY Integrated Health Systems, Ltd.*," which is dedicated to sharing his medical system under the concept of FCT – Field Control Therapy® or Guided Digital Medicine™. Since 1999, he has taught this curriculum to medical doctors and licensed health care professionals with special emphasis on energy-based diagnostic and therapeutic modalities aimed particularly at toxicological, biological or nuclear agents. These, as a rule, elude conventional and most of the alternative diagnostic methods yet represent the primary source of all chronic diseases. His book, *Biological, Chemical, and Nuclear Warfare – Protecting Yourself and Your Loved Ones: The Power of Digital Medicine* is an excellent illustration of both the scientific basis and effective practical means to combat the ravages of acute and chronic diseases in our toxic world. His system is the only alternative medical modality that has drawn attention from one of the departments of the Homeland Security Office. This year, along with several other doctors from premier medical schools in the US, he has been nominated for the prestigious Bravewell Leadership Award for "*significant contributions to the field of medicine*" and "*compelling vision for the future of medicine*."

Dr. Yurkovsky offers training to capable health care professionals.
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Pathogens in the Brain – The Oral Connection

by Blanche D. Grube, DDS, PhD

Introduction

Often times, pioneers of medicine, as well as dentistry are disregarded due to their disruption of the status quo. They become marked as rebels, controversial, and even "quacks" due to their methodologies; however, their groundbreaking ideas and discoveries sometimes come full circle. DNA testing is now proving what the science of yesteryear and clinical observation was showing, that the mouth is the key to health—good or bad.

More than a century ago, the subject of the mouth as the source of infection was being investigated by the luminaries of the day. Today this transference is referred to as "bidirectional," meaning that the microorganisms or their toxins could travel to other parts of the body.

Pioneer, Dr. William Hunter, a senior assistant physician, at the London Fever Hospital, published a paper in July 1900, titled, "Oral Sepsis as a Cause of Disease." This subject was of great interest to him for many years. His research revealed that the number of microorganisms that cause oral sepsis, and also contribute to many conditions, could be infinite. In the course of his investigation, he found pyorrhea alveolaris, stomatitis, gingivitis, erythematosa, pustulosa ulcerosa and gangraenosa. He observed that all of the various conditions were, in fact, septic in their nature and were produced by what he called "pus organisms." He continued, "These organisms were associated with every case of dental caries, no matter how slight."[1]

Hunter's message to all medical professionals such as physicians, surgeons, dental surgeons, and also patients offered solutions to help the patient recover, recommending not just a simple mouth rinse, but the following:

> (1) direct application to the diseased tooth or inflamed gum of carbolic acid (1 in 20), repeated daily for just so long a period as the patient will persist in keeping his necrosed tooth or fang; still better (2) the removal of all diseased useless stumps; (3) the most scrupulous daily sterilizing by boiling of every tooth plate worn; and (4) on the part of dentists, the avoidance of too much conservative dentistry and the use of contrivances like 'bridges', which cannot possibly be kept aseptic.[1]

Hunter's insight to the problem of oral pathogens was truly remarkable for the time. His vision of preventive medicine is where we, now a hundred years later, need to return to. A world where doctors, dentists, and all health and wellness professionals work together for the benefit of the patient. What Hunter described so long ago, is what we call a full dental revision today.

Others followed in the footsteps of Hunter such as Dr. Frank Billings, professor of medicine at Rush Medical College and Presbyterian Hospital in Chicago, who originally coined the term "focal infection." Fifteen years after Hunter's trailblazing article, Billings published *Focal Infection – The Lane Medical Lectures*.[2] Billings, using both human and animal tissues as the source in their research, remarked that there was a tremendous team effort made in order to complete this work. He made a special acknowledgement about Edward C. Rosenow, who joined the clinic in 1904, saying his work was brilliant. Billings confirmed that their conclusions were not made until a critical survey of the work and results were investigated by other qualified clinicians, pathologists, and research workers.

Billings stated, "A focus of infection may be defined as a circumscribed area of tissue infected with pathogenic microorganisms. Foci of infection may be primary and secondary."

Billings continued:

> …the incidence of infections in the mouth is enormous everywhere. In addition to the presence of innumerable saprophytes in the mouth and pharynx, one may find in the saliva and pharyngeal mucus, streptococci and staphylococci, micrococcus catarrhalis, pneumococci, diphtheria and pseudodiphtheria bacilli, meningococci, tubercle bacilli and many other pathogenic bacteria. C.C. Bass and others state that endameba buccalis was found in the mouths of 95 and even 100 percent of all adults examined.[2]

After Billings and Rosenow, came Weston A. Price, a Cleveland dentist, who along with his predecessors, looked at the connection of dentistry to nutrition and its relationship in overall health.[3] Price also praised the work of Rosenow, who by then was at the Mayo Institute. Price did extraordinary research on root canal teeth, using the methods of Rosenow, by studying bacteria and its mutations in humans and animals. He confirmed what his peers had found:

> The great majority of adults and children are, therefore, carrying as dental foci, the strains of organisms which are found in the majority of heart, kidney, joint and muscle, and nerve lesions, and which are potentially capable of producing these in the absence of an adequate defense.

Price also found that dental infections involving root canals almost always

continued on page 32 ➤

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Brain Pathogens

➤ *continued from page 30*

contained streptococci, which had many types or strains.[4] He realized that many of the methods used for sterilization of infected teeth did serious damage to the supporting structures around the teeth. Specifically, he discovered that root canal filling material rarely filled the pulp canal sufficiently to shut out bacteria, therefore, leaving room for infection.

By the 1930s the focal infection theory was falling out of favor, with some who observed: "If this craze of violent removal goes on, it will come to pass that we will have a gutless, glandless, toothless – and I am not so sure that we may have, thanks to false psychology and surgery, a witless race…."

Decades later, my friend and mentor, Dr. Hal Huggins was gifted the archival original research of Dr. Weston A. Price, which prompted Dr. Huggins to analyze the DNA of extracted root canal teeth. He discovered 83 different anaerobic bacterial species. Huggins found that many of the bacterial species that were identified over one hundred years ago were still prevalent today.

In the *Townsend Letter,* July 2017, we had written an article on Lyme disease.[5] We spoke of how Dr. Huggins developed what was then called the "Full View Test," now called the "Oral Panel" to identify the microorganisms. These organisms are present in the only part of the human body that cannot be effectively defended by the immune system; the mouth. He encouraged all dentists who were removing unserviceable root canals to send them to Dental DNA for molecular-based testing. This was the laboratory he established to identify microorganisms present in oral infections. I spent over two decades being mentored by Dr. Huggins. Together, we developed the Huggins-Grube Protocol that educates dentists, doctors, and other health care professionals, as well as consumers, on biological and holistic dentistry. When he passed away, I took over his work and am continuing the lab, which was renamed DNA Connexions.

Today we know that the pathogens in the mouth are affecting the brain and many neurodegenerative diseases have been linked to these oral pathogens.[6-11] When the brain is damaged, it can affect numerous functions in the body, including memory, sensation, and personalities.

Some of the common brain diseases are the following:

- Alzheimer's disease,
- Parkinson's disease,
- Huntington's disease,
- Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease,
- All forms of dementia,
- Memory loss,
- Forgetfulness,
- Apathy,
- Anxiety,
- Agitation,
- A loss of inhibition, and
- Mood changes.

The scientific research is now showing that oral pathogens are not only being found in the brain, but also other distant parts of the body. These microorganisms found via DNA-PCR testing are all found in periodontal disease:

- *A. actinomycetemcomitans,* a Gram-negative bacterium that is commonly found in the oral cavity and has also been found in brain abscesses;
- *P. gingivalis* and selective spirochetes that have been found in Alzheimer's disease brains;
- *P. intermedia,* a Gram-negative bacterium known to colonize in the respiratory tract and is associated with cystic fibrosis, chronic bronchitis and abscesses in the head and neck, as well as meningitis;
- *B. forsythus,* a Gram-negative bacterium linked to periodontal disease;
- *C. rectus, E.,* a Gram-negative bacterium that has been found in brain abscesses and emerging evidence shows it could become a major periodontal pathogen;
- *E. nodatum,* a Gram-positive microbe that has been found in periodontitis;
- *Treponema sp.,* a Gram-negative bacterium; compelling evidence is showing that treponemes are involved in the etiology of several chronic diseases, including periodontitis and other forms of periodontal disease.

Typically, the mouth harbors at least six billion bacteria. The red complex, which includes *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* (formerly *Bacteroides forsythus*), encompasses the most important pathogens in adult periodontal disease. Additionally, *Fusobacterium nucleatum, Prevotella species, Eikenella corrodens, Peptostreptococcus micros,* and *Campylobacter rectus* are increased in deep periodontal pockets and are implicated as possible periodontopathogens.[12] These bacteria are not usually found alone, but in combination, suggesting that some bacteria may cause destruction of the periodontal tissue in a cooperative manner.

The science shows that oral pathogens are likely to promote disease progression.

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Better Detection and Treatment for Mold Exposure: Improving Outcomes for Patients

by Matt Pratt-Hyatt, PhD

One of the hallmarks of integrative medicine is to focus on determining the underlying causes of chronic illnesses for patients, not just to treat symptoms. This has led many practitioners of integrative medicine to use testing that helps provide more personalized care protocols to their patients. It is the duty of diagnostic laboratories to deliver the most accurate test results possible and provide interpretations of the results to help practitioners understand the correlations between results and their patients' conditions. At The Great Plains Laboratory, we have been working on finding new ways to detect underlying causes of many illnesses and studying correlations between the results and conditions. Using results from both our MycoTOX Profile as well as our Organic Acids Test (OAT) (both urine tests), we have discovered correlations between them and uncovered new routes of treatment for patients with mold exposure.

For several decades, new research has gone into the detection and treatment of mold mycotoxins. These are the toxic metabolites produced by certain types of fungi. These small molecules are often carried on dust particles or food or are present in water-damaged buildings and homes. The most common routes of exposure are inhalation, skin contact, or ingestion through contaminated food.[1] Exposure can lead to different types of chronic health conditions depending on the age, sex, genetics, and health status of the patient. Common symptoms of mycotoxin exposure are fatigue, headaches, rashes, food sensitivities, joint pain, and cough.[2-4] Mycotoxins can induce disease through different routes such as cytotoxicity, immunosuppression, and DNA damage.

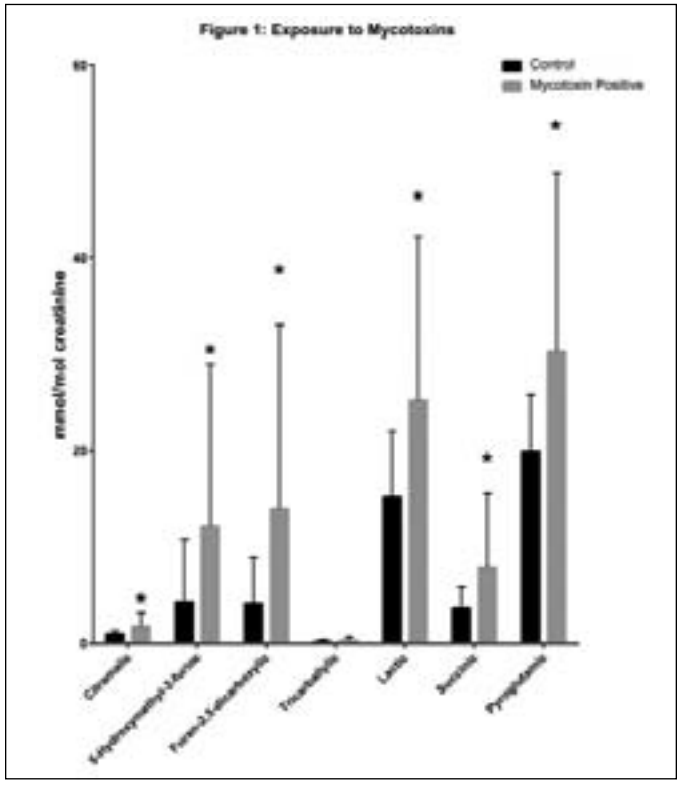
Mycotoxins can cause cytotoxicity by inhibiting multiple pathways within the cell. Mycotoxins inhibit the production of proteins by interfering with the function of the ribosome. Multiple mycotoxins bind to different subunits that are involved in protein biosynthesis, such as the 60S subunit of the ribosome.[5,6] In addition to inhibition translation, mycotoxins can also activate Jun N-terminal Kinase (JNK), mitogen-activated protein kinases (MAPKs), and p38.[7,8] Activation of these stress response elements in the cell can lead to cellular damage.

Through their mycotoxin metabolites, pathogenic fungi can reduce the efficacy of the immune system by suppressing multiple different components of it. Mycotoxin metabolites can suppress T and B lymphocyte activity, inhibit immunoglobulin production, and reduce antibody production. Some species of fungi release mycotoxins which can interfere with which genes are activated. Some also release polysaccharides which can result in the induction of neutrophil apoptosis. All these processes result in the body's inability to fight off the fungi as well as other infections.[9-11]

DNA damage caused by mycotoxins has been shown to be carcinogenic.[12] There are two different pathways in which mycotoxins can damage DNA. First is the ability for some mycotoxins to covalently bind to DNA nucleotides. Mycotoxins can covalently bind to the N-7 position of guanine and the N-3 position of adenine, both of which can interfere with DNA synthesis. These adducts can cause an incorrect substitution of a nucleotide or cause deletion in the DNA code.[13] The second cause of DNA damage from mycotoxins is the inhibition of DNA topoisomerase I and II. These enzymes are required to untangle DNA during replication, and preventing this activity can lead to the accumulation of DNA breaks.[14]

Types of Mold and Mycotoxins

Mycotoxins are produced by filamentous fungi, which are ubiquitous because of their ability to thrive in many different types of environments.[15] The most common mycotoxins are produced from the fungi genera of *Aspergillus*, *Fusarium*, *Penicillium*, and



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Stachybotrys. Many of fungi species can produce more than one type of mycotoxin (Table 1). In this table, we list ten of the most common mycotoxins, and we can depict which mold species produce these mycotoxins. *Aspergillus* is the most prevalent mold genus in the environment. The two most common *Aspergillus* mycotoxins are aflatoxin and ochratoxin, and their main target is the liver.[16,17] *Aspergillus* species are commonly associated with indoor air problems.[18] The most common route of transmission for *Aspergillus* is inhalation.[19]

Fusarium fungi grow best in temperate climate conditions.[20] *Fusarium* is present in both indoor as well as outdoor environments.[21] It also grows worldwide on many different types of grains including corn and wheat.[22] Most trichothecene mycotoxins are produced from *Fusarium* species.

Penicillium is a blue-green mold found on fruits, vegetables, and indoor environments. Many different types of citrus fruits can become contaminated with *Penicillium*, but it can also contaminate seeds and grains. Factors leading to a contamination of *Penicillium* in the home, work, or school environment include inadequate heating and ventilation, water leaks, and low sunlight.[23]

Stachybotrys is a greenish-black mold. This mold can grow on materials with high cellulose and low nitrogen content such as gypsum board, paper, fiberboard, and ceiling tiles. The humidity requirements for *Stachybotrys* are much higher than other fungi, around 93%, whereas other fungi grow at approximately 75%, and it often occurs in the presence of other fungi.[3,24] Toxicity caused by *Stachybotrys* is mostly caused by the toxins and other compounds produced, and less from particle penetration from the spores.

Detection of Mold Exposure

For decades, it has been difficult to determine if patients have been exposed to mold toxins. Research and testing in the agricultural market has proven helpful in testing and treatment methods for humans. One method of detection, which was developed a decade ago, is Enzyme Linked Immunosorbent Assay (ELISA), which has been used to detect mycotoxins in many different types of crops. There are two barriers in transferring this technology to human samples. These barriers are insufficient sensitivity and matrix effect (ME) in human samples. The first barrier is caused by the small amounts of mycotoxins in human blood and urine, which are both much less than seen in crops. The FDA action level for aflatoxin is 20 ppb (20 µg/L), which is a factor 100 times higher than seen in human samples.[25,26] Sample ranges for many mycotoxins in humans are normally in the 60-2000 ng/L (.06-2 µg/L) range.[26]

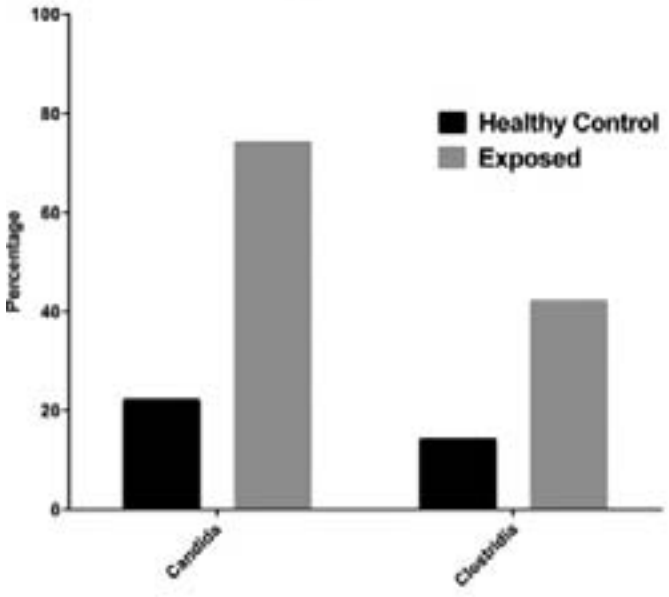
The matrix effect barrier is caused by compounds in the sample matrix that are not related to the analyte being measured but can cause a result to be either higher or lower than the actual amount. These MEs can influence any type of test, and protocols must be performed in order to separate the analyte of interest from these interferences.[27] Studies in the past eight years have focused on a new technology to access mycotoxin exposure, which is liquid chromatography mass spectrometry (LC-MS/MS).

The introduction of LC-MS/MS has allowed scientists and practitioners to quantitatively measure many different chemicals. These measurements can be done on compounds either individually or simultaneously if the compounds have similar molecular characteristics. A mass spectrometer is a device that measures the molecular mass of compounds. Many different fields have used this technology and two of the most common are drug testing and chemical exposure testing, which both need the sensitivity and selectiveness that LC-MS/MS provides.[28] Over the last 10 years in the scientific community, LC-MS/MS has become the gold standard for the measurement of mycotoxins.[29]

At The Great Plains Laboratory, we use two methods of detection to determine the best course of treatment for patients. To detect mycotoxins, we utilize LC-MS/MS technology because of its sensitivity as well as its selectivity in determining analytes. Our laboratory experts have developed a method for extracting mycotoxins out of human matrixes that provides the most sensitive and accurate data available. We recommend that all patients who take our LC-MS/MS test for mycotoxins, also take an Organic Acid Test (OAT), and both tests can be run on the same urine sample. The Organic Acids Test is a metabolic test performed on the gas chromatography mass spectrometer (GC/MS). The OAT provides a snapshot of how the body is performing metabolically and it offers four distinct areas of information that can assist in the treatment of mycotoxin exposure. These areas are fungal markers, glutathione markers, mitochondrial markers, and yeast/clostridia markers.

To better understand how the OAT and mycotoxin test overlap, we ran a study of 100 healthy patients and 150 mycotoxin-exposed patients. These results are depicted in Figure 1. All of these values were statistically significant with p-values below 0.05. The first insights that we observed in patients that took both the mycotoxin test and the OAT was that two markers in the yeast/fungal section of the OAT were statistically elevated over healthy controls. These two markers were 5-hydroxymethyl-2-furioc and Furan-2,5-dicarboxylic, which are both produced by species of *Aspergillus* (Figure 1).[30,31] Elevations in these two markers could indicate that the patient has a colonization of *Aspergillus* in the body. *Aspergillus* is the most common fungi to colonize the body. Because Aspergillus spores are smaller than most other species,

Figure 2



2 µm to 10 µm, they can reach the lower airways. This can lead to fungal colonization, which results in prolonged mycotoxin exposure and allergic responses. The most common areas of colonization are the sinus cavities, the lungs, and the gut.[32] Our data indicates that 90% of patients with elevations in these two markers also have elevations of mycotoxins. These data have been shown to be extremely beneficial in determining the best treatment of patients.

The second benefit for using the OAT in combination with the mycotoxin test is to measure detoxification capacity. In Figure 1, we demonstrate that pyroglutamic acid is elevated in mold-exposed patients, which indicates these patients have a higher usage of glutathione (GSH). Detoxification of many mycotoxins is ➤

The 40 Species of Mold and 10 Mycotoxins They Produce

	Aflatoxin	Gliotoxin	Ochratoxin	Sterigmatocystin	Zearalenone	Roridin E	Verrucarin A	Enniatin B	Mycophenolic Acid	Citrinin
Species										
Acremonium sp.				present						present
Alternaria		present								
A. flavipes				present						present
Aspergillus flavus	present									present
A. fumigatus		present								present
A. niger			present							present
A. ochraceus			present	present						present
A. parasiticus	present									present
A. sydowii				present						present
A. versicolor				present						present
A. viridictum			present	present						present
Aureobasidium				present						
Chaetomium				present						
Cladosporium				present						
Cunninghamella				present						
Cylindrocarpon						present				
Dendrodochium						present	present			
Exophiala				present						present
Fusarium avenaceum				present	present			present		present
F. cerealis				present	present					present
F. clumonrum				present	present					present
F. equiseti				present	present					present
F. graminearum				present	present					present
F. incarnatum				present	present					present
F. moniliforme				present	present			present		present
F. solani								present		
F. verticillioides				present	present					present
Myrothecium roridum						present				
M. verrucaria						present	present			
Penicillium carbonarius		present	present	present					present	present
P. nordicum		present	present	present					present	present
P. stoloniferum		present	present	present					present	present
P. verrucosum		present	present	present					present	present
Phoma sp.				present						present
Rhodotorula				present						present
Scopulariopsis				present						present
Stachybotrys				present		present	present			present
S. chartarum				present						
Trichoderma viride		present		present						
Ulocaldium										
Verticillium				present						present

➤

dependent on the endogenous molecule GSH. GSH is a tripeptide, which is made of glycine, cysteine, and glutamate. Mycotoxin toxicity is intensified in patients with glutathione transferase mutations (GSTP1 and GSTM).[33] Glutathione status is measured in the OAT with pyroglutamic acid and 2-hydroxybutyric acid. Patients that are exposed to mycotoxins can have elevated amounts of both compounds (Figure 1). High pyroglutamic acid occurs when the body has been depleted of glutathione, which then activates the γ-glutamyl cysteine synthetase, which leads to the production of pyroglutamic acid.[34] 2-Hydroxybutyric has also been linked to glutathione production. Patients with higher amounts could be glutathione deficient.[35] Using this information will allow practitioners to determine what dose of glutathione would be most appropriate for a patient.

The most important element for treatment is avoidance of further exposure to water-damaged environments as well as contaminated foods.

The third benefit of using the OAT for patients is assessing how the mold mycotoxins are affecting the mitochondrial pathways in the patient's body. Many different types of mycotoxins can bind with ribosomes in the cell as well as ribosomes in the mitochondria. These interactions can inhibit proper cellular functions.[6] The OAT assesses multiple different mitochondrial pathways. Studies done by The Great Plains Laboratory have demonstrated that patients who have been exposed to mold toxins accumulate lactic acid and succinic acid in their urine (Figure 1).

The fourth benefit of using the OAT for patients with possible mycotoxin exposure is the yeast and bacteria markers. Exposure to mycotoxins can lead to the inhibition of T helper cell function and inhibition of antibody synthesis.[36] Crucial immune organs have also been shown to decrease in size from exposure, such as the thymus, bursa of Fabricius, the spleen, and lymph nodes.[37] This can lead to the overgrowth of intestinal pathogens such as Candida or Clostridia.[38] Our data dictates that patients with high levels of mycotoxins have high levels of yeast 75% of the time and Clostridia 40% of the time (Figure 2). In this figure, we show that elevations in tartaric, arabinose, or carboxycitric acid are more common when the patient has been exposed to mycotoxins. These are serious co-morbidities that can lead to significant health issues. Diagnosis of these issues can lead to improved outcomes.

Treatment of Mycotoxins

Treatment of mold and mycotoxins must take into account possible routes of exposure; either internal colonization of mold or external exposure. Mycotoxin and fungi exposure can lead to many different symptoms including fatigue, headaches, difficulty breathing, rashes, gastrointestinal issues, joint pain, decreased libido, and more. As previously mentioned, these mycotoxins can come from water-damaged buildings or from food contamination. The most important element for treatment is avoidance of further exposure to water-damaged environments as well as contaminated foods. Using a licensed company to inspect and remediate the area is recommended. Remediation of contaminated areas is difficult because heat, ultraviolet (UV) light, bleach, ammonia, and ozone do not completely remove mold from contaminated areas.[39] Air spore counts are frequently done; however they are usually done over a short period of time and often result in false negative results. Another problem is that killing the mold does not eliminate the risk, because mycotoxins will remain in the environment.

Patients exposed to mycotoxins from mold may have two different conditions to treat. The first is the mycotoxin exposure, which can cause problems in many different tissues mentioned previously, and second is a possible infection and colonization of the fungi. To detoxify the mycotoxins, it is recommended to use a combination of glutathione, sauna, sequestering/binding agents, and antioxidants. Patients may also need to treat fungi infections and colonization. Glutathione (GSH) can be introduced in several ways, including treating with GSH precursors such as N-acetyl cysteine and whey protein or with an oral liposomal, transdermal, intravenous, nebulized, or intranasal form of GSH. It is recommended to use GSH with sequestering agents, because treatment with GSH has been shown to increase the mobilization of mycotoxins in the bloodstream.[40] Sauna therapy has been utilized for centuries for the removal of toxins from the body. Some of the most commonly used saunas are dry heat radiant saunas and far infrared saunas. Both have been shown to be equally good at removing toxins from the body. Infrared saunas have the advantage of inducing sweating at lower body temperatures. Sweating is important because many mycotoxins are lipophilic and can bind to lipid proteins, which will allow the mycotoxins to persist in the body for extend periods of time.[41]

Patients who have high levels of mycotoxins in their bodies may also be suffering from fungal infections and colonization. This is usually caused by direct exposure to elevated levels of mold spores. Fungal infections can occur in many different parts of the body. The most common areas of infection are the sinus cavities, lungs, and intestine. One Mayo Clinic study found fungal growth in 96% of patients with chronic sinusitis. The types of mold found included *Aspergillus*, *Penicillium*, *Alternaria*, *Cladosporium*, *Fusarium*, and *Cryptococcus*. All of these molds are known to produce mycotoxins and cause significant diseases.[42,43] One study demonstrated that antifungal drug therapies were useful in combating microbial pathogens detected by gas chromatography-mass spectrometry.[44]

Antifungal medications have been shown to be efficacious against mycotoxins. Multiple studies have utilized amphotericin B for the treatment of fungal infections.[45-47] Other antifungals that have been used include ketoconazole, fluconazole, and itraconazole. For intestinal fungal infections, nystatin or liposomal nystatin may be a good alternative.[48,49]

Application of Antifungal Treatment in Autism and Parkinson's Disease

Our recent work with mycotoxins and antifungal treatment has focused on two different patient populations; those with autism and those with Parkinson's disease. Our studies have found numerous patients that exhibit symptoms of either autism or Parkinson's who also exhibit colonization with mold. Results indicate that treatment with antifungal therapies has greatly improved the symptoms of patients in these categories, which strongly suggests that mold exposure may play a role in exacerbating both autism and other neurological disorders.

continued on page 38 ➤

MycoTOX Profile

Mycotoxins are metabolites produced by fungi like mold, which can infest buildings, vehicles, and food. Diseases and symptoms linked to mycotoxin exposure include pneumonia-like symptoms, heart disease, rheumatic disease, asthma, sinusitis, cancer, memory loss, vision loss, chronic fatigue, skin rashes, depression, and liver damage.

The MycoTOX Profile now screens for 10 different mycotoxins, all in one urine sample. It uses the power of advanced mass spectrometry (MS/MS), which is necessary to detect lower levels of these fungal toxins.

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Mold Exposure

➤ *continued from page 36*

Conclusions

Exposure to mold and mycotoxins can result in many different types of illnesses depending on the patient's age, sex, genetics, and environment. Determining the root causes of these illnesses is our goal at The Great Plains Laboratory. Many in the health community in the last decade have come to realize the role that mold and mycotoxins can play in the health of our patients. We believe that using the Organic Acid Test along with the LC/MS mycotoxin test can produce the information necessary to provide optimum personalized care to patients with mold exposure.

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A Mystery Answer to Restoring Brain Health

by David I. Minkoff, MD, Julie Mayer Hunt, DC, DICCP, FCCJP, and Ron Tindell

For the past 20 years I have worked with patients who have had a chronic illness. From mercury toxicity, to Lyme, autoimmune disease, and cancer, I had a stable model with which to approach them; and about 85% of the time I was successful in helping them toward healing and recovery. This approach boiled down to two basic problems. They had 1) things in their body that should not be there (toxicity/infection), and they had 2) things missing from their body that should be there: deficiency. With my early training in neural therapy, I would also address some of the structural aspects that would impair autonomic function such as scars and ganglion blockage or toxic root canal teeth or cavitations. With the four-component theory of disease 1) structure; 2) biochemical/microbiological; 3) autonomic balance; 4) spiritual, I thought I had things well understood and under control.

I was familiar with the chiropractic model of subluxation impairing nerve function, but it was out of my expertise range; and I would refer when I thought it appropriate, but usually only as an afterthought. As a medical doctor my orientation was on "more important" things that cause body disease and illness. Little did I know that there was a very significant part of the structural aspects of health that I knew nothing about nor had any inkling of how significant it was. But that was not until I met my mentor, Dr. Julie Mayer Hunt, DC, DICCP, FCCJP, a world expert in the subject; and we have partnered in helping hundreds of patients that I have referred to her for care.

How many patients do you see with headaches, head pressure, neck pain, migraine, tinnitus, vertigo, POTS, brain fog, memory loss, multiple sclerosis (MS), Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease? In how many of those have you considered that they had a structural problem at their cranial cervical junction (CCJ) that either contributed to their condition or was the actual cause of it? What is CCJ? More on that shortly.

