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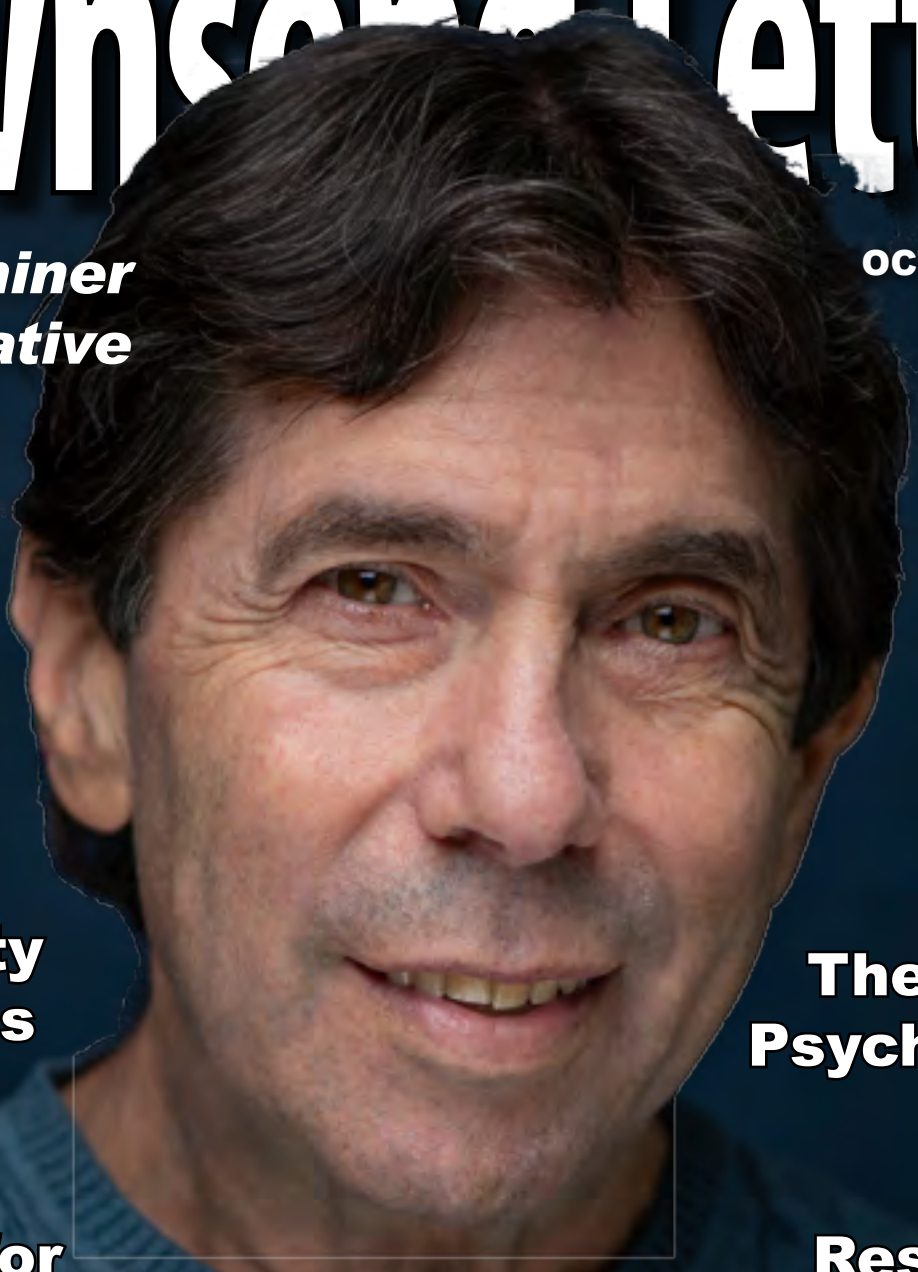

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From the Publisher

***The Whole Brain* by Raphael Kellman, MD**

While we have been preoccupied during the past 18 months with the COVID-19 pandemic, mental health issues have continued unabated. Depression and anxiety have, as expected, worsened in all age groups and among all socioeconomic groups. Our dramatic measures to control the infection, focusing on staying at home, has led to so much social isolation that it is difficult to gauge the extent of depression. Although unemployment is now beginning to reverse as the economy returns to pre-pandemic levels, many individuals remain traumatized by the ongoing need to mask up and curtail social activities as well as deal with the uncertainty of when life will return to normal.

Getting help for depression, anxiety, and more serious psychiatric disorders is difficult especially when counseling centers have cut back on in-person services. Telemedicine

and "telecounseling" are not sufficiently meeting the need. Concurrently, llicit drug use with its increased risk of suicidal overdose has worsened. Clearly primary care practitioners are being asked to take on a much greater role as psychiatrist, counselor, and social worker. What can be brought into the office to make this task any easier?

In the past decade New York City physician, Raphael Kellman, MD, developed what he calls "microbiome medicine" as an integrative health approach to managing chronic health problems. One of his earlier books, *The Microbiome Diet*, detailed a nutritional approach for patients to initiate their healing process. In 2017 he published *The Whole Brain: The Microbiome Solution to Heal Depression, Anxiety, and Mental Fog Without Prescription Drugs.* I discovered it sitting in our cache of books for review, and seeing its cover I thought why not give it a read? Written both for the patient and the practitioner, Kellman's approach to the "Whole Brain" may be just the tool to bring into the office for managing patients experiencing mental health difficulties.

Kellman asks, "What is the whole brain?" We immediately think of the organ in our skull. But Kellman thinks that our whole brain also includes the brain in our gut as well as its microbiome. We think of depression and anxiety as a malfunction of our cranial brain. Kellman would counter the malfunction exists also within the nervous system of the gut, sometimes referred to as the second brain, as well as by an imbalanced microbiome. Of course, because the microbiome resides in the gut, healing the gut not only obligates that one address intestinal permeability and digestive enzyme insufficiency, but also rebalance the bacterial denizens of the GI tract. Kellman is not so much worried about individual bacterial or viral or fungal pathogens as much as whether there is a lack of diversity as well as an excess of "harmless" microorganisms. The point is that healing the gut is not merely a means to address physical health but is critical to restoring mental well-being. Of course, when one is no longer suffering from a stomach ache, constipation, diarrhea, and bloating, physical relief is accompanied with happiness. It is quite a different matter when one ameliorates a mood disorder or cognitive dysfunction by repairing the gut.

Kellman's program to brain wellness also requires a thorough evaluation of thyroid function. He acknowledges that medicine's limited assessment of thyroid using TSH lab testing is completely inadequate. Kellman agrees that patients exhibiting hypothyroid symptomatology need to have comprehensive evaluation of their T3 and T4 functioning. An untreated hypothyroid patient will undoubtedly be depressed. Correcting thyroid function is essential to brain wellness.

Another pillar of Kellman's approach is the need to reinvigorate the patient's will to live and enjoy life. He frames this in terms of giving and receiving; one has to be freely able to receive and give in order to have the will to live life fully. Kellman asks the patient while attending to a "microbiome diet," supplementing specific probiotics to restore balance in the gut,

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Letter from the Publisher

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using thyroid hormone prescriptions, to work on dynamically interacting with others to "give" and "receive." A commitment to change in diet initially requires avoidance of gluten and dairy (except yogurt) with consumption of organic fish/beef/lamb/fowl, vegetables, some fruit, unprocessed oils, fermented foods (sauerkraut, kimchi), and nuts. He recommends an even more limited diet for those diagnosed with SIBO. Kellman uses supplemental herbs, betaine (or apple cider vinegar), enzymes, bitters and other nutraceuticals to repair the gut. He advises pre- and probiotics and also recommends very specific probiotic organisms to address depression or anxiety or obsessive-compulsive behavior. He carefully checks labs to assess and confirm thyroid functioning. Assuming compliance, Kellman sees mental health improvement appearing in weeks.

We have been quite aware that orthomolecular medicine has been an important tool for the well mind. Abrahm Hoffer, MD, PhD, advocated for dietary and nutritional supplement approaches rather than pharmaceuticals to treat mental health disorders, including psychoses. The diet Hellman advises is tough; cutting out carbohydrates is a tough sell for an anxious or depressed person. Supplement taking may not be as difficult – probiotics and digestive aids make good sense in our fast-food world. We are all knowledgeable about the benefit of thyroid treatment. Exercising our "will" (not "will power") by giving and receiving should be as much a part of our day-to-day routine as physical exercise.

The Whole Brain book is a good read for the patient who is skeptical about how diet and supplements will beat their mental health issue. For the doc, Kellman's prioritizing of the best supplementation of specific probiotics as well as herbal supplements is a very useful educational tool.

Cover Article: Alzheimer's Disease
by Michael Edson, MS, LAc

I am sure that you have had your own experiences working with patients diagnosed with Alzheimer's disease. As Michael Edson cites in his article, Alzheimer's dementia affects 10% of individuals who are aged 65 or older – 6.5 million Americans are thought to be suffering with AD. I recall when a patient brought in his middle-aged wife who was complaining about memory loss. She was lucid in her speech, well dressed and composed, intact neurologically, displaying no evidence of dementia. Yet, she was worried that she had the beginning stages of Alzheimer's, especially since her mother had died from AD some years earlier. I could not discern any signs that would suggest that her memory impairment was significantly different from what others experience in middle age – forgetting a person's name, not remembering a phone number, not recalling what she had come into a room for. It all seemed to be no different than what many of us experience as we get older. Yet, on follow-up visits she continued to complain of these recall problems and was very worried about worsening dementia to come.

A number of years passed without seeing her and then I was informed that she had been seen at the university's Alzheimer's screening clinic and was confirmed to be in the early stages of the disease. She now was very forgetful, could not drive around without getting lost, and was unable to carry on her normal day-to-day activities. Ultimately, she was placed in a home specializing in support for patients with Alzheimer's or other forms of dementia. Over the ensuing two years her disease advanced to the point where she no longer could recognize her husband and friends. She deteriorated so much that she no longer engaged in any purposeful activities and months later died. In retrospect I recognize that I missed the diagnosis of early stage Alzheimer's. On a scale of 0-10 she probably was 2-3 when I first saw her. If I had that knowledge and intervened would her disease progression have had a better outcome? It is hard to say. However, Edson would argue that, yes, intensive intervention in patients with early stage Alzheimer's will improve their prognosis.

Edson's specialty is optimizing eye care with natural approaches. He is the co-author of *Natural Eye Care: A Comprehensive Manual for Practitioners of Oriental Medicine and Natural Eye Care* (2019). He's also the author of *Natural Parkinson's Support: Your Guide to Preventing & Managing Parkinson's* (2020) as well as *Natural Brain Support: Ways to Help Prevent and Treat Dementia and Alzheimer's Naturally* (2021).

My experience with Alzheimer's disease patients has been that their conventional MDs offer Aricept® or something similar, which has very limited effectiveness. Over the summer a new drug, Aduhelm, has been approved by the FDA. However, it has limited data demonstrating effectiveness, and several major health care systems, including the Mayo Clinic, have refused to use the drug. Edson concurs with much of Kellman's thinking on improving gut permeability, avoiding allergens, restoring a balanced microbiome, removing toxins, supplementing antioxidants/herbals/nutraceuticals, exercising, reducing stress, practicing mindfulness, and using other integrative modalities.

As much as natural approaches may be helpful in preventing Alzheimer's or mitigating dementia's deterioration, it may be that routine vaccinations can be equally helpful in staving off the Alzheimer's process. The Tdap (Tetanus, diphtheria, and pertussis) vaccine was shown to reduce the risk for developing dementia by 42% in a study published by the *Journals of Gerontology* this May.[1] The authors admit that the reduction in dementia risk may be a general anti-inflammatory effect rather than specific viral protective effects of the vaccine. Similar reductions in Alzheimer's risk were seen in 2020 studies of patients receiving pneumonia and flu vaccine as reported in the 2020 Alzheimer's Association International Conference.[2] An Op-ed in the August 5 *WSJ* conjectured whether the COVID-19 vaccinations may also confer reduced risk of developing Alzheimer's.

Those not inclined to have vaccinations administered should consider diet and nutrient supplementation to prevent Alzheimer's and mitigate progressive dementia deterioration.

Jonathan Collin, MD

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1. Scherrer, JF. Lower risk for demential following adult tetanus, diphtheria, and pertussis (Tdap) Vaccination. *J. Gerontology: Series A*. 2021: 76, 8, 1436-43.
2. Flu, pneumonia vaccinations tied to lower risk of Alzheimer's dementia. *Alzheimer's Association International Conference*: 2020.

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briefed by Jule Klotter
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Acetaminophen. ADHD, and Autism

Over the last five years, several studies have reported an association between a woman's use of acetaminophen during pregnancy and the incidence of attention deficit hyperactivity disorder (ADHD) and related conditions in her offspring. Acetaminophen, aka paracetamol, is a commonly used pain reliever and fever reducer found in multiple over-the-counter products, most notably Tylenol. Rodent studies indicate that acetaminophen can affect neurodevelopment; the drug is toxic to cortical neurons and inhibits fetal testosterone production, "which would critically disrupt brain development," according to Yuelong Ji et al. Still, regulatory agencies have largely ignored the research, possibly because the studies have relied on women's self-reports instead of using more objective, precise data. Two recent studies have attempted to provide more concrete data.

A 2020 study, led by Brennan H. Baker, followed 345 children whose mothers were enrolled during the first prenatal visit or at delivery, at the Centre Hospitalier Université de Sherbrooke in Sherbrooke, Québec, Canada, between September 25, 2007, to September 10, 2009. Acetaminophen content in meconium samples, collected during delivery, was used to assess prenatal exposure. The presence of ADHD issues was determined around age six-and-a-half, using physician diagnosis/medical records and the Behavioral Assessment System for Children Parent Report Scale. Between ages nine to 11, the children underwent magnetic resonance imaging to assess resting-state brain connectivity.

The Canadian researchers found acetaminophen in 199 meconium samples (57.7%) and an ADHD diagnosis in 33 of the 345 children (9.5%): "Compared with no acetaminophen, detection of acetaminophen in meconium was associated with increased odds of ADHD (odds ratio [OR], 2.43; 95% CI, 1.41-4.21)." MRIs from children whose meconium contained acetaminophen showed less connectivity between frontoparietal and default mode network nodes and sensorimotor cortices, "which mediated an indirect effect on increased child hyperactivity (14%; 95% CI, 1%-26%)."

In another 2020 study, researchers measured acetaminophen and two of its metabolites (acetaminophen glucuronide and 3[N-acetyl-L-cystein-S-yl]-acetaminophen) in cord plasma to assess exposure. The 996 mother-infant pairs in this prospective study gave birth at Boston Medical Center and were part of the Boston Birth Cohort. In addition to multiple clinical and demographic variables, the researchers compared metabolite levels to physician diagnoses in electronic medical records: 257 of the 996 children had an ADHD diagnosis for ADHD only (25.8%); 66 had autism syndrome disorder (ASD) only (6.6%); 42 had both ADHD and ASD (4.2%); 304 had other mental, behavioral, and developmental disorders (30.5%); and 327 children (32.8%) had none of these diagnoses in their records.

All of the cord samples in this study had detectable acetaminophen, so the researchers did not have an unexposed group to act as a control. The researchers found a direct association between acetaminophen/metabolite levels and ADHD and ASD – but no association to other developmental orders. When comparing cord acetaminophen levels in the second and third tertiles to the first tertile, the odds ratio (OR) of having an ADHD diagnosis was 2.26; 95% CI, 1.40-3.69 (second tertile) and 2.86; 95% CI 1.77-4.67 (third tertile). Compared to the first tertile, the odds ratio of an ASD diagnosis was 2.14; 95% CI, 0.93-5.13 (second tertile) and 3.62; 95% CI, 1.63-8.60 (third tertile).

The authors list several limitations of the Boston study, including the one-time cord plasma measurement that cannot reflect acetaminophen exposure at various times during the pregnancy: "Whether there is a specific time window when the developing brain is most sensitive to acetaminophen exposure remains unclear." Also, the study design did not include possible confounders stemming from genetic or environmental factors.

The authors of the Boston study say their findings "warrant addition investigations." Baker and his Canadian colleagues are more precautionary; they say, "…this work suggests caution should be used in administering acetaminophen during pregnancy. Research into alternative pain management strategies for pregnant women could be beneficial."

Baker BH, et al. Association of Prenatal Acetaminophen Exposure Measured in Meconium with Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity. (abstract) *JAMA Pediatr.* September 28, 2020.

Ji Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure with Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. *JAMA Psychiatry.* 2020;77(2): 180-189.

Cannabis Use and Risks to Youth

As cannabis for medical and recreational use has become legal in more states, the perception that it is harmful has decreased. Recent studies, however, are showing that easy access to cannabis, specifically recreational cannabis with high THC levels, is dangerous – especially for young people.

On April 28, 2021, *The Denver Post* reported about the increase in psychotic symptoms among teens and young adults who consume too much high-potency cannabis. Colorado, along with Washington state, legalized recreational cannabis in 2012. Since that time, cannabis use has evolved from smoking and ingesting the botanical (e.g. in brownies) to "dabbing" oils and vapors that have high concentrations of the psychoactive component THC (tetrahydrocannabinol).

A 2020 review, led by Shweta J. Patel, looked at the relationship between cannabis use and schizophrenia, a condition with psychotic symptoms that include delusions and hallucinations. They searched for human studies published in peer-reviewed journals between 2015 and March 2020, assessed their quality, and ended up with 12 articles: five traditional reviews, two systematic reviews, two meta-analyses, and three observational studies. Ten of the 12 concluded that cannabis use, primarily due to THC content, may be a causative factor for schizophrenia – particularly "in genetically predisposed or at-risk populations." In people with schizophrenia, THC exacerbates symptoms. In addition to psychosis-like symptoms, THC impairs memory and the ability to concentrate. Adolescents with their still-developing brains are at greater risk: "Younger and more frequent users are at higher risk of developing cognitive decline. Adolescent cannabis use impacts cognition in the future." Unfortunately, cannabis use is increasing most quickly among high school students.

It is inaccurate, however, to say that the relationship between cannabis and schizophrenia is all bad. Patel et al report that the cannabis-derivative cannabidiol (CBD) has lessened psychotic symptoms in some people with schizophrenia; CBD reduces THC's effects. As they point out, "Cannabis has many strains with different ratios of components. The ratio of THC and CBD is the most important psychotomimetic [producing psychotic-like symptoms] property of any cannabis strain" – which leads back to the problems in Colorado.

"'Use and misuse has not only become increased at an alarming rate – we're seeing it in younger and younger populations,'" the legislative co-chair for the Colorado Association of School Nurses told journalist Alex Burness. And use is not just about smoking a joint or consuming brownies. Vaporized cannabis-derived concentrate, used in dabbing, can have a THC content as high as 90%, and its use has increased. Four years ago, 20% of young cannabis users reported dabbing. In the most recent Colorado survey, 52% of users reported dabbing in the previous 30 days. Parents in the article report psychotic behavior in their children.

The economic windfall from cannabis sales and the emphasis on cannabis' medicinal properties are making it difficult to address the issue of overuse by the young. Colorado state representative Yadira Caraveo, a pediatrician, unsuccessfully proposed legislation to limit THC content to 15%. Much of the cannabis sold in the state has THC content above 15%, and legislators are unwilling to curtail the state's cannabis industry. Marijuana legalization is clearly a two-edged sword; and the THC-CBD ratio lies at the heart of it.

Burness A. Colorado reckons with high-potency marijuana and its impact on children. *The Denver Post.* April 28, 2021.

Patel SJ, et al. The Association Between Cannabis Use and Schizophrenia: Causative or Curative? A Systematic Review. *Cureus.* July 21, 2020.

Shorts

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Gamma Sensory Flicker and Alzheimer's

Researchers at Georgia Institute of Technology and Emory University conducted a small feasibility study to test the safety and effect of a gamma flicker device on ten people with mild cognitive impairment due to Alzheimer's disease (AD). Exposure to flickering light and sound at gamma frequency (40 Hz) stimulates neural activity in the brain and reduces amyloid pathology, according to experiments with mouse models of Alzheimer's disease. Gamma flicker also affects microglia, the brain's primary immune cells.

In this randomized study, the participants used the flicker device, one hour a day at home, for either eight weeks or four weeks (delayed start protocol). The device consisted of light-emitting goggles and sound-emitting headphones, flickering at a repetition rate of 40 Hz. Participants were contacted each week by phone. Adherence to the protocol averaged above 88% over the eight weeks. EEG activity, measured before and after four weeks of no flicker, four weeks of device use, and eight weeks of device use, showed 40 Hz entrainment.

Participants also underwent fMRI to assess connectivity between Alzheimer's-affected areas of the brain. After eight weeks of daily flicker, the functional connectivity between the posterior cingulate cortex (PCC) and precuneus (PCu), which is weakened in AD, was stronger (p=0.016). The authors say that "…a prior small study showed PCC-PCu functional connection strength was positively correlated with cognitive function." The researchers also assessed immune data from participants' cerebrospinal fluid and found a downward trend in several cytokines and immune factors, including the cytokine TWEAK (tumor necrosis factor-related weak inducer of apoptosis; p=0.04), after eight weeks of treatment.

Adverse events were dizziness (n=3), tinnitus (n=1), and headache (n=1). The authors excluded people with a history of migraines, tinnitus, or seizures from the study because sensory stimuli could incite or worsen these conditions. A non-invasive, at-home treatment would be a boon for Alzheimer's patients, but larger and longer clinical studies are needed.

For more information about light's therapeutic effects on the brain, take a look at Dr. Peter Newsom's article "Photobiomodulation as a Treatment Modality for COVID-19 Sequelae" in this issue (page 62).

He Q, et al. A feasibility trial of gamma sensory flicker for patients with prodromal Alzheimer's disease. *Alzheimer's Dement.* May 13, 2021.

Low-Intensity Pulsed Ultrasound and Brain Injury

Researchers in China, Taiwan, and Japan have published several animal studies on the use of low-intensity pulsed ultrasound (LIPUS) to heal various types of brain injury. LIPUS reportedly increases the production of brain-derived neurotrophic factor (BDNF) in astrocytes and promotes nerve regeneration. It has also increased neurotrophins and vascular endothelial growth factor, lessening dementia in mouse models.

The use of LIPUS to address brain injuries and dementia is being investigated by a "leader in cardiovascular science," Hiroaki Shimokawa, MD, PhD. Dr. Shimokawa developed the first animal model of coronary artery spasm and has researched endothelium-derived relaxing factors for over four decades. As a possible treatment for myocardial infarction and heart failure, he developed a LIPUS machine, with the help of a Japanese-US company. The device stimulates NO release from endothelial cells and promotes angiogenesis.

Given that impaired vascular endothelial function is a risk factor for dementia and that LIPUS has shown benefits on the brain in other studies, Dr. Shimokawa and his team conducted a 2018 study that showed whole-brain LIPUS therapy (1.875 MHz, 6.0 kHz, 32 cycles) "markedly" improved cognitive dysfunctions, without serious side effects, in two different mouse models of dementia: vascular dementia from carotid artery stenosis and an Alzheimer's model. In both models, LIPUS improved cerebral blood flow, increased neurotrophins, and "significantly upregulated endothelium-related genes in RNA-sequencing and expression of endothelial nitric oxide synthase." In the vascular dementia mice, LIPUS "significantly increased CD31-positive endothelial cells and Olig2-positive oligodendrocyte precursor cells." In the Alzheimer's model, LIPUS reduced amyloid-β plaque and Iba-1-positive microglias that are signs of the illness.

Shimokawa and colleagues conducted another controlled mouse study that investigated the use of LIPUS to improve neurological function after ischemic stroke. The researchers applied whole-brain LIPUS therapy on days 1, 3, and 5 for 20 minutes after middle cerebral artery occlusion (created surgically with a suture); animals in the control group also underwent surgery but were not sutured. At day 28, infarct size was significantly less in LIPUS-treated mice compared to non-LIPUS controls (p=0.045). In addition, the treated mice showed "markedly improved neurological functions" during rotarod (running in a cylinder with increasing speed) and tightrope tests. Mice that started LIPUS therapy 28 days after the "stroke" showed no difference in function, compared to non-LIPUS mice; apparently, early treatment is key.

At this point, the use of low-intensity pulsed ultrasound therapy is still being investigated in the laboratory; I am not aware of any human clinical trials. Dr. Shimokawa and colleagues believe that LIPUS could be an effective, non-invasive therapy for stroke, dementia, as well as neurodegenerative diseases. May it be so.

Eguchi K, et al. Whole-brain low-intensity pulsed ultrasound therapy markedly improves cognitive dysfunctions in mouse models of dementia – Crucial roles of endothelial nitric oxide synthase. *Brain Stimulation.* 2018;11:959-973.

Ichijo S, et al. Low-intensity pulsed ultrasound therapy promotes recovery from stroke by enhancing angio-neurogenesis in mice in vivo. *Scientific Reports.* 2021;11:4958.

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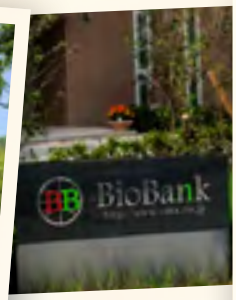

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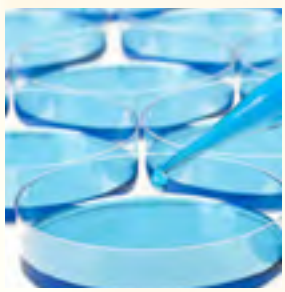

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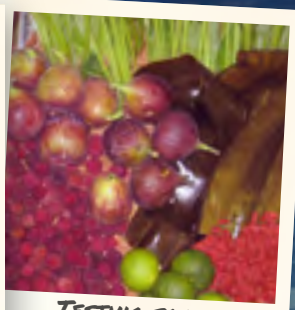

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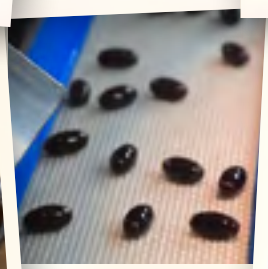

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Literature Review & Commentary

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

Riboflavin for Migraine Prophylaxis in Children

A retrospective study was conducted on 42 children (aged 6-18 years; mean, 13.8 years) with migraine (at least 4 headache days per month) who were treated with riboflavin at Dell Children's Medical Center in Austin, Texas. The dosage was 100 mg twice a day for body weight of 20-40 kg, and 200 mg twice a day for greater than 40 kg. Children were evaluated at two and four months, because the efficacy of riboflavin typically begins after one month and stabilizes after three months. The primary outcome measure was the proportion of patients with at least a 50% reduction in headache days from baseline to four months. Twenty-six children (61.9%) had at least a 50% reduction in headache days, five (11.9%) had moderate benefit (30-50% reduction), two (4.8%) had mild benefit (10-30% reduction), and nine (21.4%) had no benefit. In the group as a whole, the mean number of headache days per month decreased by 49% (from 21.9 to 11.1; $p < 0.001$), mean headache intensity decreased by 74% ($p < 0.001$), and mean duration of headaches decreased by 44% ($p < 0.001$). Some patients reported that acute medications that had previously been ineffective became effective.

Comment: Riboflavin has been shown to prevent migraines in adults, but the effect of riboflavin in children has been less clear. In the present study, riboflavin treatment was associated with marked reductions in the frequency, severity, and duration of migraines in children. These results conflict with the findings from double-blind trials in children. In one double-blind trial, 200 mg per day of riboflavin was nonsignificantly less effective than placebo for preventing migraines in children.[1] In a second trial, 50 mg per day of riboflavin was not more effective than placebo.[2] The children in the present study were older than those in the double-blind trials, and a substantially higher percentage of the children had reached the typical age of puberty. It is possible that riboflavin becomes effective for migraine prophylaxis only after the onset of puberty; that possibility warrants investigation. A double-blind trial from Iran found that riboflavin was effective for migraine prophylaxis in prepubescent children,[3] but readers of the *Townsend Letter* know that I have concerns about the reliability of studies from Iran.

Das R, Qubty W. Retrospective observational study on riboflavin prophylaxis in child and adolescent migraine. *Pediatr Neurol*. 2021;114:5-8.

Intravenous Magnesium for Acute Migraine

One hundred fifty-seven adults (median age, 36 years) presenting to an emergency department near Chicago with an acute migraine were randomly assigned to receive, in double-blind fashion, 2 g of magnesium sulfate, 10 mg of metoclopramide, or 10 mg of prochlorperazine intravenously in 50 ml of 5% dextrose over 20 minutes. The primary outcome measure was the change in pain from baseline at 30 minutes after the start of the infusion. There was a significant decrease in pain at 30 minutes in all groups, with no significant difference between treatments. There were no significant differences between groups with respect to median decrease in pain at 60 minutes, median length of hospital stay, need for rescue medication, or adverse effects.

Comment: Parenteral magnesium was mentioned as early as the 1930s and 1940s as an effective treatment for migraine. More recently, numerous clinical trials have examined the effect of intravenous magnesium in patients with acute migraine. Most, but not all, of the results have been positive.[4] Metoclopramide or prochlorperazine are effective treatments for acute migraine and are commonly used in emergency departments as an alternative to opioids. The results of the present study indicate that intravenous magnesium is as effective as metoclopramide or prochlorperazine in the treatment of acute migraine.

Kandil M, et al. MAGraine: Magnesium compared to conventional therapy for treatment of migraines. *Am J Emerg Med*. 2021;39:28-33.

Biotin and Multiple Sclerosis

Six hundred forty-two patients (aged 18-65 years) in 13 countries with primary or secondary progressive multiple

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Gaby's Literature Review

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sclerosis (MS) were randomly assigned to receive, in double-blind fashion, 100 mg of biotin three times a day or placebo for 15 months. Patients were permitted to use disease-modifying medications. The primary endpoint was the proportion of patients with improvement in the expanded disability status scale (EDSS) or the timed 25-foot walk after 12 months and confirmed after 15 months. The proportion of patients who achieved the primary endpoint was 12% in the biotin group and 9% in the placebo group (odds ratio = 1.35; 95% confidence interval, 0.81-2.26).

Comment: Biotin is a cofactor for acetyl-CoA carboxylase, a potentially rate-limiting enzyme in myelin synthesis. In an uncontrolled trial in 2015, of 23 patients with primary or secondary progressive MS, treatment with 100 to 300 mg per day of biotin for a mean of nine months resulted in various neurological improvements in 90% of cases.[5] In a double-blind study published the following year, 154 patients with progressive MS received 300 mg per day of biotin or placebo for 12 months. An improvement in disability was seen in 12.6% of patients receiving biotin, whereas no patient in the placebo group improved ($p = 0.005$).[6] Another double-blind study from 2017 found that 300 mg per day of biotin was of no benefit for patients with progressive MS.[7] The patients in that study were older, had longer disease duration, and were more disabled than patients in the studies where biotin was effective. In the present study, biotin was not significantly more effective than placebo, although the possibility of a modest benefit could not be ruled out. The negative results could not be explained by older age or longer disease duration of the subjects.

When taken together, the randomized trials suggest that there may be a small subset of patients with MS in whom biotin therapy is useful. Since biotin is safe and relatively inexpensive, a therapeutic trial would seem reasonable for selected patients. It should be noted that high-dose biotin can interfere with a wide range of laboratory tests, including thyroid function tests, 25-hydroxyvitamin D, testosterone, estradiol, progesterone, DHEA sulfate, and vitamin B12. It has been recommended that high-dose biotin be discontinued for 72 hours before blood is drawn for lab tests,

Cree BA, et al. Safety and efficacy of MD1003 (high-dose biotin) in patients with progressive multiple sclerosis (SPI2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2020;19:988-997.

Vitamin B6, Parkinson's Disease, and Levodopa/Carbidopa

Vitamin B6 levels were measured in 24 patients (mean age, 73 years) in Madrid, Spain, who had Parkinson's disease and were being treated with levodopa/carbidopa. All six patients treated with intraduodenal infusions of levodopa/carbidopa had low plasma levels of vitamin B6 and in four of those cases the vitamin B6 concentration was below the level of detection (< 9 nmol/L). Thirteen of 18 patients given the medications orally had low vitamin B6 levels. Two patients with undetectable vitamin B6 levels had electromyographic evidence of peripheral polyneuropathy.

Comment: This study found that vitamin B6 deficiency is very common in patients receiving levodopa/carbidopa, particularly if it is given by intraduodenal infusion. In rats, administration of a large dose of carbidopa decreased serum and tissue levels of vitamin B6,[8] which supports the possibility that the low levels of vitamin B6 found in the present study are drug induced. Vitamin B6 deficiency is a known cause of peripheral neuropathy, so the peripheral neuropathy found in two patients in this study may have been due to drug-induced vitamin B6 deficiency.

Physicians may be reluctant to supplement with vitamin B6 in patients who are taking levodopa because of reports that it can exacerbate the symptoms of Parkinson's disease. However, that adverse effect only occurs in people who are taking levodopa by itself (i.e., without carbidopa).[9] The apparent explanation for this adverse interaction is that vitamin B6 increases the peripheral metabolism of levodopa, thereby decreasing the amount available for uptake into the brain. In patients taking levodopa along with carbidopa (a peripheral decarboxylase inhibitor), vitamin B6 does not increase the peripheral metabolism of levodopa (because the peripheral metabolism is blocked by the peripheral decarboxylase inhibitor) and does not worsen symptoms of Parkinson's disease. To the contrary, concurrent administration of 25 mg of pyridoxine was reported to enhance the effect of levodopa in the presence of a peripheral decarboxylase inhibitor,[10] presumably by increasing the conversion of levodopa to dopamine in the brain.

The available evidence suggests that in patients with Parkinson's disease who are receiving levodopa/carbidopa, supplementation with a moderate dose of vitamin B6 (perhaps 25-50 mg/day) could correct low vitamin B6 status and potentially improve neurological symptoms.

Rojo-Sebastian A, et al. Vitamin B_6 deficiency in patients with Parkinson disease treated with levodopa/carbidopa. *Clin Neuropharmacol*. 2020;43:151-157.

Gluten-Free Diet for Cerebellar Ataxia

A retrospective review was conducted on all patients (n = 50) managed at the Sheffield Ataxia Centre over the past 25 years who had progressive cerebellar ataxia associated with antibodies against the enzyme glutamic acid decarboxylase (anti-GAD ataxia). The prevalence of anti-GAD antibodies was 2.5% among 2,000 patients with progressive ataxia of various causes. Mean age at onset was 55 and mean duration of illness was 8 years. Forty-five patients (90%) had a history of additional autoimmune diseases. Thirty-five patients (70%) had serological evidence of gluten sensitivity (presumably antigliadin antibodies, according to other research published by these investigators), and went on a gluten-free diet. Ten of those patients were diagnosed with celiac disease by duodenal biopsy. Eighteen patients (51%) had neurologic improvement, 13 (37%) stabilized, three started the diet too recently to draw conclusions, and one deteriorated.

Comment: Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme in the synthesis of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). A subset of patients with progressive cerebellar ataxia has anti-GAD

antibodies, which suggests that the ataxia in these patients is mediated by the immune system. In the present study, a gluten-free diet was beneficial for patients with progressive cerebellar ataxia associated with anti-GAD antibodies.

Hadjivassiliou M, et al. Clinical characteristics and management of 50 patients with anti-GAD ataxia: gluten-free diet has a major impact. *Cerebellum*. 2020 Oct 21 [Online ahead of print].

Does Aluminum Cause Brain Disease?

The aluminum content of the brain was measured in 20 people who had died without recognizable neurodegenerative diseases (control group). Using the same analytical method, the same research group had previously measured the aluminum content of brain tissue from people dying with neurodegenerative or neurodevelopmental diseases. The mean aluminum content of brain tissue was significantly higher in people with sporadic Alzheimer's disease, familial Alzheimer's disease, autism spectrum disorder, and multiple sclerosis than in controls.

Comment: Several lines of evidence suggest that aluminum exposure contributes to the pathogenesis of Alzheimer's disease. In some, but not all, studies aluminum concentrations in serum or brain tissue were significantly higher in patients with Alzheimer's disease than in healthy controls and patients with other types of senile dementia (alcoholic, vascular, or multi-infarct). In observational studies, higher dietary aluminum intake or higher aluminum concentrations in drinking water were associated with increased risk of developing Alzheimer's disease. In addition, injection of aluminum into the brain of rabbits produced neurofibrillary tangles in cerebral neurons (neurofibrillary tangles are a pathological change seen in the brain of people with Alzheimer's disease). In a randomized clinical trial, treatment with the aluminum-chelating drug, deferoxamine, significantly decreased the rate of functional deterioration in patients with Alzheimer's disease.[11]

The results of the present study support previous research related to aluminum and Alzheimer's disease, and raise the possibility that aluminum exposure contributes to autism and multiple sclerosis as well. Sources of aluminum exposure include beverage cans; aluminum cookware; municipal water supplies that add aluminum compounds to help remove particulate matter; food additives present in processed cheese, baking powder, and other foods; and aluminum-containing antacids and antiperspirants.

Exley C, Clarkson E. Aluminium in human brain tissue from donors without neurodegenerative disease: A comparison with Alzheimer's disease, multiple sclerosis and autism. *Sci Rep*. 2020;10:7770.

Vitamin D Improves Cognitive Function: Is This Study Legitimate?

One hundred eighty-three individuals in Tianjin, China, who were aged 65 years or older and had mild cognitive impairment were randomly assigned to receive, in double-

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blind fashion, 800 IU per day of vitamin D or placebo for 12 months. Compared with placebo, vitamin D significantly improved cognitive function as assessed by the Full Scale Intelligence Quotient ($p < 0.001$), and as determined by significant improvements in the scores on 5 of 11 subscales of the Wechsler Adult Intelligence Scale-Revised: information, digit span, vocabulary, block design, and picture arrangement.

Comment: It would be wonderful (and surprising) if a modest daily dose of vitamin D could prevent or reverse age-related cognitive decline. However, there are a number of problems with this study that cause me to question its validity.

1. Implausible recruitment of subjects: To find 183 subjects to enroll in the trial, the researchers performed a clinical, physical, and neuropsychological examination on 2,210 individuals between August 2017 and September 2017. It was not clear whether this was a one-month or two-month recruitment period. Granting the more lenient time period (2 months), the researchers would have had to conduct an average of 49.1 clinical, physical, and neuropsychological examinations per day, five days a week, for nine weeks. This study was conducted at a single center. It is implausible that a single center could evaluate so many patients in such a short period of time.
2. Implausible baseline data: In order to be included in the study, the subjects had to be 65 years of age or older. In Table 1 of the paper, the mean age in the vitamin D group was 67.22 ± 6.10 years, and in the placebo group was 66.59 ± 5.22 years. Assuming a normal (Gaussian) distribution of ages, with those means and standard deviations, approximately 16% of the participants would have had to be 61.4 years old or younger.

   In addition, the mean serum 1,25-dihydroxyvitamin D level at baseline was reported as 30.3 ng/ml. However, the reference range for 1,25-dihydroxyvitamin D is 18-78 pg/ml, so the baseline values reported in the study were more than 380 times higher than the upper limit of normal.
3. Implausible treatment effect: Considering how widely used vitamin D is, if it has a significant beneficial effect on age-related cognitive decline, it would seem that someone would have noticed that effect a long time ago. The only other randomized controlled trial that examined the effect of vitamin D on cognitive decline found no significant effect.[12] Baseline 25-hydroxyvitamin D levels were low both in that study and in the present study.

Yang T, et al. Vitamin D supplementation improves cognitive function through reducing oxidative stress regulated by telomere length in older adults with mild cognitive impairment: a 12-month randomized controlled trial. *J Alzheimers Dis*. 2020;78:1509-1518.

Curcumin and Coenzyme Q10 for Migraine Prophylaxis, or Iranian Research Fraud?

One hundred Iranian men and women (mean age, 32 years) with episodic migraine were randomly assigned to receive, in double-blind fashion, 80 mg per day of curcumin (as micellized nano-curcumin), 100 mg of coenzyme Q10 (CoQ10) three times per day, both treatments, or placebo for eight weeks. Combination treatment resulted in significant improvements in the frequency, severity, and duration of migraines, as compared with either supplement alone and with placebo ($p < 0.001$). The individual supplements were nonsignificantly more effective than placebo. The authors concluded that the combination of curcumin and CoQ10 may have an additive or synergistic effect in patients with episodic migraines.

Comment: I have noted in previous issues of the *Townsend Letter* that a large proportion of the research on natural medicine coming from Iran appears to be fraudulent. Several points in the present study raise concerns.