It was only a couple of years ago that I met Dr. Julie Hunt quite by accident when a patient told me she had seen her and got an amazing change in her condition of constant head pressure of 15 years following a whiplash injury. Dr. Hunt comes from a family of upper cervical chiropractors. Her dad started their practice 60 years ago, and now Julie, her father, and her son all work together as upper cervical specialists. They are only blocks from my office, and little did I know the miracles that they produce. Because of the incredible impact of upper cervical treatment of the CCJ on my practice, I decided to partner with Dr. Hunt in writing this article to bring awareness of ➤

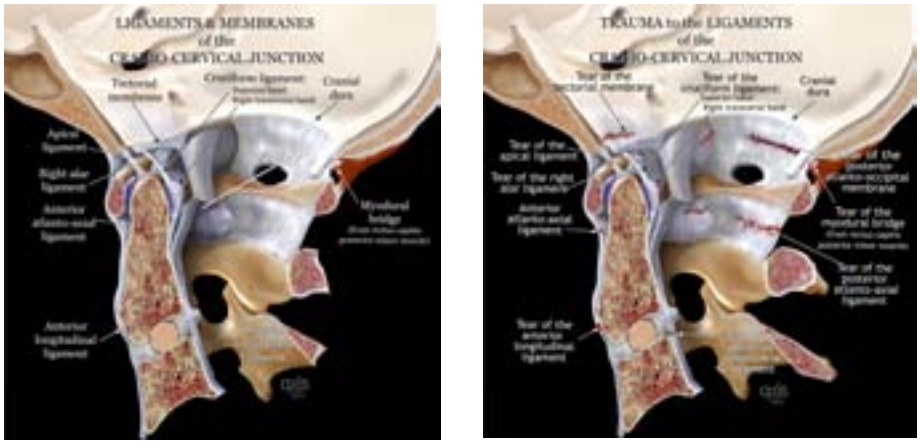

Figure 1a. (left) Basic Craniocervical Anatomy 1b. (right) CCJ Possible Trauma[3]

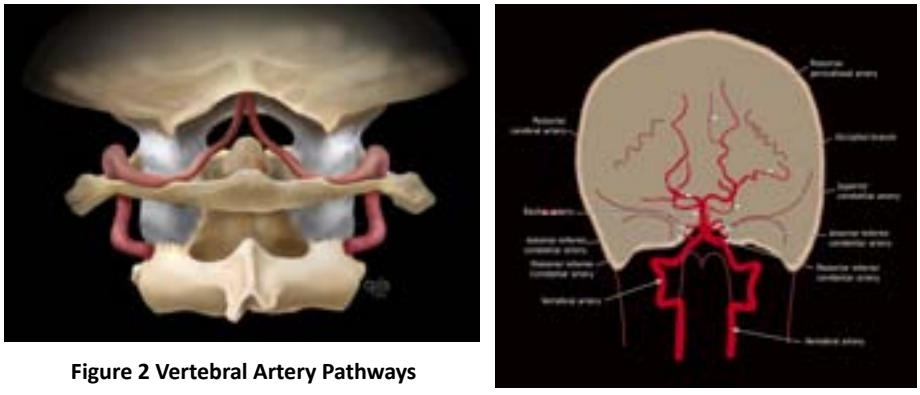

Figure 2 Vertebral Artery Pathways

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how common this problem is. I knew that if I was a medical doctor working with patients who had chronic illness for 20 years and had no idea of how important it was in health, that there were thousands more like me who would appreciate knowing the science so they could help their patients better. That is the purpose of this article.

Anatomy and Physiology of the Craniocervical Junction (CCJ)

To understand what craniocervical junction (CCJ) chiropractic care encompasses, a review of the basic anatomy is the starting point. The CCJ is the most complex joint region in the body. The CCJ, also referred to as the cranio-vertebral junction, is a collective term that refers to the occiput (posterior skull base), atlas, axis, and very importantly, the supporting ligaments. It is a transitional zone between a relatively rigid cranium and a mobile spinal column enclosing the soft tissue of the brainstem at the cervicomedullary junction (medulla, brainstem and spinal cord). It is critical to fully understand the neurology, biomechanics, and soft tissue integrity, including ligaments,[1] blood flow, and cerebral spinal fluid flow at the junction between the brain and the body.[2] Figure 1a provides details of the CCJ and the associated anterior supporting structures, including the alar ligaments, the apical ligament tectorial membrane, anterior atlanto-occipital and atlantoaxial membranes. The posterior supporting ligaments are comprised of the posterior atlanto-occipital membrane and atlantoaxial ligament. Figure 1b shows possible post trauma disruption of the posterior stabilizing ligaments of the CCJ.

As shown in Figure 2, the vascular parameters of the CCJ include the vertebral arteries which pass through the transverse processes of the atlas and make a total of four ninety degree turns. Additionally, the internal jugular veins pass just anterior to the transverse processes of the atlas vertebrae.[4] The positioning of the segments of the CCJ affect blood flow and cerebral spinal fluid (CSF) fluid flow dynamics to and from the brain.

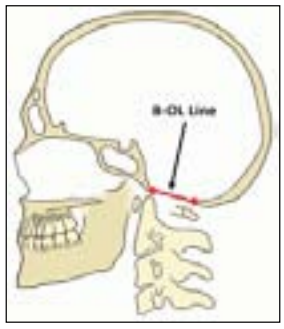


Figure 4 Basion-Opisthion (B-OL) Line

Key biomechanical stabilizers of the brainstem inside the spinal column are the dentate ligaments. These ligaments begin at the atlas level and are responsible for centering the base of the brainstem and spinal cord throughout the spinal canal. Particularly when the CCJ structures are misaligned, the dentate ligaments can create adverse tension on the lateral aspects of the spinal cord, affecting neurological impulses throughout the

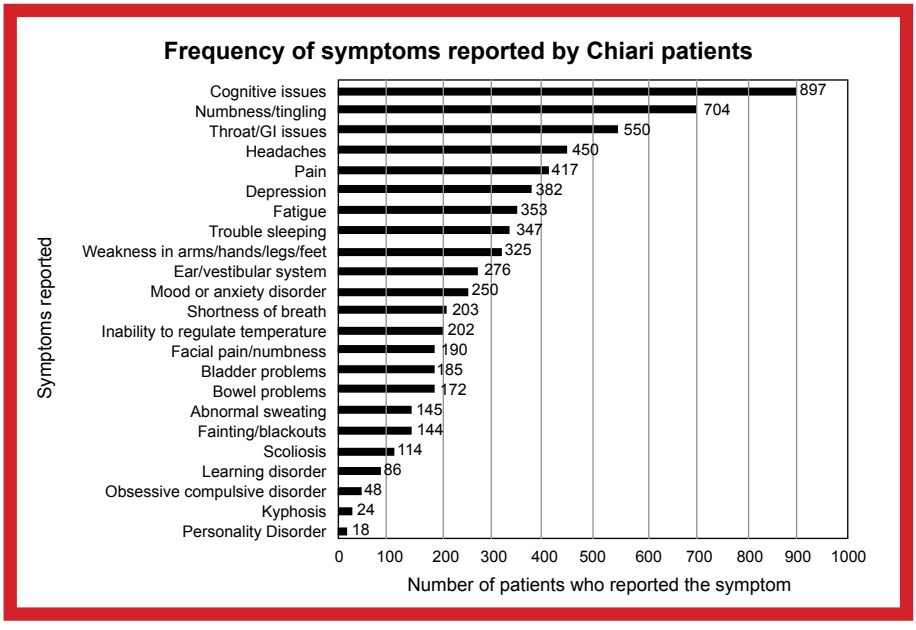
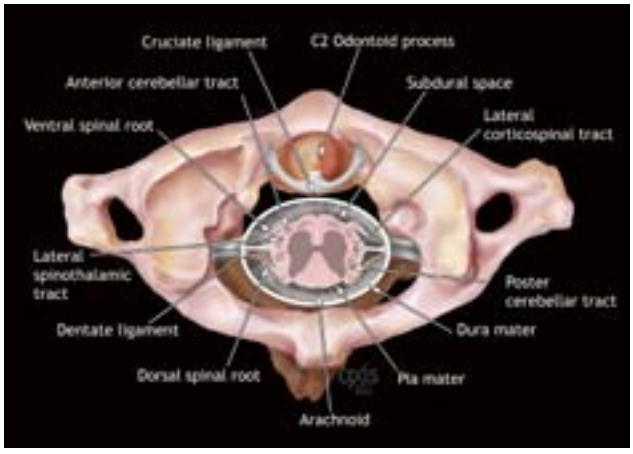


Figure 5 Reported Symptoms by Chiari Patients[7]



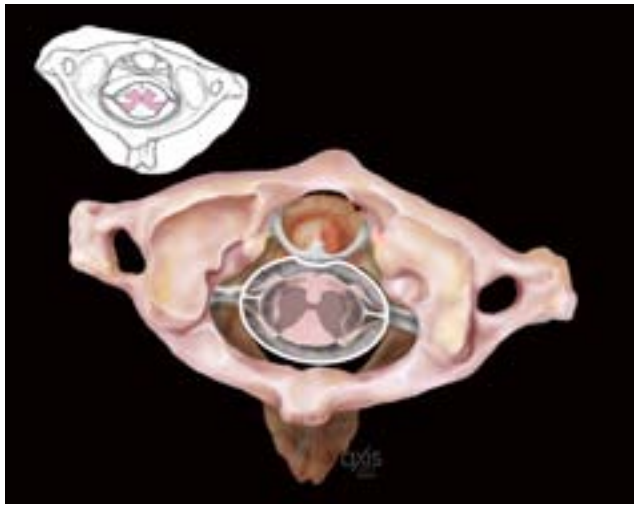


Figure 3 Normal (left)[5]; Football Shaped Spinal Cord due to Dentate Ligament Tension (right)

body and distorting the spinal cord. MRI axial presentation can be from round (normal) to almost football-shaped (abnormal), observable upon MRI imaging of the CCJ. This is shown in Figure 3 where the picture on the left shows a normal round view of the brainstem while the picture on the right shows the football shape distortion of the brainstem caused by dentate ligament tension.

The base of the brain has cerebellar tonsils, which in large part are responsible for our balance and coordination. The brain and spinal cord are one unit. Think of the spinal cord as a long-braided ponytail; it is an extension of the brain. When the base of the skull and the atlas/axis become misaligned, the dentate ligaments supporting and protecting the brainstem can potentially produce caudal tension at the skull base, creating a downward tug at the brain base. The CCJ is the main circuit breaker neurologically as well as being the "mouth" to the brain for fluid exchange, including both CSF and blood. The CCJ is best imaged upright to observe true functional positioning of key components such as the cerebellar tonsils. When MRI imaging is done in a supine fashion, the back of the head can act like something of a "bowl" and the brain tissue tends to slide into the bottom of the bowl. When MRI imaging is performed upright, the brain tissue may occupy a different position; also, spinal misalignments can be observed.

Chiari malformation is a serious neurological disorder where the bottom part of the brain (cerebellar tonsils) descend into the foramen magnum, crowding the brainstem/spinal cord and altering CSF flow dynamics, producing many disabling symptoms. Cerebellar tonsil position is commonly measured using the basion-opisthion line (B-OL, also known as the McRae Line), shown in Figure 4. When the cerebellar tonsils descend five (5) mm or less below the basion-opisthion line (skull base) and into the spinal canal, this is referred to as cerebellar tonsular ectopia (CTE) and may be listed as Chiari 0 or borderline Chiari 1 depending on the exact measurement. A Chiari 1 is measured as more than five (5) mm descent of the tonsils into the spinal canal. Symptoms can vary greatly from one person to another, and some patients may be asymptomatic until a trauma occurs.[6] The most common symptoms include cognitive issues, neck pain, headaches, visual abnormalities, poor coordination, difficulty swallowing, nausea, dizziness, anxiety, and depression as shown in Figure 5.[7]

Anatomical illustrations of the CCJ[3] are provided showing normal cerebellar tonsil positioning (Figure 6A) and low-lying cerebellar tonsils (Figure 6B). The low-lying cerebellar tonsils can potentially block cerebral spinal fluid flow and therefore affect brain health and neuroimmune function.

Sagittal MRI imaging depicting normal cerebellar position at the CCJ (Figure 7A) and abnormal cerebellar position affecting CCJ CSF fluid mechanics and brain health potential at the CCJ figure (Figure 7B) are provided as additional real-world depictions of the illustrations in Figure 6.[2]

With respect to the craniocervical junction (CCJ), most standard MRI imaging does not observe this region sufficiently. Standard axial brain MRI imaging usually terminates a slice or two under the skull base.[8] Standard axial imaging of the cervical spine usually begins at the C2 disc and proceeds caudally to the C7 region as depicted in Figure 8. Sagittal cervical MRI imaging are usually four (4) to five (5) millimeter slices which can miss detailed structures of the CCJ like cerebellar tonsils, which are small peg-like structures at the base of the brain, and CCJ ligaments, which average two (2) mm in diameter. Therefore, the CCJ soft tissue has been routinely overlooked in the mainstream medical community. Keep in mind that the medical acronym WNL, normally meaning "within normal limits," can also mean "we never looked." CCJ imaging in the past has utilized computerized tomography (CT) to rule out fracture without soft tissue considerations.[9]

CCJ Imaging Methods

For CCJ MRI imaging, the benefits of upright versus supine imaging were discussed earlier in this article. For the recommended upright imaging, patients ➤

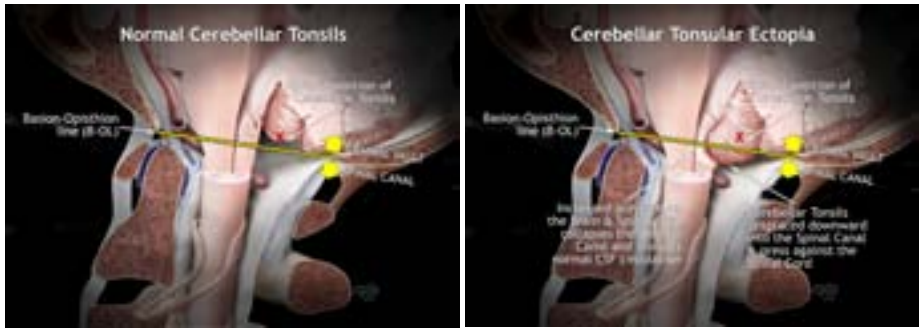


Figure 6a (Left) Normal Cerebellar Tonsil Position[3]
6b (Right) Chiari or Cerebellar Tonsillar Ectopia[3]

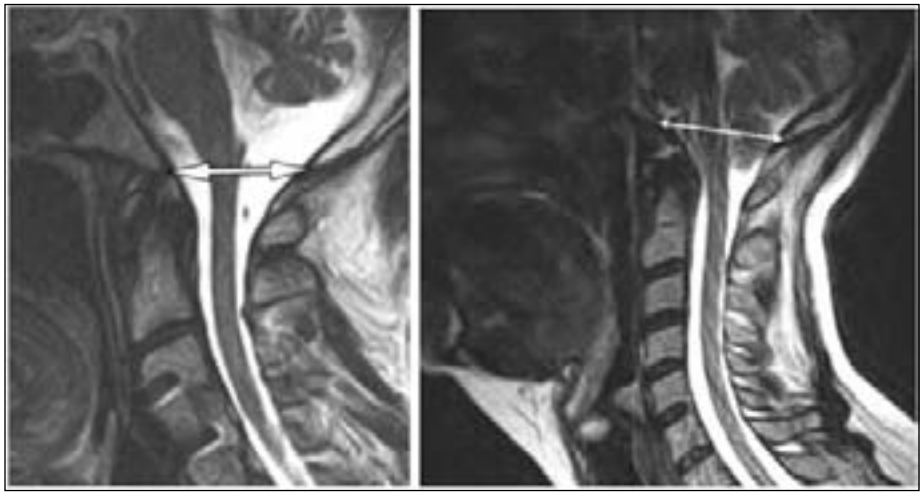


Figure 7a (left) MRI Depicting Normal Cerebellar Position[2]
7b (right) MRI Depicting Abnormal – Chiari – Cerebellar Position

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are seated; and images are obtained on the coronal, sagittal and axial planes (depicted in Figure 9) using sequences as shown in Figure 10. In these sequences:

- The slice thickness in these cases should be a maximum of 2.8 mm.
- The axial slices were obtained in proton density (PD), which is best to see ligaments.
- The sagittal slices were obtained in T1 (longitudinal relaxation time) and T2 (transverse relaxation time).
- Coronal images were obtained in T1.

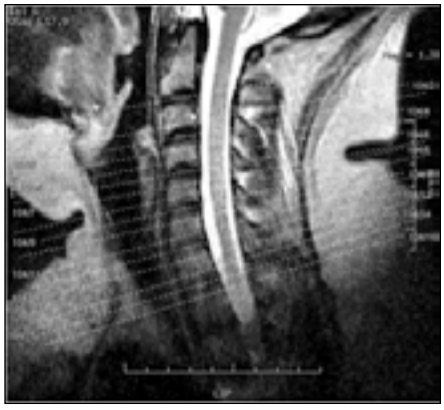


Figure 8 Typical Cervical Spine Axial MRI

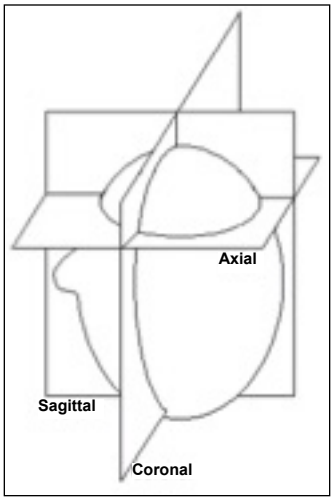


Figure 9 MRI Imaging Planes

Upright MRI imaging of the CCJ revealing low cerebellar tonsils in all three planes is shown in the Figure 11. This positioning may obstruct the normal flow of CSF. CFS obstruction may contribute to headaches, head pressure, dizziness, brain fog, and the like.

Atlas Rotation Observations: When the atlas rotates, it is plausible anatomically that the transverse process can abut the internal jugular vein. Figure 12 depicts two examples of atlas rotation misalignment. The red line highlights the rotation. The yellow arrow points to an internal jugular, which appears to have been compressed by the misaligned atlas. This compression can potentially affect venous outflow from the brain, causing backup of venous metabolic waste blood in the brain which is suggested in neurodegenerative brain diseases.[10] Also note the football shape versus a normal, round shape of the spinal cord which plausibly can suggest dentate ligament attachment tension at the brainstem.[5, 11]

C2 (Axis) rotation can be observed on CCJ oriented MRIs. Figure 13 provides several examples of axial rotational misalignment. The standard medical community cervical spine MRI misses this segment because the slices start at the C2/C3 disc. When one considers the vertebral artery pathway, illustrated in Figure 2, the axial misalignment can plausibly correlate with vertebral artery insufficiency and also the misalignments can affect dentate ligament tension of the spinal cord.[5,11]

C1 misalignment can be observed in the sagittal view with respect to the occipital condyles and the atlas lateral mass position. Figure 14a suggests anterior misalignment of the atlas lateral mass with respect to the occipital condyle. Figure 14b depicts a normal positioning of the C0/C1 articulation.[13]

Observations that can be made through upright MRI have the potential to clearly objectify spinal misalignment (Subluxation) and clarify patient care needs. The CCJ is a vulnerable region and merits special consideration for care and treatment. There are many parameters for studying the CCJ through MRI which can range from CSF and blood flow impedance, ligamentous laxity and or insufficiency, and cerebellar tonsular ectopia as well as Chiari involvement.[13]

In 2012 the glymphatic system was postulated[14] with regards to lymphatic drainage and brain health. The lymphatic system that was discovered in the brain is dependent on CSF flow. The glymphatic system, as shown in Figure 15, is a functional waste clearance pathway for the central nervous system. The CSF flow, when obstructed, appears to have negative plausible effects on brain health. Therefore, having the CCJ aligned contributes to non-obstructed flow of CSF and will plausibly contribute to improved brain health and immune function.

Craniocervical Syndrome Case Studies

Study 1, Pediatric Syrinx: A 14-year-old male presented in the office following ten days of hospitalization at a Johns

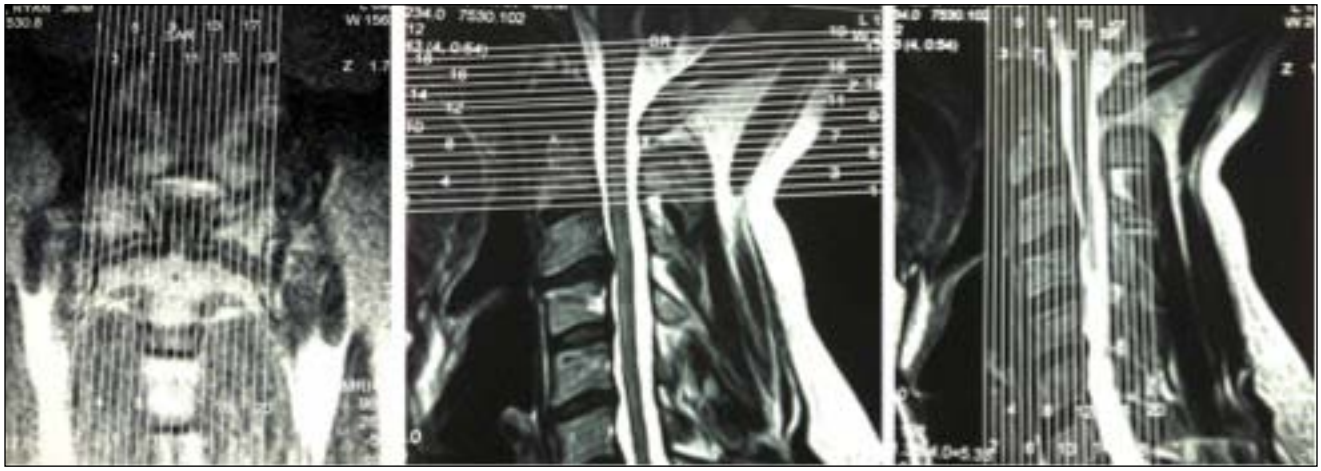


Figure 10 CCJ MRI Sequences in the Sagittal (left), Axial (middle) and Coronal (right) Planes

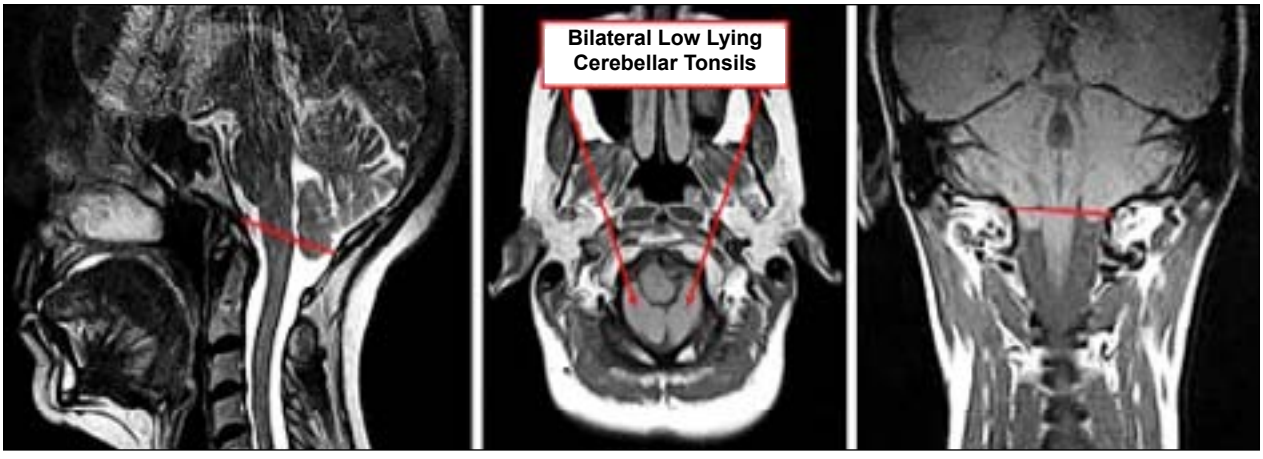
Hopkins affiliated children's hospital facility for severe head, neck, and upper extremity pain and sensitivity. On release, it was explained to him and his family that hospital protocol had been exhausted and his pain was hormonal. MRI imaging inclusive of the CCJ was ordered the day after his hospital release, which revealed a large syrinx and cerebellar tonsillar ectopia (CTE) with CCJ misalignment. We postulate that the CCJ misalignment affected the CSF hydrodynamics and the misdirected CSF played a major role in formation of the syrinx. The MRI images in Figure 16 show the location and magnitude of the syrinx as well as showing the CTE.

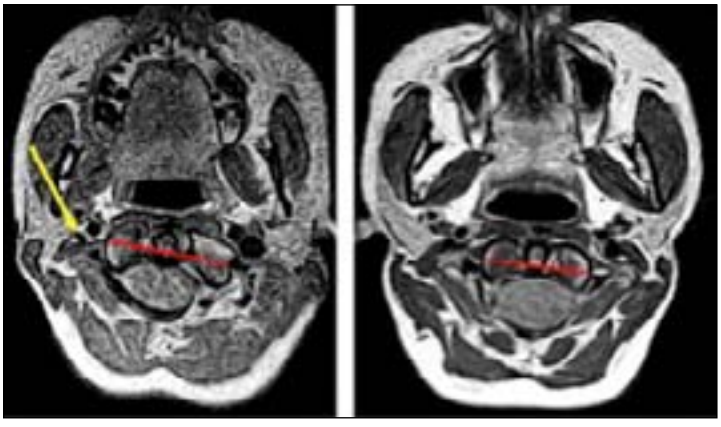
As treatment, CCJ realignment was performed and additional CSF flow imaging was obtained and utilized in the CCJ correction. The patient resolved successfully with this treatment.

Study 2, Chiari: A 19-year-old female presented to the office with eye-popping headaches, dizziness, and brain fog, which had been unremitting for the previous ten years since she had fallen on her head from a gymnastics uneven bar. She had an exhaustive list of neuro-medical consults which had provided no diagnosis or relief. She was told her issues "were all in her head." An MRI was ordered and revealed a Chiari of 22 millimeters as highlighted by the arrows in Figure 17.

She responded fairly well to CCJ specific care for three years, but ultimately had a decompression procedure that has been successful.

Study 3, Concussive Headaches: A 14-year-old male presented with constant severe head and neck pain following a concussion. MRI CCJ imaging was ordered, but the parents delayed obtaining the imaging for months. Ultimately, when ➤

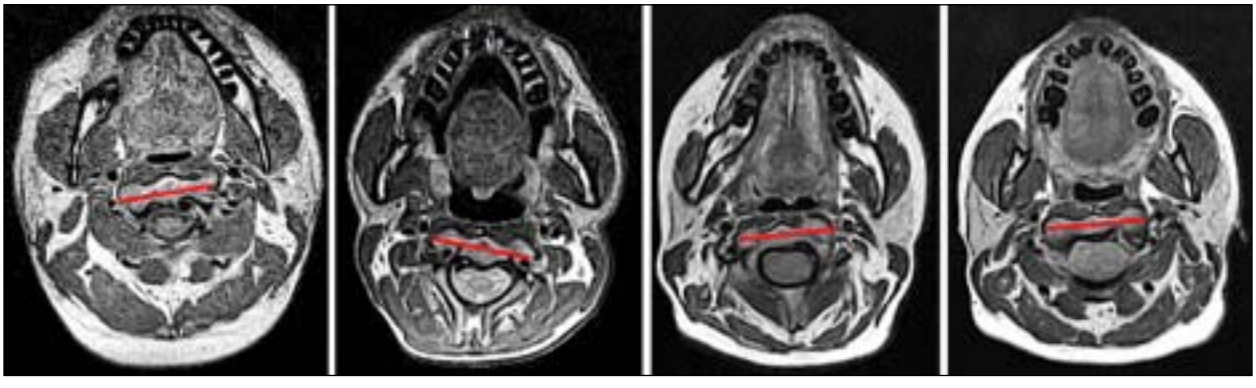




Above: Figure 11 Sagittal Tonsilar Ectopia Axial Cerebellar Tonsils Coronal Cerebullar Ectopia

Left: Figure 12 Atlas Rotation Misalignment

Below: Figure 13 Axis Rotational Misalignment



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the imaging was preformed, shown in Figure 18, a torn transverse ligament was discerned. The atlanto dental interspace is unequal (note the difference in spacing between the red marked and unmarked sides in the figure) therefore appropriate care inclusive of CCJ facet blocks are considered and possible CCJ stem cell therapy. CCJ instability is a strong consideration for his symptomatology, and the brainstem is football shaped due to dentate ligament traction parameters versus a normal round shape

Study 4, Childhood Constipation: A six-year-old male presented for treatment post-motor-vehicle accident (MVA). He presented with typical neck, head, and back post-traumatic injuries. The clinical findings included unilateral erector spinae marked spasms and spinal imbalance, with a leg length discrepancy of just over ¾". Figure 19 illustrates the possible effects on the body related to subluxation of the upper cervical spine.

Palpation of the upper cervical spine revealed unilateral articular joint pain. Figure 20 shows CCJ x-rays pre (left) and post (right) adjustment with orthospinology specific analysis of the misalignment. Post upper cervical adjustment, the upper cervical misalignment is reduced and unilateral erector spinae spasm is released and the leg length discrepancy is balanced, resolving the MVA symptomology with upper cervical chiropractic care. In addition to his injuries resolving, his mother reported that his painful constipation, experienced since birth, had also resolved under care. Balancing the central nervous system with upper cervical chiropractic care allows the body to neurologically repair itself.

Conclusion

Trauma continues to be a major player in the disruption of the CCJ integrity. Birth trauma, falls, motor vehicle crashes, sports injuries, and other traumas affecting the head and neck relationship throughout our lives play into the ability of the CCJ to facilitate the brain/body connection. All patients deserve an appropriate evaluation of the CCJ for optimal brain health parameters and brain/body for our health. There is much more that needs to be studied and understood to optimize brain health. The upright MRI imaging is a platform that potentially could allow neurology, neuroradiology and other medical specialties to work together with board-certified chiropractic CCJ procedure specialists to benefit patients and families. Understanding the complexities of the CCJ should compel all health practitioners to study further and understand how to optimize the brain/body communication of the most critical joint region of the body.