1. Issues with recruitment: Of 160 headache patients assessed for eligibility, 105 met the inclusion criteria and 100 were enrolled in the study. Patients were excluded if they used nonsteroidal anti-inflammatory drugs, which are among the most frequently used medications for migraines. Patients were also excluded if they had tension-type headaches (which, according to various estimates, affect 50-75% of the population) or if they had chronic migraines (which affect about 14% of all migraine sufferers). Another exclusion criterion was cigarette smoking (which is relatively common in migraine sufferers). Finally, patients were excluded if they used opioids. In the United States, opioids are given in more than 50% of emergency department visits for acute migraine, and these drugs are often prescribed for outpatient use. While data from Iran on migraines and opioids are not readily available, Iran is thought to have the highest per capita number of opiate addicts in the world, so one might reasonably expect that opioid use is common among migraine sufferers. With all of these exclusion criteria, it would seem highly improbable that 105 of 160 patients could have met the inclusion criteria for the study.
2. Issue regarding reporting of the data: Table 2 lists values at baseline and after eight weeks for migraine frequency (per month), migraine duration (hours), and headache diary results (HDR; which is calculated by multiplying frequency by duration). I checked the calculations for the 8 HDR values in Table 2, and not a single one matched the value on my calculator. At the very least, these errors represent sloppy data analysis and less-than-satisfactory peer review.
3. Implausible baseline characteristics: First, to be included in the study, patients had to have a body mass index (BMI) of 18.5-30.0 kg/m^2. In Table 1, patients in the placebo group had a mean BMI of 26.80 ± 5.16 kg/m^2. Assuming a normal (Gaussian) distribution of BMIs, with that mean and standard deviation, about 16% of the patients in the placebo group would have had a BMI of 31.96 kg/m^2 or higher (which would have made them ineligible to be in the study). Second, in Table 2, the mean baseline visual analogue score (VAS) for migraine severity in the CoQ10 group was 8.25 ± 1.89, which suggests that about 16% of the patients had a score of 10.14 or higher. However, the VAS scale was 0-10, so it is not possible to have a score greater than 10. The baseline VAS score is even more implausible, considering that it was determined while the patients were taking topiramate and amitriptyline, which

may have decreased VAS scores below their pre-study levels.

4. Issue regarding the treatment protocol: The trial was preceded by a four-week run-in period, in which all 100 patients were started on the combination of topiramate and amitriptyline. For that to have occurred would have required that none of the patients were already taking either of these drugs and (presumably) that none had previously taken these drugs but discontinued them because of side effects or lack of efficacy. Considering that topiramate and amitriptyline are commonly used for migraine prophylaxis, it is difficult to believe that none of the 100 patients were currently taking either of them. And, considering that the patients had been suffering from migraines for an average of nine years, it is difficult to believe that none of them had previously taken these drugs.
5. Issue regarding the medical evaluation. The paper stated that all patients were evaluated by a neurologist for eligibility. However, none of the study authors are neurologists. Considering that the neurologist agreed to prescribe topiramate and amitriptyline for all of the patients, one would think that the neurologist would have been listed as a study author.
6. Discrepancy regarding enrollment dates: The Iranian Registry of Clinical Trials document was registered on November 6, 2017. The document stated that recruitment was complete, but the published paper stated that the patients were recruited between April 2018 and November 2018.

Parohan M, et al. The synergistic effects of nano-curcumin and coenzyme Q10 supplementation in migraine prophylaxis: a randomized, placebo-controlled, double-blind trial. *Nutr Neurosci*. 2021;24:317-326.

Gaby's Literature Review

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

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Rebecca Harder, author of Gastra Girl, had been using and selling $5000 - $8000 wooden infrared saunas for 10 years in her clinics. After having turned her head every time she saw the Relax Sauna at a conference (because she had a wooden sauna she was satisfied with), she finally decided to try the relax Sauna. After 3 minutes, she could feel the difference, and writes about 20 pages on Far infrared Saunas and the Relax sauna in her latest edition of her book, giving a glowing report on the effectiveness of the Relax Sauna, and explaining why the Relax Sauna is the "Best" infrared Sauna.

Hippocrates: "Find me a way to Create Sweat or Fever, and I WILL Cure Disease!"

Hippocrates made this very powerful statement when he roamed the planet. All Cultures have used Saunas or heat in some way to increase the body temperature to stimulate the immune system to rid the body of toxins and other elements that interfered with the optimal functioning of our bodies. Dr. Bill Akpinar (who highly recommends the Relax Sauna) gives a great history of the power of sweating in his classic book, "No Sweat? Know Sweat!"

Humble Review of the Relax Sauna

In February 2017, a man posted a Review of the Relax Sauna on reddit.com. This man was very impressed with the many research articles indicating that Far Infrared Saunas were special and had the ability to revolutionize healthcare simply by using the special far infrared wave lengths to resonate with the water molecules in our bodies, thus stepping up the functioning of the immune system to detoxify the body, as well as to increase circulation with many implications on reducing pain and inflammation.

His conclusion after testing a $200 and a $500 Amazon sauna was to not waste your time on these saunas, as they were not able to increase core temperature more than ½ degree in 25 minutes. They also failed the heart rate variability tests that Research indicated Far infrared Saunas could do.

He then purchased a Relax Far Infrared Sauna and reporting glowing results: 3.2 degree increase in Core Temperature in 25 minutes, and the Heart Rate Variability Test Exceeded the results of the studies. He then wrote a glowing Relax Sauna Review. The link to this study is on: Relaxsaunas.com/superior

The Relax Sauna Technology

The Relax Sauna Company took 10 years to discover how to filter out the near and mid infrared wave lengths and generate ONLY wavelengths of 4-14 microns (4000 – 14,000 nanometers). By doing so, all of the wavelengths generated by the Relax Sauna emitters Resonate with the Water molecules in our body (8 micron Wavelength) and the organic cells in all warm-blooded creatures (9.4 microns).

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Fungi Show Early Promise for Preventing Progression of Neurodegenerative Diseases

A recently published paper has described how the inflammatory and oxidative responses to traumatic brain injury in mice were reduced using nutritional mushroom supplements.

The authors, working at the Universities of Messina and Catania in Italy, presented their latest research investigating the potential beneficial effects of *Coriolus versicolor* and *Hericium erinaceus* in preventing the development of brain pathologies similar to those found in Parkinson's disease (*Antioxidants* 2021;10:898. https://doi.org/10.3390/antiox10060898).

They induced brain injury in the midbrain region of mice through controlled cortical impact, then compared the effects of daily treatment with oral mushroom supplements. At all time points after surgery (Days 1, 7, 14 and 30), untreated brain-injured mice exhibited anxiety-related behaviors and altered cognitive function (spatial learning and memory), but mushroom-treated mice were no different to mice who had not received a brain injury. Post-mortem histological analysis showed that treated mice had less injury-induced brain tissue damage and had been protected against neuronal cell loss in the midbrain. Inflammation in the midbrain was also reduced, indicated by significantly reduced expression of the inflammatory proteins glial fibrillary acidic protein (GFAP) and ionized calcium-binding adapter molecule 1 (IBa-

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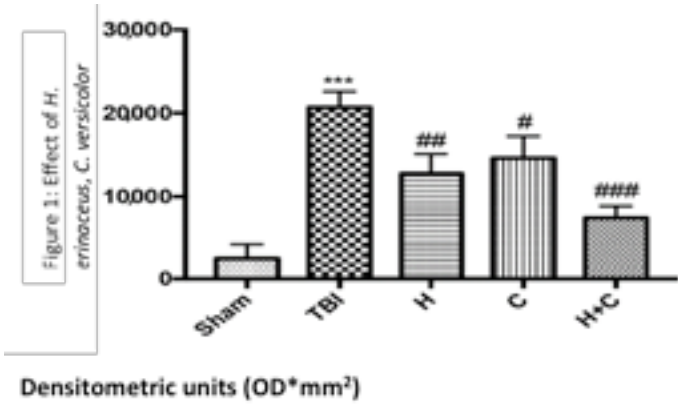
Figure 1: Effect of H. erinaceus, C. versicolor and a combination of both on α-synuclein expression in brain-injured mice (n=5 per group). Relative densitometry analysis of brain samples subjected to Western blot: ***p<0.001 vs Sham; ##p<0.01 vs TBI; #p<0.05 vs TBI; ###P<0.001 VS TBI
C, C. versicolor; H, H. erinaceus; Sham, sham-operated; TBI, traumatic brain injury



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1). Furthermore, the treated brain-injured mice exhibited a greater rise in antioxidant levels (Nrf2, HO-1, Hsp-70, γGCs and Trx) within the midbrain than untreated brain-injured mice, reflecting an enhanced protective antioxidant response; the same was found within the cortex, hippocampus, and cerebellum. As the protective response extended beyond the site of initial injury, this limited the spread of oxidative stress within the brain and the progression of neurodegenerative phenomena.

The authors showed that the inflammatory environment and oxidative imbalance following traumatic midbrain brain injury was coincident with accumulation of the protein α-synuclein and the death of dopaminergic neurons in this region (phenomena that are characteristic of Parkinson's disease). They were able to demonstrate that mushroom treatment significantly suppressed these processes (see Figure 1 for data on α-nuclein).

Although both mushroom species worked well individually in reducing and preventing the spread of inflammatory and oxidative changes within the injured brain, the combination was always more effective.

Professor Vittorio Calabrese, a senior author of the paper, said:

> The finding of this study indicates that *Hericium erinaceus* and *Coriolus versicolor* can act on specific molecular mechanisms underlying the pathophysiology of chronic traumatic brain injury and Parkinson's disease. Supplements containing these mushrooms represent a potential target of novel nutritional approaches relevant to the prevention of neurodegenerative processes associated with a brain injury.
>
> Our discovery opens up the possibility of developing new neuroprotective treatment strategies that have a beneficial impact on brain-injured patients and, moreover, are able to prevent or slow the development of neurodegenerative conditions.

Publication

D'Amico R, Trovato Salinaro A, Fusco R, Cordaro M, Impellizzeri D, Scuto M, Ontario ML, Lo Dico G, Cuzzocrea S, Di Paola R, Siracusa R, Calabrese V. *Hericium erinaceus* and *Coriolus versicolor* modulate molecular and biochemical changes after traumatic brain injury. *Antioxidants* 2021;10:898. https://doi.org/10.3390/antiox10060898

Contacts

The *Hericium erinaceus* and *Coriolus versicolor* biomass used in the study was supplied by Mycology Research Laboratories Ltd. (Luton, United Kingdom). http://www.mycologyresearch.com/; www.mrlusa.com

Luton-based Mycology Research Laboratories Ltd. was founded in the United Kingdom in 1997 with a focus on developing mushroom-based nutrition products. Over the past 20 years, Mycology Research Laboratories has had several collaborations with hospitals and universities based in the Netherlands, United Kingdom, Italy, and Portugal.

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New Breakthroughs in Treating Dementias with Light

by Len Saputo, MD, and Jerry Stine, NC

Introduction

A new era of medicine has emerged, using light to heal health conditions that have previously been essentially untreatable. The purpose of this article is to share the success we've had in treating patients with Alzheimer's disease, Parkinson's disease, stroke, traumatic brain injuries (TBI), and multiple sclerosis (MS) using a new form of photobiomodulation (PBM) device developed and refined over the past two decades.

We doubt that anyone would have been more surprised than we were at the improvements we often witnessed in just one single, fifteen-minute treatment with this novel combination of infrared, red, and blue light of many frequencies. The improvements we observed were not only unexpected but also nearly beyond belief.

The Context Within Medicine

To date, approximately 1,350 clinical trials have been conducted on light therapy for a broad range of disorders. A large number of studies on dementia, TBI, MS, and Parkinson's have shown excellent effectiveness.[2-8] Most of this research involved the use of infrared or near infrared light. Single-spectrum light devices are utilized by providers in a range of intensities and spectra (chiefly infrared, or red such as *cold lasers* or LED units used by providers such as chiropractors). Consumers have access to devices of lower power that employ near infrared light.

PBM devices are FDA approved for relief of muscle and joint pain, relief of minor neck and shoulder pain, relief of pain from arthritis, to encourage collagen growth, hair growth, and improvement of skin quality and appearance.

Safety

Treatment with light has been approved by the FDA for its safety. When used as directed, there are no significant safety issues. A review of many research articles showed some short-term discomfort from treatment, such as headaches, upset stomach, or short-term sleep issues; but the literature is remarkable free of any reports of damage or patient complaints. The major concern in maintaining safety is to make certain that the skin is not burned. The greater the intensity of light and the longer it is applied, the greater possibility for burning the skin. In people who have numbness, as is the case with neuropathies, it is especially important to start with low doses of infrared light alone.

How PBM Works

Extensive research has shown that photons have the effects listed below on the pathophysiology of the dysfunctional neurons of Alzheimer's disease and very likely in other dementias. This summary was published by a noted researcher in the field of photobiomodulation, Michael Hamblin, PhD, of Harvard Medical School, in the journal, *Photonics*[7]:

- Increases blood flow by releasing endothelial nitric oxide,
- Increases ATP production by injured cells,
- Neuroprotective,
- Decreases oxidative stress,
- Reduces inflammation,
- Attracts activated stem cells,
- Increases lymphatic drainage,
- Increases neurogenesis,
- Increases synaptogenesis,
- Stimulates gamma rhythms,
- Improves cell membrane potential.

It is easy to see how PBM's ability to stimulate all these essential cellular healing mechanisms can help to restore function to diseased or damaged cells. These are the mechanisms of action that have made effective treatment with light possible in the following neurological conditions[9]:

- Degenerative diseases: Alzheimer's disease, Parkinson's disease, and multiple sclerosis,
- Traumatic events: stroke and traumatic brain injuries,
- Psychiatric disorders: depression, anxiety, and PTSD.

In the case of Alzheimer's disease, it has been shown that when even low levels of infrared light are applied to a tissue culture of mice neurons with Alzheimer's disease, the classic pathological neurofibrillary tangles of the tau protein and beta-amyloid plaques begin to resolve within hours to days, as demonstrated in Figure 1.

Advanced PBM Device

All case histories listed below utilized a relatively new type of PBM system, the Firefly, produced by Bales Photonics. The Firefly PBM employs multispectral light frequencies (red, infrared, and blue) and features more power than previous devices.

Alzheimer's Disease

A colleague and I (Len Saputo, MD) were demonstrating the effects of PBM in a healing center in 2018. We were testing the

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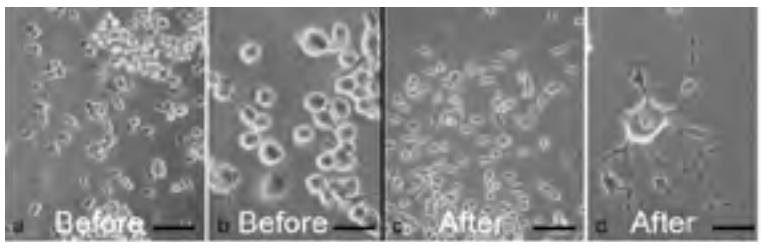
Figure 1: Neurite Elongation Experiment



In vitro post-oxidative stress. 670om, 3mW, 20 sec/day, 5 days[1]

These studies point to a viable basis to support a proposal for light energy to arrest the progression or even reverse a degenerative disease such as Alzheimer's disease by irradiating the neurons. The neurons of Alzheimer's disease patients undergo a similar loss of neurites before they progress to full apoptosis or cell death; thus subjecting these cells with *neuroblastimulation* could stimulate healing.

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first multispectral Firefly device my colleague had designed on a 91-year-old man who had advanced Alzheimer's disease. On our first evaluation, this gentleman presented with a shuffled gait, was hunched over, and could not answer most simple questions. The treatment took about 15 minutes.

This demonstration was observed by several people, including this man's wife. The results were mindboggling! Immediately afterward, the patient looked up and started telling us about his younger days when he was an electrical engineer. He then started walking with a normal gait and said he felt like dancing! It was as if we had somehow turned on a switch that allowed his brain to begin functioning again. We have followed the man over the past three years, during which he has been treating himself daily with a home light unit, and he has remained alert, coherent, and oriented.

Since that time, I have treated 25 patients with Alzheimer's disease using this device in my medical practice. About 80% have had an immediate response that was clear to the patient, to their companying family member, and to us. In general, these improvements continued with additional treatments of 10-15 minutes daily. None of the subsequent patients have had the complete response we observed with our first patient, but the improvements have made a significant difference in their quality of life.

Multiple Sclerosis

Another of our initial patients using the Firefly was a 20-year-old cheerleader who had been diagnosed with MS two years earlier. She was no longer able to cheerlead because her balance had been compromised. She was unable to walk, putting one foot in front of the other, without staggering and nearly falling. We used a protocol we designed for MS for fifteen minutes.

When we tested her balance immediately afterward, she was able to walk normally. In fact, she was able to stand for 30 seconds on one leg with her other leg raised behind her and both arms outstretched. She purchased a home unit and to our knowledge continues to do well.

Parkinson's Disease

D.S. is a 76-year-old female with an 18-year history of moderately severe Parkinson's disease. The first time I saw her on December 21, 2019, she was sitting in a chair in my waiting room. I invited her to follow me to my office and observed she could barely get up from the chair. As she began walking, she had trouble getting started but once she did, she could walk but had obvious difficulty maintaining her balance. I was relieved when she didn't fall. At that time, she was taking Stelara, carbidopa, amantidine, Requip, Wellbutrin, and thyroid hormone, and mentioned it was about time to take her medications. I asked her to hold off so we could see if the light treatment she was about to get would have an effect without the interference of her medications.

I treated her with our protocol for Parkinson's disease using our new technology for about 15 minutes. To the shock of her husband, my staff, and patients in the waiting room who had seen her struggle to get out of her chair and then struggle to walk, she bolted out of her chair and began walking with very noticeably greater coordination and balance. She also commented that the mental fog she was accustomed to had cleared, her tremor had also decreased, and she had more confidence walking.

She purchased a machine for home use and has been using it daily. She has sustained the improvements she experienced and has noted that she has been able to function with less medication.

Traumatic Brain Injury Testimonial

Ken Avery, former linebacker for New York Giants, Cincinnati Bengals, and Kansas City Chiefs: "I have been using the home light unit for over a year, integrating the therapy into my morning exercise routine, and using it again in the afternoon. The biggest improvement I have seen is in my sleep. I used to awake 10 or more times per night, required a CPAP machine, and had to take naps in the afternoon. After using the light device for a couple of months I only awake occasionally at night, no longer require the CPAP, and don't need to take an afternoon nap! My tremors have also improved significantly which allows me to operate a variety of power saws with confidence I won't cut myself. My driving has even improved as I don't have the shoulder pain I once did. Finally, I am confident the light device is slowing the progression of my diagnosis. I would recommend anyone with neurological disease to try this light device for improvements to their quality of life."

Stroke

R.M. is a 70-year-old female acupuncturist who had a right middle cerebral artery thrombosis 24 years prior to her first visit to my office on June 2, 2020. She presented with a left hemiparesis and a moderately severe expressive aphasia. She was unable to speak more than a few words without having to stop and struggled to complete most of her sentences. Frequently, she would become so frustrated that she would stop trying and would start over again. She was able to walk but limped because of the persisting hemiparesis on her left side.

She was treated on the right side of her head with light for 15 minutes using the Firefly device. Immediately after her first treatment her speech became considerably more fluent. Over the next two days we continued treatments, and she was able to complete some sentences. She continued with two-to-three treatments per month through May of 2021. Her speech has continued to improve and is now near normal. She also noted that her left-sided weakness and unstable gait have continued to improve.

What These Case Studies Have in Common

Over the past decade there have been many clinical trials that have shown that PBM can improve the health and functionality of patients with

continued on page 24 ➤

Multi-Spectrum Light for Dementia

In an initial pilot study involving nine patients and using the multi-spectrum, higher powered Firefly device, subjects received 10 treatments over the course of four weeks with a minimum of two treatments per week. PBM therapy was applied for 10 minutes over each patient's cranium.

The Mini-Cog exam (scores range from 0-5) was administered before the first treatment, one week after the tenth, final treatment (post-trial), and after a further one-month washout period. Nine subjects completed the pilot study.

The average Mini-Cog score improved by 7% from the pre-trial to the post-trial exams. The scores improved another 26% from the post-trial exam to the post washout period exam. This indicates that improvement continued even without treatment. The overall average Mini-Cog score improved by 35%.

Syed S, Bales M. info@balesphotonics.com

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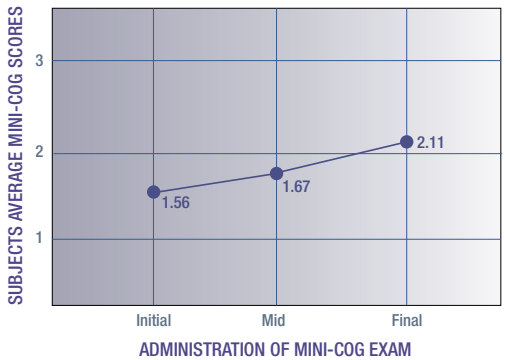

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Treating Dementias with Light

➤ *continued from page 22*

dementia. What we have discovered using our new technology is that it is possible to get faster and more impressive results. Yet, we must emphasize that our limited observations are anecdotal and need to be validated by formal scientific clinical trials.

Nonetheless, because the conditions we've treated have had such impressively positive outcomes and because there are essentially no other treatments for these often very incapacitating disorders, we believe patients should be offered PBM after fully informed consent for treatment because PBM offers the possibility of improving quality of life that is safe and affordable.

Multi-Spectrum, Higher Output PBM Devices

The impressive results in these case histories all occurred using the newest multi-spectrum, higher output device by Bales Photonics. This unit also has the capacity to modulate the light with a range of frequencies to increase effect. We have been utilizing infrared-only light devices as a major therapeutic modality for more than two decades before this newer unit became available. While we have been impressed with the results from the earlier devices, the results from the new unit were astounding. Why the increased power and multi-spectrum technology has such a powerful effect is not fully understood and calls for further investigation. There is one formal study on dementia using the Firefly by Bales Photonics. (See Sidebar.)

Physiology

In addition to biochemistry, the language of medicine is expanding to include biophysics. There is an ever-growing database of medical scientific literature documenting the effects of biophotons (photons with biological effects) in regulating how the biochemistry of the body influences physiology to promote healing. It is a language that provides a new and deeper level of understanding of how human physiology works to create healing.

*The effects of power, wavelengths, and frequencies***.** Photon energy and the depth of penetration are wavelength dependent. While shorter wavelengths, like blue light, have more energy than red or infrared light, they penetrate less deeply in human tissue. Different wavelengths of light have different depths of penetration into the underlying tissues. Blue light only penetrates 2-3 mm and delivers its heat into a very small area. Red light penetrates 2-3 cm, and infrared penetrates up to 23 cm. The greater the depth of exposure, the lower the density of heat that is delivered to the body. Therefore, blue light heats the skin much faster than red or infrared light. *It appears that different wavelengths energize different types of tissues. By running three light wavelengths at once, different tissue depths and tissue types are treated simultaneously.*

We have observed the return of function in patients treated with multi-spectrum light and theorized that the shorter wavelengths can affect deeper tissues though neural communication between nerve receptor endings in the surface of the skin and their connections to neurons deep in the body, and possibly even in the brain.

The research on basic cellular responses to photon energy in studies by Hamlin and others suggests increased cell membrane potentials and increased neuronal energy. The visible result of clinical intervention is evidence of improved nerve function in patient symptoms. Wavelength absorption is tissue dependent. For example, blue light can illuminate living teeth in the mouth, which will fluoresce in a different color, while red and infrared will not cause the same effect.

While photon intensity determines depth of penetration, water will block or attenuate some wavelengths of light. Because the body is composed of 70% water, this is an important consideration. The bones of the skull also attenuate the strength of the light, making it harder to reach brain tissue directly. A higher output device helps to compensate for this limitation.

Regarding frequencies and frequency modulation of light, our current hypothesis is that the human body has frequency dependent effects at the quantum level. When a patient experiences dysfunction, some frequencies can be attenuated or can be missing. Restoration of these frequencies may help restore function. More research is needed to test this hypothesis.

Adjunct Therapies and Clinical Integration

PBM as Additive to Other Therapies. Some practitioners have found the relief and benefit to their patients so impressive that PBM becomes the "cornerstone" therapy in their practices. For other practitioners, PBM offers an additive effect to the therapies they are currently using.

Physical Medicine. PBM strongly supports therapies that are physical in nature such as chiropractic, osteopathic, physical therapy, and body work practitioners. The ability of PBM to very rapidly reduce inflammation, mitigate pain, bring muscle relaxation, and promote tissue healing brings a high level of patient satisfaction.

Functional Medicine. The arena of functional medicine is bringing increasingly sophisticated nutritional and lifestyle therapies to neurological problems such as the work of Dale Bredesen, MD, on Alzheimer's and other dementias. These types of protocols would be well supported by PBM's beneficial effects on inflammation, oxidative stress, mitochondrial function, and tissue healing.

It Is Time for Light Therapy to Become Mainstream

At this time, there has been so much research showing good and consistently reliable results for a wide range of health conditions that a tipping point has been reached, which justifies bringing this light therapy forward into mainstream medicine. Light therapy is safe, affordable, and available. Photobiomodulation (PBM) is particularly important because it promises to provide treatment for a wide range of dementias that have previously been essentially untreatable.

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American Academy of Anti-Aging Medicine (A4M) Announces Acquisition of BodySite Digital Health

The American Academy of Anti-Aging Medicine (A4M) – the global leader for continuing medical education in longevity and whole-person medicine – has announced the acquisition of BodySite.com by its parent company Tarsus Medical Group. The acquisition marks the organization's continued movement into the ever-growing digital healthcare space.

BodySite is a world-leading digital care app and monitoring platform used by thousands of health and wellness practitioners to provide patient care. The platform combines the industry's most robust patient education content management system with remote patient monitoring through connected devices and compliance tracking to provide a complete solution for clinicians wanting to extend their care beyond the four walls of the clinic for better patient outcomes.

As an A4M offering, BodySite.com will expand its digital strategy to help providers optimize vitality for patients worldwide. The expanded platform will further allow healthcare providers of all backgrounds to better integrate remote patient monitoring, telemedicine, nutrition, and much more in between regular office visits, and thus provide more optimal patient care.

"A4M's mission has always been to redefine the standard of medicine by providing clinicians with the most cutting-edge education and resources available to deliver whole person care," said Doreen Brown, CEO of Tarsus Medical Group. "This new acquisition perfectly complements this mission. We are looking forward to further equipping our growing community of forward-thinking clinicians with such a valuable clinical tool."

"This acquisition marks a pivotal moment in our company's history that will allow us to provide even better tools and features for healthcare providers looking to make a greater impact on their patients' health as well as improve the interactions they have with their patients each day," said John Cummings, founder and CEO of BodySite Digital Health. "We very much look forward to working with Tarsus to integrate our existing offering into their medical ecosystem and expand our capabilities going forward to continue our mission to change for the better how doctors and their patients tackle health issues."

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About the American Academy of Anti-Aging Medicine & Metabolic Medical Institute:

Rooted in a forward-focused mission to redefine modern medicine, The American Academy of Anti-Aging Medicine (A4M) is the established global leader for continuing medical education in longevity medicine, metabolic resilience, and whole-person care. The Metabolic Medical Institute (MMI) serves as a branch of A4M that delivers graduate level education designed to produce the complete practitioner in all aspects of anti-aging medicine. MMI has adopted a variety of educational resources to deliver in-person, online, synchronous, and asynchronous mixed-methods learning experiences ranging from one-day workshops to month-long courses. Together, A4M/MMI is comprised of over 26,000 members and provides an advanced network of continuing medical education opportunities, including traditional CME events, intensive curriculum-based courses, university-level certification programs, in-depth workshops, and more.

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Sheldon Jordan, MD, FAAN, DABPN, DABCN, DABIPP

Abraham Morgentaler, MD

With the numerous challenges and changes that have occurred within the last two years, the healthcare field is entering a new chapter with new opportunities to build a more resilient medical system that centers on science-based, whole-person care. Themed **"The Next Chapter: Unmasking the Hidden Epidemic,"** this year's 29th Annual A4M World Congress will address many of the neglected crises within our medical system that have left patients, healthcare professionals, and our shared communities overall vulnerable. From the growing brain health crisis that permeates all aspects of health, underserved patient populations, environmental health, and more—this year's event will deliver forward-thinking insights to help clinicians confidently lead this new chapter in healthcare with the most valuable strategies, therapeutics, and resources available.

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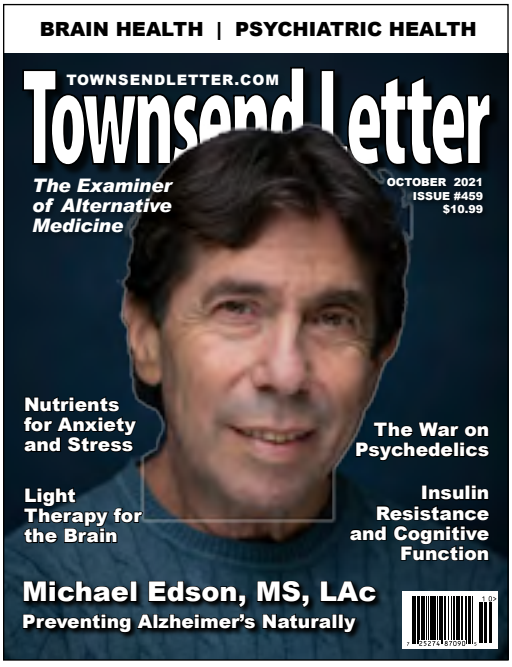

On the cover

Underlying Causes and Natural Treatments for Alzheimer's and Dementia

by Michael Edson, MS, LAc

The information and study references in this article are from my book *Natural Brain Support: Preventing and Treating Alzheimer's and Dementia and Other Related Diseases Naturally*, published in 2021, and dives into peer-reviewed, researched, natural approaches for both helping reduce the risk of onset of Alzheimer's disease and other types of dementia as well as ways to naturally help maintain and even improve healthy brain function. The article will be discussing many of the possible underlying causes or contributing factors that need to be considered as part of any treatment protocol, but also identifies essential nutrients and antioxidants found to be deficient in the brains of Alzheimer's and other patients suffering from dementia, as well as dietary and lifestyle considerations and critical foods to both eat and to avoid that contribute to either brain health or disease.

This article will focus on Alzheimer's disease (AD), being it is the most common form of dementia and the statistically fastest growing. As of 2019, an estimated 5.6 million Americans had Alzheimer's disease; and fourteen percent of those over seventy have some form of dementia.[1] It is the sixth leading cause of death, with one out of three seniors dying from AD or another form of dementia. One in 10 people, age 65 and older (10%), has Alzheimer's dementia. AD and dementia cost society 19-times more when compared with age-matched people without dementia, estimated to be around $290 billion in 2019.[2]

Yet there is much that can be done to reduce the risk of AD and even treat it naturally. The onset of dementia is connected to the health of the whole body. For example, studies have shown that illnesses such as anemia, diabetes mellitus,[3] and cardiovascular disease as well as people with fewer teeth (often related to poor health habits) all increase the risk of dementia.

The conventional treatment approach focuses primarily on preventing acetylcholine breakdown by inhibiting acetylcholinesterase and reducing excess glutamine, both critical neurotransmitters essential for healthy brain function. It is recognized that AD patients have excessive build-up of beta amyloid in the brain as well as intracellular neurofibrillary tangles (NFTs) consisting primarily of tau protein, which in normal levels provides essential functions for brain health, but excessive growth destroys healthy brain cells.

But what is the underlying cause of these build-ups and what can be done naturally to both prevent this from happening as well as reversing them naturally? This article will discuss the many variables that contribute to or may cause these excessive build-ups, as well as result in apoptosis (cell death), mitochondrial dysfunction, and excessive free radical and reactive oxygen species (ROS) exposure, as well as the effects of chronic stress and inflammation on the brain, environmental exposure to toxins, brain plasticity, neurogenesis, breakdown of the blood-brain barrier, effects of emotional imbalances, effects on emotions and socialization, and more.

A whole-body approach is needed to be more effective in preventing, managing, and treating AD. For example, the foods we eat and the health of our gastrointestinal system play a major role in our brain health because although the brain is only one to two percent of our body weight, it utilizes twenty percent of our body's energy, so any impairment in this system will effect the health of one's brain over time.

Underlying Causes or Contributing Factors

Lifestyle considerations play a critical role in our brain's health and its ability to function well. Some genetic factors can play a role in higher risk of AD onset, so does how we live our

lives though maintaining a healthy diet, exercising regularly, maintaining a positive outlook on life, and tending to one's emotional well-being, including managing excessive anger, resentment, and the effects of chronic stress.

Aging and Circulation. Aging is associated with a reduction of blood flow to the brain, which contributes to adverse changes in cognitive function.[4] A significant body of evidence points to diminished cerebral circulation as a precursor to both vascular and Alzheimer's dementia. With aging, one loses some brain plasticity, which results in a loss of cognitive function. That's why a young person, with an active, flexible brain, easily latches on to new ideas and simply thinks faster than an older person whose brain has lost plasticity and is more fixed in its patterns.[5] Loss of resilience can, for example, be counteracted by regular physical activity.[6] Brain plasticity refers to the process through which patterns of synaptic activity stimulate changes at synapses. Patterns of synaptic activity or inactivity regulate the amount of communication at the synapse. Synapses can change and the degree of change depends on how much they are used.[7]

Self-Help: Keep doing regular exercise and eat an alkaline diet, which includes avoiding most sugar and refined carbohydrates (see more on diet below). Nutrients that help improve circulation include bilberry, *Gingko biloba*, vinpocetine, lutein, zeaxanthin, saffron, nattokinase.

Free Radicals. Free radicals are considered a key factor in the aging of brain cells (as well as overall aging). In the central nervous system (CNS), cellular damage due to free radicals may be responsible for neurodegeneration.[8]

Free radicals exist throughout one's body and are a natural part of physiological activity. They contain an extra electron on their outer orbit, so seek to steal an electron from a healthy cell, resulting in cell damage and cell death. The body produces some of its own antioxidants that neutralize free radicals before they destroy healthy cells, but it also needs antioxidants from food. If antioxidants are missing in the diet, then higher levels of oxidative stress exist within the brain.[9]

Stress. Healthy stress reactions help one deal with emergency situations, allowing us to spring into action. Once over, the body returns to homeostasis. This is often referred to as the "flight and fight mode," resulting in allostatic overload.[10] In modern life, the daily challenges often leave one in a constant state of flight and fight mode, ultimately causing a variety of health issues, including having damaging effects on the brain.

Studies have shown that stress can cause functional and structural changes in the hippocampus,[11] including atrophy and neurogenesis disorders.[12] Chronic stress and, consequently, an increase in plasma cortisol, leads to a reduction in the number of dendritic branches,[13] and neurons,[14] structural changes in synaptic terminals,[15] and decreased neurogenesis in hippocampus tissue.[16]

When chronic stress is experienced, the body makes more cortisol than it has a chance to release, which can over time wear down the brain, disrupt synapse regulation,[17] kill brain cells,[18] and actually shrink the size of the brain.[19]

Chronic stress causes an increase in excitatory amino acids, particularly glutamate,[20] which play a key role in structural as well as functional changes in the brain. Glutamate is the major excitatory transmitter; excess glutamate causes damage and inflammation.[21] Chronic stress results in immune suppression,[22-23] as well as many other health conditions, including high blood pressure and digestive disorders.

Chronic stress can negatively affect different parts of the brain, including the amygdala which helps us manage our so-called "fight or flight" response, as well as regulate emotions such as fear and aggression. It ties our emotional meaning to our memories. reward processing, and decision-making.[24] The effects of acute and chronic stress on the amygdala can result in stress-induced loss of spines[25] and shrinkage of dendrites.[26]

Reduced blood flow to the brain contributes to loss of cognitive function.

Spines are neuronal protrusions and are essential for synaptic function and plasticity. They function to obtain information from other cells and carry that information to the cell body. Dendrites are critical for synapsis, the transmission of nerve impulses between neurons.

Two other hormones essential for memory and normal brain function are noradrenaline, which is both a hormone and neurotransmitter, creating emotional aspects of memories stored in the basolateral amygdala area,[24] and corticosteroids that facilitate the memory process. If high levels of chronic stress cause excessive release of corticosteroids, noradrenaline effectiveness is suppressed causing a negative effect on memory formation in the amygdala.[25] Glucocorticoids are hormones secreted by the adrenal glands *(*also called glucocorticosteroids, corticosteroids or steroids) and are present in almost all organs and tissues, including brain. They affect homeostasis, the body's ability to adapt to stress, and mediate hormonal activity through the stimulation or suppression of target gene transcription.[26] This increase in glucocorticoids is postulated to be a key step in the irreversible activation of the cascade leading to Alzheimer's disease, involving inactivation of the adaptive insulin receptor mechanism.[27]

Glucocorticoids can diffuse through the blood-brain barrier and exert long-term effects on processing and cognition.[28] Excess chronic stress causes the increased release of glucocorticoids, which in turn causes changes seen in AD patients in glutamate neurotransmission in the prefrontal cortex and the hippocampus, thereby influencing some aspects of cognitive processing.[29]

A decrease in the secretion of glucocorticosteroids causes preservation of spatial memory in adults and has also been shown to have neuroprotective effects. Lifelong corticosterone levels determine age-related decline in neurogenesis and memory.[30]

Chronic Inflammation. In AD, damaged neurons and neurites and highly insoluble amyloid beta peptide deposits and neurofibrillary tangles provide stimuli for inflammation, which then exacerbates more deposits and tangles resulting in a degenerative cycle. Exaggerated oxidative stress in AD[31-36]

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leads to overproduction of amyloid beta protein-associated free radical production and cell death,[37-38] causing yet more oxidative stress[39] – a dangerous cycle.

Inflammation in the brain causes shrinkage, decreased neurogenesis, and neurodegeneration in pathologically vulnerable regions of the brain, as in AD.[40-42] Chronic intestinal inflammation is associated with decreased neurogenesis in the subgranular region of the hippocampus, which is responsible for learning, memory, and mood control.[43]

Many studies have shown a connection between inflammation and Alzheimer's, dementia, and cognitive decline, including circulating inflammatory markers.[44-47] Inflammation in AD pathology is linked to activated inflammatory cells (microglia and astrocytes) and inflammatory proteins (e.g. cytokines), which surround amyloid plaque and neurofibrillary tangles.[48]

Chronic inflammation[49] and oxidative stress[50-51] are prominent issues related to contributing nerve damage and the onset of AD, and may play a role in other forms of dementia.[52]

Neuroinflammation has been tied to disease progression and severity in AD, where misfolded and aggregated proteins trigger an immune response resulting in neuronal death and progressive cognitive decline.[53-56]

Microglia are a collective type of neuroglia (glial cell) located throughout the brain and spinal cord. Microglia account for ten to fifteen percent of all cells found within the brain. In normal conditions microglia perform significant functions in maintaining healthy brain functions, including disposing of dead neurons, breaking down amyloid beta plaque (a causative factor in AD), and disposing of other brain debris. A hallmark of brain damage is an increased inflammatory response capable of activating microglial cells. Microglial activation has also been linked with brain diseases.[57]

Many studies have proposed that inflammatory dysfunctions are associated with psychiatric disorders and neurodegeneration in both animal models and human patients.[58-59]

Self-Help: A strong alkaline, anti-inflammatory diet is critical as part of an overall treatment strategy.

Neurogenesis and Brain Plasticity. The human brain is capable of forming new connections between neurons. When we take in new information, an electro-chemical signal is sent across the space between neurons (called the synaptic space). This ability of the brain to form new connections or neural pathways to communicate with each other is often referred to as brain plasticity. Brain plasticity is now understood to be the very foundation of learning and memory.

Neurogenesis is the brain's ability to product new brain cells. Researchers noted in the 90s that neurogenesis decreases with aging.[60] But the number and type of stem cells in the neurogenic region of the hippocampus apparently does not decrease with aging, rather they become inactive or dormant.[61] Neurogenesis occurs through stem cells that can differentiate into many other types of cells, including nerve cells.

Neurotrophic factors are molecules produced by the body (biomolecules), mostly peptides and proteins. The three known neurotrophins are brain-derived: neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and nerve growth factor (NGF). Loss of neurotrophins cause impaired brain plasticity, which results in loss of cognitive capacity expressed in conditions like Alzheimer's disease. These growth factors are responsible for the ability to utilize and put into action essential proteins in the brain and the promotion of health and re-growth of neurons.

Neurotrophic factors keep the brain nourished. When they are working well, our ability to think and process information stays healthy. When their action is impaired, learning and remembering becomes more difficult, and the brain actually withers and shrinks over time. Neurotrophic factors are positively affected by having a healthy diet, being emotionally balanced, managing stress, and exercising regularly. Negative influences include an unhealthy diet, sedentary lifestyle, tobacco and alcohol use, mood disorders, oxidative stress, emotional imbalances such as excessive fear or anger, chronic pain, deficiencies in certain essential vitamins, and some medications.

Brain derived neurotropic factor (BDNF) regulates hippocampal neurogenesis.[62-63] It is required for the development of the nervous system, proper cognitive function, and memory formation, and is known to be critical for the development of the brain, neuron survival,[64] neuronal regeneration, and synaptic plasticity.[65-68] When BDNF levels are irregular or declining, neurological diseases such as Alzheimer's, Parkinson's, Huntington's disease, and amyotrophic lateral sclerosis can develop.[69]

Nerve growth factors (NGF) have been shown to improve neural regeneration in neurodegenerative diseases, such as Alzheimer's,[70] Parkinson's,[71] and Huntington's disease.[72] Neurotrophins have also been found to be located in adult stem cells niches and therefore may promote tissue regeneration outside of the nervous system.