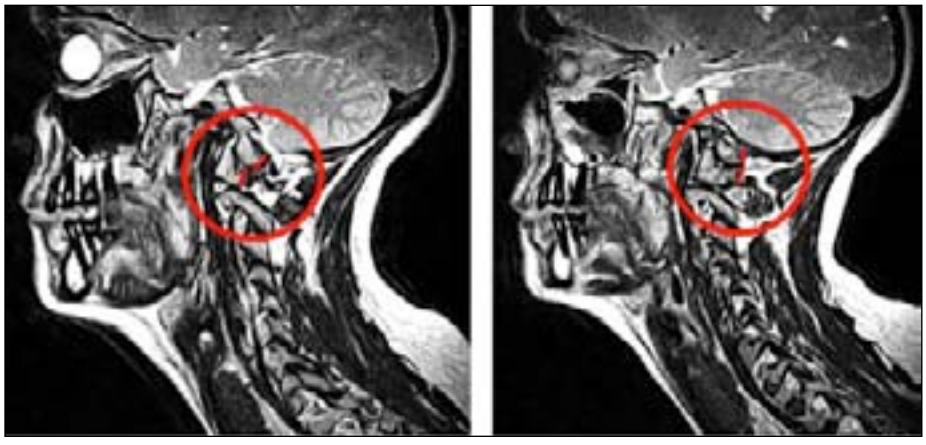

Figure 14a Sagittal Atlas Misalignment (left), 14b Normal Alignment (right)

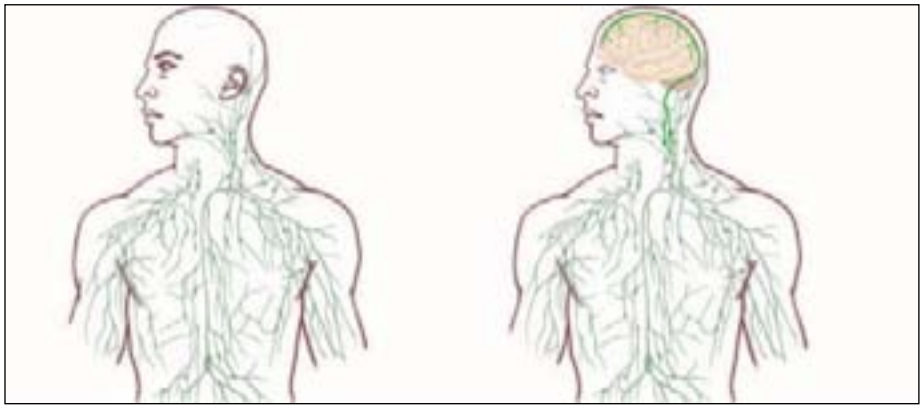

Figure 15 Lymphatic (left) / Glymphatic with Lymphatic System (right).
Image Courtesy of University of Virginia School of Health.

Parting Thoughts

I'd like to emphasize guidelines for practitioners who are on the front line to have high index of suspicion when they see patients with history of head or neck trauma, or autonomic symptoms involving the brain stem or cranial nerves, vertigo, brain fog, head pressure or pain of any kind, or anything from chronic constipation to cardiac arrhythmias. Autistic children should all be referred as early as possible.

Unfortunately, there is an epidemic of young infants being diagnosed with GERD by pediatricians and pediatric gastroenterologists. These infants are symptomatic, but to put a two-month-old baby, who has just been through a birth process that more than likely affected his CCJ, on Pepcid or similar acid blocking drug is not good medicine, especially if his problem can be cured with a couple of gentle movements to his upper cervical spine.

Once the brain has been decompressed and CSF flow re-established, then detoxification and healing can occur if the required nutrients are supplied. Primary to this are essential amino acids and essential fatty acids with vitamins and minerals. Neurons that have been under stress require optimal nutrition to heal. My standard approach for supplying required nutrients consists of the following:

1. Paleo or Ketogenic diet,
2. Supplemental amino acids in the form of Perfect Amino,
3. Omega 3 supplement,

4. Probiotic,
5. Complete multivitamin like BodyHealth Complete that contains 5000 u Vitamin D3 and K and activated folate.
6. If chemical or heavy metal toxicity is part of the picture, then Metal Free and Body Detox can be added.

In summary, it is the doctor's obligation to find the actual diagnosis that the patient has if he is to help the patient. All too often in complex cases the workup by the traditional doctor is too superficial to really do this and patients get put on symptomatic medication that has no chance of reversing the process, and a good chance that the medication will further complicate the problem. Meanwhile the actual cause has never been found.

It is my experience now that very few doctors consider that CCJ pathology could be the underlying cause and, without knowing this, never pursue this as a possible diagnosis. Dr. Hunt and her team have trained up an expanding group of doctors who know this technology and who can be consulted to help you out.

Whenever I hear on my initial interview any of the symptoms from the patient listed in Figure 5, I refer them to the upper cervical specialist for proper exam and, if needed, X-rays to confirm if there is a problem at the CCJ. This has been the most significant breakthrough in my education in many years, and it has upgraded my success results with patients tremendously. For me this has meant an upgrade in my listening skills so that when the patient mentions a key symptom(s) or answers one of my questions that my index of suspicion jumps into action and I refer them.

I know if you learn from this to listen for it and pursue it, it will do the same for you.

Good luck,
Drs. Minkoff and Hunt

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3. Illustrations courtesy of Ron Tribell; Medical Illustrator; Axis Arts; Little Rock, AR
4. Bulut MD, et. al. Decreased Vertebral Artery Hemodynamics in Patients with Loss of Cervical

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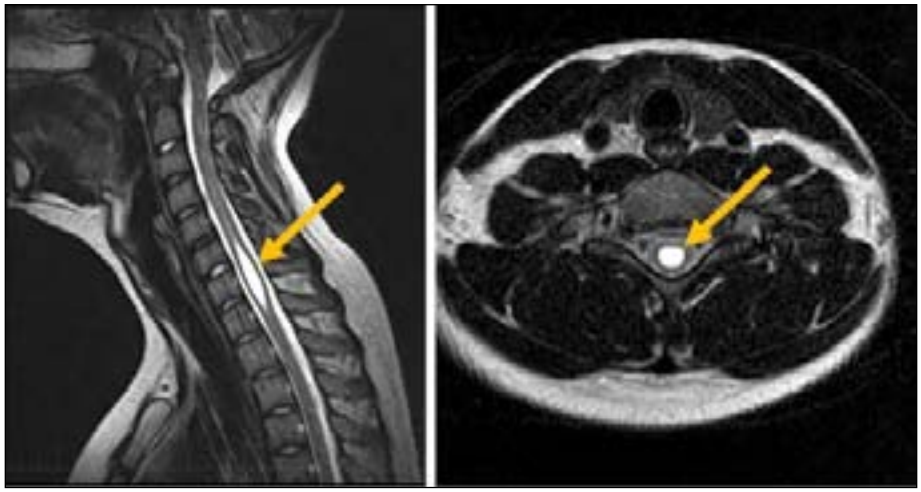

Figure 16a (left) Sagittal MRI Showing Syrinx; 16b (right) Axial MRI Syrinix

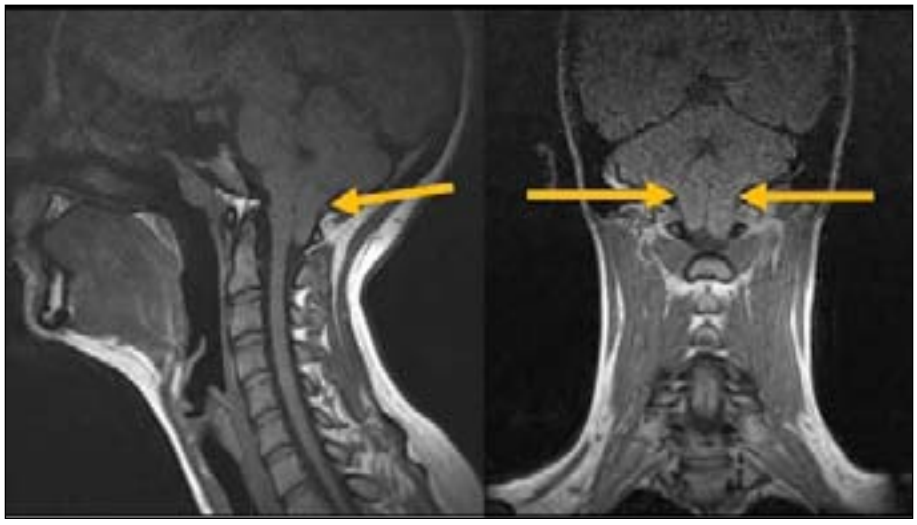

Figure 17
22 mm Chiari in a 19-Year-Old Female Patient – Sagittal View (left), Coronal View (right)

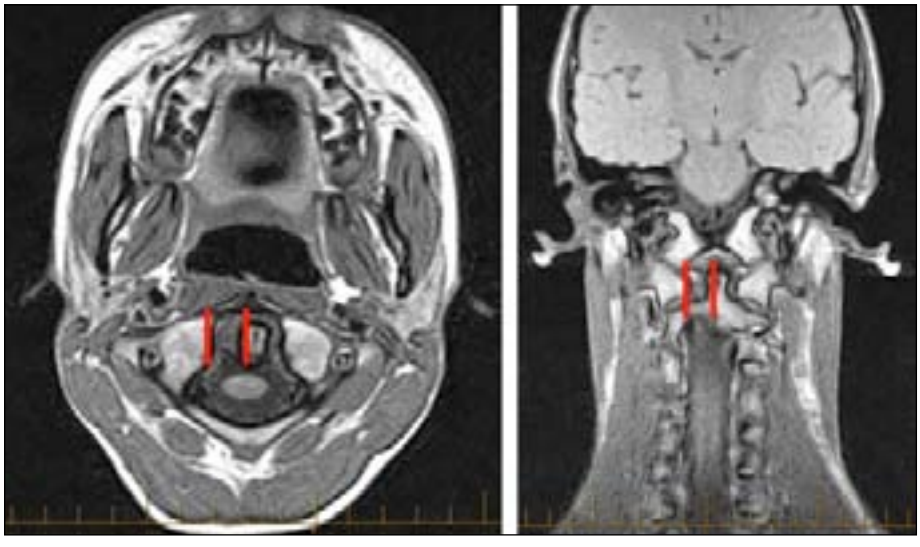

Figure 18 Axial (left) and Coronal (right) CCJ MRI Showing Abnormal Parodontid Spacing

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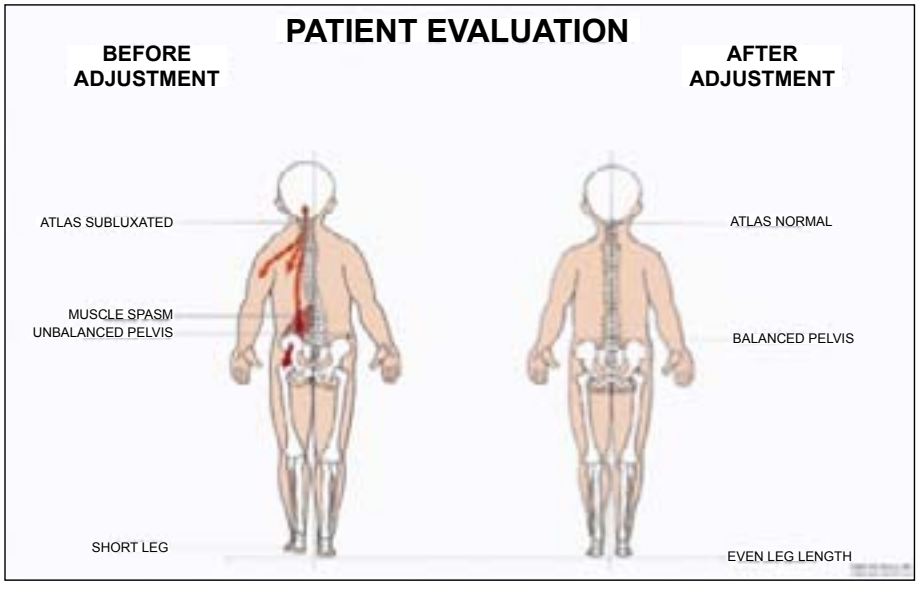

Figure 19 Possible Effect of Upper Cervical Subluxation on Spinal Dysfunction and its Idealized Correction(adapted from 5)

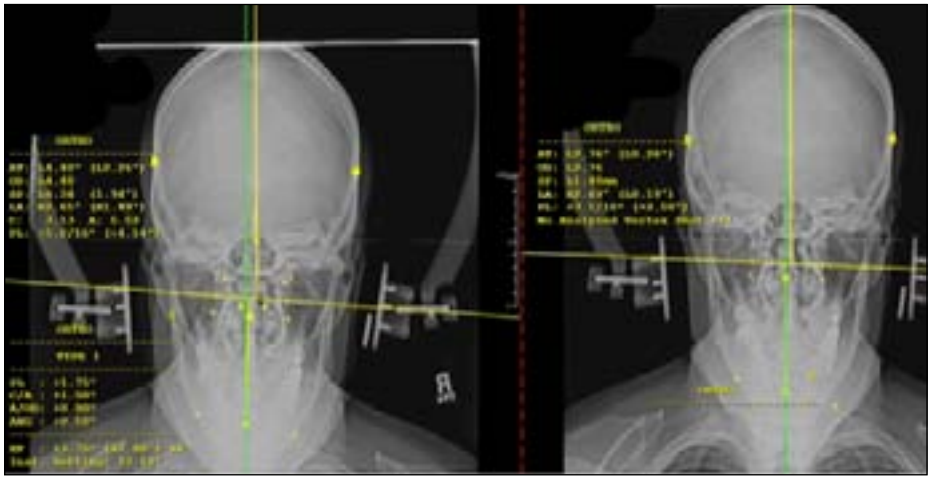

Figure 20 CCJ X-Rays Showing Pre (left) and Post (right) Upper Cervical Adjustment

Acknowledgements
Parts of this paper 'borrow' content from a paper written by Dr. Hunt for the International Chiropractors Association (ICA) digital magazine, *The Chiropractic Choice*, reference 14. Dr. Hunt thanks the ICA for allowing use of this content. Dr. Hunt also acknowledges the excellent illustration inputs from Ron Tribell of Axis Arts (reference 3) which help visualize the most complex joint region of the body.

◆

Dr. David Minkoff graduated from the University of Wisconsin Medical School in 1974 and was elected to the "Phi Beta Kappa" of medical schools, the prestigious Alpha Omega Alpha Honors Medical Fraternity for very high academic achievement. He then worked for more than 20 years in the area of traditional medicine before making the switch to alternative medicine when he and his wife, Sue, founded LifeWorks Wellness Center in Clearwater, Florida. LifeWorks is now one of this country's foremost alternative health clinics, offering a wide range of cutting-edge protocols.

In 2000, Dr. Minkoff founded BodyHealth, a nutrition company which offers a unique range of dietary supplements to the public and practitioners. Dr. Minkoff is passionate about fitness and is a 42-time Ironman finisher, including eight appearances at the Ironman World Championships in Hawaii. He also writes two weekly newsletters, *The Optimum Health Report* and the *BodyHealth Fitness Newsletter*.

Dr. Julie Mayer Hunt is a second-generation upper cervical care chiropractor in Clearwater, Florida. She graduated from Life University in 1981 and started practicing with her father, Dr. David Mayer, at Mayer Chiropractic, which celebrated its 60th anniversary in February 2018. In 2000, Dr. Hunt completed her Diplomate in Clinical Chiropractic Pediatrics (DICCP), becoming the first board-certified pediatric chiropractor in Florida. In 2013, Dr. Hunt was appointed to the Florida Board of Chiropractic Medicine by the Governor and continues to serve on that board today. In 2016, Dr. Hunt was awarded her Fellow in Craniocervical Junction Procedures (FCCJP). Dr. Hunt has presented at seminars and conferences concerning upper cervical care across North America and in Europe for the ICPA, the ICA, Society of Orthospinology, The Florida Chiropractic Society, Academy of Upper Cervical Chiropractic Organizations, and many other Upper Cervical and State organizations.

Dr. Hunt has published several papers in a peer-reviewed journals and is a contributor to several chiropractic textbooks.

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L-Valine
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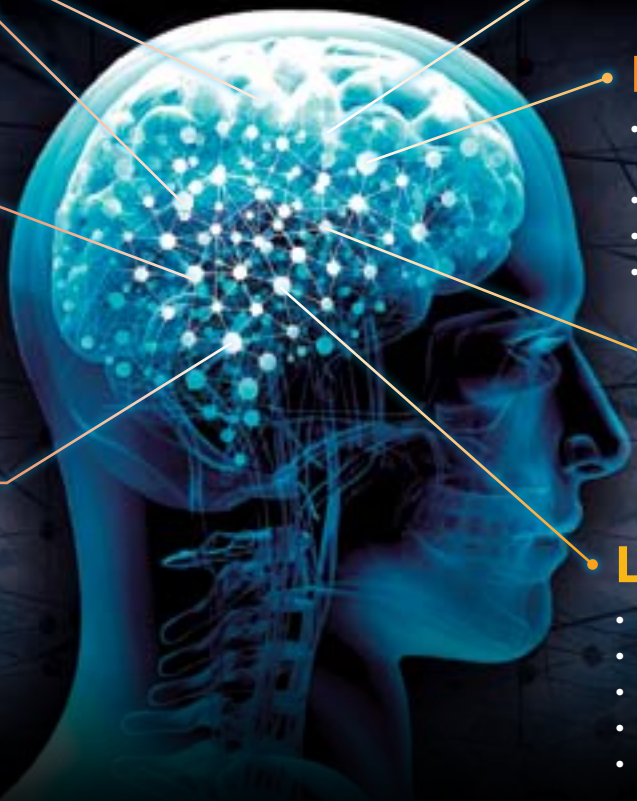
- Promotes normal growth & repair of tissue
- Can help with insomnia
- Is one of the three BCAAs



L-Threonine
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- Immune booster
- Sleep aid

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- Blood sugar regulation
- Promotes repair of muscle
- Is one of the three BCAAs

L-Tryptophan
- Precursor to melatonin, serotonin & niacin
- Helps regulate sleep

L-Methionine
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- Influences adrenaline
- Helps sleep
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- Supports liver detox

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- **Supports energy production at the mitochondrial level ***
- **Enhances quality of life ***
- **May replace specific nutrients that may be depleted during certain therapies ***

■ Studies evaluated the effects of LAMC and radiation in various animal models. Whole-body gamma radiation exposure once a week for 2 weeks and daily after 4 Gy of irradiation protected DNA damage in the peripheral blood. It also rendered protection against radiation-induced lowering of platelet count and appears to be responsible for its radio sensitizing and protective effects while supporting mitochondrial remodeling.

■ Dr. Paul S. Anderson has worked with LAMC in various clinical settings (neuro-degenerative illnesses, chronic fatigue/fibromyalgia and mitochondrial dysfunction) and has documented the following:

- Poly-MVA shows consistent safety and efficacy in all its uses
- Poly-MVA improved quality of life in the oncology population
- Poly-MVA added to multi-agent therapies for chronically ill patients led to improved outcomes, positive responses and quality of life.

■ Dr. Paul S. Anderson, NMD has shown the clinical synergy between LAMC and DCA; LAMC is neuroprotective and uniquely supportive in mitochondrial upregulation.
■ Ischemia studies demonstrated improvement and protection.
■ Phase One human safety trials in hypertension completed.
■ A 1000-patient oncological animal study resulted in an 86% improved quality of life.

Neuroscientist Dr. Frank Antonawich notes:

■ **This complex enhances the enzymatic activities of multiple Krebs cycle enzymes while upregulating mitochondrial function at complex I-IV.**

■ **With its powerful antioxidant properties, such as scavenging of free radicals, lowering lipid peroxidation, increasing the levels of glutathione, glutathione peroxidase, manganese superoxide dismutase, and catalase, it gives us a powerful complex to combat fatigue associated with numerous mitochondrial abnormalities.**

■ **The complex also modulates mitochondrial dysfunction, acts as a prophylactic for neuronal and radio protection, supports DNA repair, and improves the quality of life.**

"The therapeutic function /potential of this complex can be utilized in the various applications for supporting neurological injury resulting from TBI's, transient ischemic attack, death of neurons and other progressive loss of structure or function of neurons associated with any neurological event." - Dr. Paul S. Anderson, AMSA Clinic

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Lipoic Acid Mineral Complex Modulates Free Radicals in Neurodegenerative Diseases

by Frank Antonawich, PhD,[a,b*] and Merrill Garnett, DDS[a]

Introduction

Oxidative stress is caused by the chemical imbalance between reactive oxygen species (ROS) production and their breakdown by reducing agents or antioxidants. Over-abundance of ROS has been found during neuronal development, as well as in numerous neuropathological conditions. A predominant feature of neuronal injury is the onset of oxidative stress [Higgins et. al., 2010].

Oxidative stress and mitochondrial dysfunction have been closely associated in many sub-cellular, cellular, animal, and human studies of both acute brain injury such as ischemia and stroke and neurodegenerative processes such as Parkinson's, Alzheimer's and Huntington's. While the oxidative stress occurs chronically in Alzheimer's disease, it is more acute in ischemic reperfusion injury. The consequences of mitochondrial dysfunction include DNA and protein damage, lipid peroxidation, disruption of the mitochondrial permeability transition, Ca^{2+} homeostasis, and triggering apoptosis. It is essential to have healthy mitochondria contributing substantially to the physical, mental, and emotional elements needed to support the well-being of patients suffering from brain injury or neurodegenerative diseases [Krishnan et.al., 2011, 2012].

Energy metabolism, calcium regulation, and apoptosis-signaling pathways are the major roles of mitochondria. Energy requirements dictate the number of mitochondria in a cell [Alberts et. al., 1989; Voet D. & Voet J. G., 1995; Beattie, 2002; Nagley et. al., 2010]. Cardiac and skeletal muscles, the brain, and the liver have the most mitochondria because of their high metabolic activities. These cells are also exposed to the most oxidative stress because the source of free radical production is also the mitochondria. Due to low levels of antioxidants in neurons, they are intrinsically ill-equipped to defend against an increase in oxidative stress. Glial cells including astrocytes play a supplementary role in antioxidant defense of neurons [Higgins et. al., 2010].

Alpha lipoic acid is extensively studied as a potent mitochondrial nutrient for improving memory deficit, oxidative stress and mitochondrial dysfunction.

Our search for an extremely safe (up to 40 mL/day, 0.037 M aqueous solution) and nontoxic therapeutic agent resulted in the development of a novel redox molecule, "Lipoic acid mineral complex," that is active in mitochondrial cellular metabolism and other functions. The selection of the naturally occurring coenzyme, α-lipoic acid, as our ligand was based on its safety as well as its redox, antioxidant, and fatty acid properties. After selecting the ligand that plays a critical role in biological energy metabolism and numerous other functions, we wanted to tweak the properties of the ligand by complexing it with a metal that is safe and has very high catalytic and electronic properties. After numerous investigations with a variety of metals, the final selection was made to use palladium, a transition mineral.

The properties of the resulting lipoic acid mineral complex were remarkable in many ways and have been reviewed recently [Krishnan et. al., 2011]. Briefly, this complex enhances the enzymatic activities of Krebs cycle enzymes, isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, succinate dehydrogenase, and malate dehydrogenase and mitochondrial respiratory enzymes, complex I, complex II, complex III, and complex IV. These enzymatic activity enhancements by the metal complex were, in general, much greater than that of the ligand, α-lipoic acid. Coupling this increase in the efficiency of the aerobic metabolic cascade with its powerful antioxidant properties, such as scavenging of free radicals, lowering lipid peroxidation, increasing the levels of glutathione, glutathione peroxidase, manganese superoxide dismutase, and catalase, gave us a powerful weapon to combat fatigue associated with numerous mitochondrial

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abnormalities [Sudheesh et al., 2009, 2010; Ajith, 2014]. The complex also modulates mitochondrial dysfunction, acts as a prophylactic for neuronal protection from transient ischemic attack, repairs DNA damage resulting from radiation, acts as a prophylactic for protection from radiation, and improves the quality of life. The therapeutic ability/potential of this complex may be exploited in its applications for combating brain injury resulting from transient ischemic attack, death of neurons, and other progressive loss of structure or function of neurons associated with diseases such as Parkinson's, Alzheimer's, and Huntington's.

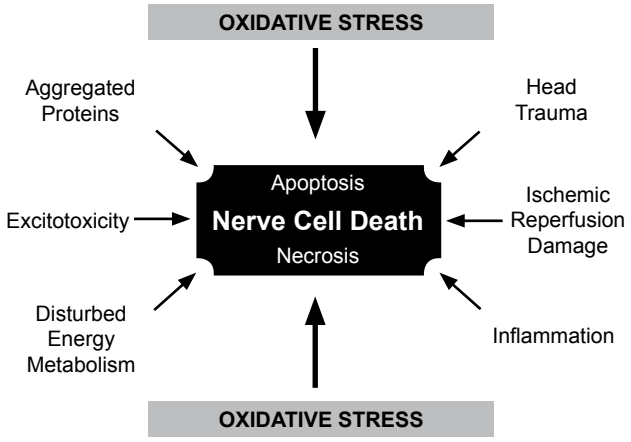
Mitochondrial Dysfunction in Neurodegenerative Diseases

Since different organs can rely on mitochondrial energy to different extents, mitochondrial defects can cause organ-specific phenotypes. The organ system most reliant on mitochondrial energy is the central nervous system. The consequences of mitochondrial dysfunction are numerous and include oxidative stress, loss of cellular Ca^{2+} homeostasis, promotion of apoptosis, and metabolic failure. Hence, evidence continues to accrue implicating mitochondrial dysfunction in the etiology of a number of neurodegenerative conditions such as Parkinson's, Alzheimer's, and transient ischemia.

In transient ischemia, a lack of oxygen and glucose delivery compromise the integrity of aerobic metabolism, while reperfusion potentiates injury via the generation of free radicals. Superoxide, nitric oxide and peroxynitrite production in the brain is increased during reperfusion following 30 minutes of global ischemia. In patients with Parkinson's disease, excess Fe^{2+} can reduce peroxide and produce hydroxyl radicals**.** These radicals and their reactions cause oxidative stress and consequent mitochondrial damage resulting in mutations. Evidence for mitochondrial dysfunction in Alzheimer's disease pathogenesis comes from impaired activities of three key Krebs Cycle enzyme complexes and reduced respiratory chain complex I, III, and IV activity observed in postmortem Alzheimer's disease brain, and oxidative damage to both mtDNA and nDNA.

Apart from ATP production, mitochondria also produce reactive oxygen species (ROS). Some electrons escaping or leaking from the electron transport complexes, mainly from complexes I and III, during respiration react with oxygen to form superoxide radicals. However, it may be possible for mitochondrial DNA (mtDNA) mutations to disrupt the normal electron flow and seriously affect energy production. Oxidative damage and the resulting serious consequences have been extensively reviewed recently [Singh, 2006]. Compared to nuclear DNA (nDNA), mtDNA is far more susceptible to mutations due to their being present in a highly oxidative environment, a lack of protective histones and limited repair capacity [Carew & Huang, 2002; Singh, 2006]. In aging and neurodegenerative disorders, apart from inherited defects, mDNA deletions and point mutations within neurons are well recognized.

Figure 1. Endogenous and Exogenous Triggers of Nerve Cell Death in Neurodegeneration [adapted from Behl & Moosmann, 2002]



Alzheimer's Disease

The most common cause of loss of brain function or dementia is Alzheimer's disease (AD). It is an age-related progressive and irreversible neurodegenerative disease resulting in impairments of cognition, memory and behavior. Available drugs do not offer significant benefit and seem to be ineffective against progression of the disease [Barnes & Yaffe, 2011]. The Alzheimer's Disease International Conference, held in Paris, France, show cased certain advancements for early detection of AD, via the high rate of falls, an early blood test of nine hormones and proteins that predict amyloid levels in the brain, and imaging of the retina to look for the width of certain blood vessels. A mathematical model revealed seven factors that contributed to the risk worldwide: lack of education (19.1%), smoking (13.9%), lack of physical activity (12.7%), depression (10.6%), high blood pressure at midlife (5.1%), diabetes (2.4%), and midlife obesity (2.0%) [Barnes & Yaffe, 2011].

Alzheimer's disease is a protein misfolding disease resulting from the accumulation of abnormally folded amyloid-β protein (Aβ) and hyperphosphorylated aggregates of the microtubule-associated (tau) proteins in the brain. Beta-amyloid plaque, made up of small peptides, is a fragment from the larger amyloid precursor protein (APP) that penetrates through the neuron's membrane. This type I transmembrane protein, APP, is needed for neuron growth, survival and post-injury repair. Enzymes divide this APP into fragments by proteolysis. One of these fragments forms fibrils of beta-amyloid. The extracellular deposition of diffuse and neuritic plaques containing amyloid-β peptide, the intracellular accrual of neurofibrillary tangles containing tau protein, and selective nerve cell loss in certain brain regions are the histopathological features of AD [LaFerla, 2002]. These are formed selectively in the hippocampus and neocortex of the brain.

Dysregulation of Ca^{2+} homeostasis is implicated in the pathogenesis of AD [Khachaturian, 1989]. Every gene that is known to increase the susceptibility to AD also modulates Ca^{2+} signaling [Laferla, 2002]. Increased intracellular Ca^{2+} increases accumulation of amyloid-β, hyperphosphorylation of tau protein, and neuronal death. Disruption of Ca^{2+} regulation in the endoplasmic reticulum mediates signal transduction cascades

that are associated with AD [LaFerla, 2002].

Neuronal cell survival and death are regulated by the pivotal role of mitochondria that also regulate energy metabolism and cell death pathways. Numerous studies have established that mitochondrial dysfunction has an early and preponderant role in AD [Moreira et. al., 2010a, b]. Oxidative damage to both mtDNA and nDNA has been examined in several studies [Mecocci et al., 1994; Gibson et al., 2000; Castellani et. al., 2002; Bubber et. al., 2005]. Significant, three-fold, increases in the amount of 8-hydroxy-2′-deoxyguanosine have been demonstrated in the mtDNA within the parietal cortex of Alzheimer's patients. A smaller, but significant increase, in oxidative damage to nDNA has also been observed [Mecocci et al., 1994]. A deficiency in cytochrome c oxidase has been reported in Alzheimer's disease [Castellani et al., 2002]. In addition, significant decreases were observed in the activities of pyruvate dehydrogenase complex (-41%), isocitrate dehydrogenase (-27%), and α-ketoglutarate dehydrogenase complex (-57%). A strong correlation exists between the diminished activity of these enzymes and the Clinical Dementia Rating [Gibson et al., 2000; Bubber et al., 2005]. On the other hand, the activities of succinate dehydrogenase (complex II) (+44%) and malate dehydrogenase (+54%) were increased.

Decreased glucose metabolism has been found to correlate well with the clinical deterioration [Minoshima et. al., 1997]. Diminished metabolism leads to hyperphosphorylation of tau proteins and increased production of amyloid-β peptide [Bubber et. al., 2005]. Oxidative nerve cell death in Alzheimer's disease and the role of antioxidants as neuroprotective compounds have been examined [Behl and Moosmann, 2002].

Alpha lipoic acid is extensively studied as a potent mitochondrial nutrient for improving memory deficit, oxidative stress and mitochondrial dysfunction [Liu, 2008]. It is used to treat peripheral neuropathy, cardiac autonomic neuropathy, insulin resistance in type-II diabetes, retinopathy and cataract, glaucoma and Alzheimer's type dementia. All the data suggest that lipoic acid mineral complex functions are far superior to that of α-lipoic acid. The complex is extremely safe with practically no side effects and has numerous properties, including enhancement of activities of Krebs cycle and mitochondrial respiratory chain enzymes, free radical scavenging properties, and DNA repair. We strongly believe in its potential for ameliorating some of the deleterious effects of AD. However, there are currently no clinical data available on its effects on cognitive functions except some preliminary promising data from patients with Stage IV cancer and under palliative care.