Microglia. Microglia are the resident macrophages (large cells) and primary immune cells of the brain, and they have a multitude of functions, including attacking and consuming bacteria (phagocytosis), removing waste, providing neuroprotection, and contributing to the growth of new neurons. They interact with a number of cell types, including astrocytes, neurons, and endothelial cells. In conditions such as AD, they fail to clear away waste, including beta-amyloid deposits.[73]

Glial Cells. Glial cells maintain homeostasis, form the myelin sheath that protects nerve cells, and provide support and protection for neurons. In addition, they support synaptic contacts and the signaling abilities of neurons. Glia are more numerous than nerve cells in the brain, outnumbering them by a ratio of perhaps 3 to 1.

Glial cells include astrocytes, which are essential in maintaining brain homeostasis and neuronal metabolism. They support brain plasticity and synaptogenesis, provide neurons with mechanical support, control neuronal cell development, release nutritional and energy substrates like glucose and lactate that regulate neurotransmission, vasomodulation, and repair, and protect neurons from oxidative damage, and control

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FREQUENCY SPECIFIC MICROCURRENT FOCUSING ON BRAIN HEALTH

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

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

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

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

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

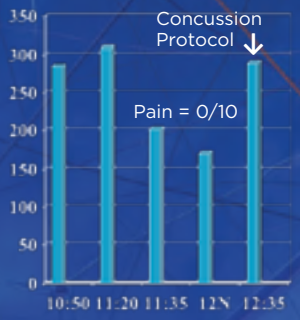
2013: only specific frequencies targeting the sympathetic and parasympathetic nervous systems changed autonomic function and heart rate variability dramatically and quickly.

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

ONLY ONE FREQUENCY SEQUENCE INCREASED SEROTONIN

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

Serotonin
normal=100-300 ng/ml



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

TREATING PTSD WITH FREQUENCIES ALONE

Case #1 Combat exposure score 28 (high)

4 years chronic (2006)
5 Treatments

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

Case #2 Combat exposure score 35 (Heavy Exposure)

3 years chronic (2007)
4 Treatments

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

Case #3 Combat exposure score 27 (high)

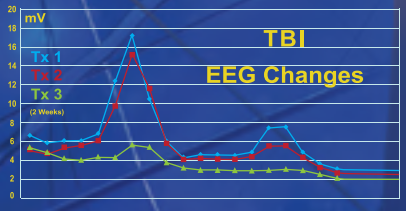
DOI 2005, Dx 2007
4 Treatments

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

THE PERFECT COMBINATION

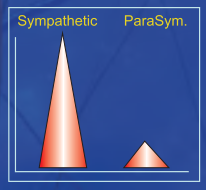
- **Specific frequencies change cell signaling to reduce inflammation**
- **Frequencies change neurotransmitters quickly and safely**
- **Specific frequencies change the brain**
- **Support those changes with nutrition and lifestyle**

Frequencies Change The Brain

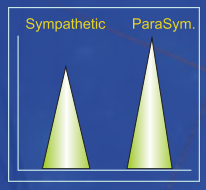


Change Autonomic Balance

Pre-Treatment

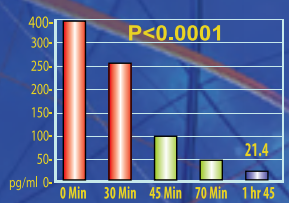


Post-Treatment

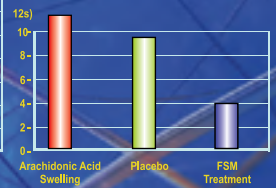


Reduce Inflammation

Reduce IL-1



Reduce LOX 62%



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the blood brain barrier and blood flow.[74-75] Oligodendroglia cells are found in the central nervous system. Their main function, along with Schwann cells (found in the peripheral nervous system), is the formation of myelin, the protective covering of nerve cells. Satellite cells are glial cells that cover the surface of nerve cell bodies in sensory, sympathetic, and parasympathetic ganglia, and help regulate the external chemical environment. Like astrocytes, they are interconnected by gap junctions and respond to ATP (as a neurotransmitter) by elevating intracellular concentration of calcium ions.

Epigenetics. The study of epigenetics has shown that gene expression could change throughout one's lifetime, determined by many environmental factors, including diet, emotional nurturing, social interactions, exercise, smoking, alcohol consumption, air pollution and other exposure to toxins, working habits (particularly those who have shift work), chronic stress, and even how one sleeps. In diseases such as cancer, congenital diseases, neurodegenerative diseases, and neuropsychiatric disorders,[76-79] various genes are switched into an opposite state, away from the normal/healthy state. Numerous historical studies show that patterns of famine, smoking, or breast feeding, affect future generations related to potential impact on development and health,[80] especially during critical developmental periods.[81]

Vascular Risk. Chronic high blood pressure in which blood vessels lose their elasticity cause the muscular layer of the vessels to enlarge, making it more difficult for the body to get the blood effectively to the brain. Hypertension may contribute to cognitive decline by causing cerebral small vessel pathology and increasing neurofibrillary tangles and amyloid plaques.[82] Elevated plasma homocysteine is an independent risk factor for cardiovascular disease, stroke, and dementia, including AD.[83]

Environmental Toxins. Children and young adults who live in areas with significant air pollution are much more likely to have the hallmarks of Alzheimer's. These include twisted protein fibers, deteriorating neurons, and amyloid beta plaque deposits.[84-86]

Exposure to toxins in the environment can have a substantial effect on brain functioning. For example, high levels of blood lead (Pb) are associated with reduced ability to recall and define words, identify line-drawn objects, and difficulty in a perceptual comparison test,[87] as well as fatigue, decreased processing speed, fine and gross motor deficits, and generally decreased cognitive functioning.[88] These declines are greater than changes observed with normal aging alone.[89]

Cumulative lead exposure is associated with an increased risk of amyotrophic lateral sclerosis[90-91] and Parkinson's disease.[92] In regions with high levels of air pollution even children exhibit the hallmarks of Alzheimer's: twisted protein fibers, deteriorating neurons, and amyloid plaque deposits.[93-95] The same is true of industrial-, combustion- and friction-derived nanoparticles.[96]

Cholinergic Circuit Dysfunction. Problems of the cholinergic circuit, such as with the neurotransmitter acetylcholine, are important factors. Cholinergic circuit dysfunction has been associated with neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's as well as psychiatric disorders such as schizophrenia.[97]

Blood Sugar Imbalances. A strong school of thought is that insulin resistance[98] with chronic blood sugar elevations are involved in depression and neurodegenerative disorders such as Alzheimer's disease.[99-101] Insulin regulates glucose (sugar) and directs the body to store energy. In the brain, insulin not only breaks down glucose but also regulates the clearance of b-amyloid protein and tau phosphorylation (essential for avoiding AD). Insulin supports healthy blood flow and the removal of fats from the brain, inhibits apoptosis (cell death), manages the response to inflammation, supports the ability for the formation of new synapsis, and supports new memory formation. It can also facilitate neurotransmitter receptor trafficking.[102] Therefore, any change in insulin balance can have serious consequences. There is a great similarity between AD and type 2 diabetes as both ultimately result in one's body becoming resistant to insulin, thereby reducing its effectiveness. In both conditions, inflammation with increased levels of oxidative stress occurs. The b-amyloid levels increase in both the brain and pancreas along with hyperphosphorylated tau protein and cognitive decline. Fifty percent of Americans between the ages of forty-five to sixty-four and seventy-six percent of those over sixty-five have an insulin imbalance, which becomes a critical health issue for Americans.

High Cholesterol and Homocysteine Levels. One study concluded that high total cholesterol levels at midlife have been associated with a nearly threefold increase in the likelihood of developing AD, even after controlling for ApoE genotype.[103]

High homocysteine levels double the risk of Alzheimer's.[104] Elevated plasma homocysteine is an independent risk factor for cardiovascular disease, stroke, and dementia, including AD.[105-106]

Mitochondria. Mitochondria are the energy batteries of our cells, producing ATP, which powers metabolic processes. Mitochondrial dysfunction appears to be a critical factor in the pathogenesis of AD.[107-108] This results in reduced membrane potential, increases permeability, and produces excess free radicals, which damage proteins, lipids, and nucleic acids.

Nutrients that support mitochondrial function (and against mitochondrial dysfunction) include vitamins B1, B2, B6, C, D, and E, l-carnosine, l-taurine, CoQ10, benfotiamine, alpha-R-lipoic acid, PQQ (pyrroloquinoline quinone), luteolin [from orange extract fruit), l-carnitine, trans-resveratrol, curcumin, magnesium, and schisandra.

Blood Brain Barrier Compromise (BBB). The BBB is critical for preventing particles and pathogens for reaching the brain, allowing only essential nutrients to pass through. Astrocyte destruction is associated with BBB (blood-brain-barrier) disruption.[109] Astrocytes induce and maintain the BBB, and in particular form the glia limitans.[110-111]

Immune reactions to gluten (see Celiac Disease below) can break down the blood-brain barrier, increasing autoimmune reaction risk in the brain and nervous system.[112]

Nutrients that support the BBB include resveratrol and baicalein.

Glymphatic System. The glymphatic system is a waste clearance pathway for the central nervous system and may play a significant role in clearing waste build-up in the brain. It is most active during sleep and may have implications in headache and in neurodegenerative diseases associated with pathologic protein aggregation, including Parkinson's disease and Alzheimer's. disease. The glymphatic system functions much like the lymphatic system but is managed by the glial cells within the brain. Glial cells are non-neuronal brain cells with several regulatory and protective roles, including destruction of pathogens and removal of dead nerve cells.

The Gut-Brain Axis. Through two-way communication with the brain via the nervous system, endocrine system, and immune system, the gut and central nervous system form a gut-brain axis. They communicate with each other constantly, in both sickness and health.[113] Researchers have concluded mechanisms that degenerate the neurons in the brain also degenerate neurons in the enteric nervous system.[114] The enteric nervous system (ENS) is a large division of the peripheral nervous system (PNS) that can control gastrointestinal behavior independently of central nervous system (CNS) input.

Changes in gut microbiota affect the nervous system, and dysfunction of the delicate interconnections between the two are closely associated with neurodegenerative conditions such as Parkinson's and Alzheimer's diseases.[115] In this way intestinal microbiota are directly linked to various forms of dementia because of the action of metabolic disease and chronic low-grade inflammation.[116]

Candidiasis and leaky gut syndrome are two common forms of flora imbalances in the gut. Brain infection was found in half of patients with systemic candidiasis.[117] Leaky gut is often associated with fungal infections. Fungal proteins and diffuse mycoses in the blood of AD patients suggest that chronic fungal infection associates with high risk of AD.[118]

Celiac Disease (CD). CD is an immune-mediated affected by the intake of gluten (a protein present in wheat, rye, or barley) that occurs in about one percent of the population.[119-120] **Non-celiac gluten sensitivity** (NCGS) also remains undertreated and under-recognized as a contributing factor to psychiatric and neurologic manifestations. NCGS is estimated to occur six times greater in the general population than CD.[121]

Data suggests that up to twenty-two percent of patients with CD develop neurologic or psychiatric dysfunction,[122] and as many as fifty-seven percent of people with neurological dysfunction of unknown origin test positive for anti-gliadin antibodies. A 2006 study identified a number of patients who had cognitive impairment due to CD[123-124] or dementia.[125]

Non-celiac gluten sensitivity can trigger neuroinflammation, gut-brain axis dysfunction, leaky gut, and vulnerability for dementia.[126]

Essential nutrients for celiac patients include vitamins B6, B12 (cobalamin), and folate, as well as iron, calcium, selenium, and vitamins D and K.[127-128]

Drug Contraindications. There are many drugs that may be contraindicated for AD; discuss with your doctor. For example, anticholinergic drugs are those that block the neurotransmitter acetylcholine in the central and the peripheral nervous system.[129] They are typically used to treat a variety of conditions such as urinary incontinence, overactive bladder, chronic obstructive pulmonary disorder (COPD), and certain types of poisoning. Although brain dysfunction systems can often disappear after discontinued use of these drugs, sometimes the damage is more permanent and can look like Alzheimer's disease[130] and/or they may be associated with increased dementia risk. A well-known risk with anticholinergic medications is acute impairment in specific aspects of cognition (e.g., working memory, attention, psychomotor speed) which has been demonstrated in single dose experimental studies[131] and cohort studies.[132] In addition, anticholinergics may be associated with global cognitive impairment.[133]

Changes in gut microbiota affect the nervous system.

Natural Approaches

Lifestyle considerations play an essential role in brain and overall health. Risks include long-term consumption of high-fat, high-sucrose, refined-grains diet, poor nutrition and/or nutrient absorption, sedentary lifestyle, chronic insomnia, social isolation, chronic stress, cognitive inactivity, and epigenetic (environmental) factors.

More specifically, research points to genetic inheritance, cardiovascular and cerebrovascular problems, excessive alcohol consumption, traumatic brain injury, chronic inflammation, compromised blood-brain barrier, biochemical imbalances, oxidative stress, and having one or two copies of the APOEε4 genetic variant.

Exercise. Normal brain aging involves potentially reversible loss of resilience, which, for example, can often be counteracted by regular physical activity,[134] as well as regular forms of meditation, stress management, a healthy diet, and targeted supplementation, particularly related to deficiencies in certain nutrients. Sedentary behavior increases the risk of Alzheimer's as much as genetic factors because inactivity may negate the protective effects of healthy genes.[135] Moreover, and even more encouraging, they found that people who didn't get in shape until middle age or later still enjoyed the benefits of markedly lowered risk of dementia.[136]

Do not smoke. Nicotine can kill brain cells, stop new neurons forming in the hippocampus, and significantly impact the ability to promote new neurons.[137] Smoking may affect plasticity and refinement of cortical connections,[138] and may have functional implications for maturation and function of the prefrontal network.[139]

Learning. The process of learning new knowledge, skills, and information also stimulates hippocampal neurogenesis.[140] Learning tasks that are related to the hippocampus are linked to new cell generation there, while learning tasks that do not

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require the hippocampus do not alter the number of new cells.[141] Learning, spaced over time, induces more enduring memory, which is linked to the number of new cells in the hippocampus.[142]

Healthy Diet. Scientists agree that nutritional factors have a role in protecting and enhancing neurogenesis.[143-144] Diets that include lots of sugars and high fats reduce neurotrophic factors in the hippocampus, nerve plasticity and learning capacity.[145]

Social Support. Mood may influence social behavior, and social support is one of the most studied psychosocial factors in relation to health and disease. Lack of support can possibly result in mimicking symptoms of dementia.

Sleep. Not getting enough sleep at night and chronic insomnia cause many cognitive and related problems.

Top Brain Nutrients

These top four nutrients or foods are the most important for supporting neurogenesis and/or BDNF. They are discussed in detail in the diet and nutrition chapters.

- **Blueberries.** The polyphenols contained in blueberries support neurogenesis,[146-147] and protect cognitive capacity.[148-149]
- **Curcumin** induces neurogenesis,[150-151] protects against fat oxidation, and reduces neuron deterioration due to free radicals in neurodegenerative conditions.[152-153]
- **Goji Berries** (*Lycium barbarum*). Goji berry supports neurogenesis,[154] and protects against chemical-caused neurogenesis suppression.[155] Goji contains high amounts of antioxidants, and other vitamins and flavonoids.
- **Omega-3 Fatty Acids.** Not only do omega-3s induce neurogenesis via synapse support and neurite growth,[156-158] but they also reduce inflammation, are neuroprotective,[159] and enhance BDNF synthesis. They are essential for learning and memory.[160-161]

Other important nutrients and foods to support brain health and neurogenesis include acetyl-l-carnitine, apigenin, ashwagandha, other berries, choline, cruciferous vegetables, garlic, ginkgo, ginseng, grapeseed extract, green tea, glutathione, green, leafy vegetables, gut microbia, hesperidin, huperzine A, iron, lecithin, lotus root extract, lutein, magnesium, magnolol, melatonin, milk thistle extract, mulberry, mushrooms (lion's mane, shiitake, reishi), olive leaf extract, PQQ (Pyrroloquinoline quinone), quercetin, red sage (salvia), resveratrol, taurine, vinpocetine, zeaxanthin and vitamins A, B6, B12, E, and D.

Most Important Brain Foods/Herbs

Top brain foods include ashwagandha, avocado, blueberries (and other dark berries) dark chocolate, eggs, fish, fruits and vegetables, ginseng, goji berry, green and black teas, nuts, mulberry, mushrooms (reiki, shitake, and lion's mane for example), olive oil, pomegranate juice, prunes, pumpkin seeds, yogurt (organic plain), and walnuts. These foods along with others contain high amounts of flavonoids that have many potent benefits to the brain, including reducing beta amyloid and fibril formation.[162-166]

The body produces some of its own antioxidants that neutralize free radicals before they destroy healthy cells, but it also needs antioxidants from food. If antioxidants are missing in the diet, then higher levels of oxidative stress exist within the brain.[167]

Diets that are rich in omega-3 fatty acids and antioxidants, epidemiological studies indicate that diets with high contents of trans and saturated fats adversely affect cognition.[168]

Eat more raw or slightly steamed vegetables and fruits to supply digestive enzymes. The typical Western diet does not provide enough antioxidants to support proper digestion, enzyme production, or to support normal metabolic activity. The nutrient composition of processed foods in the Western diet can also negatively affect the brain and contribute to the development of degenerative diseases.[169-170]

Juicing is an excellent way to get essential antioxidants, enzymes, and other nutrients into one's body. Whenever possible, juice with organic products.

Exercise

Exercise daily which can include fast walking, swimming, tennis, or other sports, work-outs at the gym, yoga, etc. Not only does exercise strengthen the physical body but improves neurogenesis (the growth of new nerve cells).[171] Participants of the study did at least 150 minutes per week of walking, running, swimming or other exercise. They experienced lowered levels of key biological markers of Alzheimer's disease in their cerebrospinal fluid, including tau (a protein that builds up in the brains of people with Alzheimer's).[172] Another study showed that people with a history of exercise that have the ApoE4 gene (increases the risk of AD onset 10-30 percent) did not develop dementia and had less *b*-amyloid in their brains.[173]

Foods to Avoid

A diet high in "junk food" and saturated fats elevates the neurological burden that is associated with brain injury, as evidenced by a worse performance in learning tasks and a reduction of BDNF-mediated synaptic plasticity.[174-175] This type of diet increases the vulnerability of cells to damage[176] by causing free-radical formation that surpasses cellular buffering capacity. The nutrient composition of processed foods in the Western diet can negatively affect the brain and contribute to the development of degenerative diseases.[177]

In a similar study with over five-thousand people, it was found that a diet high in red meat, processed meat, baked beans and fried food was associated with inflammation and a faster decline in reasoning over ten years.[178]

Diets high in sugar (including refined carbohydrates) can be highly detrimental to brain health. High sugar levels (as in uncontrolled diabetes) cause oxidative stress, which produces high amounts of free radicals (damaging healthy cells).[179] Research strongly supports the fact that people without diabetes but with above normal blood sugar levels have an increased risk of developing dementia.[180]

Avoid artificial sweeteners. Artificially sweeteners such as used in diet soft drinks are associated with an increased risk of

ischemic stroke, and all types of dementia including AD.[181,182] Some of the adverse effects on the central nervous system caused by the intake of aspartame are headaches, mood changes, insomnia, and seizures.[183]

Avoid canned foods as aluminum can leach out and has been implicated as a causative factor of AD.

Nutrients Found to Be Deficient in the Brains of AD Patients

Deficiency or low levels of specific vitamins such as vitamin D3 and B vitamins can result in cognitive difficulty, mood swing, and depression. These deficiencies can mimic symptoms of dementia and AD. Specific nutrient deficiencies such as zinc, vitamins B1, B2, B6, B12, D3, can result in cognitive difficulty, mood swings, and depression; and magnesium deficiencies can contribute to brain dysfunction and reduced learning, memory, and cognitive function. Magnesium helps suppress amyloid beta build-up in the brain. Zinc deficiency may induce learning and memory impairment. B12 deficiency has been linked to mental decline (which can often be mistaken for dementia). Deficiency in melatonin, produced by the pineal gland and essential for a good night's sleep, may be directly related to age-related cognitive impairment.[184-186] Note that exposure to blue light (computers and mobile devices) inhibits the production of melatonin.[187]

DHA (Docosahexaenoic acid) is found in higher concentrations in brain synapses than any other tissue in the body and found in highest concentrations in the hippocampus of the brain. DHA concentrates in the structures involved in forming new memories, such as synaptic membranes and tiny outgrowths called neurites.[188-189] Those at risk for AD and those with cognitive impairments often have a DHA deficiency.[190-191] AD patients have significantly lower levels of DHA in the neurons of their hippocampus.[192] Changes in DHA levels in cerebral spinal fluid (CSF) were inversely correlated with CSF levels of total and phosphorylated tau.[193]

Glutathione is especially important as it is the antioxidant in the greatest quantity in the brain and found to be deficient in the brains of AD and Parkinson's patients.[194] Glutathione is referred to as the "anti-agent" antioxidant due to its effectiveness in neutralizing the full spectrum of free radicals.

Several studies have documented the positive impact of mindfulness-based programs on symptoms of anxiety and depression[195-196] and improvements in sleep patterns,[197-198] and attention.[199]

Some Top Essential Oils

Use of essential oils has many benefits, including reducing anxiety, depression, improving mood and sleep, stimulating the mind and improving cognitive function, reducing stress, improving digestion and loss of appetite, and much more.

There is some evidence that aromatherapy using various essential oils may have some potential for improving cognitive function, especially in patients with AD.[200-203] Used with massage, they may help to calm agitated people with dementia.[204]

The book goes into greater depth into different essential oils and best ways to apply them, but here are a few great ones.

One study looked at the effects of massage with a cream containing lavender, sweet marjoram, vetiver, and patchouli on dementia patients in a residential care facility. They saw a decrease in "dementia-related behaviors.[205]

Lemon balm and lavender are the most used aromatherapeutic treatments for behavioral and psychological symptoms in dementia.[206-208]

Bergamot can be used to relieve anxiety,[209] agitation, mild depression, stress, and relieve insomnia (in a study, combined with lavender and ylang ylang).[210]

Frankincense helps relieve chronic stress and anxiety, reducing pain and inflammation, boosting immunity.[211]

Saffron is an antibacterial, blood purifying, antioxidant, decongestant, and memory enhancer.[212]

Other Modalities

Other modalities shown to be helpful in managing Alzheimer's and dementia include Ayurvedic and Chinese medicine, craniosacral treatments, yoga, qigong, tai chi, and meditation practice.

There are many studies regarding Chinese medicine and herbs for brain issues, including post-traumatic stress disorder, dementia and AD discussed in the book, but here are a few. In a randomized, controlled, parallel-group study of over twelve weeks with a twelve-week follow-up, it was found that acupuncture treatment improved cognitive function more effectively than Donepezil.[213]

A 2019 review of acupuncture and acupressure techniques for behavioral and psychological symptoms of dementia found that there were statistically significant improvements in activities of daily living (75% improvement), agitation (100%), anxiety (67%), depression (100%), mood (100%), neuropsychological disturbances (67%), and sleep disturbances (100%).[214]

Regarding Parkinson's disease, some Chinese herbal medicines are useful as an adjunct to help improve both motor and non-motor symptoms, permit lower doses of dopaminergic drugs, and reduce dyskinesia.[215-216]

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References and article are available online at www.townsendletter.com.

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Treating Stress and Anxiety with Functional Medicine

by James Greenblatt, MD

Unfortunately, the state of our collective mental health has been deteriorating. While normal, external stressors are still taking a toll, when combined with a global pandemic, political, and recent social upheavals, the last year has taken a profound toll on the mental health of the world's population. In particular, stress levels are hitting the younger generation the hardest with one-third stating their mental health is worse than last year and seven out of ten reporting concerning symptoms linked to depression.[1]

When excessive, stress often becomes a core contributing factor to anxiety. External factors that cause stress can upregulate pathways in the brain that contribute to vigilance, excessive worry, and fear. If the emotional reaction to stress persists even after external stressful circumstances have passed, an anxiety disorder can result.[2] Helping to improve stress tolerance and slowing overactive worry and fear circuits in the brain are core components of a functional treatment approach to anxiety disorders.

In my experience, several treatments for anxiety and stress stand out, including vitamin B3, magnesium, and ashwagandha. These treatments can help reduce and resolve anxiety. While other factors may need to be considered, these three supplements combined can often help individuals to reduce their experience of stress and anxiety on a daily basis.

Vitamin B3

Vitamin B3 has a long history of use for mental health conditions. Originally explored as a treatment for schizophrenia in the 1950s, several double-blind trials found benefits for high doses of the vitamin.[3] Recent reports of mental health benefits with vitamin B3 strongly suggest a need for further research on its relationship to schizophrenia, bipolar, and other mental health conditions.[4-6]

In order to understand the effects of niacin on schizophrenia, researchers began exploring the effects of large doses on animals. Initial evidence of sedative or tranquilizing effects of niacin began to emerge.[7] After the discovery of the benzodiazepine receptor in 1977, reports of niacin having benzodiazepine-like activity began to follow.

Benzodiazepines act through benzodiazepine receptors that are part of the gamma aminobutyric acid (GABA) receptor complex. Injections of vitamin B3 into the spinal cord were shown to give similar physiological reactions as injected benzodiazepines, although the necessity of large doses was noted.[8] In contrast, a separate study at the same time found only antagonistic effects with niacin on benzodiazepine receptors when injected into the pallidum of the brain.[9]

However, continuing research found that giving rats systemic niacin in large doses had very similar effects to diazepam, confirming vitamin B3's anxiolytic effects.[10] One of the clinical uses of benzodiazepines is for reducing seizures. Studies in mice have found similar anti-seizure activity with vitamin B3. Some studies went on to suggest that the anti-seizure effect appears to be mitigated through the same receptor, although with selective dosing differences based on the type of seizure-inducing agent administered.[11,12] Further research in Ukraine and Russia continued to find similarities between niacin and benzodiazepines, especially around anti-seizure activity.[13,14]

Confusingly, some research suggests the benzodiazepine-like activity of niacin may not act directly through benzodiazepine receptors.[15] Yet other research suggests that niacin's direct binding to benzodiazepine receptors may not always act through GABA modulation.[16] More research is clearly needed to understand niacin's anxiolytic activity on the central nervous system. Unfortunately, research on the exact physiological effects of niacin has been languishing for decades since its initial discovery.

Practically, case studies of anxiety disorders have demonstrated that some individuals respond to niacinamide treatment. Several authors have noted significant potential for niacinamide in high doses for relieving anxiety symptoms,[17-19] although not all cases were found to respond.[20]

In my clinical experience, niacinamide (the no-flush version of niacin) benefits a significant subset of patients struggling with anxiety disorders. High doses are needed but have been shown to be safe up to 3000 mg per day and may provide benefits for osteoarthritis as well.[21,22]

Magnesium

Of all the nutrients, magnesium seems to be one of the most commonly deficient. Research suggests around half of individuals don't consume enough of the mineral, with deficiencies becoming even more prevalent in the elderly.[23]

Evidence from paleolithic diets suggest stone age humans consumed four times more magnesium as compared to current consumption levels.[24] Further complicating matters, serum magnesium levels are tightly regulated, so serum measurements can be normal in cases of significant deficiency.[25]

Magnesium is the second most abundant intracellular cation and plays a role in over 300 different enzymes.[26] The mineral is critical for muscle relaxation and energy production, with deficits increasing vulnerability to stress.[27,28]

In the brain, magnesium is also crucial for normal function. Magnesium plays a central role as a calcium channel blocker, inhibiting the N-methyl-D-aspartate (NMDA) receptor. This effectively blocks glutamate-induced excitatory neuronal signaling. Glutamate signaling can lead to excitotoxicity, increased free radical burden, and neuronal cell death.[29] As such, magnesium acts as a neuroprotective molecule, blocking this excitotoxicity.

Magnesium also has an important role as an anti-inflammatory compound. Deficiency can play a role in numerous diseases, including arthritis, heart disease, asthma, hypertension, metabolic syndrome, diabetes, and stroke.[30,31]

With the far-reaching effects of magnesium, it shouldn't come as a surprise that magnesium plays a role in mental health. When replete, magnesium helps calm and balance the nervous system. However, it's worth noting that stress causes depletion of the mineral and increased needs for the nutrient.[32-33]

Magnesium deficiency has been associated with numerous mental health symptoms, including anxiety, depression, irritability, weakness with lack of energy, agitation, and psychosis.[34,35] While research is not robust, it is still strongly suggestive that magnesium supplementation improves depressive symptoms. The majority of studies on magnesium levels in depression have found correlations between deficiency and symptomatology.[36] While not all clinical trials have shown benefits for depression, several have found improvements in symptoms with magnesium treatment.[37-39]

As for anxiety, clinical research is thin, but clinical experience and biochemistry clearly reveal the needs for the mineral. With the well-documented increased needs for magnesium associated with stress, combined with deficiency states contributing to anxiety, the need for magnesium is obvious. Magnesium deficiency in animals has been shown to dysregulate the stress response through the hypothalamus-pituitary-adrenals (HPA) axis, and the authors conclude that this dysregulation is likely relevant in "hyper-emotionality" due to low magnesium intake.[40] A recent systematic review found that evidence is suggestive of benefits with magnesium for anxiety, but the quality of research is poor.[41]

Anyone under increased stress and anxiety will likely benefit with additional magnesium. Supplementation is safe as long as kidney function is intact. For supplementation you want to use better absorbed forms of magnesium, typically amino acid chelates which also decrease gastrointestinal side effects. Dosing between 400-600 mg per day is not unusual. Some benefits occur quickly, while others may be slower as it takes time for intracellular magnesium levels to increase.

Ashwagandha

Too much stress just seems to make everything worse. Higher stress levels have been shown to worsen heart disease, cancer, inflammatory bowel disease, infectious disease, autoimmune conditions and mental health.[42-47] Helping individuals cope with stress is often a major part of treating anxiety and restoring wellbeing.

As such, targeting the physiology underlying the stress response is often key. The HPA axis is the major player in the stress response, culminating in the release of cortisol and other stress hormones from the adrenal glands. While magnesium is also key, ashwagandha has been shown to modulate the stress response, reducing reactivity and stress hormone levels while improving stress tolerance.

In rats, random foot shocks induce a chronic stress state. This chronic stress profoundly affects biochemical and neurological functioning, leading to blood sugar dysregulation, increased stress hormones, depressive behaviors, cognitive deficits, gastric ulceration, and immune suppression. Ashwagandha, especially in higher doses, significantly ameliorates the negative consequences of stress, in some cases almost normalizing function.[48] A more recent trial of ashwagandha in stressed horses also found significant improvements in stress hormone levels, blood sugar, immune response, and liver function.[49]

Ashwagandha, combined with magnesium and niacinamide, can reduce anxiety symptoms.

One recent study found that after two months of ashwagandha extract, stressed, but healthy adults saw decreases in anxiety with lowered first morning cortisol.[50] In stressed, overweight individuals, ashwagandha significantly decreased perceived stress, cortisol levels, and body weight, while improving Oxford Happiness Questionnaire scores.[51] In an earlier study on chronically stressed individuals, ashwagandha significantly improved dry mouth, sleeplessness, forgetfulness, irritability, and concentration. In addition, fatigue, poor appetite, and body aches also improved.[52]

Beyond stress, research on ashwagandha for mental health conditions has also yielded positive results. A study on schizophrenia used ashwagandha as an add-on treatment during symptom flares combined with standard antipsychotic medications. Negative symptoms, general symptoms and total symptoms all improved significantly.[53] The same group did further analysis of patient results and found improvements in both depression

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and anxiety levels.[54] However, a smaller, earlier study only found benefits for blood sugar and triglycerides but not for schizophrenia symptoms with ashwagandha.[55]

Obsessive compulsive disorder has also been shown to respond to treatment with ashwagandha. In patients already on medication, the addition of ashwagandha almost halved remaining symptom scores, while the placebo had minimal impact.[56]

For anxiety, ashwagandha has been shown to yield improvements as well. An early trial in ICD10 anxiety disorders found an 88.2% response rate for ashwagandha and only 50% response with placebo.[57] A trial that used ashwagandha as part of a naturopathic protocol for anxiety treatment compared to psychotherapy, deep breathing, and placebo found a 56.5% decrease in anxiety scores as compared to 30.5% in the control group.[58] In patients with both anxiety and insomnia, ashwagandha was able to significantly improve both sleep and Hamilton Anxiety Rating scores.[59] As an adjunctive treatment in generalized anxiety disorder, ashwagandha was also effective at reducing anxiety symptoms over placebo.[60]

As an herb with a long history of safe use, ashwagandha has some distinct advantages in treating mental health symptoms. With its ability to improve physiologic responses to stress, many patients can benefit from supplementation. When combined with magnesium and niacinamide, you can typically reduce symptoms of anxiety for the majority of patients.

Conclusion

Stress and anxiety are endemic in today's society. Unfortunately, standard pharmaceutical treatments don't address many of the underpinning problems for patients struggling with anxiety symptoms. Patients often continue to suffer, in need of additional treatment. By slowing down brain activity with niacin and maximizing tolerance to stress with magnesium and ashwagandha, patients will typically find their anxiety symptoms improve as their tolerance to stress is restored. Best of all, side effects are minimal with this effective combination.

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Causes of TechStress and 'Technology-Associated Overuse' Syndrome and Solutions for Reducing Screen Fatigue, Neck and Shoulder Pain, and Screen Addiction[1]

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Abstract

The COVID-19 pandemic, almost overnight, has transformed our relationship with technology as we sheltered-in-place. Computer, laptop, tablet, and cellphone screen use has become the main method for maintaining work, education, and social connections virtually. The result has been an increase in symptoms that are physical, behavioral, and emotional in nature. Physical complaints include various neck, shoulder, back, and eye discomfort or pain. Behavioral experiences include insomnia, fatigue, and exhaustion, overindulging on snacks, or skipping meals. Psychological concerns can include making worse symptoms associated with attentional deficits and hyperactivity disorders (ADHD), anxiety, depression, and loneliness. Sometimes, patients or clients use the term Zoom fatigue or COVID stress to refer to a set of symptoms associated with overusing technologies while sheltering in place. Discussed are the following: 1) factors that explain why working with digital devices (computers, laptops and cellphones) can more directly cause and/or indirectly make worse the computer-related disorders; and, 2) evolutionary factors that prime people to respond to phone and computer software notifications and contribute to screen addiction; and, 3) practical suggestions for how to optimize health while using digital devices in a virtual environment.

The COVID-19 pandemic has rapidly transformed our lives in the modern era compared to our ancestors who spent most of their day hunting and gathering resources for survival. Computers, laptops, tablets, and smartphones with large screens have become ubiquitous tools for working, learning, and for connecting, both professionally and socially. Even though some people are already spending a large number of hours with digital devices – and some might say spending too much time using social media apps, or distracting themselves with continuous streams for entertainment – technology is convenient and, for some has become the primary or only way to connect. The result has been an increase in, to coin a phrase, 'technology-associated overuse' (TAO) syndrome, marked by physical, behavioral and psychological symptoms such as: neck, shoulder, and back discomfort/pain, eye irritation, insomnia, fatigue and exhaustion, overindulging on snacks, or skipping meals, attentional-deficits and hyperactivity disorders (ADHD), anxiety, depression, and loneliness.[1-8]

People use digital devices all day, every day with little awareness of the toll associated with continuous screen interactions. Some people amplify their habits of continuously and/or unconsciously checking for text messages multiple times an hour, descending into a rabbit hole of 'click-bait,' following link-after-link, or playing countless rounds of computer games for hours without a break.[9] On the average we now check our phones 96 times a day – about once every 10 minutes and an increase of 20% as compared to two years ago.[10] For many students, the last thing before sleep and the first thing before getting up is checking the phone. Even during social interactions with other people, we may automatically check our phones for social media and text notification. Thus, we engage in a form of 'semi-tasking' (e.g. doing twice as much, half as well), not fully paying attention to the people we are with or to the people at the other end of a text message.

Even though digital communication has numerous benefits (e.g., connecting with friends and family on social media, reduction or elimination of commuting), 94% of our college students report that online synchronous learning while sheltering in place (e.g. via Zoom) is more stressful and challenging than in person learning.[11] Similarly, many

1. Adapted from: Peper, E., Harvey, R. & Faass, N. (2020). *TechStress: How Technology is Hijacking Our Lives, Strategies for Coping, and Pragmatic Ergonomics.* Berkeley: North Atlantic Books.
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faculty report that teaching remotely (e.g. via Zoom) is more exhausting. Some of the factors that contribute to this exhaustion includes the following:

- Lack of movement as the person sits with minimal movement.[12]
- Near-field vision stress as the person looks at the screen. The eyes converge and accommodate, without allowing the eye muscles to relax by looking at the distance.
- Difficulty in sensing nonverbal communication cues (body movement, breathing patterns, eye movement, body odors, etc.).[13,14]
- Reduced facial feedback (non-responsive face, reduced screen resolution, the face appears dark because of back lighting, or in gallery view the face picture is very small). For the viewer (e.g. a teacher) non-responsive faces covertly evokes the feeling of danger.[15]
- Incorrect ergonomics (arrangement of chair, keyboard, monitor, lighting, etc.).[16]
- Lack of somatic awareness of static muscle tension and shallow breathing (shoulder muscle tension while mousing, head forward or downward to read the screen or look at the cellphone).[17]

The COVID-19 pandemic super-charged a social trend of the last 20 years towards encouraging working and learning from home. One benefit is the reduced expenses associated with commuting, office rent, or room and board in dorms, as well as to provide increased access to the information (e.g. more people can work and learn from home).[18] Similarly, telemedicine and teletherapy are transforming health care delivery, including facilitating on-screen diagnoses using high-definition cameras, and real-time (synchronous) interactions with therapists.[19,20] Unfortunately, the overuse and over dependency on screens (e.g. digital devices with screens) for work, education, entertainment, and socializing contributes to an increase in tech stress symptoms.

This article explores why people may develop discomfort while using digital devices as compared to a time in history when technology included working on a typewriter. Strategies to reduce discomfort and enhance health with digital devices are presented next.

Why do some people develop symptoms of stress and strain, dubbed 'technology-associated overuse' while working at the computer compared to working at a device such as a typewriter?

Although data entry with a typewriter (typing) and data entry at the computer appear similar, there are differences worth noting.

Movement differences. Typing incorporates episodic motor movements (e.g., carriage return, inserting single sheets of paper and filing the typed papers) that interrupts the static arm, back, legs, neck, and shoulder tension. On the other hand, computer data entry is predominantly a static sitting task as illustrated in Figure 1a and 1b.

Computer keyboarding and mousing typically involves only finger and arm movement for data entry. The data entry tasks can continue for extended time periods while the person sits without large motor movements. The computing task does not intrinsically incorporate body movements to interrupt static muscle tension as the use focuses on the screen, captured by the content or task.

It is no wonder that for some people hours pass before taking even the briefest movement break (a micro break for a few seconds), or a longer mini or macro break such as stretching in place or getting up out of our seats for a short walk. Modern interactions with digital devices lead to increasing muscle tension without awareness and a significant decrease in blood flow. Unfortunately, blood and lymph fluids may pool in the lower portion of the body from lack of leg movement, which is so important that the muscles of the calf have been called the second heart because they help return the blood against gravity back to the core.

Even when 'interrupt' programs are used to remind us to move our bodies, we often ignore them or turn them off because it is inconvenient or, just easier to continue to work. No wonder that more and more people experience discomfort all day long while using digital devices. Technology-associated overuse results in an increase in "sitting diseases" such as hypertension and musculoskeletal pain disorders, where people who sit six hours a day have a 19 percent increase in death rate from all causes as compared to those who sit less than three hours a day.[21,22] To repeat a generic phrase, *sitting is the new smoking.*

Vision differences. Typists usually could look alternately at near and far distances when engaging with the material on the page. For example, a typist would focus on things farther away each time they changed the paper in the typewriter. Every time the eyes could focus on a far distance, the eye muscles could relax, and therefore reduce near-field visual stress.

Today, most computer screens are typically positioned about 18 inches from our eyes. People typically only look at near-field objects displayed on the screen, or look at a wall, or at a partition right behind the screen. When looking at a cellphone screen, we look ever closer, about 10 to 15 inches away. The muscles that cause the eyes to converge and the lenses to focus have no opportunity to relax, which can only occur by looking away at

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Figure 1a. 1940 working at a typewriter Figure 1b. 2020 working at a computer

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the far distance. At the same time, our blinking rate is reduced when we attend to new stimuli.[23] Consequently, many people suffer from eyestrain and dry eyes in addition to muscle strain from immobility of sitting for hours working at a computer.[24,25]

Taking timeout to regenerate differences. Today, modern work can be performed anywhere and anytime 24 hours a day, 7 days a week, and 365 days a year. At home we often continue to do more office work, email a friend, text, read digital books, search the internet, and participate in social media, all in a fluid continuum of never-ending digital screen interactions – and some might say digital distractions. Even when on holiday, we may keep in contact with the office. The consequence of the conveniences of being able to access many activities instantly may mean there is less time to regenerate physically and mentally and spiritually, seldom stopping to ask, "why am I feeling so tired."