Parkinson's Disease

The second most common neurodegenerative disease after Alzheimer's disease is Parkinson's disease (PD). This disease increases with aging ➤

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exponentially in incidence above the age of 65 [Chan et. al., 2009]. This disease, associated with movement disorder, is characterized by the loss or degeneration of dopaminergic neurons in the substantia nigra pars compacta. This leads to a dopamine deficit in the striatum. The most common motor symptoms such as bradykinesia, hypokinesia, rigidity, resting tremor, and postural instability are all manifestations of this deficiency resulting in the dysregulation of basal ganglia circuits. At the time of clinical presentation, ~ 50-70% of dopaminergic neurons in the nigrostriatal system have been lost [Orth & Schapira, 2002]. The presence (in the surviving neurons) of Lewy bodies or proteinaceous deposits within neuronal perykarya and processes (Lewy neurites), mainly composed of α-synuclein, ubiquitin, neurofilaments, and molecular chaperones are viewed as pathological hallmarks of PD [Schapira, 2007, 2008; Winklhofer & Haass, 2010]. Autosomal forms of PD seem associated with a gain of function mechanism arise from mutations in the genes encoding α-synuclein and leucine-rich repeat kinase 2 (LRRK2). Similarly, autosomal recessive PD seems connected to a loss of function mutations in the genes encoding parkin, PINK1, DJ-1 and Omi/HtrA2 [Gandhi et. al., 2009]. The presence of activated microglial cells in the Parkinsonian substantia nigra is reported [Ruberg et. al., 1998]. These cells synthesize a known apoptogenic substance in the immune system, cytokine TNF-α.

Oxidative stress, the pathogenic outcome of reactive oxygen and nitrogen species overproduction beyond the capacity of their clearance (by antioxidants) in cells [Niizuma et. al., 2010], is implicated in the pathogenesis of Parkinson's disease (PD) [Olanow & Lieberman, 1992; Weiner et al., 2007]. Inhibition of complex I activity of the electron transport chain induces PD. An age-dependent increase in somatic mtDNA deletions associated with a respiratory chain defect has been identified in dopaminergic neurons from the substantia nigra. Also, several genes associated with sporadic and familial PD interface with pathways regulating the mitochondrial function, morphology, and fission-fusion dynamics have been closely scrutinized [Parker et al., 1989; Greenamyre et. al., 1999; Schapira, 2007; Winklhofer & Haass, 2010].

Excess Fe^{2+}, also found in patients with Parkinson's disease, can reduce peroxide and produce hydroxyl radical (HO**-**). The hydroxyl radical can lead to lipid peroxidation and alter the structural integrity of neural membranes. Dopamine undergoes auto-oxidation, producing superoxide, H_2O_2, semiquinone radical and finally a quinone [Olanow and Lieberman, 1992].

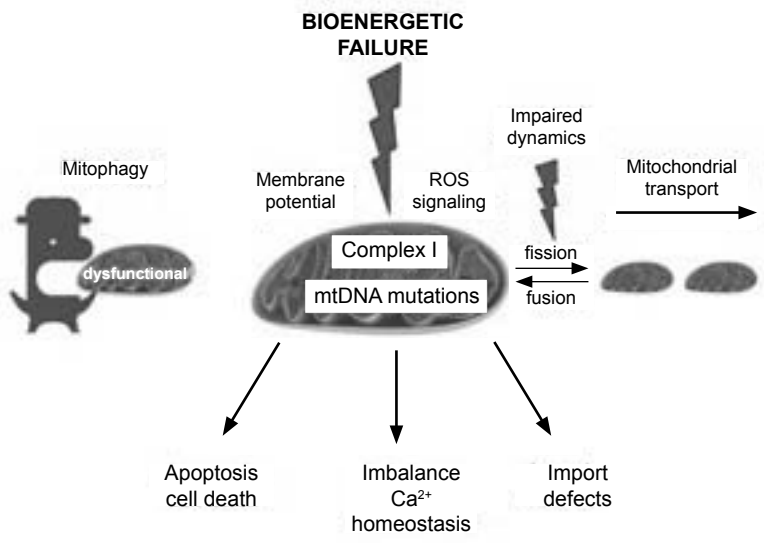
The central nervous system contains high levels of polyunsaturated fatty acids. They are susceptible to attack by free radicals, especially $HO^{\cdot}$, because the high consumption of oxygen in the brain facilitates more free radical production. The brain is relatively deficient in defending against oxidative stress. It has relatively low catalase activity and moderate SOD and GSHPx activities [Moreira et. al., 2010a]. Lipid peroxidation by the hydroxyl radical can alter the structural integrity of membranes. The excess Fe^{2+} can reduce hydrogen peroxide and produce $HO^{\cdot}$. These radicals and their reactions (reactions 13-20) cause oxidative stress and consequent mitochondrial damage resulting in mutations and probably cancer.

Vitamin E can break the chain propagation reaction by reacting with lipid peroxyl radicals. Other small molecules such as ascorbate (vitamin C), reduced coenzyme Q10 ($CoQH_2$), GSH, and α-lipoic acid also "repair" oxidizing radicals directly. Under normal physiological conditions, SOD converts the superoxide to H_2O_2 and O_2 catalytically, and H_2O_2 is cleared by GSH catalyzed by glutathione peroxidase. The oxidized glutathione (GSSG) is reduced back to glutathione by NADPH, which is catalyzed by glutathione reductase.

Table 1. Levels of Ferritin, Fe^{3+}, Glutathione and Ascorbic acid in Substantia Nigra from control and Parkinson's Disease [Prasad et. al, 1999].

	Control, µg/g fresh tissue	Parkinson's Disease, µg/g fresh tissue
Ferritin	223 ± 22	288 ± 27
Fe3+	16 ± 4	42 ± 5
Glutathione	57 ± 13	30 ± 12
Ascorbic acid	309 ± 47	271 ± 15

Figure 2. Probable mitochondrial alterations associated with Parkinson's disease [adapted from Winklhofer & Haass, 2010].



The probable mitochondrial alterations associated with PD are schematically shown in Figure 2. Neuronal cells may die because the structural integrity of neuronal membranes may be compromised by any one of these stress factors.

There are reports of oxidative stress to dopaminergic neurons [Ruberg et.

al., 1998]. The oxygen consumption of these neurons is very high because of the presence of a large number of mitochondria. There are reports of a decrease in glucose metabolism as evidenced by an increased lactate/N-acetyl aspartate ratio in the occipital cortex of demented patients with PD as well as an increase in lactate/creatine ratio in the striatum. Complex I activity or mitochondrial NADH ubiquinone reductase activity in post mortem tissue samples of the substantia nigra compacta of PD brains is also found to be about 35% less [Ruberg et. al., 1998; Chan et. al., 2009]. It is also reported that the post-mortem brains from PD patients contain increased levels of malondialdehyde, and lipid hydroperoxides. There are also reports of oxidative damage to DNA, lipids, proteins, and somatic DNA mutations in dopaminergic neurons [Chan et. al., 2009].

Autopsy sample of substantia nigra from PD brains showed increased levels of oxidants, and decreased antioxidants [Table 1]. Increased levels of free iron were seen in autopsy samples as well as in brains of living PD patients by iron-mediated contrast magnetic resonance imaging.

The role of multiple antioxidants in the prevention and treatment of PD has been reviewed [Prasad et. al., 1999]. Since α-lipoic acid is heavily involved in the attenuation of free radical related disorders including Alzheimer's disease, it is possible for it to have a positive influence in the amelioration of PD as well. But there are no well documented data. We have demonstrated that the properties of lipoic aciid mineral complex formulation are far superior to that of the ligand in every respect. Thus, we are confident that the oxidative stress associated with Parkinson's disease may be attenuated by the use of this complex. In addition, based on our data with ischemia in gerbils, the efficacy of the remaining dopaminergic neurons may be potentiated.

Multiple Sclerosis

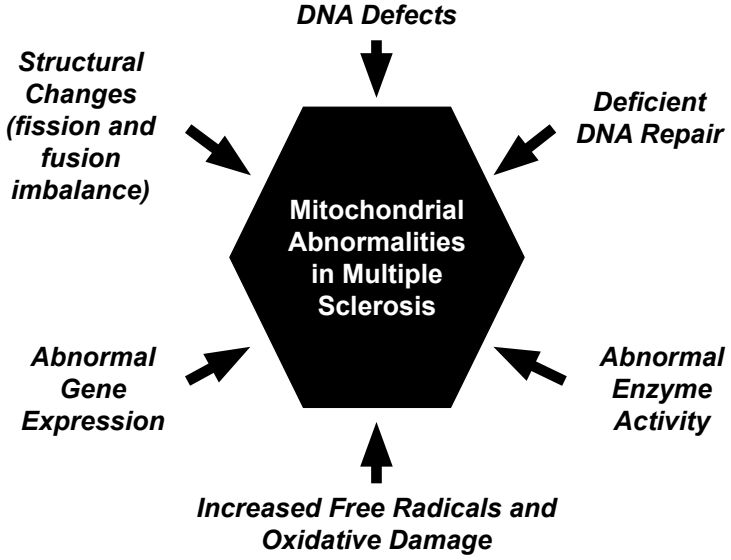
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. It is associated with demyelination and a variable degree of axonal and neuronal degeneration. Demyelination decreases nerve impulse conduction velocity. Also, the axons become vulnerable to inflammatory conditions. The mechanisms of tissue injury and neurodegeneration in MS are still under active investigation. Most multiple sclerosis (MS) patients initially experience relapsing-remitting episodes of neurologic deficits that last for six to eight weeks. The initial relapse rate is about 0.3/year. This rate declines progressively with time [Siffrin et. al., 2010]. This is followed by a gradual progression of irreversible neurological impairment or secondary progressive multiple sclerosis (SPMS) [Campbell et. al., 2011]. With advancing disease, the observed increase in gray matter atrophy, which is indicative of the loss of neurons and axons, correlates well with the corresponding clinical disability.

Apart from the consistent features, neuroaxonal injury and dysfunction in MS, the vascular aspects of MS, an increased risk for ischemic disease, global cerebral hypoperfusion, and a chronic state of impaired venous drainage are receiving a great deal of attention [D'haeseleer et. al., 2011; Filippi & Rocca, 2011].

Based on current research, it has been proposed that mitochondrial abnormalities are involved in the development and progression of multiple sclerosis (Figure 3), including mitochondrial DNA defects, abnormal mitochondrial gene expression, defective mitochondrial enzyme activities, abnormal or deficient mitochondrial DNA repair mechanisms, and mitochondrial dysfunction. Studies suggest that abnormal mitochondrial dynamics (imbalance in mitochondrial fission and fusion) plays a key role in tissues affected by multiple sclerosis. Furthermore, mitochondrial abnormalities and mitochondrial energy failure may impact other cellular pathways including increased demyelination and inflammation in neurons and tissues that are affected by multiple sclerosis [Mao & Reddy, 2010].

Mitochondrial injury and subsequent energy failure have been implicated in the pathogenesis of MS [Lu et. al., 2000; Dutta et. al., 2006; Mahad et. al., 2008, 2009; Haider et. al., 2011; Campbell et. al., 2011]. Proteins and DNA in mitochondria are highly vulnerable to free radical damage and consequent mitochondrial injury in MS. The likely candidates involved in tissue injury in MS are the reactive oxygen species and nitric oxide intermediates. These are produced by activated macrophages and microglia. In the brain tissue of patients with MS, oxidized DNA and oxidized lipids have been detected [Lu et. al., 2000]. Oxidized phospholipids and malondialdehyde (lipid peroxidation-derived structures) data from MS lesions of different activity of ➤

Figure 3. Mitochondrial abnormalities in multiple sclerosis [adapted from Mao & Reddy, 2010].



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patients with acute, relapsing, remitting and progressive disease were found to be concentrated in active MS plaques, in areas known as initial demyelinating lesion or the "prephagocytic" stage of active MS lesions [Haider et. al., 2011]. There was good correlation between inflammation and the extent of DNA and lipid oxidation.

So far, the efforts for complete restoration of axonal mitochondria following remyelination have not been successful. Thus, the need for preservation of myelinated axons is exemplified by the fact that remyelinated axons have increased energy demand. This may also result in deficient neurons and reach detrimental levels in the long term. Mitochondrial DNA deletions have been found in the neurons in the progressive stage of MS [Campbell et. al., 2011]. The pathological features of MS lesions include demyelination and oligodendrocyte apoptosis, preferential destruction of small-caliber axons, differentiation arrest of oligodendrocyte progenitor cells and remyelination failure, and astrocyte dysfunction [Haider et. al., 2011].

In view of our data with palladium α-lipoic acid formulation on the enhanced enzymatic activities of Krebs cycle and electron transport chain enzymes in animals, anti-oxidant activity and the ability of this formulation to repair DNA, we had decided, as a preliminary step, to investigate its usefulness in ameliorating the fatigue conditions in 15 MS patients. At the completion of this IND study there was a statistically significant decrease in MS-associated fatigue in all three clinical scales evaluated.

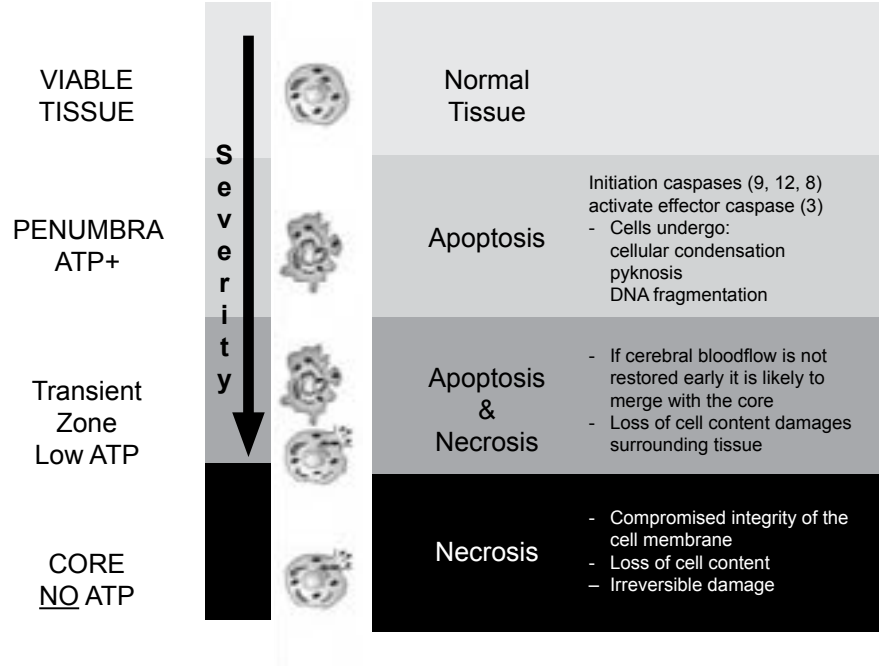
Cerebral Ischemia

An insufficient or reduced blood flow to the brain to meet the metabolic demand will result in cerebral or brain ischemia. The normal cerebral blood flow is ~ 50 to 60 mL/100g/min. Death of brain tissue is a consequence of poor oxygen supply or cerebral hypoxia resulting from the insufficient blood flow. A prototype of brain damage during cerebral ischemia is shown in Figure 4 [adapted from Mehta et. al., 2007]. Maximum damage occurs as a result of ischemic necrosis (infarction) at the "core" or "focal" tissue region, where the blood flow is < 7 mL/100g/min. Since the cellular integrity is compromised during necrosis, cellular damage repair at the core is extremely hard. The blood flow in the surrounding less-severely ischemic boundary ("penumbral" or "perifocal" tissue) is ~ 7 to 17 mL/100g/min. The penumbra is metabolically active but electrically silent [Mehta et. al., 2007]. More moderate alterations develop in this region because of the near normal glucose use, but the oxidative metabolism is still impaired. Different mechanisms contribute to cell death in the core and penumbra due to differences in the severity of ischemia.

While focal ischemia is confined to a specific region of the brain, global ischemia encompasses wide areas of the brain tissue. Focal ischemia occurs in a region when a blood clot has occluded in a downstream region of artery in the brain (ischemic stroke). This occlusion or blockage may be caused by thrombosis (a blood clot formed locally obstructing the blood flow) or arterial embolism (obstruction of blood flow due to an embolus from elsewhere in the body). While ischemic strokes are caused by interruption of the blood supply, hemorrhagic strokes are the result of rupture of a blood vessel. Hemorrhagic strokes result in areas of friable tissue, containing areas of both viable and dead tissue. Transient global ischemia involves a brief interruption in blood flow usually in a larger cerebral vessel, e.g. middle cerebral artery, resulting in primarily apoptotic cell death.

More than 80% of all strokes are due to focal ischemia. Unless treated, the occlusion of an artery produces tissue infarction resulting in a loss of all cells including neurons, astrocytes, oligodendrocytes, microglia and endothelial cell [Sims & Muyderman, 2010]. The stroke results in mitochondrial impairment because the blood flow becomes < 20% of the normal and a consequent reduction in glucose and oxygen supplies ensue. This attenuates ATP and reactive oxygen species production as well as apoptosis. Lack of ATP production disrupts the ionic gradients across the plasma membrane. The net result is marked losses of intracellular K^+ and a large influx of Ca^{2+} into cells [Doyle et. al., 2008]. Thus, there is heavy involvement of the impaired

Figure 4. A prototype brain damage during cerebral ischemia: core, a region where cells undergo necrosis. The region surrounding the core is called ischemic penumbra, a site of delayed mode of cell death (apoptosis) due to availability of ATP. Further, a transient zone in-between the core and penumbra is likely to merge to the core if the cerebral blood flow is not restored early. The penumbral region is surrounded by a region of viable tissue [adapted from Mehta et. al., 2007].



mitochondria in the development of the tissue injury after ischemic attack, due to modifications in ATP production and other mitochondrial changes leading to apoptosis and necrosis.

Ischemic cell death is also attributed to abnormal activation of enzymes such as poly-ADP ribose polymerase (PARP) and the caspases. Oxidative stress, which produces free radical nitric oxide ($NO^{\cdot}$) and reactive peroxynitrite ($ONOO^{-}$), is implicated in both necrosis and apoptosis in focal ischemia. Peroxynitrite is formed by the reaction of $NO^{\cdot}$ with superoxide. Mitochondria are targeted by peroxynitrite and the resulting mitochondrial dysfunction during severe hypoxia-ischemia increases generation of oxygen free radicals. This leads to dysfunction of cellular membrane causing necrosis [Mehta et. al. 2007]. An additional consequence of ischemia involves the dissociation of the electron transport chain within minutes of the insult. Ubiquinone and cytochrome C, which serve as electron shuttles, translocate from the inner mitochondrial membrane. This is of particular consequence upon restoration of blood flow. While reperfusion limits some damage, oxidative stress is increased under these conditions. It has been found that over expression of Mn^{2+}-superoxide dismutase, which converts superoxide to hydrogen peroxide results in moderate reductions in the size of infarction in temporary ischemia [Sims & Muyderman, 2010]. Addition of the mitochondrial uncoupling agent, dinitrophenol, was found to modulate the Ca^{2+} content and production of free radicals in the mitochondria of penumbra [Korde et. al., 2005].

The reduced delivery of oxygen and glucose to the tissue in focal ischemia affects the function of the mitochondria. Mitochondrial properties undergo further changes depending on the severity and duration of ischemia and also following reperfusion. Development of cell death pathways depends on the impaired mitochondria's ability to generate ATP.

The changes in energy-related metabolites and in the contributing metabolic pathways in brain tissue in the first 2 h of ischemia and reperfusion for 1 h are summarized in Table 2 [Sims & Muyderman, 2010]. In the core, the ATP and glucose content falls significantly in the first 5 min of occlusion and then ATP stabilizes to ~ 15-30% of normal for at least the first 2 h and then reaches about 50%. The initial rapid decrease is attributed to the major redistribution of ions across the plasma membrane of cells. The adenylate energy charge decreases rapidly to ~ 0.4-0.5 during the initial hours and remains above 0.8 after 2 h compared to the normal value in the brain of ~ 0.93. While adenylate kinase catalyses the conversion of some ADP to AMP to meet short term energy needs of the brain, in ischemic tissue, the adenine nucleotide pool is depleted by the conversion of AMP to inosine and hypoxanthine. Phosphocreatine, the short-term energy reserve of the brain falls quickly to <30% of normal during ischemia. Phosphocreatine stabilizes to about 70% of normal after ~ 2 h of ischemia. ATP regeneration from ADP is catalyzed by the enzyme creatine kinase. Lack of oxygen forces glucose to go the glycolytic pathway creating a 10-fold increase in lactate and consequent lowering of pH. Of course, lack of removal of lactate due to limited blood flow may also be contributing to this accumulation. In addition, restricted blood flow appears to have a greater effect on the delivery of oxygen to the tissues versus glucose, since penumbral glucose levels are either the same or slightly higher, while lactate levels are much higher (however less than in the core).

During the first 2 h following reperfusion, phosphocreatine and adenylate energy charge are recovered to >90% of normal compared to ATP values of 50-70%. This resistance of ATP for restoration is attributed to the depletion of the adenine nucleotide pool. In the penumbral tissue, phosphocreatine and adenine nucleotide balance, but not ATP are recovered almost completely within 1 h of reperfusion for ischemic periods of 3 h or longer [Sims & Muyderman, 2010]. The glucose utilization is less in the penumbral region during the first hour of reperfusion. The lactate, on the other hand, is decreased during this period.

The reduction in ATP production in the ischemic brain may be associated with decreased neuronal activity of the post-ischemic brain as a result of the enzyme AMP-activated protein kinase enzyme [Sims & Muyderman, 2010].

It must be mentioned that there is a complete or near complete recovery of mitochondrial respiratory function in core and penumbral tissues within the first hour following reperfusion. This is followed by a secondary deterioration, ➤

Table 2. The effects of focal ischemia for up to 2 h and of subsequent reperfusion for 1 h on the content of energy-related metabolites and pathways of energy metabolism [Sims & Muyderman, 2010].

	Focal ischemia		Reperfusion	
	Core	**Penumbra**	**Core**	**Penumbra**
Metabolites				
ATP	↓↓↓	↓↓	↓↓	↓
Adenylate energy charge	↓↓	↓	↓/N.C.	N.C.
Total adenine nucleotides	↓↓	↓↓	↓↓	↓
Phosphocreatine	↓↓↓	↓	↓	N.C.
Lactate	↑↑	↑↑	↑↑	↑/N.C.
Glucose	↓↓↓	N.C.	N.C.	N.C.
Metabolic activity				
Glucose use	↓↓↓*	N.C.	↓↓	↓↓
Oxidative metabolism	↓↓↓*	↓↓↓	↓↓	↓↓

Differences are shown compared to non-ischemic tissue. ↓: decreased to >65%; ↓↓: decreased to between 35% and 65%; ↓↓↓: decreased to less than 35%; ↑: increased less than four-fold; ↑↑: increased greater than four-fold; N.C.: no significant change. Two symbols indicate findings that differ between published reports. *, direct evaluation of these properties in severely ischemic tissue may not give reliable information. The magnitude of these reductions is assumed from the large decrease in substrate delivery and large changes in ATP and phosphocreatine content [Sims & Muyderman, 2010].

➤

indicative of the development of irreversible cell dysfunction.

One neuroprotective approach involves the use of anti-oxidants. As an example, α-lipoic acid reduced the mortality rate of male Sprague-Dawley rats from 78% to 26% during 24 hours of reperfusion. It was found effective in improving survival and protecting the rat brain against reperfusion injury following cerebral ischemia [Panigrahi et. al., 1996]. In another study rats that received subcutaneous treatment of R-or S-lipoic acid for 2 hours before ischemia significantly reduced the infarct volume [Wolz & Krieglstein, 1996]. Similar results with mice were obtained with 100 mg/kg of lipoic acid given subcutaneously 1.5 hours before ischemia [Clark et. al., 2001]. Transient global ischemia also benefits from pretreatment with α-lipoic acid. Administration of 40 mg/kg for 7 days protected from ischemic damage when gerbils were tested for locomotor behavior and morphological damage to the CA1 region of the hippocampus. [Cao & Phillis, 1995].

Animal studies, using adult male Mongolian gerbils, demonstrated that acute, post ischemic and prophylactic administration of lipoic aciid mineral complex formulation limits ischemic damage [Antonawich et. al., 2004]. Following bilateral carotid artery occlusion in the gerbil, the lipoic acid mineral complex formulation was administered intraperitoneally (IP) immediately after surgery, then once daily for 3 days. The control group received saline. Palladium lipoic acid complex formulation treatment significantly protected CA1 hippocampal pyramidal cells from transient global ischemia at 30, 50, and 70 mg/kg per 24 h.

While a delayed application of the lipoic acid mineral complex formulation after 48 hours of ischemic attack had no significant effect in protecting CA 1 cells, a delayed administration after 6 hours of ischemic attack was as good as giving it immediately after ischemic attack in minimizing cell death.

Five minutes of carotid artery occlusion was sufficient to hinder the characteristic nesting behavior of gerbils for approximately 3 days. Their nesting behavior was observed to improve significantly after treatment with palladium lipoic acid complex formulation (50 mg/kg every 24 h and 30 mg/kg /24h at 24 and 72 hours after ischemia. The lack of nesting behavior at 70 mg/kg-treated animals was attributed to their excessive energy and consequent ignoring of the nesting material.

It was observed that preventive or prophylactic treatment with 10 mg/kg gerbil (or allometric scaling equivalent of 10 mL-human dosage) offered significant behavioral and morphological improvement from transient global ischemia.

Our studies demonstrate a greater protective effect of lipoic acid mineral complex versus α- lipoic acid alone (Cao & Phillis, 1995). Four times more α-lipoic acid and for a longer period of pre-treatment were necessary to obtain morphologiocal protection. Furthermore, immediate administration of lipoic aciid mineral complex formulation protected over 70% of the CA1 neurons, and administration delayed up to 24 hours after the TIA still offered significant protection (30% of the CA1 pyramidal cells) [Antonawich et. al., 2004]. This mechanism of action appears to be related to stabilizing the electron transport chain, in addition to quenching radical formation.

Conclusions

At the heart of a number of neurodegenerative disorders is mitochondrial dysfunction. Lipoic acid mineral complex is formulated to combat mitochondrial dysfunction. The unique electronic properties of palladium modulating the properties of α-lipoic acid appear to be a key to this physiological effectiveness.

Lipoic acid mineral complex facilitates aerobic metabolism much more than that of α-lipoic acid, by significantly enhancing the enzymatic activity of isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, succinate dehydrogenase, and malate dehydrogenase at the Krebs cycle and mitochondrial complexes I, II, III, and IV of the electron transport chain. The electronic properties of palladium also appear to modulate the antioxidant properties of α-lipoic acid in that lipoic acid mineral complex formulation enhances the activities of catalase and glutathione peroxidase more than that of α-lipoic acid. The level of glutathione also was significantly improved, and the level of lipid peroxidation was decreased in the heart mitochondria of aged rats.

Lipoic acid mineral complex formulation is similar to a multi-spectrum drug. Since it targets the mitochondria, it is able to carry out several functions such as combating age-related as well as disease-associated fatigue and minimizes the effects of ischemic injury. Being a powerful free radical scavenger, it may also be effective in combating death of neurons and other progressive loss of structure or function of neurons caused by free radicals.

Dr. Frank Antonawich completed his undergraduate training at the University of Rochester, earned a PhD in neuroscience from New York University and completed his post-doctoral fellowship in the Department of Neurology at Stony Brook University. He is a professor of biology at St. Joseph's College in New York, as well as the chair of the biology department. Dr. Antonawich serves as a senior scientist and the clinical research administrator at Garnett McKeen Laboratory Inc. in Bohemia, New York.

Dr. Merrill Garnett is the founder and director of Garnett McKeen Laboratory, Inc. Holding a DDS from New York University, and graduate study in chemistry and biochemistry, Dr. Garnett has had research laboratories at the Central Islip State Hospital, Waldemar Medical Research Foundation, Northport Veterans' Administration Medical Center, and the High Technology Incubator of The State University of New York at Stony Brook.

Dr. Garnett's principle laboratory discoveries reveal the presence of corollary dynamics of the genetic code by which specific DNA coded segments and cell membranes exchange ultra-low frequency sinusoidal electrical currents.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Carotenoids Play a Role in Cognitive Function

Ninety-one healthy individuals (mean age, 45 years) with low concentrations of macular pigment were randomly assigned to receive, in double-blind fashion, a daily supplement containing 10 mg of lutein, 10 mg of *meso*-zeaxanthin, and 2 mg of zeaxanthin or placebo for 12 months. Compared with placebo, supplementation with the carotenoids resulted in significant improvements in scores on four tests that measured memory function out of a total of seven tests that measured cognitive function.

Comment: Lutein and zeaxanthin are dietary carotenoids that have been shown to prevent age-related macular degeneration. The beneficial effect of these carotenoids in the retina appears to result from their capacity to filter the phototoxic blue-light portion of the sun's rays. Lutein and zeaxanthin have also been identified in the hippocampus, cerebellum, and frontal, occipital, and temporal cortices of the human brain. The concentrations of these carotenoids in the brain correlate with their respective concentrations in the retina. The results of the present study indicate that the combination of lutein, zeaxanthin, and *meso*-zeaxanthin can improve memory in healthy individuals with presumed suboptimal intake of lutein and zeaxanthin (as suggested by low concentrations of these carotenoids in macular pigment). The supplement used in this study also contained *meso*-zeaxanthin, which is not a major dietary carotenoid, but which can be synthesized in the retina from lutein. To what extent, if any, the improvement in cognitive function observed in the present study was due to *meso*-zeaxanthin was not investigated.

Power R, et al. Supplemental retinal carotenoids enhance memory in healthy individuals with low levels of macular pigment in a randomized, double-blind, placebo-controlled clinical trial. *J Alzheimers Dis*. 2018;61:947-961.

Wernicke's Encephalopathy: Both Thiamine and Magnesium Are Important

A 34-year-old male developed signs of Wernicke's encephalopathy that failed to respond to high-dose intravenous thiamine. Serum magnesium was found to be below normal. Intravenous administration of both magnesium and thiamine resulted in a resolution of symptoms after his serum magnesium level became normal.

Comment: Wernicke's encephalopathy is a neuropsychiatric disorder that results primarily from thiamine deficiency. The condition is common among chronic alcoholics and has also been observed in people with persistent vomiting (including hyperemesis gravidarum), advanced cancer (particularly in patients who have had surgery for gastrointestinal cancer), Crohn's disease, or a history of bariatric surgery.

Magnesium is required for the conversion of thiamine to its biologically active form.[1] Furthermore, some thiamine-dependent enzymes also require magnesium. In patients who are deficient in both thiamine and magnesium, symptoms of thiamine deficiency may not respond to thiamine supplementation unless magnesium deficiency is also corrected. In addition, administration of large doses of thiamine can exacerbate magnesium deficiency. Magnesium supplementation should therefore be considered for patients being treated with thiamine.

Coughlan JJ, et al. Thiamine refractory Wernickes encephalopathy reversed with magnesium therapy. *BMJ Case Rep*. 2016;2016:bcr2016218046.