Sitting difference (e.g. slouched and collapsed). When sitting and looking at the screen or cellphone many people tend to slouch and bring their head forward to read the screen. The slouched posture with a head forward position tends to increase neck muscle tension leading to muscle tension headaches, with accompanying decreases in subjective energy and reduction of positive thoughts.[26-29]

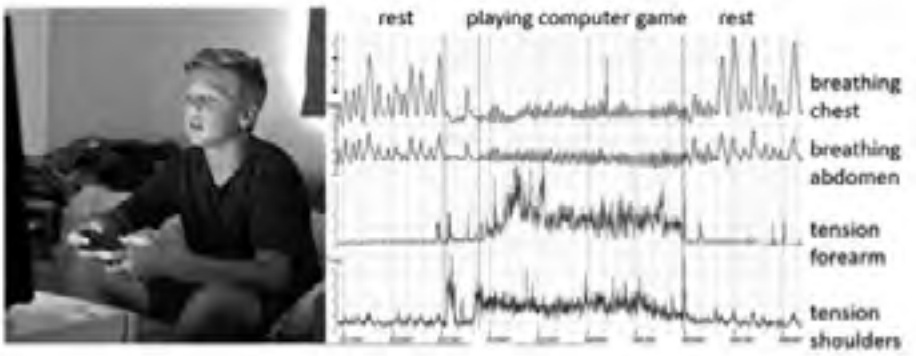

Figure 2. Representative recording of a boy playing a computer game with engaging content. During the entire duration of gaming some children will breathe rapidly with static tension in their forearm and neck and shoulder muscles
(by permission from Peper, Burke & Peper, 2002; Peper, Harvey, & Faass, 2020).

Impact on Children's Health

In the past, children's daily life included more outside play which supported many kinds of muscle development.[30-32] Without awareness, children developed motor coordination, alternated between looking at near and far objects that reduces near visual stress, and played 'freeze, stop and start' movement games that developed self-control. Children did not learn to use a typewriter until they were in their middle or high school years.

Today, babies and children are often given a cellphone or tablet early in life, which serves as a digital 'baby-sitter' since visual displays capture their attention. Unfortunately, overuse of technology can result in spending hours looking at screens without interruption. The result? Predominantly near-vision focus that affects eye development and increases near-vision stress (e.g. increased convergence and accommodative dysfunction) to the point that there is an increased prevalence in developing early onset myopia.[33-35] For example, over 85% of Singapore's young people today wear glasses, related in part to technology-associated overuse.[36,37] Arguably, schoolchildren in many parts of the world, including East Asia, spend their childhood predominantly looking at screens instead of playing outside and relaxing their eyes by looking at far distances, possibly contributing to myopia.

As children become 'captured' by the screen, they tend to stay in the same static position often resulting in little or no change in body movement with an increase in static muscle tension.[38] At the same time, the multimedia content in the screen captures their attention and increases their arousal as indicated by their shallow, rapid breathing (see Figure 2).

Increased screen time has been identified as a cofactor in developing sleep disturbances, attention deficit disorders, hyperactivity disorders, overweight and obesity disorders, and Asperger's syndrome.[39-41]

Why are we so easily captured by the screen's content and by digital notifications (e.g texts or instant messages)? Computer displays, cellphone apps, and social media capture our attention without awareness because the visual and auditory signals activate physiological responses that in ancient times supported our survival. Continuous overuse of the automatic response patterns that supported our survival may unintentionally contribute to various kinds of physical symptoms because of the overuse. The hijacking of the body's responses that evolved to get us out of danger by the audio, video and vibratory signals from modern digital devices have been described by Peper, Harvey and Faass (2020) in their book, *TechStress: How Technology is Hijacking Our Lives, Strategies for Coping, and Pragmatic Ergonomics,* and include the following:

We are wired to identify danger, which means we tend to react to *any* stimuli that suggests potential danger as well as the presence of food sources (e.g. game animals). Whether the stimuli is auditory, visual, tactile, or kinesthetic, those stimuli trigger arousal. This arousal occurs to both real as well as virtual stimuli *because our biology compels us to respond to virtual stimuli presented on digital devices.* Because digital content can be omnipresent, always beckoning, 'come hither and stick around' it evokes 'screen addiction'. From an evolutionary perspective, even though we were once triggered to move our bodies in response to 'real world' survival signals, today we may not have an opportunity to move our large muscles as much

or as often, and instead get to hold ourselves fixed in place, moving only our hands or fingers. Unfortunately, we never get to complete the range of actions and movements that co-evolved to support our survival during a time when we had to hunt and gather food, or fight or flee to survive predators or enemies. In ancient times, the signals that identified danger or were tied to our survival led to relatively short-lived experiences. Today, we may be exposed to a continual stream of stimuli that evoke arousal associated with survival; however, instead of hunting and gathering, or fighting or fleeing, we stay seated, relatively immobilized, and do not act or move our large muscles for defense or survival. Unfortunately, the ongoing arousal and vigilance triggered by modern digital device content is coincident with static muscle tension, such as tightening our neck and shoulders muscle, (e.g. increased low-level trapezius muscle tension) and changes in heart rate and breathing patterns (e.g. decreased HRV and increase shallow breathing).

We are wired to conserve energy in order to heal and regenerate. Not moving our bodies, because we are sitting all day looking at screens. reduces energy expenditure. The biological consequence can include increases in fat storage, arguably a physiological mechanism that evolved that allows people to survive longer when food is scarce. Unfortunately, the ability to preserve energy stores (e.g. increase fat stores) combined with lack of movement and sedentary lifestyle (e.g. 'sitting disease') contributes to development of obesity, diabetes, and cardiovascular disease.

We are wired to see digital images and sounds as if they are real. The brain does not discriminate between actual and visual-auditory images that are artificial, digital recreations, which explains one aspect of our attraction to our phones, to binge watching, and to gaming. Our bodies, nervous system, and emotions respond to virtual content in the same way as real, lived experiences, which contributes to ongoing, continual arousal and physiological stress for as long as we use digital devices, and arguably longer than the time it takes to hunt and gather, or fight or flee.

We are wired to be active during daylight. Blue-white light sources from our phones and computers stimulate the central nervous system as if it were daylight. Watching a screen before going to sleep inhibits melatonin production and increases arousal as we react to the updates on social media or watch arousing media. Even when there are apps that change our screens' frequency of light (e.g. to a 'night-mode'), the content of the visual images and sounds may represent daylight activity, so the body responds by keeping us awake contributing to disordered sleep.[42,43]

We are wired to attend to social information about power structure and hierarchy. The particular cues in social media related to power structures and hierarchy contribute to social media addiction because we continuously feel the need to know who has power and be updated about what is going on regarding who may have power over us. Unfortunately, even with friends or family with whom we feel safe and secure in our relationships, we feel the urge to check the notification or social updates to make sure that our social status in some hierarchy has not shifted.

Although many response patterns that evolved for our survival are evoked by the content of work or media presented on digital devices, we tend to blame the individual for lacking control (e.g., they are addicted, lazy or lack self-control) over their responses. The blame may be more justly placed on the technology companies who have designed the hardware platforms and software content to capture our attention by exploiting the human evolutionary response patterns. We need to move away from blaming the individual for responding automatically to the stimuli to recognizing that the companies have developed the displays and notification to trigger these evolutionary survival responses – these automatic responses have become evolutionary traps. It is similar to blaming a child for wanting candy at the supermarket checkout counter. Instead, we should blame the store and the food industry for evoking the child's response. Solutions need to include reducing the exposure to the stimuli, especially for young children.

Figure 3. Candy displayed to evoke the evolutionary survival response. https://live.staticflickr.com/4036/4628145997_f1789aa24e_b.jpg

Teaching Awareness with Biofeedback to the Rescue

When working at the computer, most people are unaware of the low levels of chronic muscle tension in their shoulders and their forearm during data entry. They also breathe shallowly and rapidly. Even when they think they are relaxed, their muscles are still slightly contracted as shown in Figure 4.

In almost all cases, the person is unaware of the physiological changes such as increased muscle tightening and reduced breathing that occur. The biofeedback monitoring of respiration and muscle tension make the invisible visible and the covert overt. The visual and auditory feedback provides evidence and a rational of why physical symptoms may develop such as chronic low-level muscle tension and increased sympathetic arousal. More importantly, feedback training can support strategies for learning how to work with less static muscle tension/overexertion

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and healthier breathing (e.g. lower and slower breathing). With regular feedback, people can learn awareness of muscle tension and work without tightening unnecessary muscles. For detailed instructions how to use devices that provide muscle feedback (e.g. EMG protocols) for assessment and training see Peper, E. & Gibney, K. H. (2006). *Muscle Biofeedback at the Computer: A Manual to Prevent Repetitive Strain Injury (RSI) by Taking the Guesswork out of Assessment, Monitoring and Training*. Biofeedback Foundation of Europe. (Free download available from: http://bfe.org/helping-clients-who-are-working-from-home/)

How to Thrive and Survive in a Digital Environment

Maintaining health and preventing discomfort at the computer is more than learning muscle awareness and physiological control. Healthy computing and digital device use need to include a 'systems perspective' that accounts for the triggering of evolutionary traps, lack of body awareness while focusing on the work task, and training in awareness with biofeedback to enhance health.

Implement the following camera and sound recording guidelines to improve communication and teletherapy for your clients and patients.

- Arrange the camera so that your face is clearly visible (eliminate back lighting and provide light onto the face. Be aware when the camera records from the side because the viewer may believe you are looking away from them and are not attending to them directly.
- When possible, use a separate microphone for better sound quality.
- If the screen freezes or the sounds warbles (possibly due to WiFi bandwidth issues) turn off the screen so that the sound is better and upgrade internet connection.
- Ask people to sit further back so that you can see non-verbal communication cues such as arm, trunk, leg and breathing movements.
- Review ergonomic guidelines to optimize health at the keyboard. Finally, implement the following pragmatic suggestions to enhance health at the computer and optimize bio and neuro-teletherapy and telebio-/neurofeedback.
- Use biofeedback to demonstrate or model or 'show and tell' for your clients and patients how your body responds during interactions with digital devices, before guiding them in learning a technique.
- Incorporate many movement breaks is a series of microbreaks (e.g. 30 seconds or less), minibreaks (a few minutes or less) and longer breaks (e.g. more than a few minutes). Every few minutes move and wiggle so that the muscles can relax (think of the typist inserting a new sheet of paper in the typewriter).
- Practice deliberate large movement breaks to interrupt sitting disease (think of the typist getting up and filing the paper, or walking to the next room to the printer).
- Learn slow diaphragmatic breathing that lasts at least 10 seconds, breathing in and out. When you become aware of shallow rapid breathing or breath holding, pause to practice slower breathing through the nose.
- Optimize the ergonomics for your particular needs by avoiding 'one-size-fits-all' equipment. Remember that if the chair does not fit your body, it is incorrect, and you can only sit uncomfortably. Even when a chair is ergonomically correct, it does not mean that you will sit in it correctly, so take the time to adjust the chair to your needs. Unfortunately, you may still tend to slouch and work under stress, thus, pay attention to your work style.
- Schedule uninterrupted work time so that your productivity is not disrupted by notifications, emails, or phone calls except for a "true" emergency.
- Turn off digital 'distraction' devices when socializing such as during dinner, talking with friends, or playing with children.
- Limit any digital device exposure for children. Let them entertain themselves by playing actual physical movement games. Outdoor games facilitate motor development and also teach children impulse control mastery. Games, such as red-light green-light or hide-and-seek, encourage children to stop and freeze or stay totally quiet so not to give away their location.
- Avoid arousing content and bright digital screens an hour before going to bed to reduce blue exposure and sympathetic arousal.
- Practice daily relaxation/meditation exercises to quiet the emotions and mind.

For the comprehensive background and guidelines see the book, *TechStress-How Technology is Hijacking our Lives, Strategies for Coping and Pragmatic Ergonomics*, by Peper, Harvey and Faass (2020). ◆

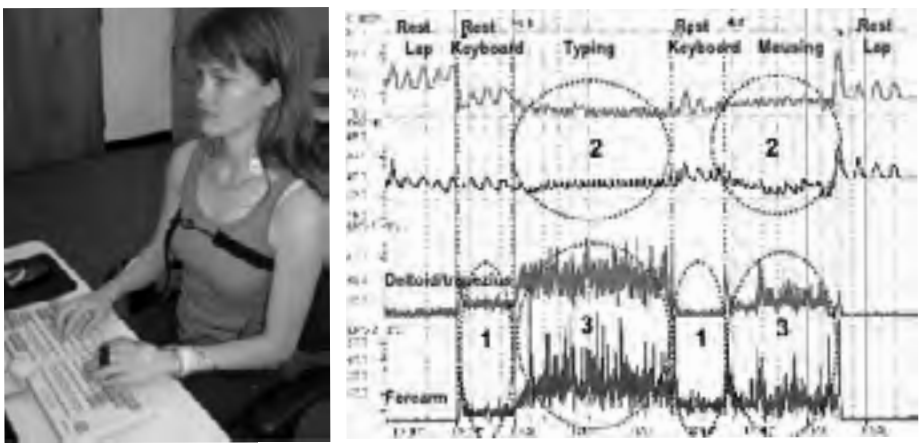

Figure 4. A representative recording of a person working at the computer. Note the following: 1) forearm and shoulder (deltoid/trapezius) muscle tension increased as the person rests her hands on the keyboard without typing; 2) respiration rate increased during typing and mousing; 3) shoulder muscle tension increased during typing and mousing; and, 4) there were no rest periods in the shoulder muscles as long as the fingers are either resting, typing, or mousing (reproduced from Peper & Harvey, 2008).[44]

References and article are available online at www.townsendletter.com.

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Tim Horton's Roll Up to Win and Operant Conditioning

by Douglas Lobay, ND

After a long and dreary winter of COVID isolation, I was excited and happy to participate in the iconic but albeit online Tim Horton's Roll Up to Win contest. (Tim Horton's is "home of Canada's favourite coffee.") Of course to minimize public health risks, the traditional Roll Up the Rim to Win on the paper cups was replaced with just the online Roll Up to Win contest. As I make my customary stop at Tim Horton's during my morning walk before work, I made a curious and peculiar observation while picking up my medium half-caf with two shots of cream. Excited as I was to scan my Tim's bar code before ordering inside at the service counter, I watched a particularly long and steadfast lineup of vehicles going through the Tim's drive-through, ordering then receiving their morning caffeine fix and maybe breakfast. Like lab rats in BF Skinner's box, I observed people methodically scanning their reward cards with their cell phones, paying a paltry piece of silver equal to about a toonie, then receiving their reward of fresh-brewed coffee and a free play on the Tim Horton's app. As I received my coffee, I came to the insightful conclusion that Tim Horton's Roll Up to Win contest is a classic example of the psychological principle of operant conditioning.

I took a first-year introductory psychology course at the University of British Columbia in the mid-1980s. Among the concepts we were introduced to was a learned and modified behavior in animals and humans called operant conditioning. Operant conditioning is a fancy term that basically describes a modifiable behavior that is changed by associating it with a positive or sometimes a negative reinforcement. BF Skinner was an American psychologist who pioneered research into the burgeoning field of modifiable behavior. In his classic experiment, he placed laboratory rats in a cage, colloquially known as a Skinner box. He had made a lever in the box that dispensed a morsel of food when pressed. He taught the rats that in order to receive the treat they would have to press the lever. He conditioned their behaviors and made the rats learn that by pressing the lever they would be rewarded. This is an example of a behavior that is modified by positive reinforcement. Pressing the lever more would result in more morsels of food being dispensed. Conversely, behavior can also be modified with negative reinforcement with a negative outcome for a certain behavior. I surmised that I was something akin to a lab rat in Skinner's box receiving my coffee and Tim's roll.

Behavior psychology is a somewhat complex yet archetypically simple and adaptable evolutionary concept in which an animal or person acts in response to a particular situation or stimulus. I must confess that I have gone to Tim Horton's quite a few more times than normal when they opened up the Roll Up to Win contest. I normally consider myself level-headed and perhaps somewhat addictive in personality. However, I like to maintain that I am in control of my behavior no matter what the circumstance. I was happy and excited to participate in the contest. After all I would receive a coffee that I would normally pay for with no questions asked if that is what I wanted. Additionally, I would receive a free lottery ticket and a chance to win one of many prizes, including a Volkswagen Toas vehicle, weekend getaways at a Fairmount resort in Canada, Samsung smartphones, flat screen TVs, and many other prizes. It seemed like a win-win situation hands down. Besides I rationalized that I was helping the economy during these troubling times.

Like a rat in Skinner's box, I modified behavior to increase my once daily purchase at a local Tim Horton's restaurant. I scanned my Tim's app at the time of purchase over my cell phone. I received my coffee that I enjoyed anyways and got the chance of rolling or tapping for a prize. I liked the colorful cups that were adorned with all sorts of teasers about the prizes to be won. I excitedly opened the Tim's app and pressed the Roll Up to Win icon on my cell phone and waited for the result. At this time I probably got a hit of the pleasurable neurotransmitter dopamine in the amygdala or other part of the limbic system of my brain. The reward immediately popped up. Of course, after all, they said every roll or tap is a winner. And like they said, it seemed like I won every time. From more commonly a paltry five Tim's points to occasionally a free coffee or donut, I did win. So far I have also won a twenty dollar discount at an online store called Skull Candy and a six-month free subscription to SportsNet Now. However, as the contest rolls on I seem to be a little less excited. I still like to purchase my one daily medium-sized coffee. I limit my purchases and like to think I am in control of my behavior.

As the Roll Up to Win contest comes to end shortly, I would like to make conclusions from my observations. To state again, the contest is a classic example of the effect of operant conditioning on behavior. Buying a coffee from this coffee company is implicitly associated with the positive reinforcement of also having a chance to win a prize. If I am any indicator, it is probably an advertising juggernaut for the company. I am not suggesting that the practice is right or wrong, moral or immoral, or promoting addictive gambling behavior. It seems to be innocent enough, and I still like to think I am in control of my responses. I make a conscious choice to limit my behavior in cost and frequency. After all I am supporting the economy, getting a beverage that I paid for, and engaging in a little fun lottery of sorts.

After taking a break to ponder on my observations, I realize I am less enamored with the contest, and now it is time to move on. I like to think I am in the driver's seat and in control of my response. I believe I make my choices no matter whether operant conditioning is involved. After all I am not a laboratory rat. I am almost done with the Tim's Roll Up to Win contest. Besides the contest ends in early April 2021. I think it is almost time to move on. Besides I think I will start going to McDonald's and get my morning coffee there for a while. They have stickers there that I can collect, and when I get seven I am eligible for a free coffee. ◆

Hormone Therapies to Strengthen Our Immune Resistance to Viral Infections, Including COVID-19

by Thierry Hertoghe, MD
International Hormone Society

The best way to control the COVID-19 pandemic is to prevent people from becoming infected. Aside from putting on a mask, keeping social distance, and being vaccinated against the SARS-Cov-2 coronavirus, almost no measures of prevention are advocated by governments and in the media. Fortunately, most physicians working in the integrative or holistic field of medicine have a better overview of the problem. They are aware that the best prevention starts with stimulating a patient's immune system so that masks, social distancing, and vaccines might then become unnecessary. These measures could be reserved for the most fragile individuals of our society, patients of all ages with serious diseases as well as very old adults.

How can physicians help patients increase their resistance against infections? In my experience, making changes in three domains significantly increases the immune system: diet, nutritional supplements, and hormone treatments. In this article, we will mainly examine what is possibly the most essential intervention to boost the immune system efficiently, the hormone therapies.

The first step is to obtain that patients **improve** their **diet**. Scientific studies tell us that a diet rich in fresh vegetables and fruits, sufficient protein-rich foods cooked at low temperature (and, thus, not burned) improves the immune system and decreases the number of infections. Avoiding sugar, sweets, and bread, which is made of hard to digest non-sprouted grains, has been shown to reduce the incidence of infections. Equally, the incidence of infection drops when people stop consuming dairy. Cow milk and its derivatives are not designed for human consumption but are mainly adapted to the digestive system of calves.

The second step is to take **immune-enhancing nutritional supplements.** Among the nutrients that show immune-stimulating potency against viral infections are zinc, iron, iodine, and vitamins A, C, and D.