Fatty Acids Improve Reading Ability in Children

One hundred fifty-four children (aged 9-10 years) in Sweden were randomly assigned to receive, in double-blind fashion, three capsules twice a day of omega-6 and omega-3 fatty acids

or placebo (palm oil) for three months. The active treatment provided daily 558 mg of eicosapentaenoic acid, 174 mg of docosahexaenoic acid, and 60 mg of gamma-linolenic acid. One hundred twenty-two children completed the trial. In both intent-to-treat and per-protocol analysis, active treatment was superior to placebo for improvement in phonologic decoding time and visual analysis time. For children with ADHD-Rating-Scale-IV scores above the median (indicating more attention deficit-hyperactivity disorder [ADHD] symptoms), compared with placebo, active treatment improved visual analysis time ($p < 0.01$), reading speed ($p < 0.01$), and phonologic decoding time ($p = 0.006$).

Comment: The results of this study indicate that supplementation with the combination of eicosapentaenoic acid, docosahexaenoic acid, and gamma-linolenic acid improved certain parameters of reading ability in schoolchildren in Sweden, particularly those with attention problems. In previous uncontrolled[2] and two double-blind trials,[3,4] supplementation with docosahexaenoic acid or with a combination of fish oil and evening primrose oil (which contains gamma-linolenic acid) improved reading skills in children with dyslexia. Additional research is needed to determine which regimen of fatty acids is most effective and which children are most likely to benefit.

Johnson M, et al. Omega 3/6 fatty acids for reading in children: a randomized, double-blind, placebo-controlled trial in 9-year-old mainstream schoolchildren in Sweden. *J Child Psychol Psychiatry*. 2017;58:83-93.

Biotin and Multiple Sclerosis

Forty-three patients (median age, 61 years) with progressive multiple sclerosis (median disease duration, 23 years; 26 secondary progressive, 7 primary progressive, 10 relapsing remitting with progression) were asked to take 300 mg of biotin once a day for at least one year. Twenty patients were on disease-modifying drugs and continued those drugs during biotin treatment. Twenty-four patients completed one or more years of biotin treatment. Discontinuation of biotin was almost always due to lack of perceived benefit or perceived worsening of symptoms. High-dose biotin was safe and well tolerated, and no new lesions were seen on brain MRIs. None of the patients improved according to the Expanded Disability Status score (EDSS). Some 38-43% of the patients became worse, most often with increased lower extremity weakness, worse balance, and more falling. Several patients who had become worse while taking biotin improved after stopping it.

Comment: Biotin is a cofactor for acetyl-CoA carboxylase, a potentially rate-limiting enzyme in myelin synthesis. In a previous uncontrolled trial, 90% of 23 patients with multiple sclerosis (primary or secondary progressive) experienced various neurological improvements while taking biotin (100-300 mg per day for a mean duration of 9 months).[5] However, in a follow-up double-blind trial, high-dose biotin (300 mg per day for 1 year) produced clinical improvement in only 13% of patients.[6] In the new study, biotin treatment was not beneficial. As compared with the other trials of high-dose biotin for multiple sclerosis, the patients in the present study were older, had longer disease duration, and were more disabled.

Despite its uncertain efficacy, biotin is safe and relatively inexpensive, so a clinical trial in selected patients with multiple sclerosis seems reasonable. Supplementation with large doses of biotin may interfere with laboratory tests for vitamin B_{12}, certain steroid hormones, and thyroid function (potentially leading to an erroneous diagnosis of Graves' disease). It has been recommended that people taking high-dose biotin discontinue it for 72 hours before having blood tests.

Birnbaum G, Stulc J. High dose biotin as treatment for progressive multiple sclerosis. *Mult Scler Relat Disord*. 2017;18:141-143.

Alpha-Lipoic Acid for Schizophrenia

Twelve Brazilian patients (aged 18-60 years; mean age, 38.5 years) with chronic schizophrenia (mean disease duration, 18.7 years) who had been on stable doses of antipsychotic medication for at least one year received 100 mg per day of alpha-lipoic acid (ALA) in open-label fashion for four months. Ten patients completed the trial. All patients improved; the mean improvement in the Brief Psychiatric Rating Scale (BPRS) score was 63.9%. All domains of the BPRS showed improvement in the mean score (percent improvement in parentheses): negative symptoms/disorganization (69%), excitement (76%), depressive symptoms (47%), and positive symptoms (52%). A significant improvement in extrapyramidal symptoms was also seen.

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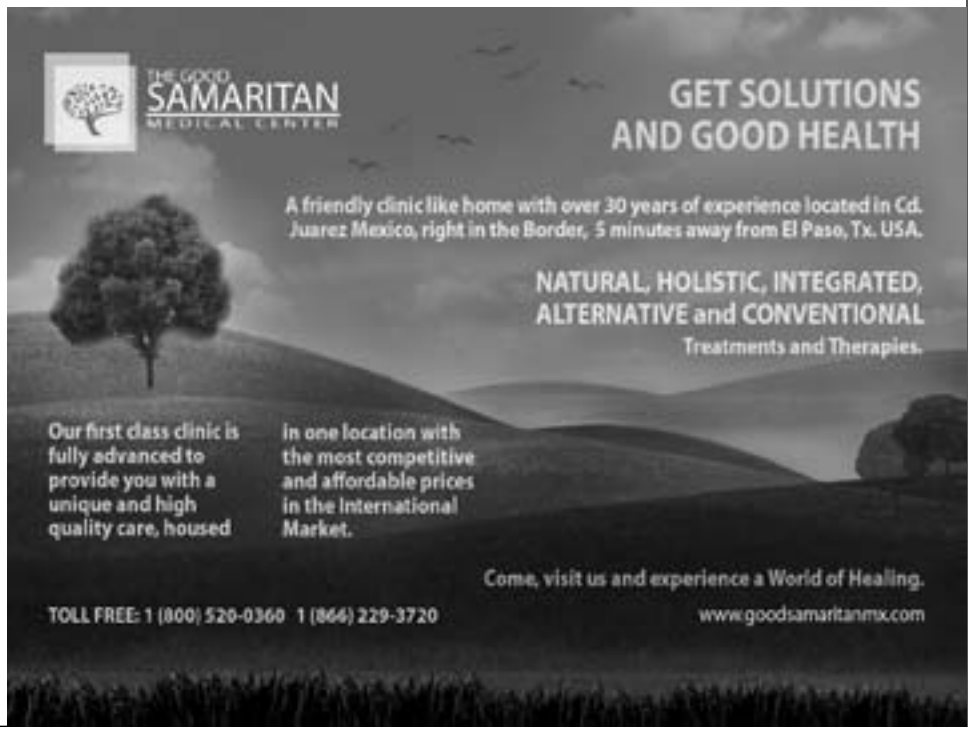

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Comment: The authors of this report cited two studies from the 1950s in which ALA improved symptoms in at least half of patients with schizophrenia. In those studies, two of three patients who improved on a dose of 100 mg per day deteriorated when the dose was increased to 200 mg per day. In more recent studies, ALA at a dose of 300 or 1,200 mg per day did not improve symptoms in patients with schizophrenia. Taken together, these findings raise the possibility that there is a "therapeutic window" for ALA in the treatment of schizophrenia, such that doses either above or below the therapeutic window are less effective than the optimal dose. Additional controlled trials are needed to investigate that possibility.

Sanders LLO, et al. Alpha-lipoic acid as adjunctive treatment for schizophrenia: an open-label trial. *J Clin Psychopharmacol*. 2017;37:697-701.

Vitamin B3 for Bipolar Disorder

A 60-year-old man had a long history of bipolar disorder that had been treated with lithium and other psychotropic medications. These medications had had beneficial effects but at times were insufficient. The man was prescribed sustained-release niacin at a dose of 1 g twice a day to treat anxiety. He experienced a marked improvement in both anxiety and depression and was able to wean off all psychotropic medication over a period of about one year. The patient has remained well for 11 years while taking niacin, currently 1 g three times per day of the regular-release form. On a few occasions, discontinuation of niacin resulted in a return of anxiety and depression within two to three days, which again resolved within one day of resuming niacin.

Comment: Vitamin B3 (niacin or niacinamide) plays a role in serotonin metabolism, and has been reported in uncontrolled trials to be of value in the treatment of depression, anxiety, and insomnia. This case report suggests that vitamin B3 is also useful for selected patients with bipolar disorder. The authors of the report suggested that this patient had a vitamin dependency (i.e., an unusually large requirement for vitamin B3, possibly genetically determined). The patient had a strong family history of depression and other psychiatric disorders, and it would be interesting to determine whether other family members would have a positive response to niacin or niacinamide.

Jonsson BH. Nicotinic acid long-term effectiveness in a patient with bipolar type II disorder: A case of vitamin dependency. *Nutrients*. 2018;10:E134.

Subtle Hypothyroidism and Infertility

A cross-sectional study was conducted on 239 infertile couples in which the female partner had a normal thyroid-stimulating hormone (TSH) level. One hundred eighty-seven women (mean age 31.5 years) had unexplained infertility and 52 women (control group) (mean age, 30.1 years) had no other cause of infertility than a partner with sperm abnormalities (azoospermia or severe oligospermia). The median TSH level was significantly higher in the women with unexplained infertility than in the control group (1.95 vs. 1.66 mIU/L; p = 0.003). The proportion of women who had a TSH level of 2.5 mIU/L or greater was significantly higher in the women with unexplained infertility than in the control group (26.9% vs. 13.5%; p = 0.003).

Comment: Hypothyroidism is a known cause of infertility. In the present study, unexplained infertility in women was associated with higher TSH levels in the normal range. That finding raises the possibility that some women with unexplained infertility have subtle hypothyroidism. In my experience, some infertile women have normal thyroid-function tests but clinical evidence of possible hypothyroidism (e.g., cold extremities, fatigue, depression, edema, constipation, delayed Achilles tendon reflex return). In many of these women, a clinical trial of low-dose thyroid hormone is followed by an improvement in the various signs and symptoms and a successful pregnancy. The evaluation and management of "sub-laboratory" hypothyroidism has been discussed elsewhere.[7,8]

Orouji Jokar T, et al. Higher TSH levels within the normal range are associated with unexplained infertility. *J Clin Endocrinol Metab*. 2018;103:632-639.

Tea and Iron Absorption: Timing Matters

Twelve iron-replete non-anemic women (mean age, 25 years) consumed a standardized porridge meal extrinsically labeled with ^{57}Fe as ferrous sulfate on three separate occasions, with a 14-day interval between each test meal. The meal was administered with water during the first test, with 200 ml of black tea consumed simultaneously with the meal during the second test, and with 200 ml of tea consumed one hour after the meal during the third test. Fractional iron absorption was 5.7% with the water test, 3.6% with simultaneous tea ingestion (37% inhibition), and 5.7% when tea was ingested one hour after the meal ($p < 0.05$ comparing simultaneous tea ingestion and 1-hour postprandial tea ingestion).

Comment: Black tea (and, to a lesser extent, green tea) has been shown to inhibit nonheme iron absorption, but it has not been clear whether the timing of tea consumption relative to a meal influences iron bioavailability. The results of the present study indicate that the inhibitory effect of black tea on nonheme iron absorption can be prevented by consuming the tea one hour after the meal.

Ahmad Fuzi SF, et al. A 1-h time interval between a meal containing iron and consumption of tea attenuates the inhibitory effects on iron absorption: a controlled trial in a cohort of healthy UK women using a stable iron isotope. *Am J Clin Nutr*. 2017;106:1413-1421.

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On the cover

The Biology of Hope

by Leigh Erin Connealy, MD

Introduction

We are at a point in time where medicine is coming back to whole body health care from a reductionist view that has dominated the conventional medicine world for the past several hundred years. Just like a pendulum that swings back and forth, science has also swung from one point of view to another throughout history, from healing through shamanic rituals to using pharmaceutical drugs to make a change in the body at the molecular level. As the pendulum slows down, we are able to integrate worldviews of both conventional and integrative/functional medicine into an integrative whole person model that utilizes the best of both worlds without sacrificing one or the other. There is a place for chemotherapy, radiation, and surgery for treatment of cancer; but based on latest research, we know that there is a place for the mind and the spirit as well. Integrative and functional medicine incorporate and realize that healing, with a whole being platform or the seven pillars of health, takes place on all levels and includes spirituality, mind-body, immunity, nourishment, detox, lifestyle and targeted therapies.[1] In fact, in psychosomatic medicine, it's often understood that a person's mental state and outlook on life, such as having hope, could have an influence on the course and severity of a physical disease such as cancer.

Conventional Approach

Western science has been divided ever since the seventeenth century when Rene Descartes, the philosopher and founding father of modern medicine, developed his theory on the mind-body problem known as the Cartesian dualism, in which the body and the mind are viewed as separate entities. Interestingly, this happened when Descartes was forced to make a deal with the Pope in order to get the human bodies that he needed for dissection. He agreed he wouldn't deal with the soul, the mind, or the emotions, which were under the jurisdiction of the church at the time, if he could claim the physical body for his own study. And sadly, it has been like this for Western science and medicine ever since, where most of the medical establishment has been forbidden to bring the mind into discussion.

Today, conventional oncologic treatment consists of chemotherapy, radiation, and surgery. But my experience with thousands of patients over the years has solidified the belief that they aren't enough to cure cancer or other medical problems. In the conventional approach, a patient is tested for cancer by mammogram, ultrasound, confirmed by biopsy, and then given a cancer diagnosis with a prognosis that has a time limit. When a time limit is given, all the patient hears in their mind is a death sentence and this fear in itself prevents the patient from healing. In other words, the mind has a powerful impact on the outlook of the course of the disease and this, of course, is not taught to the doctors or mentioned to the patients in the conventional world.

Integrative Approach

Cancer is a disease of the whole person, not just one body part; and yet most conventional oncologists treat cancer as a separate entity or as a specific problem in the body. Their aim is to kill the cancer cells and remove the tumor from the body rather than heal the body from within and understand the environment and condition of the patient, to understand what set the stage for the cancer to develop in the first place. If the tumor is just removed but the environment stays the same, the cancer is sure to develop again. Circulating tumor cells (CTCs) or cancer stem cells (CSCs) are cells

that break off from the original tumor and float around in the bloodstream looking for their next "nest" to settle in and are responsible for 95% of all metastases and cancer deaths.[2] Scientists have not figured out how to eliminate them through chemotherapy, radiation, or surgery. Instead of building up the immune system to help the body heal on its own and fight the cancer, conventional treatments tear it down and can sometimes create new health problems for the person due to immune suppression.

If we re-frame our mind to look at the whole person and the environment for what caused the cancer to develop in the first place, then that's where all these other factors such as stress, diet, environment, the mind, the spirit, and all other aspects of the patient come into play. The body is an intelligent organism with a magnificent biochemistry and has a self-healing capacity. And it's possible that cancer is one way that our body lets us know that something is off-balance, or maybe the cancer itself is a healing mechanism for warding off an outside invader, or for holding an emotional trauma. Whatever the case may be, we need to re-frame our mindset as medical doctors and scientists and help to revolutionize the thinking pattern of our patients if we truly want to treat the origin of the illness or the cause of the cancer.

The Science Behind the Mind-Body Connection

The idea that emotions are linked to cancer has been around since the 1940s and has been well studied in research studies for a long time.[3–9] Temoshok from UCSF showed that cancer patients who didn't express their anger had slower recovery rates than those who were more expressive,[10] while Spiegel's study showed that expressing emotions like anger and grief improved survival rates of cancer patients.[11,12] As Candace Pert states, "Repressed traumas caused by overwhelming emotion can be stored in a body part, thereafter affecting our ability to feel that part or even move it."[13] Dr. Hamer developed testicular cancer after his son was shot dead; and after investigating over 15,000 cases of cancer, he found that every cancer could be traced back to a traumatic event such as a loss of a loved one, rape, or other traumatic event in the patient's life, which Dr. Hamer calls a conflict-shock-experience. He, interestingly, further noticed that the theme of the psychic conflict correlated with a specific location of the cancer.[14]

Some emotional risk factors for cancer include chronic exposure to stress hormones, adverse childhood experiences (ACEs), depression, post-traumatic stress disorder (PTSD), alexithymia (inability to express one's emotions), attitudes/beliefs/nocebo effect, and lack of meaningful connections. Bruce Lipton, PhD, presents in his book *The Biology of Belief* that it isn't our DNA that control our biology, but our environment, thoughts, and beliefs that can turn our genes on and off through epigenetics.[15] When someone falsely believes that they're getting a medication and gets better symptomatically, when in fact they're getting a sugar pill, it's known as the placebo effect.[16,17] This placebo effect or belief effect as Bruce Lipton calls it, stresses that our perceptions, whether they are accurate or not, impacts our behavior and health. When a person perceives love, it was found that the growth genes were activated through the placebo effect. Similarly, when a person perceived a negative environment such as fear, anger, or hatred, the body went into fight or flight mode and the immune system and vital organs were neglected. Just as much as someone could get better with the placebo effect, the opposite can happen through what's called the nocebo effect, when someone believes that they will get worse or will die from a disease. A study found that patients who thought that they were going to die from cancer were more likely to do so than those who didn't have these thoughts.[18,19] Therefore, a patient's belief and perception of their diagnosis is very important in the course and outcome of their disease.

It wasn't known until after 1973 when Candace B. Pert, PhD, discovered the opioid receptor, that the body makes its own opioid called endorphins that act like morphine. Known as the mother of psychoneuroimmunology (PNI) and someone who brought the gap between the mind and body closer, Candace Pert calls these neuropeptides the "molecules of emotion" due to the fact that these molecular peptides have an effect on our mind and emotions.[13] According to Pert, our emotions are what glues the body and the mind together and runs all the systems in the body since emotional expressions are always tied to a specific flow of peptides in the body and the spinal cord site that filters all incoming bodily sensations have receptors for almost all these peptides. For example, it's through these molecules of emotions or peptides that an embarrassing thought can turn a face red.

But how do emotions have an effect on our health? These neuropeptides are in constant communication with our immune system, and the immune system itself produces peptides as well to modulate our health. Interestingly, viruses use the same receptors as these neuropeptides to enter into a cell; and depending on how much of the natural peptide is present, the virus will have either an easier or harder time entering a cell. This means that the state of our emotions will have an effect on the level of neuropeptides produced and thus whether we succumb to a viral infection or not. It can be deduced from this that being in a certain emotional state, such as an elevated mood, may protect against certain viruses. In 1990, Hall's study showed that psychological factors such as relaxation and guided imagery, self-hypnosis, biofeedback, and autogenic training, could directly affect the cellular function of the immune system i.e. the stickiness of the white blood cells as measured by saliva and blood tests.[20] And knowing that cancer is tightly linked with the immune system, it's easy to extrapolate that our emotions may be linked with cancer development. The immune system is what's responsible for the constant destruction of erroneous cancer cells that are developing in each one of us at every moment.

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Based on an analysis of over 1,500 cases of radical remission of cancer patients and research in 10 different countries, Kelly Turner, PhD, found that there were nine common healing factors in most of these remission cases.[21] Only two of the nine factors were physical (diet and supplements) and the remaining seven all had to do with emotions, mind-body connection, and spirituality, i.e. releasing suppressed emotions, increasing positive emotions, taking control of your health, following your intuition, embracing social support, deepening your spiritual connection, and having strong reasons for living.

Neuro Emotional Technique (NET) is one mind-body intervention developed in the early 1980s that helps to reduce stress. In a recent 2017 study, researchers found that cancer patients who had NET treatment, their reactivity in a number of brain structures associated with the perception of emotional traumas was reduced on fMRI brain imaging compared to those who didn't get the NET treatment. This study result shows that NET works to reduce stress on a physiological level and that it has potential in the treatment of cancer by reduction of emotional distress in patients.[22]

Patient Case

We have seen similar amazing remission cases at the Cancer Center for Healing as well that have demonstrated the power of positive thinking on the patient's healing journey. For example, a 54-year-old female diagnosed with ductal carcinoma of both breasts in April 2016 did not want conventional treatment. After being on an integrative treatment protocol for six months, the cancer mass in her left breast disappeared, and the 10 cm x 8 cm mass in her right breast disappeared after 10 months of being on the protocol. The patient always had a positive attitude throughout this whole time and had a belief that she would treat her cancer naturally.

Conclusion

Cancer is a multi-factorial disease and requires a multi-faceted treatment approach that integrates the mind, body, and spirit. Conventional treatment deals with the physical body only and forgets to address the mind and spirit, which we know from Kelly Turner's book that seven out of the nine healing factors were all emotional and spiritual in nature. As it can be seen in the above patient example and from Kelly Turner's analysis of numerous remission cases, the mind is powerful. To summarize, our beliefs lead us to feel emotions, such as fear, stress, joy, and hope, which creates hormones/peptides that direct our bodies to either fight or flight or go into repair mode. Therefore, it's important for us to revolutionize our ways of thinking as doctors and to revolutionize the thinking pattern of our patients for them to have hope, to manifest love and joy, instead of instilling fear in them by giving a time limit without any alternatives. If we are to treat cancer and heal the whole person, it will be imperative for the practitioner to recognize that the mind plays a powerful part in the success of the patient's healing and to take this into consideration when talking with the patient and to also bring this knowledge to the patient in a way that they can utilize.

Leigh Erin Connealy, MD, is a prominent leader in the integrative/functional medicine medical field (taking the best of all sciences, including homeopathic and conventional treatments). She is the medical director of two amazing clinics: "The Cancer Center For Healing" & "Center For New Medicine." The combined clinics have become the largest integrative medical clinic in North America, and visited by patients from all over the world.

Dr. Connealy is the author of two books, *The Cancer Revolution* published in 2017, and prior to that the *Be Perfectly Healthy* book in 2009, and has revolutionized the landscape of medicine. In 2017, she was named one of the top 50 functional and integrative doctors in the country. Dr. Connealy feels we must treat "the whole person," the patient with the disease and not the disease of the patient, while determining the "root cause of the illness." Dr. Connealy begins a TV Series "Dr. Detective" airing on the JUL-TV Television Network beginning in June 2018.

She has discovered that many factors contribute to the disease process; therefore, many modalities must be used to reverse it, spending the proper time with each patient to allow for reversal of the disease. Dr. Connealy and her team of practitioners make this happen each and every day at her multi-disciplined "state-of-the-art" clinic, while providing quality of life treatments.

Dr. Connealy has 31 years of experience and has taken numerous advanced courses, including homeopathic, nutritional and lifestyle approaches, while studying disease, chronic illness, and alternative or integrative/functional medicine cancer treatments. In addition, Dr. Connealy imparts her wisdom in educating medical practitioners from all over the world as well as, public speaking engagements, webinars and podcasts. She offers the most scientifically and technologically advanced equipment and protocols at her clinic located in (Southern California) Irvine.

To learn more visit: www.connealymd.com

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MSG Excites Us, But How About Glutamine and Glutamate?

by Sue Visser

Should we ban all forms of MSG from food and take L-glutamine supplements instead? A number of conflicting professional views on MSG (monosodium glutamate) makes it difficult to take sides based on hearsay, scholarly articles or the internet. I noticed that MSG-based condiments were recently removed from our supermarket shelves, yet I found a jar of L-glutamine selling at ten times the price in a health shop next door. Both of these products are precursors to free-form glutamate. As a neurotransmitter, glutamate activates over 45% of the brain's neural synapses and thereafter it is used as a precursor for the inhibitory neurotransmitter known as GABA (gamma aminobutyric acid) to inhibit the stimulus. Glutamate provides both the accelerator as well as the brakes of our neural synapses. Most people with mental disorders or poor muscle control are primarily suffering from the effects of excessive neural stimulation called excitotoxicity that destroys neurons. Normally, glutamate and GABA are not allowed to cross the blood brain barrier, so what is the problem? It has a lot to do with a leaky brain.[1-3]

Glutamate/MSG plus a lack of its processing and controlling factors in the food chain – as well as the body – affect excitotoxicity. Glutamate is assembled and broken down within the brain; and ideally, no other glutamate should be present after a neural synapse activation takes place. Calcium activates channels on dopamine receptors to allow glutamate to stimulate or excite the neuron. To end the synapse, magnesium deactivates or blocks the calcium channels. The remaining glutamate is processed in two ways. Either it is transformed into GABA, assisted by pyridoxine (vitamin B6) and the decarboxylase enzyme, or it reverts to glutamine and is returned to the glial cells for future use. GABA is an inhibitory neurotransmitter, the antithesis of the glutamate and calcium combination that stimulates (or over excites) neurons. Most of the GABA that calms us down, induces sleep, and alleviates depression is made in the gut out of glutamate that comes from the food we eat.[4,5]

Some practitioners treat motor neuron diseases with drugs that remove glutamate from the brain; but an overdose will cause neural stimulation as well as the GABA production to fail. It is not a cure for a leaky gut or brain! There is no one off-patent remedy for a disturbed glutamate/GABA axis. Muscle spasms, jerking, twisting, writhing, tics, rigidity, falling and difficulty in speaking or swallowing typify symptoms of both Huntington's and Parkinson's disease whereby neurons are over- or under-activated. The signalling between the brain and muscles depends on the supply of glutamate in the right amount at the right time. Doctors who embrace alternative or complementary modalities prefer to investigate the patient's causative factors – the ones that drugs can't alleviate. For instance – gut health, diet, genetics, nutritional deficiencies, and toxic load to track down the effects that glutamate/GABA imbalances have on particular ailments.[6-8]

Within the brain the excitotoxicity potential of glutamate arouses justifiable concern in cases where the conversion of glutamate into GABA is impeded or when the glutamate influx and engagement is excessive. However, not everybody is affected by these chemical imbalances, so it makes no sense to universally condemn all sources of glutamate. For some, a glutamate deficiency can impede GABA production – leading to depression, anxiety and insomnia. A few people, especially those with a leaky brain may have an adverse reaction to MSG and they do experience headaches, heart palpitations, blood pressure fluctuations or even asthma. They may be particularly vulnerable to excitotoxicity. At the same table, others enjoy the umami or savoury taste that is imparted by MSG or free glutamate. Whether supplied by condiments, food sources, glutamine supplements, or made in the body, glutamate plays a key role in many essential neural, motor and metabolic processes.[5,7,9-11]

Whether supplied by condiments, food sources, glutamine supplements, or made in the body, glutamate plays a key role in many essential neural, motor and metabolic processes.

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The Glutamic Acid-Glutamine-Glutamate-MSG Family Tree

Glutamine is the most abundant free-form amino acid in the human body. Depending on how its chemical structure is modified, glutamine can convert to glutamic acid or to glutamate. There are glutamate receptors throughout the body; and the digestion of food, especially, is stimulated by those that are present on the tongue. We need to understand that the body uses glutamate – lots of it every day, whether it comes from glutamine, the MSG shaker, or from a plate of food. The digestive system breaks down MSG into glutamate and sodium. Getting to grips with the basic chemistry will give us a better overview of the relationship between these controversial chemicals.[4,12-14]

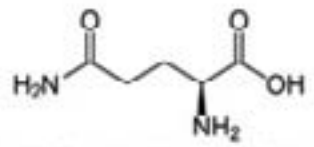
Glutamate is part of our food chain as well as body chemistry – and it tastes good! During digestion MSG loses its sodium atom and receives one of hydrogen to release free glutamate that is taken up by the bloodstream. Two forms of glutamate – both bound and free – can be present in the same food sources, but only free glutamate enhances its flavour. It augments (excites) the savoury sensation on glutamate receptors that are present on the tongue. The savoury taste is called umami and is different to the sweet, sour, bitter or salty signals we get from our taste buds. As a result of the savoury sensation, the brain orchestrates the release of digestive enzymes, hydrochloric acid, and insulin to help us digest the incoming food. Glutamate derived from either L-glutamine supplements or MSG also helps the gut to ferment and break down fibre. (This also helps to reduce the gassy effects of baked beans I discovered. I believe that it is unwise to eat them without a dose of glutamate.)[15,16]

When food manufacturers are told to remove MSG from their ingredients, they often add others that are rich in natural sources of glutamate such as yeast extracts, hydrolysed protein, and so on. MSG forms naturally when fermented food dries out and those controversial white crystals appear. Fermented food like yoghurt, kimchi, and pickles are rich in glutamate; and during digestion gut bacteria set the glutamate free to aid digestion and supply the body with glutamate that is mainly used by muscles. Cabbage, when fermented into sauerkraut, is a good source of glutamate as well as vitamin C and valuable probiotics like *Lactobacillus plantarum*. Scientists have found this microbe to be one of the best for releasing glutamate. There is 10 times more free glutamate present in breast milk as opposed to cow's milk. An infant can detect the taste of naturally occurring free glutamate and ingests more of it per kilogram of body weight than during any other period of its life. The baby prefers mother's milk to MSG-free infant formulas.[2,8]

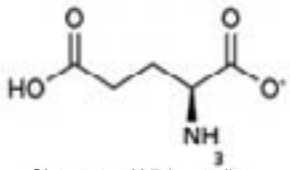
They say that the Japanese brought MSG to America to be sold as a flavour enhancer, but the MSG pettifoggers accuse them of causing the excitotoxicity problem. Sugar beets and sugar cane are typically used as raw materials to harvest MSG crystals that are formed out of molasses. Ironically, in the USA, the same sugar cane and sugar beets are used to excite our taste buds in a different way. They produce white crystals that excite sweetness – to make us addicted to sugar and consume vast quantities of it, leading to insulin resistance in many cases. Sugar addicts are morbidly obese as a result of consuming too many calories and refined carbohydrates. Yet some medical experts say that MSG is one of the worst food additives on the market. Worse than sugar or high fructose corn syrup? What causes insulin resistance, heart disease, obesity, cancer, liver failure and tooth decay – sugar or MSG?[3,15]

What happens to neurons during a spell of excitotoxicity? Glutamate levels rise in the brain for a number of reasons. Firstly, we know that MSG can trigger excitotoxicity within a leaky brain whereby a damaged blood brain barrier allows toxins, microbes

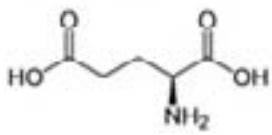
Glutamine and the different forms it takes.



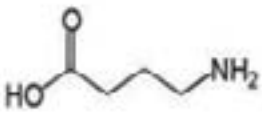
The amino acid L-Glutamine with a pH of 5.65 has two variants: Glutamate is neutral with a pH of 7 and it is an excitatory neurotransmitter



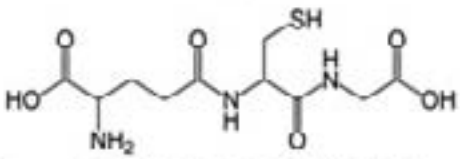
Glutamate pH 7 (neutral)



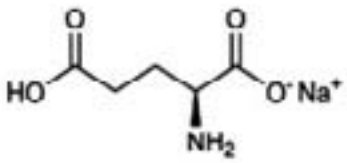
Glutamic acid pH 3.22



Gamma-aminobutyric acid (GABA) pH 7.3 alkaline
GABA is a calming neurotransmitter that opposes glutamate on the receptors



Glutathione has a pH of 7.2 and is alkaline.
It is also derived from glutamate. This antioxidant helps to detoxify, reduce inflammation and protects cells from free radical damage.



Monosodium Glutamate (MSG) pH 7 (neutral)
See left: A sodium (Na) molecule drops off during digestion and MSG reverts to glutamate by adding another hydrogen molecule. Free glutamate then enters the bloodstream, but only glutamine can enter a neuron. There is no MSG present in the brain.

and especially glutamate to enter the grey matter. When a large quantity of foreign glutamate floods onto a dopamine receptor, the antagonists and anti-agonists, GABA conversion, and glial uptake mechanisms will fail to shut down the synapse. Another reason for synapses to be overwhelmed by glutamate happens within the brain when glial cells are damaged. These cells store glutamine that is converted temporarily by the enzyme glutaminase into glutamate during synapse activation, and then it reverts to glutamine for uptake and storage. If glial cells are injured or die due to a lack of oxygen or glucose, they spew out their glutamine and it reverts to glutamate. As a result of trauma from head injuries, concussion or extreme emotional stress, strokes or a diabetic coma that lead to the destruction of glial cells, glutamate will inappropriately form inside the brain – regardless of blood brain barrier protection.[18-21]

From either cause, the unsolicited glutamate will remain in the extracellular fluid, and unopposed will continue to stimulate cells to death – a state of excitotoxicity. A lack of magnesium and an excess of calcium contributes to the mayhem. A cascade of glutamate arises when surrounding glial cells also begin to die off and spill out their contents. This is what happened, as I discovered, when a friend of mine –already traumatised by his failed marriage – collapsed as a result of a blood sugar-related incident. He was insulin resistant, and as a result of a perpetual stress-related cortisol overload, he began to suffer from bouts of hypoglycaemia (low blood sugar) alternating with hyperglycaemia (high blood sugar). Stress and trauma can trigger inflammation and may also damage the blood brain barrier.[20,22]

Glial cells throughout the body, especially in muscles that are starved of glucose (hypoglycaemia) will die, spilling out their carefully guarded reserves of glutamine and the enzyme glutaminase – a deadly duo that becomes glutamate and joins up with calcium, its excitable partner. Excitotoxicity is the result. Excessively high blood sugar also damages nerves. Their outer myelin coating can degenerate, resulting in neuropathy. The nerves are no longer properly insulated, and fingertips, toes, and extremities are the first to feel the stinging and the pain. Then the numb feeling as the nerves begin to die. Some cells are very sensitive to an overload of glucose and do not develop enough insulin resistance over time. They are thus unable to prevent a burnout within the mitochondria. Retinal cells are especially vulnerable to hyperglycaemia. Whenever nerves die, the glial cell at the synapse will provide a lethal dose of glutamate and this excites the neurons to death, causing a domino effect on neighbouring cells. My friend never fully recovered from this setback; despite the attempts of his doctor friends, our endless suggestions and bottles of supplements. When you have experienced excitotoxicity to this extent, what can you do?[23]

GABA Helps to Control Excitotoxicity

The body is protected from excessive glutamate exposure in a number of ways within the brain and on its neuro receptors throughout the body. GABA helps control excitotoxicity and calms us down, alleviates insomnia, and uplifts depression. While the glutamate/GABA axis mechanism helps to forestall neural excitotoxicity, it is also the target of abuse. Unfortunately, the class of depressant pharmaceutical drugs, such as barbiturates (sleeping pills), and anti-anxiety, anti-depressant drugs as well as alcohol, that target GABA receptors tend to reduce their sensitivity. Constant consumption of these downers also destroys GABA receptors and leads to an increased dependence on drugs. GABA levels are also vulnerable to stress, loud noises, radiation, toxins, and trauma. Within the gut, the *Bacterioles fragilis* KLE1758 microbe consumes GABA. In 2011 an American university rat trial aimed at increasing gut levels of GABA succeeded by introducing the *Lactobacillus rhamnosus* (JB-1) strain. ➤

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The conclusion was that it lowered stress-related behaviour such as anxiety and depression.[24-27]

Our brain is connected to the gut via the vagus nerve and when this channel was severed in the newly de-stressed rats, they reverted to a stressful and anxious condition. Certain Lactobacilli strains have the highest GABA production potential. They reside in a healthy bowel and the best natural source comes from fermented dairy products. The supplementation of *Lactobacillus rhamnosus* and the Bifidobactera strains especially can improve all types of mental and neurological disorders. It is also important to attend to micronutrients and their food sources that assist the precursors of GABA such as magnesium, zinc, vitamin B6, progesterone, and taurine.[28,29-33]

Other Ways to Prevent Excessive Neuro-Excitability

Glutamate receptors or landing sites are distributed throughout the body – wherever there are bundles of nerves – as for example, in muscles, the digestive system, and also the brain. Glycine that shares some types of glutamate receptor sites also provides an inhibitory effect and is called an anti-agonist. In other words, glycine also helps to shut down the excitement caused by glutamate activated by its agonist – calcium. Magnesium is an antagonist, a substance that opposes glutamate. It is present at the entrance of calcium channels as a natural glutamate blocker as well as a calcium channel blocker. Magnesium keeps both glutamate and calcium under control and guards their transportation channels to prevent nerve cells from exciting themselves to death. People who are deficient in magnesium are more prone to headaches, blood sugar imbalances, muscle cramps, dyskinesia, and insomnia. Diabetics, especially, are deficient in magnesium.[34]

The Day I Excited My Digestion with L-Glutamine and Discovered a Way to Treat Diabetes

L-glutamine powder that people take as a health supplement can also have some remarkable effects on blood sugar. What glutamine does when you lick, taste and then swallow a teaspoon (5 grams) of it mixed with water caught me by surprise. At the time I did not realise that glutamate receptors on the tongue respond to glutamine, to excite the digestive system as they do with MSG and glutamate. After tasting the L-glutamine powder and finding it to be slightly savoury, I had inadvertently stimulated my digestive system, between meals, and it caused a nasty hypoglycaemic episode. I am not sure if it was the teaspoon (5 grams) of the powder, the tongue stimulation or the combination of the two that caused the whoosh of insulin and a flood of digestive enzymes. According to the label on the jar, the five-gram serving of L-glutamine was best taken between and not with meals. There were no warnings or contraindications.[35,36]

Half an hour after tasting and ingesting the glutamine, I began to lose my mojo. My head was spinning, the lights were flickering. I felt limp, blurry, and began to get the shakes. My tummy was growling, I was starving and along came the familiar feeling of hypoglycaemia – this time a near blackout. If you eat sugar on an empty stomach, it may cause reactive insulin spikes and hypoglycaemia for people like me, with average but sometimes low blood sugar. But why did this happen after a dose of glutamine? I am not sure what taking 5 grams of MSG would have done to me on an empty stomach because we usually only have it with food. So, watch out for glutamine supplements because tasting them also triggers the glutamate receptors on the tongue. I can only assume that glutamine mimics the effects of glutamate and MSG in this respect.[37]

I had a similar experience when I tested a new formulation I was working on to use as a pain supplement. The main ingredients were MSM (methylsulphonylmethane) mixed with vitamin C in equal quantities. I mixed a teaspoon of it with water on an empty stomach, 2 hours before lunch and also had a serious bout of hypoglycaemia. I figured that if it did that to somebody with normal to low blood sugar, it could be of benefit to diabetics. A doctor tried it to help a patient with gestational diabetes. It lowered her blood sugar to an acceptable level after other medications had failed. That was many years ago; and although I cannot make such claims, yet I have to warn customers that this product has a, well, beneficial side effect! These simple, albeit naïve observations of patients and laymen are often overlooked by scientists in their obsession to patent drugs that do the same thing.

Blood Sugar Regulation with L-Glutamine Supplementation

I thought that perhaps diabetics could also take advantage of my recent discovery and use glutamine or glutamate (or MSG) to help regulate their blood sugar. They could also introduce it directly to the tongue and taste buds. I was joking at the time, but it is true that diabetics often suffer from sub-optimal levels of glutamate. About 2 kg of our body weight is made up out of glutamate where it is mainly present in muscles, the brain, kidneys and the liver. Our reserves are rapidly depleted during exercise, illness, trauma and other stressful conditions. Doctors recommend L-glutamine supplementation for patients with intestinal disorders, to boost immunity, and to help patients with AIDS and cancer. Sportsmen take extra glutamine to compensate for the loss of muscle tissue during exercise.[38]

Not many people (including me) knew that diabetics respond favourably to glutamate, and it helps to lower their fasting blood sugar and improve HbA1c readings. In 2014 after a six-week placebo controlled study in Iran, the diabetics who took 30 grams of glutamate with their meals experienced improved blood sugar as well as blood pressure control. Their muscle mass increased and waistlines were trimmer. Glutamine converts to glutamate, as we now know and stimulates the pancreas to lower blood sugar by improving

insulin release and sensitivity. In this case 30 grams a day with meals was recommended, but it is best for your practitioner to determine the ideal dose. This discovery about glutamine helps to clear up the mystery of why I experienced a bout of hypoglycaemia when I took it between meals![35]

A healthy natural diet also provides tongue-tingling umami enhanced foods that provide adequate sources of glutamate. That's why babies love breast milk, and we love tomatoes, dairy products, meat, fish and green vegetables. Other sources include hydrolysed vegetable protein, yeast and soy extracts and protein isolate. If you are sensitive to glutamate, there is little point in avoiding MSG and all these food items and then supplementing with L-glutamine. If you have a leaky brain and are wary of an attack of excitotoxicity, it is important to attend to the blood brain barrier, otherwise glutamate will keep on flooding in.[39,40]

Having a leaky brain is like leaving your front door open to allow your house (brain) to be invaded by the neighbourhood, then trying to chase them all out. Only your family belongs inside your house, so close the door to keep out the strangers.[2]

Let glutamate be in your food and let it also be your (dose-related) medicine. Glutamate remains elusive – troublesome in excess yet essential for survival. It needs to be present in the right proportion at the right time, in the right place. From latching onto a neuro receptor to healing the gut, mopping up ammonia and helping muscles to move, this versatile yet controversial chemical is a true multitasker. Glutamate also bucks up the brain, enhances the taste of food and relieves flatulence, as does MSG its precursor – the notorious scapegoat of excitotoxicity.[41]

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A Case of Essential Tremor Resolved by Chelation of Toxic Metals

by Davis W. Lamson, MS, ND

Tahoma Clinic, Tukwila, Washington

"Benign essential tremor" is a somewhat common disorder of tremors, mostly in the upper extremities and neck, resulting sometimes in shakiness of the head. In most cases it is described as being of unknown origin. There are several reports of association between essential tremor and high lead levels in blood, and reports of other toxins.[1-5] But there seems to be no reports showing resolution of tremor with reduction in lead or other toxic metal levels. This may be the first report on such resolution.

A woman, age 77, consulted regarding several problems including previously diagnosed essential tremor. She had pronounced shaking of the head and impaired handwriting from tremor of the hands. In the course of assessment, a thyroid profile revealed elevated reverse T3 of 41 (range 6.7-21.8). There are extensive, but yet unpublished, records at this clinic showing a high correlation (~98%) of elevated rT3 with five or more toxic metals being quite elevated.

An intravenous chelation challenge with EDTA (ethylenediamine tetraacetic acid) and DMPS (dimercaptopropanesulfonic acid) was followed by a six-hour urine collection for metal analysis (January 2014). Metal analysis showed substantial levels of nine toxic metals with aluminium, cadmium, gadolinium, lead, and platinum in the highest range. (She was previously treated with platinum chemotherapy.) Mercury, nickel, thallium, and uranium were mid-range.

Chelation therapy was continued on a twice monthly schedule with occasional mineral replacement and with the urine collection for metal analysis performed following a chelation about every four months. After 22 chelation treatments (April 2015), the periodic urine analyses for metal discharge showed almost no change instead of the usual reduction of levels. (This phenomenon is interpreted as having such high metal burden that reduction in levels thus far was small compared to the total amount in the body.)

However after 22 chelation treatments, there was complete resolution of head tremor with notable improvement in handwriting (by patient report). Chelation therapy was continued, to observe whether further benefit to hand tremor could be achieved and whether laboratory indication of reduced metal levels would occur.

The patient discontinued chelation therapy in 2016 by personal choice. She returned to the clinic in May 2018 reporting that tremor of the head was still absent, but that there was a tendency to tremor in the hands and handwriting quality had declined. She resumed treatment in May 2018.

Regarding essential tremor overall, there is not enough evidence to claim that metal toxication is a major cause. A review of essential tremor in 2014 indicates that there have been no highly successful pharmaceutical treatments.[6] More recently the application of high intensity focused ultrasound guided by magnetic resonance imaging for essential tremor, called Neuravive, has been approved by the FDA. Even if this or some pharmaceutical treatment is successful at relieving this troublesome neurological condition, such would not be relieving any toxicity as underlying cause.

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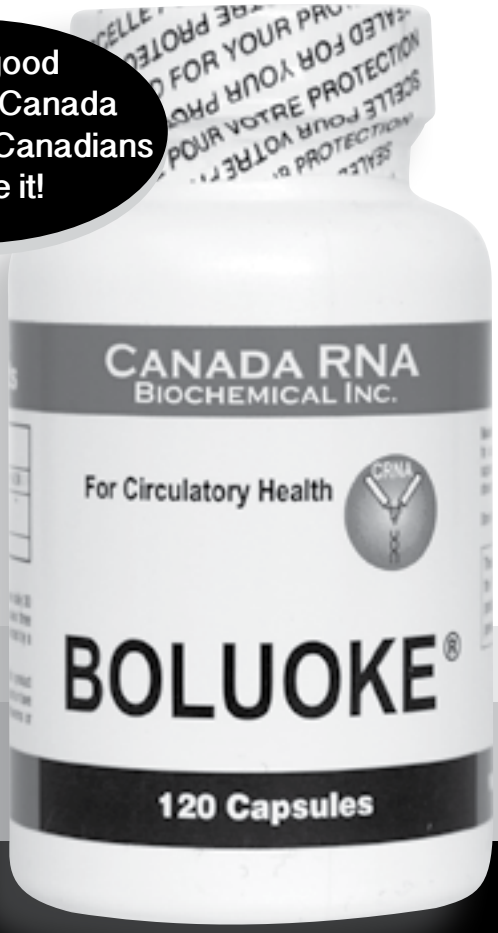

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Bastyr University San Diego Clinic: Student Case Reports

edited by Baljit Khamba, ND, MPH

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

Student Case Report: Late Post-Traumatic Epilepsy in An Elderly Male

by Fernanda Gallo Moreno

Abstract

The purpose of this case report is to investigate the prognosis, outcome, and naturopathic treatment available for the elderly population experiencing post-traumatic epilepsy. The case discussed in this paper is of an 85-year-old male diagnosed with late post-traumatic epilepsy, which began in 2013 after a single trauma to the top of his head. The elderly population is the most vulnerable to post-traumatic epilepsy, though only about 4% of epilepsy is due to trauma.[1] The initial treatment for epilepsy due to trauma is immediate anti-seizure medication, which has been shown to improve seizure remission rate; this medication is often prescribed prophylactically when trauma occurs to an elderly person to prevent the onset of an initial seizure.[1] Anti-seizure medication, unfortunately, has been known to cause extensive and persistent side effects; therefore, research has investigated a natural alternative for children with epilepsy. The effects of cannabidiol (CBD) oil in epilepsy has been shown to improve remission rates and symptomology associated with seizures in children, though the mechanism of action is not yet fully understood.[2] The ketogenic diet has been shown to improve neuro-degeneration, epileptiform activity, and side effects from anti-epileptic medication by optimizing energy output by the mitochondria in all cells.[3] It is still unclear if CBD oil is effective in seizure remission in adults. Further research is highly suggested to address the lack of knowledge in natural alternatives for epilepsy treatment in the elderly population.

Introduction

When treating seizures in the elderly, many factors should be considered: predisposition to epilepsy and trauma, the natural aging process, the increased risk of polypharmacy, drug-to-drug interactions, increased susceptibility to side effects, and multiple comorbidities. Older patients experience a loss of independence and have an increased risk of falls and physical injuries. A seizure diagnosis may further exacerbate their already declining quality of life. The standard of care for post-traumatic epilepsy, particularly in the elderly, is to prescribe anti-epileptic medication to prevent future incidences of seizures. Epilepsy is a condition where recurrence of unprovoked seizures are expected in the absence of treatment; therefore, treatment is highly indicated.[4] Natural therapies have not been studied in the elderly population and are not considered alternative or adjunctive treatment for epilepsy.[1] There is a clear need for alternative treatment to pharmaceuticals for elderly experiencing epilepsy in order to avoid drug interactions, drug side effects, and to increase quality of life.

There is currently no drug cure that exists for epilepsy. Symptomatic relief has been achieved through antiepileptic drugs (AEDs) for up to 70% of patients; however, only two-thirds of patients with epilepsy are successfully treated by the AEDs. The

remaining 30% of epileptic patients, both adult and children, with intractable seizures not controlled by AEDs seek treatment available to them in the medical system that is often invasive, requires surgical resection, or neuro-stimulation.[4]

Current Research of Treatment

Recent research suggests that cannabis may be a potential alternative treatment for refractory epilepsy. There are two chief cannabinoids present in marijuana, or cannabis: D-9-tetrahydrocannabidinol (THC), the main psychoactive component, and cannabidiol (CBD), the main non-psychoactive component. CBD has been shown to be an antiepileptic, though the exact mechanism is not yet understood. CBD has a low affinity for CB1 and CB2 receptors found in the body; both receptors are linked to Gi protein-coupled receptors and inhibit adenylyl cyclase activity. Activation of CB1 receptors inhibits glutamate release. The presence of CB1 receptors in the basal ganglia, cerebellum, neocortex, spinal cord, hippocampus, and amygdala may explain why CBD has shown improvements in children with epilepsy; the direct effect on the nervous system is being investigated. CB2 receptors are found mainly in peripheral tissues of the immune system, such as monocytes, B-cells, T-cells, and macrophages, which may explain their role in cytokine release.[5]

A 2016 study investigated the effects of CBC oil (CBD:THC at a 20:1 ratio dissolved in olive oil with a dose ranging from 1 to 20 mg/ kg/d) in 74 children with retractable epilepsy, who failed treatment with ketogenic diet and vagal nerve stimulation implantation. Of the 74 children, 89% reported reduction in seizure occurrence with 18% reporting 100% reduction; 7% reported aggravations, which led to CBD withdrawal. Other symptoms that were observed were improvements in behavior, alertness, language, communication, motor skills and sleep.[2] Larger double-blind clinical trials are indicated. Despite positive findings, a survey conducted by Epilepsia showed that fewer practitioners specializing in epilepsy support prescribing CBD products and medical marijuana to patients compared to other medical doctors, due to a lack of conclusive data on its effects.[6]

It is known that traumatic brain injuries (TBIs) have many repercussions, including what is known as mitochondrial disease, which is caused by mitochondrial dysfunction. One of the most common presentations of mitochondrial disease is epileptic seizures and encephalomyopathy; whether one is the cause or effect is still debatable.[6] It is clear that lipid peroxidation during seizure activity could be responsible for neuronal damage in the hippocampus, as seen in a rat model.[7] For this reason, it is critical to aim for complete seizure remission in all vulnerable patients. To date, the only proven treatment to aid in recovery are anticonvulsant medication, vitamins, nutritional supplements, and the ketogenic diet; there is no known cure.[6]

This case report will investigate the prognosis of a person with late-onset post-traumatic epilepsy and the impact that CBC oil and a ketogenic diet may have on prognosis and quality of life.

Case Description

The patient is an 85-year-old male who experienced a head injury to the top of his head while swimming laps in a swimming pool on June 2013. Twenty-four hours after the impact, the patient experienced his first seizure. He was taken to his medical doctor that day where he was diagnosed with adult epilepsy. He is currently seeing a neurologist, a cardiologist, an endocrinologist, a doctor of oriental medicine and now, a naturopathic doctor, to address all aspects of his health. His wife, who has been his primary caretaker since the start of his health concerns, accompanied him at every visit.

In the span of two and a half years, from the initial impact in 2013 through December 2015, the patient had a total of five seizures. After the first seizure, the patient began taking gabapentin; after the second seizure on December 2013, he was prescribed a different AED; after the third seizure on July 2014, he was prescribed another AED. Finally, on December 2015, he experienced two seizures back-to-back, 45 minutes apart. He was instructed to begin taking levetiracitam 250 mg, four times per day, and has not had a seizure since. Every seizure, excluding the first, had occurred between 1 to 3 am and was preceded by stomach upset, extreme fatigue, decreased appetite and choking on heavy, viscous, yellow phlegm. His wife reports that during the seizures, he was gasping, coughing, and experienced full body convulsions for less than five minutes. After the event, the patient had difficulty breathing, erratic snoring and had no recollection of the event after a 25-minute postictal phase.

Naturopathic Doctor Prescribing Rights

The patient and his wife presented to clinic with the goal of seeking help to completely wean off of levetiracetam, which he believed was causing him extreme fatigue, and to seek guidance in obtaining and dosing CBD oil as alternative treatment. The laws in California do not permit licensed naturopathic doctors to alter or prescribe Schedule I or II drugs; naturopathic doctors are allowed to prescribe legend or Schedule IV and V drugs only under the supervision of an MD/DO, and schedule III drugs under patient-specific protocol checked by a supervising MD or DO.[8] The Federal Drug Agency (FDA) and the Drug Enforcement Agency (DEA), work together to categorize drugs that are then put on the market for use. If the FDA has labeled a drug a 'controlled substance', due to potential for abuse, the drug is sent to the Drug Enforcement Agency (DEA) to be put into a "schedule" before it is available for use. Some drugs used for epilepsy, like phenobarbital, are considered controlled substance, though most anti-epileptic medications have not been shown to be abused or have addictive properties. Forms of cannabis, including CBD oil, is currently considered a schedule I substance, is illegal under federal law, and is considered by the FDA and DEA to have no therapeutic benefit.[9] For this reason, our naturopathic team, researched a medical doctor in the area who is not only qualified to wean this patient off of levetiracetam, but also willing and experienced in prescribing CBD oil for epilepsy.

History of Present Illness

The patient presented with an initial chief complaint of excessive mucus, which began the day after the initial impact. The mucus was thick, ropy, yellow, began in the chest, and took great force to expel. Patient wakes at night to expel ¼ to ½

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cup of mucus every night. He has attempted therapies such as prednisone, Flonase, and hydrogen peroxide mouth rinse, with no avail. Eliminating sugar, corn, and dairy has helped improve the mucus. His second chief complaint is extreme fatigue, which he believes, is a side effect to the medications he has been taking. He rates his fatigue an 8 out of 10. He experiences depression, which he describes as constant "melancholy." He states that he did not experience fatigue or depression prior to the head trauma. The biggest detriment to his overall wellness has been his inability to swim, jog, or do Pilates, like he used to.

Past Medical History and Review of Systems

The patient was taking the following medications and supplements managed by his medical doctor: levetiracetam (Keppra) 1000 mg daily (250 mg 4x/day); levothyroxine (Synthroid) 125 mg tablets daily; tamsulosin HCl 40 mg daily; cholecalciferol (vitamin D3) 50,000/week; fluoxetine (Prozac) 20 mg daily; glucosamine chondroitin (Osteo Bi-Flex) 1200 mg daily. Though the mechanism of action of levetiracetam is not entirely understood, scientists speculate that it may inhibit sodium channels, inhibit calcium channels, cause GABA-ergic inhibition, reduce the potassium current, and modulate neurotransmitters. Some of the many side effects from levetiracetam alone include impaired coordination, abnormal gait, fatigue, dizziness, somnolence, toxic epidermal necrolysis and Steven-Johnson syndrome, decrease in red blood cells, in hemoglobin and in hematocrit, hypersensitivity reaction, hypertension, and psychiatric conditions including suicidal ideation.[10] The former of these symptoms pertain to this case.

The patient has a past medical history of hypothyroidism, squamous cell carcinoma, arthritis, and has had monoclonal gammopathy detected—Waldenstrom's macroglobulinemia will be ruled out by bone marrow biopsy. He is a retired pilot and has four healthy children. His lifestyle includes a pescatarian diet, lowered hydration status, about 30 minutes of slow walking per day, and one normal bowel movement per day. The patient takes up to two hours to fall asleep every night, wakes up two to three times per night, and sleeps two to three hours during the day. Review of systems is positive for weakness, fatigue, decrease appetite, changes in sleeping habits. He experiences heavy eyelids, pressure behind his eyes, hearing impairment, frequent tinnitus, and decreased sense of smell. He experiences shortness of breath much sooner and more often with exercise, as well as cough, sputum production, bilateral tremors, memory loss, and depression.

Physical Examinations

Physical examinations presented as follows: vitals within normal limits; blood pressure: 110/70; pulse: 66 bpm; temperature: 97.5 ° Fahrenheit; weight: 189 lbs; height: 5'11"; and BMI: 26.30 kg/m^2. Previous workup with medical doctor showed high MCV, low vitamin D, high LDH, and high beta-2-microglobulin. Physical exams revealed multiple crowns on all wisdom teeth and canines, multiple mercury fillings; tongue displayed involuntary shaking and difficulty with voluntary movement; tongue with thick yellow white layer; bilateral tonsils at a +3, posterior oropharynx with some erythema, and left pharyngeal arch unable to rise. Cardiovascular exam with normal heart sounds with diminished sounds. Respiratory exam revealed no wheezing, rales, or tenderness; diminished breath sounds, and restricted chest movement. Neurological exam revealed that the patient was alert and oriented of place and timing; abnormal coordination, postural tremors, slight shuffling gait, hunched over posture, and minimal arm swing, all of which are reflective of parkinsonism.

Diagnosis

The differential diagnosis includes mitochondrial dysfunction, psychogenic non-epileptic seizures, drug-induced symptomology, drug-induced parkinsonism, vasovagal response and syncope, and systemic infection secondary to oral microbial toxins. The working diagnosis being late post-traumatic seizures, considering there was an initial head trauma involved and no pertinent family history, as well as, diagnoses of fatigue due to old head trauma, and chronic mucus hyper-secretion.

Treatment and Future Plan

On the initial visit, the take home plan involved a three-day diet diary including bowel movements, water intake, physical activity, and mood. Patient was instructed to increase his water intake. The patient, his wife, and the naturopathic team agreed to research medical doctors in the area qualified and experienced in safely weaning off anti-seizure medication and prescribing and dosing with CBD oil.

Three weeks later the patient reports that him and his wife and the naturopathic team had both coincidentally decided on the same medical doctor in the area. Patient had begun to decrease his anti-seizure medication and had started taking 15 mg of CBD oil twice per day the night before the second visit. Patient reported that his morning walk went noticeably better than usual. After reviewing his diet diary, we strongly suggested he completely eliminate inflammatory foods such a gluten and dairy. The patient was asked to begin the ketogenic food plan in order to encourage healthy energy production and removal of offending foods. A handout and complete instructions by Institute for Functional Medicine on a mitochondria-supporting diet were provided. The patient was asked to carefully observe the changes he experiences for the next two weeks with the new diet changes and with daily doses of CBD oil.

Six weeks after beginning treatment with CBC oil and discontinuing levetiracetam, we recommended alternating 'smooth move' tea, initially used to aid in producing daily bowel movements, with organic psyllium fiber. Patient had eliminated dairy from his diet, with only occasional goat cheese, and increased his daily proportion of vegetable intake. An internal referral was made for intravenous therapy (IV) infusion therapy for nutrient and glutathione antioxidant support for the purpose of preventing further neuro-degeneration due to TBI and medication, and to provide powerful antioxidant protection to his central nervous system.[11]

Future treatment may involve the consideration of acetylated glutathione, if IV therapy is less preferred by patient.

Future treatment may also involve CoQ10 supplementation and respiratory chain cofactors, such as, riboflavin, tocopherol (vitamin E), succinate, ascorbate (vitamin C), menadione, and nicotinamide. It is also highly indicated to address sleep, immune modulation, dental hygiene, past and current environmental exposures, and the consideration of homeopathy as adjunctive treatment.

Outcomes

Subjective patient recall after only one day of CBD oil and discontinuation of levetiracetam shows he is slightly more physically able. Upon six-week follow up, patient reported improved mucus production and change in color of mucus from yellow to clear. Patient continues to wake at night from excess mucus production, which he manages with mouthwash; otherwise, he reports improved sleep with recent negative sleep study results. Patient reports a decrease in resting and postural tremors, which he attributes to the change in medication. Patient's chief complaint of fatigue remains the same despite these changes, though patient has once again began to do physical exercise twice per day, including Pilates and weight lifting. Patient continues to be seizure free without the help of AEDs. The patient seems very hopeful about this treatment and plans to continue to return to Bastyr University for follow-up treatment.

Discussion

Research has shown that when CBD is taken orally, it has a bioavailability as low as 6% after it has undergone first-pass metabolism, with a half-life of only one-to-two days. CBD is a powerful inhibitor of cytochrome P450 isozymes; therefore, caution should be taken when paired with medications.[5] For this reason, it was of great importance to find a medical professional who is trained and experienced in not only pharmaceuticals, but also in CBD.

The patient may likely experience benefits from a consistent ketogenic diet, which includes high-fat, low-carbohydrate diet, and high antioxidant content. The ketogenic diet not only aids in neuroprotection and seizure control, it is now understood that it may also improve mitochondrial redox status. A 2008 study in rats, showed an increase in hippocampal mitochondrial glutathione (GSH) production, increase enzymatic activity of glutamate cysteine ligase, increased hippocampal reduced CoA, and lipoic acid, as well as a decrease in H_2O_2 production and mtDNA damage. There are indicators that the ketogenic diet aids in GSH biosynthesis, enhances mitochondrial antioxidant status, and protects mDNA from oxidative damage.[3] It is important in this case to also consider the long-standing side effects of not only the initial TBI, but also the effects of the anti-seizure medications taken for several years. Though the patient is 85 years old, the Parkinson-like symptoms he is now experiencing are a drastic change from ➤

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the physical and mental ability that he had just prior to taking medications. In the Substancia Nigra – the area in the brain impacted in Parkinson's disease – the antioxidant defenses are more vulnerable to low levels of GSH than other areas of the brain.[13] It is possible that the neuro-damage from the TBI and from the AEDs has lowered the intrinsic oxidant defenses in his brain making him susceptible to potential drug-induced parkinsonism.

Diagnostic Process and Outcomes of Disease

Post-traumatic epilepsy (PTE) is considered 'late' when seizures occur more than one week after head injury and 'early' if they occur within the first week of injury. Late post-traumatic seizures often present with more permanent structural and physiological changes to the brain typical of a TBI. Of those suffering from PTE, up to 80% will experience a seizure within two years. Those with more severe TBIs are at risk for late-PTE for a longer span of time; a mild TBI leaves a patient at risk for five years versus a severe TBI with a 20-year risk. Risk of recurrent seizures without treatment is up to 86% in the first two years. For this reason, long-term anticonvulsant medication is recommended for patients with an initial seizure and used prophylactically for patients at risk of seizures who experience a TBI. Over 13% of patients with prophylactic anti-seizure drug trials had seizures even with aggressive pharmaceutical treatment. The remission rate for PTE is about 25 to 40% with initial anti-seizure treatment.[12]

Limitations and Biases

This particular case is still in progress and may require time in order to investigate the impact that both anti-seizure medication and CBD oil may have on symptoms. It is still unclear how severe and how long-lasting the side effects of the medications are, and whether these changes are permanent. Future studies investigating the impact of CBD oil as initial treatment or as initial adjunctive treatment have yet to be studied. Most medical doctors in California do not advocate the use of any cannabis products and do not offer this as an option to patients as part of the treatment regimen for epilepsy. Many people suffering from seizure disorders and epilepsy are not made aware of the potential benefits of CBD through the medical system. Most studies on human trials have focused on children and have not demonstrated the effects on adults and seniors. Further research on the impact that CBC oil may have on seniors with epilepsy, as well as a comparison of effects between anti-seizure pharmaceuticals and CBC oil is indicated.

Conclusion

It is still unclear whether this patient will experience complete remission from seizures from the transition from leveteracitam to daily doses of CBD oil capsules. There are many variables to consider that may have contributed to the patient's symptoms of fatigue, seizures and excess mucus production; therefore, it may take months to assess complete effects of the given treatment. Potential modifications of treatment based on individual need may be necessary. The patient demonstrates a great desire to recover from the side effects of the various anti-epileptic medications he has taken in the span of four years; his persistence and the support from his wife is not to be under-estimated as a significant factor in his recovery. The patient has received careful guidance on weaning off of anti-epileptic medication and dosing with CBD oil by his medical doctor, in conjunction with guidance by a naturopathic team, who is addressing the side effects from the TBI and pharmaceuticals through a ketogenic diet and antioxidant support. This may provide a good foundation for neuro-regeneration and complete seizure remission. Future research on the impact of these therapies on the elderly population are in great need.

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New Hope for Alzheimer's Disease: Nutritional Lithium as the Foundation for Prevention, Part 1

by James Greenblatt, MD

In the United States, someone develops Alzheimer's disease every 67 seconds. The disease affects more than 5.7 million Americans; this year Alzheimer's and other dementias are expected to kill more than 700,000 Americans over 65. In this country, Alzheimer's disease is the sixth leading cause of death. One in three seniors dies with Alzheimer's or another dementia. Alzheimer's is the only cause of death in the top ten that cannot be prevented, cured, or even significantly slowed by pharmaceutical intervention (Centers for Disease Control).

The burden of Alzheimer's is increasing. Older adults will soon outnumber children in America for the first time. The cost of treating and caring for people with Alzheimer's disease will surpass $1 trillion dollars this year (Alzheimer's Association).

No Pharmaceutical Cure

Despite the increasing population of older adults, accelerating rates of Alzheimer's, and mounting costs of treatment, no drug has been approved to treat memory loss since 2003. A plethora of clinical trials have been launched in recent years, all with the goal of finding effective pharmacological interventions to stop or slow the progression of neurodegenerative disorders like Alzheimer's disease. Between 2000 and 2012, however, 99.6% of drug studies aimed at preventing, curing, or mitigating Alzheimer's symptoms were either stopped or discontinued for lack of effectiveness. Of 413 trials of proposed Alzheimer's drugs, only one drug made it to market (Devlin 2015).

These failures do not result from lack of money or effort. Pharmaceutical companies are acutely aware they would reap billions in profits if they could develop a drug effective against Alzheimer's. The history of clinical trials of Alzheimer's drugs, however, is littered with fizzled attempts. In 2018, Eli Lilly terminated a phase III clinical trial for a drug to clear beta-amyloid plaques from the brain. The drug, which Lilly had been testing since 2012, had failed. During the past 3 years, Axovant, Biogen, and Prana Biotech all reported similar failures of compounds in the pipeline that had first appeared to have potential for treating Alzheimer's. After a setback with a drug in advanced stages of testing, Pfizer dropped out of the Alzheimer's disease market altogether in January 2018. Merck abandoned a Phase III trial in June 2018.

Prevention Is Critical

A.D. Korczyn, chairman of the neurology department at Tel-Aviv University Medical School, posed the question, "Why have we failed to cure Alzheimer's disease?" He concluded:

> Attempts to find cures for Alzheimer's disease have. . . failed so far, in spite of enormous investments, intellectual and financial. We therefore have to reconsider the problem from new angles. Alzheimer's is regarded as a disease because of its clear manifestations and underlying pathology. However, this combination does not define a disease but rather a syndrome. . . It is probable that senile dementia is the result of a combination of several processes, working differently in each person Thus, a concerted effort to fight the dementia epidemic must be made by aggressive action against its risk factors, and this battle must begin in midlife, not old age. (Korczyn)

Despite billions of dollars of investment, the combined efforts of pharmaceutical companies have produced no cure. One explanation for this abundance of failures is the nature of the disease itself. Alzheimer's is asymptomatic until its damage may be irreversible. Secondly, scientists do not yet understand the mechanisms behind the damage that results in this disease. For a long time, researchers believed that plaques of beta-amyloid and tangles of tau protein that jammed the signaling of neurons caused Alzheimer's disease. Yet no pharmaceutical intervention to target plaques and tangles seems to slow brain atrophy. Scientists now believe the damage of Alzheimer's occurs through multiple and complicated pathways. Therefore, this complex disease is a formidable opponent for scientific researchers trying to discover ways to stop the deterioration of the brain.

The current absence of effective treatment for Alzheimer's makes prevention even more critical. We know that the brain degeneration that eventually manifests as Alzheimer's symptoms may be three to four decades in the making. Clearly, the focus of combatting Alzheimer's disease needs to be on prevention. The best intervention for preventing the multiple mechanisms that lead to Alzheimer's is the element lithium.

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Nutritional Lithium

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Discovering Lithium's Capacity for Regenerating Brain Cells

In 2000, researchers at Wayne State University School of Medicine made an accidental discovery while studying lithium's mechanism of action on bipolar disorder. When they examined the MRI scans of the brains of patients treated with lithium, they found something they had not been looking for. The gray matter in the brains of the bipolar patients taking lithium had actually increased by an average of 3%. This was evidence that contradicted accepted wisdom: scientists had always thought the adult brain could only lose cells, not gain them. But the scans were tangible evidence that the adult brain can regenerate cells (Moore, G.,et al.).

This finding was especially striking because patients with bipolar disorder have a higher risk of Alzheimer's disease than the general population. Researchers began to investigate rates of Alzheimer's in bipolar patients on lithium. One research group compared the rates of Alzheimer's in 66 elderly bipolar patients on chronic lithium therapy with 48 similar patients not taking lithium. The differences were impressive: in patients receiving continuous lithium, the prevalence of Alzheimer's disease was 5%, compared with 33% in the group not taking lithium (Nunes et al., 2007). Further studies confirmed this phenomenon using different study designs but yielding strikingly similar results. In one study, investigators surveyed the records of more than 21,000 bipolar patients who had received lithium treatment. They found lithium associated with decreased levels of both dementia in general and Alzheimer's disease in particular (Kessing et al., 2008). These results confirmed lithium's potential for preventing and treating the brain atrophy caused by Alzheimer's disease.

Once research confirmed that bipolar patients treated with lithium had lower rates of Alzheimer's than other bipolar patients, studies were designed to test the effectiveness of lithium against Alzheimer's disease in the general population. Unfortunately, the first clinical trials testing lithium with Alzheimer's patients proved disappointing. Researchers tested lithium on patients who already had fully developed Alzheimer's disease. At this point, the damage to the brain was simply too great to turn around. One group tested lithium on participants with early stage Alzheimer's over a 10-week period. This group, too, failed to find significant effects of lithium on cognitive performance or related biomarkers (Hampel et al., 2009). The problem with this trial was the length of treatment. It takes months, if not years to see significant cognitive improvement.

The best intervention for preventing the multiple mechanisms that lead to Alzheimer's is the element lithium.

A research group led by Forlenza in 2011 corrected for these initial design flaws. These researchers focused on sustained prevention instead of brief, late-stage treatment. A group of 45 high-risk individuals were randomized to receive either lithium or a placebo. After the 12-month trial, those in the lithium group had lower levels of destructive tau proteins compared to their pre-study levels. This finding was in stark contrast to the tau levels of the placebo group, which had increased steadily over the course of the study. Moreover, the lithium group performed better on multiple cognitive scales. The researchers conclude that lithium has a significant disease-modifying effect on preventing Alzheimer's when initiated early (Forlenza , 2011).

After completing the first meta-analysis of many studies exploring a link between lithium and Alzheimer's treatment, Matsunaga found that lithium improves cognitive performance in patients with mild cognitive impairment and Alzheimer's disease. It has as much efficacy in inhibiting progression of cognitive decline as currently approved pharmaceutical compounds for slowing dementia. The effectiveness of lithium was assessed in this study based on participant scores on the Mini-Mental State Examination. The positive effects of lithium demonstrated by this research were not found in studies assessing the benefits of anticonvulsants, antidepressants, or antipsychotic drugs (Matsunaga, 2015).

Since the discovery that lithium protects brain cells from deterioration and even spurs cell regeneration, scientific studies have outlined lithium's mechanisms of action specific to Alzheimer's.

Lithium fosters neuroprotection, neurorepair, and neurogenesis. While scientists once believed any malfunction in adult brain tissue was irreversible, recent research shows that neurons and neural connections can be created over the course of a lifetime. Neurotrophic factors are proteins that regulate growth and survival of neurons. Lithium stimulates the circulation of several key neurotrophic factors, including brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) (Leyhe et al., 2009; Walz et al., 2008, Fukumoto et al., 2001). The BDNF protein is directly involved in the growth, maturation, and maintenance of nervous system cells. It is found primarily in the synapses, or spaces between neurons, where it enhances cell-to-cell communication and signaling. Nerve cell synapses can strengthen and weaken over time in response to lived experience, a process of adaptation called synaptic plasticity. BDNF regulates synaptic plasticity, an important biochemical underpinning of learning and memory.

NT-3 is closely related to BDNF. It promotes survival and differentiation of neurons in specific sections of the central nervous system. NT-3 supports cellular resilience and helps protect neurons from the harmful effects of stress and injury.

Not only does lithium increase the circulating levels of these proteins, but it also sensitizes the receptors that draw them into tissues. When the neurotrophic receptors are more alert,

greater amounts of BDNF and NT-3 are drawn to help nervous system cells. Lithium thereby amplifies the effects of the brain-protecting neurotrophic system by increasing levels of neurotrophic factors and by allowing these proteins to work on cells more easily.

Lithium increases a marker of nerve cell function. Lithium increases concentrations of N-acetyl-aspartate (NAA) in the brain, a molecule that is critical for nerve cell metabolism. High levels indicate increased brain cell and viability (Moffett et al., 2007). At least 20 studies of the function of NAA in neurological disease have concluded that higher NAA counts predict better long-term cognitive function (Yildiz and Ankerst, 2006). Lithium safely and effectively raises NAA concentrations in people of all ages.

Lithium inhibits glycogen-synthase kinase-3 (GSK3). Lithium modifies activity of the enzyme GSK3. In the nervous system, GSK3 helps coordinate neural growth and development by activating proteins in the cells. It is involved in the biological process that drives memory formation and influences processes that fail in patients with Alzheimer's disease (Jope and Roh, 2006; Hooper at al., 2008). Overactivity of GSK3 in the brain areas that control memory and behavior, such as the hippocampus and the frontal cortex, leads to production of proteins at too rapid a rate. Beta-amyloid and tau proteins are among the key proteins activated. They begin to accumulate, creating plaques, and neurofibrillary tangles form in brain tissue.

Finding ways to inhibit GSK3 is a goal for Alzheimer's researchers. Fortunately, lithium is a well-established GSK3 inhibitor. By dimming GSK3 activity, lithium slows the production of beta-amyloid and tau proteins and prevents related damage (Hooper et al., 2008; Wad, 2009; Engel et al., 2006).

Lithium removes plaques and tangles from cells. In addition to slowing beta-amyloid and tau protein production, lithium promotes their removal from cells by repairing damaged "cleaning systems" in the neurons. Nerve cells regularly undergo autophagy, the process by which unwanted or dysfunctional cell components are broken down and removed. In patients with Alzheimer's disease, however, autophagy is disabled. This allows peptides and tau proteins to accumulate much faster and with more destructive effects (Cheung, 2011).

Lithium stimulates autophagy. It thereby corrects the waste removal process in cells so that lesion-causing proteins are eliminated (Sarkar et al., 2005; Ravikumar et al., 2010).

Lithium prevents neuronal destruction. When cells are too damaged to be cleaned or repaired, they begin to die. They shrink, condense, and disassemble. The process of apoptosis, or cell death, clears cells that have been overrun with misfolded proteins and can no longer carry out their functions.

Apoptosis becomes dysregulated in many patients with Alzheimer's. Cell death is triggered in random nervous system cells (Shimohama, 2000). Lithium counterbalances this effect by suppressing the pro-apoptotic molecules that initiate cell death. Simultaneously, lithium ions support the expression of anti-apoptotic molecules, which mark cells as healthy so they are not mistaken as candidates for apoptosis (Manji, 1999; Chen et al., 1999; Liechti et al., 2014). By recalibrating the rate of cell death, lithium slows the accelerated tissue loss that accompanies Alzheimer's disease.

Lithium regulates glutamate. Glutamate is the most important neurotransmitter for normal brain function. More than half of all brain synapses release the chemical glutamate in order to communicate. Under healthy conditions, glutamate promotes biological processes involved with learning and memory and leads to high-level cognitive integration. However, because glutamate is a strong excitatory chemical, it must be swiftly

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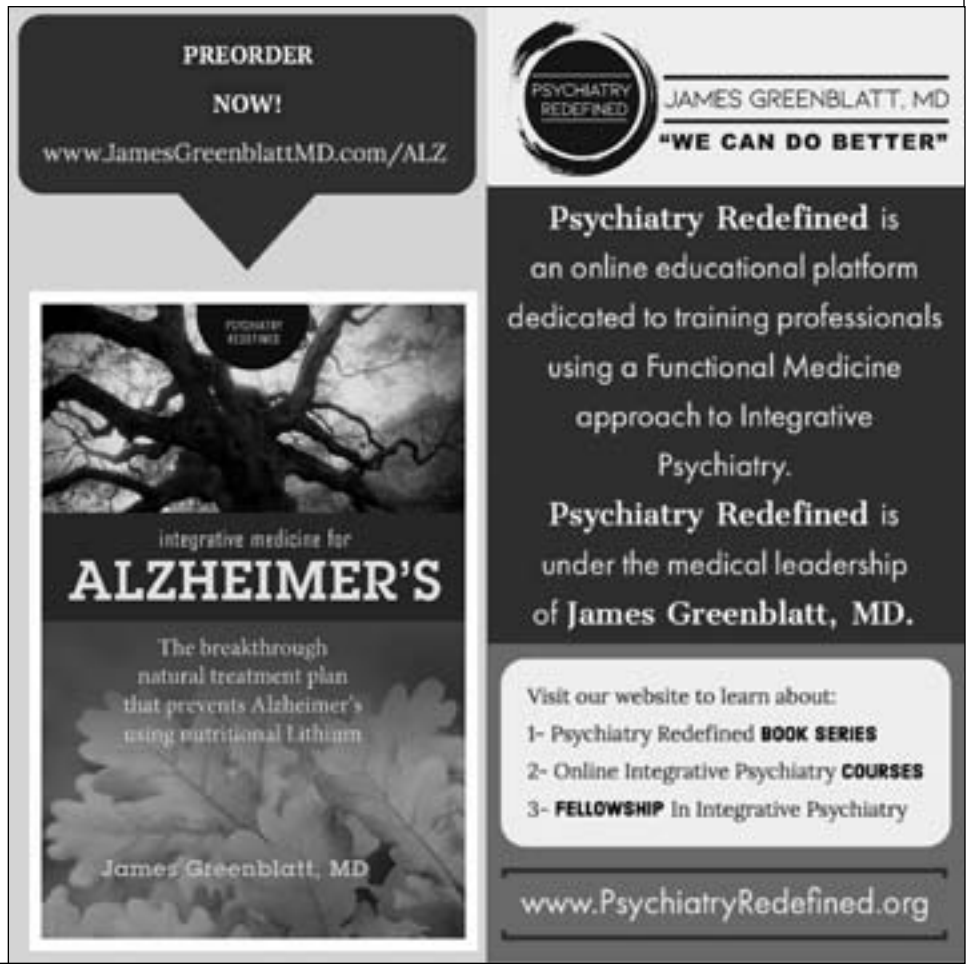

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cleared from the nerve cell junctions to keep messages brief. Excess glutamate can overwhelm the neurons, leading to agitation, injury, and eventually cell death (Hamilton et al., 2015). This often occurs in the Alzheimer's brain, where an overabundance of excitatory glutamate floods cells.

Lithium prevents glutamate uptake into the cells by deactivating N-methyl-D-aspartate (NMDA) receptors, the main class of glutamate receptors in nervous tissue. This action protects neurons from its potential excitotoxic effects (Hashimoto et al., 2002).

Balancing intracellular glutamate levels is another pathway through which lithium may prevent cell death associated with Alzheimer's and related symptoms of cognitive decline.

Lithium decreases inflammation. Neuroinflammation, or inflammation of nervous tissue, occurs normally as a protective process coordinated by the immune system in response to an infection or injury. It then stimulates repair and recovery by delivering white blood cells. If not controlled, however, this process can be very damaging. Scientists now believe that inflammation is a key component in Alzheimer's disease, in which the inflammatory response becomes disrupted and proceeds in an out-of-control way Control over this process may help arrest neuron destruction and stabilize brain health. Cells in the immune system communicate by releasing and responding to chemical messengers such as cytokines. Lithium moderates inflammation by dampening cytokine reactivity (Moore and O'Banion, 2002).

In addition, lithium changes fatty acid metabolism in the brain in a way that protects against inflammation. By shifting various points in the inflammatory chain, lithium diminishes neuroinflammation, protecting neurons from devastating effects.

Lithium's influences on genes can protect against Alzheimer's disease. Genetics is one of the factors that can increase or decrease an individual's risk of developing Alzheimer's disease. Lithium can actually contribute to genetic changes that diminish the severity of the disease. Lithium changes gene expression through two basic channels: DNA methylation and acetylation. Lithium prevents DNA methylation of the BDNF gene promoter. In other words, it increases the expression of the BDNF gene. The increased synthesis of BDNF contributes to robust neural growth and healthy dendritic branching. By ensuring that the BDNF gene is left in the "on" position, lithium promotes consistent release of protective neurotrophins that protect and nourish the brain (Dwivedi and Zhang, 2015).

BDNF levels are diminished both in the brain and serum of patients with Alzheimer's. In one study, Alzheimer's patients treated for 10 weeks with lithium showed a significant increase in BDNF serum levels. They also displayed less cognitive impairment than a similar group of patients with Alzheimer's who were treated with placebo (Leyhe et al., 2009).

Lithium also acts through histone modification. Histone function is especially important for encoding high-level cognitive functions like learning and memory. In fact, diminished memory in Alzheimer's patients has been linked with problems in histone metabolism. In laboratory animals, lithium increased histone acetylation by weakening the binding of the DNA to its spool, making it more available to proteins that enhance memory (Lee et al., 2015). Although studies in humans are needed to further delineate the exact mechanism, lithium may prevent genetic changes associated with Alzheimer's and other neurogenerative conditions.

Lithium, then, has been shown through research from the last three decades to arrest destructive processes that result in Alzheimer's disease. It can generate new neurons and restore damaged ones, thereby increasing gray matter and brain volume. Pharmaceutical treatment of Alzheimer's disease has failed, as scientists do not yet fully understand the complicated interaction of processes that converge in the deterioration of the brain. Unlike drugs, which have one mode of action, lithium affects multiple cascades. The simple element lithium, sprinkled throughout the earth as cosmic dust by the Big Bang 13.8 billion years ago, has been shown in studies from Texas to Lithuania to lower rates of mental illness, violent crime, and suicide. It also provides our best hope against Alzheimer's by interrupting multiple pathways to disease.

Dosage

Lithium may be most effective in preventing and treatment of early Alzheimer's disease when used at micro-dose or supplemental levels, similar to those found naturally in some water and foods. In a study reported in *Alzheimer's Research*, a tiny dose of 0.3 mg lithium was administered once daily to Alzheimer's patients for 15 months. The patients receiving lithium had stable results on cognitive performance tests throughout the study, while the cognitive test results in the control group demonstrated progressive decline. In addition, three months into the study, the seemingly impossible occurred: the patients with Alzheimer's got better. Those treated with lithium scored higher on standardized assessments of cognitive function than they scored before the study began (Nunes, 2013).

These indications that low-dose lithium is effective in preventing cognitive decline followed four large studies of the effects of lithium in tap water, conducted in the US, Denmark, and Japan. Each of these studies confirmed an association between lithium at trace doses in drinking water and low levels of Alzheimer's disease and dementia. A very large study conducted in 2017 in Denmark matched the cases of 73,731 patients with dementia and 733,653 controls according to presence or absence of lithium in their local water supply. Those who lived where water contained lithium had lower rates of dementia than controls. The researchers concluded that lithium in drinking water is linked to longer life in patients with Alzheimer's (Kessing, 2017).

To date, then, a drug used in higher doses to treat patients with bipolar

disorder has turned out to slow and even reverse the devastating effects of Alzheimer's. The researchers at Wayne State, who were trying to understand lithium's efficacy against bipolar disorder, happened to see unexpected results and to realize the potential of what they had seen.

We now know that the processes that culminate in Alzheimer's disease are active in the brain 30-40 years before symptoms develop. Studies reported in reputable academic journals show unequivocally the effectiveness of lithium against multiple cascades that contribute to the disease.

James Phelps, a nationally renowned expert in bipolar disorder, posed the question, "Why is there so little clamor from patients at high risk for Alzheimer's disease and their families for microdose lithium? Might it be because this is lithium, with all its historical baggage and the stigma of being associated with bipolar disease?"

As a nutritional psychiatrist, I have been prescribing lithium for more than 30 years. The biological benefits of lithium affect many of the processes that cause brain cell degeneration. Even at pharmaceutical doses, I have not seen the severe side effects from lithium treatment that seem to cloud its reputation. And the question of side effects is irrelevant when lithium is used at microdose levels.

The accumulated failures from pharmaceutical trials reveal that a model of prevention is the only window of intervention to slow Alzheimer's disease. The research on lithium has been extensive and includes animal, epidemiological and clinical studies. Given the low cost of nutritional lithium, the safety profile and the long, silent progression of Alzheimer's disease before symptoms occur, it is imperative that we shift research priorities.

We hear little about lithium's potential only because it is neither patentable nor lucrative and therefore does not reward a lavish marketing and advertising investment. Ironically, we may be slow to recognize the enormous benefits of lithium because it has been right in front of us all the time.

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The Endocannabinoid System's Intriguing Role in Gut Health

by Chris D. Meletis, ND, and Kimberly Wilkes

Cannabis has been used medicinally for centuries in people suffering from disorders associated with the gastrointestinal tract (GI), including abdominal pain, cramps, diarrhea, nausea, and vomiting.[1,2] An extensive amount of recent research offers justification for the traditional use of not only cannabis but also other phytocannabinoids such as cannabidiol (CBD) for GI health. This research points to a strong connection between the endocannabinoid system and various aspects of gut health. The gut-brain axis, which refers to the ability of intestinal function to alter various aspects of mental and cognitive health, has drawn considerable attention in the medical literature. New research indicates that actions of the gut-brain axis may be in part mediated by the endocannabinoid system.[3]

The endocannabinoid system refers to cannabinoids produced within the body (endocannabinoids), neurotransmitters that bind to cannabinoid receptors 1 and 2 (CB_1 and CB_2), thus regulating many aspects of health. Enzymes that play an important role in the synthesis and breakdown of endocannabinoids and molecules required for endocannabinoid uptake and transport are also involved in the endocannabinoid system. Phytocannabinoids like CBD may exert their health benefits in part through their actions on this system. It has long been known that the endocannabinoid system regulates many functions in the body including mental health and pain control. Its role in other areas of health has only recently begun to be appreciated. One of those areas is the role it plays in the intestines.

The Endocannabinoid System's Role in Gut Health

An extensive amount of evidence indicates the endocannabinoid system plays a significant role in intestinal health. High concentrations of the endocannabinoids 2-arachidonoyl-glycerol (2-AG) and anandamide are observed in the colon along with significant fatty acid amide hydrolase (FAAH) activity,[4] which is involved in the breakdown of anandamide.

The enteric nervous system (ENS) of the GI tract contains approximately 500 million nerve endings.[5] The highest levels of immune cells in the body are also found in the gastrointestinal tract.[5] Roughly 20% of the nerves in the GI tract are intrinsic primary afferent neurons, which alert the brain when subtle changes within the GI tract occur.[5] This communication occurs through the vagus nerve. Endocannabinoids may regulate neurotransmission in the gut, as indicated by the presence of the CB_2 receptor on enteric neurons and its expression by immune and epithelial cells in the GI tract.[6,7] Furthermore, altering the activity of CB_1 receptors can regulate sensory processing from the gut, brain integration of the brain-gut axis, extrinsic control of the gut, and intrinsic control by the enteric nervous system.[4]

The effect of both endocannabinoids and phytocannabinoids on colon carcinogenesis in rodents further supports the role of the endocannabinoid system in gut health. Studies using CBD or a *Cannabis sativa* extract with high cannabidiol content inhibited the initiation of aberrant crypt foci, polyps, and tumors in the colon of mice.[8,9] Cannabidiol also suppressed cell proliferation in colorectal carcinoma cell lines.[8]

The Endocannabinoid System and Gut Motility

Endocannabinoids are known to regulate gut motility, the time it takes for food to move through the intestines. Slow gut motility is more commonly called constipation and fast gut motility is known as diarrhea. Evidence indicates that the endocannabinoid system plays an important role in gut motility. In obese mice fed high-fat diets, the endocannabinoid system in the gut underwent alterations, leading to an increase in gut motility.[10] Many studies also indicate that CB_1 receptor activation suppresses peristalsis and gastrointestinal contraction. The CB_1 receptor is activated by THC, the psychoactive component in marijuana.[11,12] Because CBD does not directly affect the CB_1 receptor it may be less likely to produce constipation. This was indicated in a mouse model of sepsis, which demonstrated that CBD slowed gastrointestinal motility in the animals with sepsis but did not affect motility in normal mice.[13] Furthermore, CBD regulates the activity of FAAH, an enzyme involved in gastrointestinal motility through its actions on anandamide.[13] Additional evidence

that the endocannabinoid system is involved in gut motility was provided by a mouse model of constipation in which inhibiting diacylglycerol lipase (DGL), the enzyme responsible for the synthesis of the endocannabinoid 2-AG, improves gut motility.[14]

Endocannabinoids, the Gut, and Obesity

Through pathways associated with the gut-brain axis, alterations in the endocannabinoid system can result in obesity and accompanying inflammation.[15] Endocannabinoid signaling in the gut may modulate food intake and energy balance by indirectly interacting with the vagus nerve,[16] which permits neurotransmission between the gut and brain.[17]

A rodent model found fasting leads to the synthesis of 2-AG and activates the CB_1 receptor through efferent vagal activation of receptors in the small intestine, which may signal hunger.[18]

The endocannabinoid system's role in food intake was shown in a study demonstrating increased endocannabinoid signaling occurs after hedonic eating (consuming food for pleasure).[18] In both normal-weight and obese humans, thinking about eating or eating a highly palatable food such as chocolate or pudding, leads to circulating levels of endocannabinoids that are higher compared with a nonpalatable control diet.[19-21]

The Endocannabinoid System and Inflammatory Bowel Disease

Endocannabinoids and phyto-cannabinoids are involved in inflammatory regulation in the gut. Endocannabinoids help signal immune cell movement to intestinal inflammation sites.[22,23] Cannabidiol has been shown to suppress the synthesis of proinflammatory cytokines, such as TNF-α and IFN-γ, and reduce intestinal inflammation.[24,25] Due to its role in regulating gut inflammation, it's not surprising that the endocannabinoid system has also been shown to modulate inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). Tissue from humans with IBD is characterized by increased epithelial CB_2-receptor expression, suggesting CB_2 receptors act in an immunomodulatory capacity in this disorder.[26] This in turn affects mucosal immunity in the inflamed colon and interacts with the actions of CB_1 receptors in the colonic lining to promote wound healing.[26] In fact, CB_1 receptors play an important role in gut health as evidenced by the increased incidence of diarrhea in people administered CB_1 receptor antagonists.[27]

Other evidence supporting the endocannabinoid system's role in modulating colonic inflammation was provided by rodent models showing that suppressing FAAH, leading to a rise in anandamide levels, stops the development of colitis.[28,29] Likewise, inhibiting FAAH and the inflammatory enzyme cyclooxygenase (COX) in mice with colitis reduces the severity of the disease by elevating anandamide levels

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and acting on the CB_1 receptor.[30] Blocking FAAH and COX correlated with higher concentrations of the endocannabinoids palmitoylethanolamide (PEA) and oleoylethanolamide. In intestinal tissue from ulcerative colitis patients, PEA levels are 1.8-fold higher compared with healthy patients, likely a result of the PEA attempting to help heal the inflammation.[31] PEA has pronounced anti-inflammatory properties that inhibit features of colitis in mice as well as the synthesis of inflammatory cytokines.[32]

The phytocannabinoids CBD, THC, and cannabigerol have significantly reduced intestinal inflammation in animal models. In one of those models, both CBD and THC proved beneficial.[33] However, THC was the most effective in rats with experimental colitis, although CBD enhanced the effects of an ineffective THC dose to the point where the combination of CBD and lower-dose THC was the equivalent of a higher THC-only dose.[33] The phytocannabinoid cannabigerol (CBG) has also proved beneficial in rodent models of colitis. In one study, CBG inhibited colitis in mice and lowered the synthesis of reactive oxygen species in intestinal epithelial cells.[34]

Polymorphisms in the gene encoding CB_1 receptors are associated with irritable bowel syndrome, further establishing the link between the endocannabinoid system and this disease.[35] Variants of the CB_1 receptor gene (*CNR1)* and *FAAH* genes have been noted in individuals with diarrhea-predominant and alternating forms of IBS.[36,37] In intestinal tissues of patients with constipation-predominant IBS, lower levels of *FAAH* mRNA were observed.[38] In a study of patients with constipation predominant IBS (C-IBS), diarrhea-predominant IBS (D-IBS), and mixed IBS (M-IBS) who suffered from chronic abdominal pain and functional dyspepsia, there was a relationship between the non-wild type *FAAH* genotype and functional bowel disease phenotypes and with increased colonic transit in IBS-D patients.[39] Likewise, in another study, there was a pronounced association between a polymorphism in the cannabinoid receptor 1 (*CNR1)* gene and IBS symptoms, colonic transit in IBS-D, and intestinal gas.[40] However, pain was not associated with this polymorphism. Furthermore, researchers found that the *CNR1* mutations correlated with the emergence of IBS symptoms, as observed in two studies of a Korean and Chinese population with IBS.[41,37]

Rodent models indicate that early-life stress alters the endocannabinoid system, which increases the susceptibility to IBS [irritable bowel syndrome].

Human research using a CBD supplement further corroborates the potential benefits of modulating the endocannabinoid system in IBD/IBS. In a 10-week study of patients with ulcerative colitis given a CBD-rich botanical extract, the primary endpoint of percentage of patients in remission after treatment was similar between the placebo and CBD group.[42] However, subjective physician's global assessment of illness severity, subject global impression of change, and patient-reported quality-of-life outcomes were improved in the CBD group. Additionally, the placebo group experienced more gastrointestinal-associated adverse effects. Furthermore, in human colonic cultures derived from ulcerative colitis patients, CBD suppressed enteric reactive gliosis and reduced inflammation, thus inhibiting intestinal damage.[25] The researchers concluded, "Our results therefore indicate that CBD indeed unravels a new therapeutic strategy to treat inflammatory bowel diseases." Clearly, as another group of researchers stated, the endocannabinoid system "in the gut is a potential therapeutic target for IBS and other functional bowel disorders."

Psychological Stress and the Endocannabinoid System

The endocannabinoid system regulates abdominal pain (visceral hyperalgesia) caused by chronic stress and may explain, at least in part, the relationship between chronic stress and IBD/IBS.[27,43] Rodent models indicate that early-life stress alters the endocannabinoid system, which increases the susceptibility to IBS.[44] The endocannabinoid system is a key player in the regulation of visceral pain and the means by which psychological stress impairs GI function may involve this system.[44] Chronic stress reduces levels of the endocannabinoid anandamide while elevating 2-AG in the brain and downregulating CB_1 receptors in sensory ganglia, which regulate visceral pain.[45] During chronic psychological stress, CB_1 receptor activity is altered through epigenetic pathways, which may explain the association between stress and abdominal pain.[46] Epigenetics refers to the alteration of gene expression through pathways other than the genetic code. It refers to the changes that occur in our genes due to lifestyle or environmental factors. Through these epigenetic actions, chronic stress affects the CB_1 gene promoter, leading to lower levels of CB_1 in sensory neurons that innervate the colon and other pelvic organs.[47]

The Microbiota and the Endocannabinoid System

Perhaps one of the most interesting aspects of the endocannabinoid system's role in gut health is its interaction with the gut microbiota. The gut microbiota can modulate intestinal endocannabinoid tone.[48] A microbiota profile associated with obesity also correlates with an increased intestinal concentration of anandamide, which leads to increased gut permeability (leaky gut).[48] In fact, the link between the gut microbiota and obesity may be mediated by the endocannabinoid system.[48] The results of a study where the bacterium, *Akkermansia muciniphila*, was administered to obese and type 2 diabetic mice daily support this concept.[49] In that study, the bacterium reversed diet-caused obesity.

It accomplished this by increasing intestinal levels of endocannabinoids that control inflammation, the gut barrier, and gut peptide secretion.

On the other end of the spectrum, endocannabinoids from adipose tissue can also modulate the composition of the gut microbiota.[35] This indicates there is bidirectional communication between the microbiota and the endocannabinoid system.[35] Evidence of this cross-talk between the endocannabinoid system and the microbiota is reinforced by studies showing that the beneficial effects of probiotic supplementation on gut health may in part involve this system. The probiotic *Lactobacillus* given orally to rodents reduced visceral pain while simultaneously upregulating CB_2 receptors in the intestinal epithelium.[50] Inhibiting CB_2 eliminated the beneficial effects of the probiotic. In a model of chronic colonic hypersensitivity, *Lactobacillus acidophilus* NCFM resulted in analgesia.[50] This study also indicated that CB_2 receptors may be involved in the association between gut microbiota and visceral hypersensitivity. Furthermore, dysbiosis of the gut microbiota caused by antibiotics correlates with a general inflammatory state and alteration of certain endocannabinoids in the gut of mice as well as accompanying depression.[51] However, in a human study of individuals consuming *Lactobacillus acidophilus* NCFM over a period of 21 days, CB_2 receptors were not upregulated in colonic mucosal biopsies.[52]

Conclusion

An abundance of evidence is pointing to the conclusion that the endocannabinoid system is involved in gut health and that it may even be an important mediator of the actions of the gut-brain axis. The damaging effects of chronic psychological stress on the intestinal tract may also be driven by the endocannabinoid system. Targeting this system by the use of CBD oil or other phytocannabinoids may be one way to reduce colonic inflammation and reduce the effects of stress on the gut. In my clinical practice I also use a specific high potency PEA that has helped many patients.

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Letter to the Editor

Homeopathy as Psychotherapy and Props

It will be no surprise to readers that I am writing a response to Dr. Douglas Lobay's article slamming homeopathy. A 1983 Bastyr graduate, I am a confessed homeopathy fanatic. Since Dr. Lobay dismisses homeopathic medicine as "psychotherapy with props," I feel well suited to comment since I am also a University of Washington MSW grad of '76 specializing in psychiatric social work. From the day I was introduced to homeopathic philosophy in my first year at Bastyr (1979), it made perfect sense to me. And now, 34 years and however many thousands of patients later, I am more convinced than ever of its effectiveness.

Rather than cite scientific articles in support of homeopathy, which abound and have been more than effectively documented by Dana Ullman, MPH, I refer readers to a recent film, *One Drop Homeopathy* (https://www.justonedropfilm.com/), and you can see for yourselves the prejudice against homeopathy, to the point of dishonesty, in the scientific research community. As long as this bias and dishonesty exist, the results of homeopathy will not be honestly represented in scientific literature.

The homeopathy that I learned in my naturopathic education was nowhere complete enough to produce effectiveness with my patients. After studying with all of the top homeopaths of that time, I, to my great fortune, found Dr. Rajan Sankaran of Mumbai, India, and had the remarkable fortune to study with him and his close colleagues intensively for a good ten years. I changed my practice completely, which produced much greater success, then went on, with my husband, to write seven books on homeopathy documenting many of our successful cases.

I do not know how intensively Dr. Lobay has studied homeopathy nor with whom. Nor his style of practice. It is sad to me that one of my fellow NDs has used the platform of the *Townsend Letter* to demean homeopathy. He is entitled, of course, to his professional and personal opinion. But to dis homeopathy as "psychotherapy with props" is, to me, naïve and less than fully informed. I used various types of cutting edge psychotherapy in my practice for many years and I can share, unquestionably, that one could never achieve the same results without the correctly selected *simillimum* (one correct homeopathic remedy for each individual). Has Dr. Lobay attended a clinical seminar with a homeopathic doctor at the level of Dr. Sankaran and spent days watching before-and-after videos of patients? Has he studied any clinical cases presented in our books and by so many other competent homeopaths? Rather than regurgitating the same, often flawed, studies disproving homeopathy, I would ask that he have an open mind about its effectiveness. Each doctor, naturopathic or other, needs to choose the modalities and style of practice which best suits him or her. I don't criticize NDs who choose a practice style far different from mine nor make them wrong for doing so. I would hope to have that same collegial respect and open mindedness from Dr. Lobay.

Judyth Reichenberg-Ullman, ND, MSW

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Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Ketogenic Diet Shifts Gut Microbiome to Improve Seizures

A new study confirms what clinicians have known for nearly a century. Wu, Wang, Fan et al reported in April 2018 that a ketogenic diet was helpful in about 60% of the 52 kids who had followed the diet to treat seizures. These weren't just any epileptic kids; they were notable because their seizures were not responding to drug treatment. The trial lasted 12 weeks, but those who responded did so in the first two weeks. The kids ranged in age from three months old to seven years.

The treatment was considered effective in 29 of the 52 kids or 56% of the cases at the end of 12 weeks of treatment. Fifteen of the kids were doing better in the first week. At the end of the study, 14 participants were seizure free, nine had a marked reduction in the number of seizures, and six kids were having half the number of seizures or less than before treatment started. The treatment was 'ineffective' in 23 kids but keep in mind the bar for being effective was set high, a 50% reduction in the number of seizures from baseline.[1]

Modern interest in diet to treat epilepsy began with fasting; two French physicians, Guelpa and Marie, wrote a paper in 1911 and reported seeing improvements in 20 children they had treated but provided little detail.[2] Hugh Conklin, a doctor in Battle Creek, Michigan, popularized therapeutic fasting in the United States in the early 1900s. Conklin worked as an assistant to Bernarr Macfadden, the 'fitness guru' behind *Physical Culture* magazine. Macfadden claimed fasting could cure just about anything but especially epilepsy. Macfadden was a character; he apparently shortened his first name from Bernard so he could pronounce it like a lion's roar.

Conklin fasted epileptic patients in his practice, and Rawle Geyelin an endocrinologist in New York noticed and adopted the practice as well. He reported his patient experiences in 1921.[3] This spread further to Harvard where Cobb and Lennox began studying fasting. They were the first to observe how rapidly improvement happened; the effects of starvation caused seizure improvement in just two to three days.[4]

Two important observations on fasting were published in 1921. Woodyatt noted that in normal people a diet that had too low a proportion of carbohydrate and too high a proportion of fat caused similar changes as a starvation diet, that is the appearance of acetone and beta-hydroxybutyric acid in the blood.[5] Wilder at the Mayo Clinic suggested that similar benefits to fasting were achieved if ketonemia was reached through dietary manipulation and that fasting was not necessary.[6] Wilder went on to coin the term 'ketogenic diet' and treated patients at the Mayo Clinic using it.

In 1925 Peterman, also at the Mayo Clinic, published the formula that is still used today. One gram of protein per kilogram body weight in children and only 10-15 grams of carbohydrate is consumed per day with the remainder of calories coming from fat.[7]

The ketogenic diet was described in almost every medical textbook on epilepsy published between 1940 and 1980. Livingston at Johns Hopkins reported that in over 1,000 children he had treated, 52% had complete symptom control and 27% had symptom improvement following the diet.[8] These percentages are remarkably similar to those reported in the new Wu study.

Awareness of the ketogenic diet and research interest was revived by a *Dateline* TV show broadcast on NBC in October 1994. The TV program followed the story of a two-year-old boy named Charlie, treated at Johns Hopkins by Millicent Kelly (a dietitian who had worked with Dr. Livingston). Charlie became seizure-free, and his father formed The Charlie Foundation, which disseminated informational videos for parents about the ketogenic diet, published a book about the diet,[9] and even produced a TV movie (starring Meryl Streep) and funded research that showed the diet produced significant benefit.[10,11]

Although the ketogenic diet has been effective in treating childhood seizures for nearly a hundred years ago, no one has been certain why it works.

In late May 2018, a study published in the journal *Cell* explained that the ketogenic diet's impact on epilepsy is related to its effect on the human intestinal microbiome. That sentence needs to be written a second time; the ketogenic diet may reduce seizures because it changes the gut biome. This is exciting news, a paradigm shift in our understanding on how diet affects mental function.

Wu et al in discussing their findings do not mention this biome idea in their discussion; they instead expressed uncertainty why the diet works suggesting that shifting the brain to using ketones as an energy source or perhaps the caloric restriction might have something to do with the benefits. Neither explanation was convincing.

Earlier mice experiments have demonstrated that ketogenic diets prevent development of epilepsy,[12] improve symptoms of autism,[13] improve motor symptoms in Alzheimer's disease,[14] and reduce epileptic activity in the brain.[15]

This biome theory appeared in the May 24, 2018, issue of *Cell*. Christine Olson and colleagues at Elaine Hsiao's lab at UCLA claim that the ketogenic diet quickly alters the gut biome in a specific way so that it provides protection against both electrically induced seizures and spontaneous tonic-clonic seizures in mouse models of epilepsy.

The ketogenic diet does not provide seizure protection to germ-free mice, raised in a germ-free environment or who have been heavily treated with antibiotics. The effect requires gut bacteria to be present. However, transplanting these germ-free mice with populations of *Akkermansia* and *Parabacteroides* bacteria confers protection against seizures.

Olson et al propose a simple mechanism of action. The high-fat, low-carb ketogenic diet shifts the gut biome, decreasing diversity and increasing populations of *Akkermansia muciniphilia* and *Parabacteroides spp.* bacteria. These bacteria decrease gamma-glutamyltranspeptidase activity, decreasing gamma-glutamyl amino acids in the blood, which in turn increases GABA levels in the brain. Increased GABA in the brain offers the protection against seizures.

Hsiao's lab has been producing a steady stream of interesting research related to the gut biome and its impact on the brains of mice and humans for years. In 2013 Hsiao reported that in a mouse model of autism, alterations in microbiota and GI barrier could be corrected using *Bacteroides fragilis*, which "corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like and sensorimotor behaviors."[16] In simpler words, modifying the gut biome reduced the autism-like symptoms. Hsiao's work on autism continues. Because of her work, it is now widely accepted that "immune dysregulation and gastrointestinal issues are common comorbidities" in the autism spectrum.[17,18]

UCLA has already granted licensing rights to a start-up company that plans to develop a probiotic treatment for epilepsy. The idea is that the right formulation of bacteria will modulate GABA, "thereby conferring the neuroprotective effects of the ketogenic diet in a pill. The pill regimen would be easier to comply with than the diet and potentially have fewer side effects."[19]

There may be other strategies to increase gut populations of these bacteria and so increase GABA. Metformin, a drug used to treat type-2 diabetes, has been reported to increase populations of both these bacterial species in mice.[20] Yang et al reported in 2017 that chronic use of metformin does have some anti-seizure effect on mice.[21] Consumption of certain 'resistant starches' designed to reach the large intestine and 'feed' certain bacteria may also increase populations of these bacteria. [22]

We really don't understand the relationships between various bacteria species and disease as yet. We are just getting hints as to the profound impact they may have.

Both *Akkermansia muciniphila* and *Acinetobacter calcoaceticus*, were found to be four times more abundant in multiple sclerosis patients than in healthy people, while *Parabacteroides distasonis* is four times more abundant in healthy people than in MS patients. *Akkermansia* and *Acinetobacter* are associated with inflammatory responses in MS while *Parabacteroides* appears to have an anti-inflammatory action.[23] We probably do not want to rush into force-feeding all of our patients with every species of bacteria that improve life for a mouse.

Treatment of epilepsy may be on the verge of shifting to a focus on altering the gut microbiome by using a combination of probiotics, ketogenic diet, and possibly eating foods containing resistant starches. If this strategy does indeed increase GABA levels in the brain, a long list of other possible conditions might be improved by such a treatment strategy.

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Functional Gastroenterology Bolus

by Steven Sandberg-Lewis, ND, DHANP

Collagen, Joint Hypermobility, Digestion, and Psychology

The spectrum of rare, genetic, altered collagen syndromes (i.e. Marfan's) has particularly garnered the attention of rheumatologists and cardiologists. In gastroenterology, Ehlers-Danlos syndromes have major significance – particularly the more common joint hypermobility form of Ehlers-Danlos syndrome (hEDS), which has multiple effects on digestive anatomy and physiology. Common examples are hiatal and abdominal/pelvic hernias; gastric, small bowel, colonic or rectal prolapse; intussusception; and weakness of the lower esophageal sphincter and ileocecal valve. Digestive symptoms commonly associated with hEDS include dysphagia, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, recurrent abdominal pain and either constipation or diarrhea.[1] The screening for hEDS begins with the Beighton score – an easy 3 minute in-office joint flexibility test. See https://www.ehlers-danlos.com/assessing-joint-hypermobility/ for details. I do a Beighton score on every new patient. A positive score is 5 or more hypermobile joints for those ages 10-59, and 4 or more for those over age 60. To open the discussion with adults, you may ask about a history of being able to perform "the splits" or other "double-jointed" activities when younger.

hEDS may also have psychological manifestations. Examples of these emotional states include depression, anxiety,[2] low self-confidence, hopelessness,[3] and negative thoughts. A recent paper points to a possible connection between attention deficit hyperactivity disorder and hEDS.[4] Sleep quality is frequently poor and leads to fatigue in this population.[5] In addition, women with hEDS are much more prone to balance issues and falls.[6] Chronic pain and its effect on stress hormones and the HPA axis may be a major factor in the mood disorders of hEDS. Because most physicians neglect to screen for hypermobility syndrome, they do not know that some of their patients have it. Patients may feel misunderstood, marginalized and that their real concerns are not taken seriously by the healthcare practitioners.[2]

When I know that the patient has hEDS it affects my management and treatment in several ways. First, I will make sure to screen them for hiatal hernia and hiatal hernia syndrome (for more detail see chapter 12 of my textbook – second edition) and ileocecal valve syndrome (for more detail see chapter 15 of my second edition). It tempers my expectations for results of treatment since hEDS presents key structural changes ("floppy" collagen). This not only creates instability of joints but also laxity of sphincters, the omentum, ligaments, and tendons, which often creates a life-long tendency for GI issues. I may review imaging reports to check for prolapse and tortuosity of the intestines.

The presence of hEDS will inform my recommendations for bodywork personally and by other practitioners the patient may visit. Spinal manipulation using force (grade 5) should generally be reserved for rare situations. Myofascial work should also involve less force and shorter duration. Musculoskeletal techniques that preserve and enhance stability of joints, such as prolotherapy, platelet-rich plasma (PRP) injections, and toning exercises should be first choices.

It will also remind me to include nutritional treatments that have the potential to support collagen. These include vitamin C, bone broth, collagen extracts, and methylsulfonylmethane, although formal nutrition research is speculative.[1,7,8]

Along with my colleagues, I suspect that the lack of joint integrity in the cervical spine becomes a strong risk factor for traumatic brain injury. Perhaps even the slightest whiplash (shaking the brain) may become a source of significant neuronal reorganization or degeneration.[9]

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MARCH 1-3: CALIFORNIA NATUROPATHIC DOCTORS ASSOCIATION 21st MERGING MEDICINE CONFERENCE – Autoimmunity in Palm Springs, California. CONTACT: https://www.calnd.org/ce-events

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JUNE 7-9: COLLEGE OF NATUROPATHIC DOCTORS OF SASKATCHEWAN HEALING SKIES CONFERENCE in Saskatoon, Saskatchewan, Canada. CONTACT: http://sanp.ca/healing-skies-conference.html

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Breast Related Issues

Fibrocystic Breast Changes and Nutrient Solutions

Fibrocystic breast change (FBC), aka fibrocystic breast disease (FBD), is a benign disorder of the breasts that can result in lumpiness, nodules, and/or pain. It is not associated with breast cancer risk, but it makes it hard to decipher if a nodule is benign or cancerous because it is not easy to distinguish these lumps from solid tumors that might be malignant.

Conventional treatments include nonsteroidal anti-inflammatory drugs (NSAIDS) and, in severe cases, even some strong hormonal medications.

Historically, there have been studies of evening primrose oil or various forms of iodine to reduce breast pain that have showed benefit, but some doses of iodine that lead to relief, exceed recommended safety limits. The current study was a multicenter, prospective, randomized, double-blind, controlled parallel-group study in the United Kingdom. Women were randomized to receive a liquid formulation that contained 1 gm of gamma-linolenic acid (GLA), 50 mcg of iodine, and 70 mcg of selenium; or they received the liquid formula without the GLA, iodine, or selenium. They were given 4 oz of the liquid formula daily for three menstrual cycles. Breast pain, medications, and menstrual signs were recorded. Nodularity of the breasts was determined with a clinician exam.

Breast pain scores decreased similarly in both groups, by about 30%. Nodularity was reduced in the treatment group but not the control group; and the amount of pain medication was reduced in the treatment group relative to the control group. The amount of nodularity reduction was 53% in the number of women with the most severe breast nodularity where breast pain was the most severe.

Commentary: The strengths of this study lie in the combination of the GLA and the iodine, both known to reduce mastalgia. This study showed the strongest benefit in reducing nodularity, a condition associated with less cyclic breast pain. In addition, women who were in the treatment group used less pain medications over time to manage their breast pain.

The strongest studies prior to this for cyclic mastalgia include those with chaste tree berry, evening primrose oil, vitamin E, and iodine. It is important to be very cautious with iodine, as over 1100 mcg/day is considered above the tolerable upper limit of safety.

Mansel R, et al. A randomized controlled multicenter trial of an investigational liquid nutritional formula in women with cyclic breast pain associated with fibrocystic breast changes. *J Women's Health*. 2018;27(3):333-340.

Reduce Breast Density to Reduce Breast Cancer Risk

Breast density status is now typically reported on the screening mammogram report, and approximately 50% of women who undergo screening mammography have either heterogeneously or extremely dense breast tissue. Dense breast tissue is defined as a greater amount of fibrous or glandular tissue than fatty tissue in the breasts. Women with dense breast tissue have a modestly elevated risk for breast cancer, and the sensitivity of screening mammography is reduced by dense breasts.

One of the goals of natural medicine is to reduce the risk for chronic disease, and if someone has extremely dense breasts on mammography, and/or a first degree relative with breast cancer, I recommend strategies that might reduce breast density, and thus reduce the risk of breast cancer. One of those strategies is N-acetylcysteine (NAC). A 2012 study included 25 postmenopausal women randomized to receive either 1 – 1.5 g metformin or 400 – 600 mg of NAC over an average of 10 months. Mammographic breast density was measured before and after completion of the study. Both groups exhibited reductions in mammographic breast density. The metformin group had a 28.5% reduction and the NAC group a 27.3% reduction. While this is a small study, NAC supplementation may represent a useful strategy to reduce breast cancer risk in those who are above-average risk of breast cancer.

Bershtein, LM, et al. The influence of metformin and N-acetylcysteine on mammographic density in postmenopausal women. *Vopr Onkol.* 2012;58(1):45-49.

Do Oral Contraceptives Affect Risk for Breast Cancer?

The issue of whether or not oral birth control pills increase the risk of breast cancer has been confusing and contradictory for at least the last 20 years. It is certainly an ongoing concern

in the minds of many women and clinicians. This recent prospective cohort study from the Denmark national data base attempted to determine if there was any association between use of hormonal contraception and risk for invasive breast cancer in women aged 15-49. Approximately 1.8 million women were followed for an average of 10.9 years from 1995-2012.

In that period of time, 11,517 breast cancers were diagnosed. Most of the hormonal contraceptives were oral formulations and then secondarily, progestin IUDs. The relative risk for breast cancer in current or recent users of these products was compared to those women who never used hormonal contraception and found to be 1.20 with an absolute risk of 13 additional cases of breast cancer per 100,000-person years. Current or recent use of the progestin IUD was associated with a similar, 1.21 relative risk. Breast cancer was uncommon in women who used contraceptive implants or injections.

Commentary: The authors of this study adjusted the findings for many things, including duration of hormonal contraceptive use, age, education, parity, polycystic ovary syndrome, endometriosis and a family history of breast or ovarian cancer. What they did not adjust for was clinical breast examinations, screening mammograms and lactation history, all of which are considered potential issues that confound the results. In addition, it must be factored in that > 80% of breast cancers are in women older than 49, and in the current analysis, they limited their aged group to women between 15 and 49.

Researchers consider that a relative risk of less than 2 or 3 should not be interpreted as a indication of causation; so in this study, with the results of 1.21, it could not be concluded that current or recent use of hormonal contraception was the cause of their breast cancer.

In one of the definitive studies on this topic, conducted by the Centers for Disease Control and published in the *New England Journal of Medicine* in 2002, there was no suggestion of an excess risk for breast cancer with use of oral contraceptives.

The current study does indicate the possibility of a very small increase in risk, the best available data on this topic does shows that they do not have an impact on the risk of breast cancer. With increased understanding of numerous genes on breast cancer risk, not just BRCA genes, and an increased attention to the effect of environmental pollutants, it is likely that this is where we should be putting our attention. However, it may also be true that in women who take oral contraceptives, these medications may provide some kind of fertile environment, an added negative influence for the genetic issues as well as environmental exposures, two areas that currently leave us asking more questions. In the meantime, there are numerous non-hormonal options for contraception; and pregnancy is a risky enterprise in and of itself, with medical risks that outpace the POSSIBLE very small increased relative risk of birth control pills and breast cancer.

And don't forget…there is good published scientific evidence that the following reduce our risk of breast cancer: exercise at least 3.5 hours per week; less alcohol – not more than seven drinks/week (some data says 0-3/week); avoid being overweight/obesity. While the research is not as robust, there is also evidence that we can reduce our risk of breast cancer by eating a Mediterranean diet, fish and/or fish oil supplements, higher fiber diets, olive oil, green tea, and getting more sunshine (adequate vitamin D levels).

Morch L, et al. Contemporary hormonal contraception and the risk of breast cancer. *NEJM*. December 7, 2017; 377:2228.

Hunter D. Oral contraceptives and the small increased risk of breast cancer. *NEJM*. December 7, 2017;377:2276.

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Lion's Mane Mushroom

by Ward W. Bond, PhD

In my research of the Lion's Mane mushroom, we find that its fruiting body contains at least two types of bioactive substances – the *hericenones* and *amyloban* – that strongly stimulate NGF synthesis and protect neuronal cells from oxidative stress-induced cell death.

Potentially, both can cross the blood-brain barrier. The question is, do these substances work when given orally to human patients?

To answer this question, a study was done in a rehabilitative hospital in the Gunma prefecture in Japan, with 50 patients in an experimental group and 50 patients used as a control. All patients were elderly and suffered from cerebrovascular disease, degenerative orthopedic disease, Parkinson's disease, spinocerebellar degeneration, diabetic neuropathy, spinal cord injury, or disuse syndrome. Seven of the patients in the experimental group suffered from different types of dementia. The patients in this group received 5 g of dried Lion's Mane mushroom per day in their soup for a six-month period. All patients were evaluated before and after the treatment period for their Functional Independence Measure (FIM), which is a measure of independence in physical capabilities and in perceptual capacities.

The results of this preliminary study show that after six months of taking Lion's Mane mushroom, six out of seven dementia patients demonstrated improvements in their perceptual capacities, and all seven had improvements in their overall FIM score.

One of the most exciting areas of potential is its ability to help combat some of the symptoms and underlying causes of dementia and Alzheimer's disease as well as peripheral neurological dysfunction.

About Ward W. Bond, PhD
Author of *The Power of the Lion's Mane Mushroom: Regenerate Your Brain with Lion's Mane*
Dr. Bond hosts the daily television show *Think Natural* and the weekly radio program *Life Changing Wellness*. DrWardBond.com

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➤ *continued from page 96*

include avoiding large meals, eating slowly, and not eating within two-to-three hours of lying down. From 2013 to 2015, 99 patients (median age, 57 years) were treated with alkaline water (pH above 8.0), a Mediterranean diet containing 90-95% plant foods, and standard reflux precautions (AMS group). The Mediterranean diet consisted mainly of vegetables, fruits, whole grains, and nuts, with two-to-three meals per week containing 3-4 ounces of meat and minimal intake of dairy products. It was thought that consuming a primarily plant-based diet, which has relatively low protein content, would lead to less secretion of pepsin, compared with a higher-protein omnivorous diet. Patients on the Mediterranean diet replaced all beverages with alkaline water. The primary outcome measure was the change in the Reflux Symptom Index (RSI), which was measured at baseline and after six weeks of treatment. The proportion of patients who experienced a clinically meaningful improvement of 6 points or more in the RSI was nonsignificantly higher in the AMS group than in the PS group (62.6% vs. 54.1%). The mean improvement in the RSI was significantly greater in the AMS group than in the PS group (39.8% vs. 27.2%). These results indicate that consumption of a plant-based Mediterranean diet plus alkaline water is at least as effective as, and possibly more effective than PPIs in the treatment of LPR. The authors of this study pointed out that this approach could avoid the costs and adverse effects of PPIs, as well as providing the additional health benefits associated with a plant-based diet.[2]

Once again, diet and lifestyle modification have demonstrated promise as an effective alternative to potentially dangerous medications in the treatment of a common health condition.

Alan R. Gaby, MD

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

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.

Laryngopharyngeal Reflux: A Common Condition Treatable by Diet

Laryngopharyngeal reflux (LPR) is a common medical condition characterized by daytime (upright) acid reflux, frequently without heartburn or esophagitis. It is sometimes called silent reflux. Symptoms of LPR may include hoarseness, chronic cough, frequent throat clearing, sore throat, a sensation of a lump in the throat, difficulty swallowing, chronic sinusitis, halitosis, and exacerbation of asthma, emphysema, or bronchitis. Chronic LPR is also thought to increase the risk of developing cancer of the larynx.

As with gastroesophageal reflux disease (GERD), proton pump inhibitors (PPIs) are one of the mainstays of treatment for LPR. However, PPI therapy is frequently unsuccessful, and long-term use of these drugs is associated with potential adverse effects such as nutritional deficiencies, small-bowel bacterial overgrowth, and increased risk of developing pneumonia. There is disagreement about whether the use of acid-suppressive medication is appropriate for patients with LPR. The American Gastroenterological Association advises against the use of PPIs in patients with LPR who do not have symptoms of GERD. In contrast, the American Academy of Otolaryngology-Head and Neck Surgery recommends that most patients with LPR undergo a trial of a PPI twice a day for at least six months.

The pathophysiology of LPR differs somewhat from that of GERD, in that injury to laryngeal tissue appears to be due primarily to pepsin, rather than to acid. Because pepsin is active up to a relatively high pH (6.5 to 8.0), even mildly acidic foods may cause problems in patients with LPR.

One practitioner measured the pH of common foods and recommended that patients with LPR avoid all items with pH below 5.0. This approach appeared to produce marked improvement in many cases. With additional experience, it was found that some nonacidic foods (such as eggs and red apples) also triggered symptoms in some patients. In 2011, this practitioner reported on 20 patients (mean age, 54 years) with LPR who had failed to respond to acid-blocking medication.[1] Using the abovementioned dietary approach, 19 of the 20 patients improved and three became asymptomatic. Mean symptom severity improved by 42%. Carbonated beverages were the most common symptom-evoking substance, and in some cases patients found relief simply by avoiding these drinks. The pH of carbonated water is around 3 or 4, because the infusion of carbon dioxide into the water results in the formation of carbonic acid. Many other foods that are bottled or canned today have a pH below 4, because of additives such as acetic acid, ascorbic acid, citric acid, and other acids.[1]

A study published in 2017 followed up on the concept of decreasing the acidity of the diet as a method of treating LPR. The study was a retrospective evaluation of 184 patients who had been treated for LPR between 2010 and 2015 and who complied with the treatment recommendations. From 2010 to 2012, 85 patients (median age, 60 years) were treated with a PPI and standard reflux precautions (PS group). Standard reflux precautions included the avoidance of coffee; tea; chocolate; soda; greasy, fried, fatty, and spicy foods; and alcohol. Other common recommendations to minimize reflux

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