The third and, in my experience, most important intervention to stimulate the immune system is to **correct deficiencies in immune-stimulating hormones** in patients. The most significant immune-stimulating hormones are likely as follows. Thyroid hormones are potent hormones to improve our resistance against viral infections. Thymosin alpha-1, the number one hormone of the thymus, might, in my experience, be the most potent of all the hormones that stimulate the immune system. Cortisol, at physiological doses, also enhances the immune system, particularly against viral infections. DHEA, melatonin, estrogens, and testosterone may be considered additional immune-stimulating hormones that help fight off viral infections.

First, let's discuss **thyroid hormones.** Patients with hypothyroidism are easily infected. In one study, about half of the participants complained of nasal obstruction (48%), one-sixth complained of rhinorrhea (16%), and one-fifth complained of headaches (20%), typical symptoms of the common cold. Thyroid therapy can efficiently make these complaints disappear.[1] The same might be valid for the flu. Patients infected with influenza (A) reportedly have T3 and T4 serum levels below the lower reference limit. [2] In my experience, thyroid therapy with recurrent flu can considerably decrease the incidence and recurrence of the flu in hypothyroid patients.

Some data suggest that thyroid hormones might help against coronavirus infections. In an observational study of 50 hospitalized patients with severe COVID-19 in Wuhan, China, the place of origin of Sars-CoV-2, most patients had serum levels of total T3 and TSH below the lower reference limit. Both of these levels normalized in people who survived the infection.[3] This suggests that the coronavirus affects the pituitary gland or the hypothalamus, resulting in a reduced secretion of TSH, itself causing a reduction of the secretion of thyroid hormones, including of T3. However, coronaviruses may also profoundly affect the thyroid gland.

During the SARS-CoV-1 pandemic in 2002-2004, also in China, two studies showed that the coronavirus profoundly damaged the thyroid gland of the patients who died from the infection. The follicular cells, which produce thyroid hormones, and the parafollicular cells, which produce calcitonin, in the thyroid gland are severely injured and tend to disappear.[4-5] Reports in the media related the cases of two men who were dying from COVID-19 infection but who dramatically improved and survived with T3 supplementation.[6] A randomized controlled study is ongoing to determine whether providing T3 as a nasal spray during the first 7-10 days of COVID-19 might improve the survival rate of severely ill patients.

Thyroid therapy may also display beneficial effects against herpes infections. Rats rendered hypothyroid by taking the antithyroid drug methimazole accumulated 10 times more of the herpes simplex virus in their spleens than euthyroid rats did. In contrast, rats rendered hyperthyroid accumulated almost no herpes simplex

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virus: approximately 1,000 times less herpes simplex virus in their spleens than were found in euthyroid rats (and 10,000 times less than hypothyroid rats).[7] In hypothyroid patients, thyroid supplementation can reduce by 40% the risk of herpes zoster infection (shingles).[8] Interestingly, children with autoimmune thyroiditis have a 40 to 60% increase in prevalence of IgG antibodies against Epstein-Barr (also called herpes 4) virus in their serum. Because patients with autoimmune thyroiditis usually have lower thyroid hormone levels and a higher TSH serum level than healthy individuals, the high frequency of Epstein-Barr IgG antibodies may signify that lower thyroid activity may have contributed to infection by Epstein-Barr virus in these children.[9]

Hypothyroidism may also allow easier development of viral hepatitis. Patients with viral hepatitis have been reported to have lower serum T3 and T4 levels, as well as higher serum TSH and reverse T3 levels, [10] indicating a lower thyroid function. The lowest T3 levels and highest levels of reverse T3, which blocks T3 action, are found in patients affected by fulminant viral hepatitis, the life-threatening form.[11] The opposite is true when thyroid therapy is given to hypothyroid patients with hepatitis: clinical improvement, stimulation of liver and immune functions, and amelioration of their hormone status.[12]

Further evidence of protective effects of thyroid hormones against hepatitis viruses may be found in the laboratory tests of patients with chronic hepatitis B: a mean of 58% increase in serum TSH in the most ill patients whose livers have become fatty (steatohepatitis).[13] Thus, a lower thyroid function may facilitate the progression of the disease. The risk that hepatitis B progresses into the dangerous fulminant form increases at progressively greater drops of the serum T3 level and increasingly higher levels of the antagonistic reverse T3. The lower the serum T3 level is in patients with fulminant hepatitis, the less chance they have of surviving massive necrosis of the liver.[14] Patients infected by the hepatitis C virus also tend to have a certain degree of hypothyroidism, which may weaken their immune systems. One study reported that hepatitis C patients are at a three-fold higher risk of overt hypothyroidism and about two times higher risk of having antithyroid antibodies (as well as antithyroglobulin as antithyroid peroxidase antibodies) in their serum.[15] The lower the serum T3 total is, the more likely these patients present a severe form of cirrhosis and, thus, of dying. In general, the severity of viral hepatitis appears to depend on the level of free or total serum T3.[16]

HIV infections are also associated with an increased incidence of free serum T3 and T4 levels below the lower reference limit and a TSH above the upper reference limit. For each of these levels, approximately 20% of HIV patients are in the overtly pathological level versus 2.5% of the overall population.[17]

In my experience, the most efficient thyroid preparation to improve the immune system is desiccated thyroid at doses between 30 and 180 mg/day, depending on the patient's degree of hypothyroidism. The additional presence of T3, T2, T1, and T0 thyroid hormones next to T4 in the preparation makes this therapy more efficient at stimulating the immune system than T4 (thyroxine) alone, the usual medication for hypothyroidism. (Note that each number following the capital T indicates the number of iodine atoms incorporated into each different type of thyroid hormone.)

Thymosin alpha-1 is the most potent immune-stimulating hormone I know, particularly against the flu. Many of my patients who take subcutaneous injections of thymosin alpha-1 at a dose of 0.3 to 0.5 mg per day no longer seem to catch flu. If they do, tripling the dose in the early stage of the flu usually makes the infection disappear within hours. Treatments with a single but higher dose of 3.2 mg of thymosin alpha-1 together with the influenza vaccine have been shown to increase antibody production substantially in reaction to the influenza virus vaccination in patients who are vulnerable to infections, such as uremic patients (patients with kidney failure).[18] Such beneficial effects might, in my opinion, also occur with COVID-19 vaccination when thymosin alpha-1 is given simultaneously on the same day as the vaccine injection.

Thymosin alpha-1 is also a potent treatment for coronavirus infections. In 2002, thymosin alpha-1 was given to coronavirus patients who developed a severe acute respiratory syndrome during the first outbreak of a coronavirus pandemic in China. The hormone was found to control the development of the disease efficiently.[19] Thymosin-alpha-1's efficacy seems to be even more evident with the coronavirus that causes COVID-19. A controlled trial first published in May 2020 on 76 patients hospitalized for severe COVID-19 showed that the 36 patients who received 10 mg/day of subcutaneous injections of thymosin alpha-1 for seven days were three times less likely to die than the controls without the treatment (11% of treated patients died vs. 30% of controls). In addition, thymosin alpha-1 virtually eliminated the need for mechanical ventilation in these severely infected patients. Eighty-two percent fewer patients who received thymosin alpha-1 needed non-invasive mechanical ventilation than the controls did. Hospitalized patients with COVID-19 suffer from severe lymphopenia. The main effect of thymosin alpha-1 was to restore lymphocyte count, particularly the T lymphocytes CD4+ and CD8+ cells, which fight off viruses.[20]

Thymosin alpha-1 is, in my experience, surprisingly efficient in herpes infections. All my patients with recurrent and treatment-resistant herpes infections report important progress with thymosin alpha-1, having no or almost no infections, on condition they follow a healthy diet and avoid consuming sweets, chocolate, and alcohol. Studies in mice infected with herpes viruses confirm this finding. Subcutaneous injections of thymosin alpha-1 to mice infected with herpes simplex 1 and herpes simplex 2 viruses substantially decreased the morbidity and mortality of these infections.[21] In cell cultures, thymosin alpha-1 can decrease the replication of herpes simplex 1 and 2 viruses.[22] In kidney transplant patients with acute respiratory distress syndrome due to cytomegalovirus infection, thymosin alpha-1 treatment significantly increased survival and decreased morbidity. Doses were either 1.6 mg a day of thymosin alpha-1 or 1.6 mg every two days. These doses increased the survival with an additional + 56% compared to patients who only received standard treatment. In survivors of the cytomegalovirus

infection, thymosin alpha-1 increased the CD4+ lymphocytes and the immune ratio of CD4 to CD8 cells.[23]

Thymosin alpha-1 is also beneficial in patients with viral hepatitis. The hormone has been officially accepted by healthcare systems throughout the world for its potency to help patients survive and heal from viral hepatitis, particularly hepatitis B and C pathologies where levels of thymosin alpha-1 may be lower. In patients with chronic hepatitis B, serum titers of thymosin alpha-1 are approximately 30% lower.[24] For treatment of hepatitis B, thymosin alpha-1 has been reported to be more efficient than interferon-alpha. In one controlled trial, 50% of patients had complete remission with thymosin alpha-1 compared to 27% in the group taking interferon alpha at 12 months (6 months after the end of the treatment). [25] These superior effects of thymosin alpha-1 alone have been confirmed in other studies.[26-30] Thymosin alpha-1 has also been reported to improve the antibody production to hepatitis B vaccination.[31,32] For hepatitis C, thymosin alpha-1 alone is less efficient as a treatment. It should be considered an adjuvant treatment next to other therapies in contrast with its effects on hepatitis B where alone it may be very efficient. [33-37]

In HIV infections, the serum thymosin alpha-1 titer is paradoxically higher.[38,39] The higher level is a false positive result due to cross-antigenicity of thymosin alpha-1 with molecules produced by HIV patients. The last 18 amino acids of one end of thymosin alpha-1 have a 50% similarity with the last 18 amino acids of the HIV P 17/18 protein. [40] Thus, much of the higher level of thymosin-alpha-1 that is measured in the serum consists in fact of HIV P 17/18 proteins, not thymosin-alpha-1. Can thymosin-alpha-1 help HIV patients? Yes, in association with antiviral medication (azidothymidine) and interferon alpha, thymosin-alpha-1 increases the number of T cells and the CD4 to CD8 ratios in AIDS patients.[41,42] Moreover, in cultures of macrophages and peripheral blood mononuclear cells, thymosin alpha-1 treatment inhibits HIV infection.[43]

The third most important hormone for the immune system is **cortisol**. Since its discovery at the end of the 1940s, cortisol has been used efficiently to overcome viral and bacterial infections, particularly the flu. Before cortisone became available, influenza almost invariably killed patients with adrenal insufficiency.[44-45] During an outbreak of avian influenza in Malmo, Sweden, in 1957, autopsy studies of each of the five patients who died from influenza showed untreated adrenocortical insufficiency.[46] Dr. William Jeffries, an expert in cortisol treatment, reports that in the acute stages of the flu, there are remarkably low serum cortisol levels, while at the same time the cortisol secretion to ACTH injections is normal. This means that these patients with the flu have an ACTH deficiency. The virus blocks the production of ACTH by the pituitary gland. The lack of ACTH causes a drop in cortisol production by the adrenal glands and puts the patient in adrenal deficiency. In his famous book *Safe Uses of Cortisol*, Jefferies points to the great similarity between symptoms of acute flu and those of acute adrenal deficiency. He reports that taking cortisol supplements, even transiently, can impressively improve the outcomes of patients infected by the flu.[45]

Correcting hormone deficiencies may prevent many patients from getting viral infections and may save lives.

The strategy to get rid of a flu infection is to make adrenal-deficient patients who are already taking cortisol increase the dose of hydrocortisone by 5 mg every 30 minutes (during a maximum of 2-3 hours) within the first minutes up to first six hours of the first symptoms of flu. When taken early, this treatment is very efficient. When cortisol is taken later (e.g., 1 to 2 days after the start of the infection), it is a too late to achieve quick results by increasing the cortisol dose. In this latter case, I recommend cortisol-deficient patients increase their hydrocortisone dose by 50% over three to five days. People who are not under glucocorticoid treatment and who acquire the flu or other types of infection may transiently take a single dose of 20 to 30 mg in the first hours of the flu. This method may help them overcome the infection quickly in two-to-three hours. I also advise patients to take an additional and equivalent (to the cortisol) dose of DHEA. For example, if the additional dose of hydrocortisone is 20 mg/day, then the patient should take an additional 20 mg/day of DHEA. This helps to avoid excessive tissue breakdown. Several studies report that supraphysiological doses of glucocorticoids together with antibiotics accelerate and improve the recovery of acute pneumonia due to the flu.[47-50]

The intake of glucocorticoids has also been shown to decrease the duration of the common cold caused by rhinovirus. The treatment suppresses nasal inflammation and cold symptoms during the first two days of the infection.[51] In patients with suspected or confirmed severe COVID-19 infections, two studies have shown that the use of glucocorticoids decreases mortality by 20 to 30% and the need for mechanical ventilation by approximately 20 to 50%. Efficient doses of intravenous hydrocortisone were 200 mg per day. If dexamethasone is administered, then the dose is 6 mg per day. The duration of both types of treatment is 7 to 10 days.[52,53]

For shingles (herpes zoster infection), methylprednisolone, a synthetic glucocorticoid, at supraphysiological doses has been shown to reduce the persistence of pain when given within the first 5-10 days of the infection.[54.] For herpes zoster infection, Jefferies proposes to do it with hydrocortisone and provide 4 x 20 mg per day to patients during the two-to-seven days of acute pain until a substantial decrease in pain is obtained, which is when a progressive decrease in dose can be implemented. The dosage should be tempered off progressively over two-to-seven days with 4×5 mg less each time.[55] At that stage, I would also add an equivalent 4×20 mg/day of DHEA, then 4x10 mg/day, etc., to protect the body from excessive catabolism.

Cortisol also helps to fight off other types of virus infections. Patients with viral hepatitis B and cirrhosis have lower levels of cortisol than patients without cirrhosis. The lower the cortisol level is found in patients with hepatitis B, the more they suffer from a progressive

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increase in cirrhosis (liver fibrosis).[56] This suggests that cortisol might slow down the progression of hepatitis B. In cell cultures, cortisone has been shown to inhibit proliferation of polio, rabies, and yellow fever viruses.[57] Cortisol deficiency also plays a role in HIV infections. More than a quarter (27%) of patients with HIV infection have been reported to have adrenal deficiency and show symptoms of cortisol deficiency.[58] Physiological, but not supraphysiological, doses of cortisol to these patients help them better overcome the infection and have, in my experience, an immune-stimulating effect rather than an immune-depressing effect.

DHEA is a fourth important immune-stimulating hormone. DHEA blocks excessive immune-suppressing effects of cortisol. DHEA alone can stimulate the immune system and resistance against viral infections. For example, a DHEA analog has been shown to decrease the replication of influenza A virus in mice.[59] Subcutaneous DHEA injections have been shown to decrease the mortality from herpes simplex 2 virus infection substantially in mice, increasing their survival from 60 to 92%.[60] Subcutaneous injections of DHEA also substantially increased the survival of mice infected with Coxsackie virus from 0% survival to 80%.[61] Interestingly, androstenediol, a metabolite of DHEA, is even more potent. The skin possesses the enzymatic equipment to make androstenediol from DHEA.[62] In the same experiment with Coxsackie virus, androstenediol treatment kept all mice alive. It is likely that most of DHEA's anti-infectious potency is obtained through its transformation into androstenediol because all the experiments with DHEA on infections in mice involved subcutaneous injections.

In one observational study, pregnant women with cytomegalovirus infection presented low serum DHEA sulfate levels. The authors of the study suspect that the cytomegalovirus decreases the synthesis of DHEA sulfate. They also observed that cytomegalovirus damaged the adrenal glands of the fetus.[63]

DHEA may counter a number of other viral diseases. For example, in vitro DHEA reduces the replication of the genital herpes virus.[64] In patients with hepatitis C virus, low serum DHEA sulfate levels are found, possibly contributing to the appearance or aggravation of the liver infection.[65] In patients with HIV who are showing a lot of symptoms in pain from the disease, serum DHEA sulfate levels drop to less than half of the DHEA sulfate levels in HIV patients without symptoms.[66-67] Moreover, a level of DHEA lower than 100 µg/dL or 2.7 µmol/L, which corresponds to the average at age 65, significantly predicts future aggravation into AIDS.[67-70] Other studies have shown that the lower DHEA sulfate levels are in HIV patients, the weaker their immune systems are with increasingly lower numbers of CD4 cells and differentiated and aggressive cytotoxic CD8 cells and with higher HIV viral load.[71] In HIV patients, each progression into a more advanced stage of HIV disease, is accompanied by a progressively greater decline in DHEA sulfate levels in the serum and a worse prognosis over the next year. Can DHEA treatment oppose HIV progression? A hint of an answer is given in several in vitro studies, which show that DHEA and a DHEA analog reduce the replication of the HIV virus at concentrations on the average five times higher than the average physiological level in adults.[72-74]

Melatonin is a fifth hormone that may help to increase our resistance against viral infections. Melatonin is found in every living being. In mice, melatonin has been shown to reduce substantially the severity and mortality of deadly encephalitis-inducing virus infections, such as with the West Nile virus, encephalomyocarditis virus, Semliki forest virus, and Venezuelan equine encephalitis virus, thereby improving survival by three to 13 times.[75-78] In the Aleutian mink inoculated with the Aleutian mink virus, subcutaneous implants of melatonin considerably reduced the animals' mortality rate.[79] In rabbits infected with the rabbit hemorrhagic disease virus, melatonin supplementation has been shown in three studies to decrease both morbidity and mortality of the rabbits considerably.[80-82]

The most important researcher in melatonin, Prof. Russell Reiter, published several studies presenting evidence that melatonin treatment may help prevent viral infections in general. He hypothesize that melatonin also increases patients' survival of Ebola virus and COVID-19 infections.[83-84] In patients with herpes infection, 2.5 mg per day of melatonin can produce complete regression of symptoms in 96% of patients, a result more efficient than 200 mg of the antiviral drug acyclovir (85% of patients have complete regression).[85] Melatonin can possibly also reduce the severity and duration of herpes infection because low melatonin levels have been found in patients with herpes zoster. In this study, the lower the melatonin levels were, the more severe the rashes and pain of herpes zoster were.[86] Can melatonin treatment increase our immune resistance to HIV infection? Observational data suggest yes. HIV-infected patients have lower salivary and serum melatonin levels. In AIDS, the advanced stage of HIV infection, the appearance of lipodystrophy is a sign of further aggravation and associated with significantly lower serum melatonin levels.[87,88]

Estradiol is a sixth potent hormone to stimulate the immune resistance against viral infections. In mice made estrogen-deficient by removal of the ovaries, estradiol supplementation reduces the morbidity and increases the survival during an influenza A virus infection.[89-90] Estradiol treatment also significantly stimulates the production of antibodies against the influenza virus in estrogen-deficient mice. When estrogen-deficient mice receive the flu vaccine, estradiol treatment significantly stimulates the mice's production of antibodies against the influenza virus.[91] However, we are lacking data from human trials. A prospective cohort study did not show that estrogen therapy could significantly increase the production of anti-influenza virus antibodies in postmenopausal women after vaccination.[92]

Estradiol may also be helpful against hepatitis C. Patients with chronic hepatitis C have significantly lower 17-beta-estradiol levels than healthy controls.[93] In cell cultures, estradiol can reduce the replication of the hepatitis C virus.[94] Can estradiol also boost the immune resistance of women against HIV? The answer is likely a yes. In an interesting experiment, female monkeys (macaques) were made estrogen-deficient by removal of their ovaries. Without estradiol treatment, all monkeys became infected by inoculation

of the simian immunodeficiency virus (SIV similar to HIV) into their vagina. However, estradiol treatment prior to the vaginal inoculation of the SIV, completely blocked transmission of the SIV. This protective effect was obtained by an effect of estrogen either within the vagina or, more likely, on the vaginal epithelium, because there is no inhibition of HIV transmission when the virus is inoculated with a syringe in the tissues situated beyond the vaginal epithelium inside the body.[95]

Testosterone is a seventh interesting hormone that may improve the resistance against viral infections, but perhaps less efficiently in the flu and more efficiently in coronavirus and hepatitis infections. In a trial on aged male mice with influenza, testosterone treatment modestly decreased the morbidity and mortality of influenza virus infection.[96] In men with hepatitis C, the effects of testosterone are more important. Fifty percent of men with active hepatitis C have low serum free testosterone levels. Progressively lower total testosterone is found when the hepatitis infection gradually worsens.[97] A small study of men with recurrent viral hepatitis C and who got a failing liver transplant for serious third or fourth stage of cirrhosis (liver fibrosis) is enlightening. Treatment of nine of the men with 1% testosterone gel for six months kept them alive with significant improvements in albumin, muscle strength, well-being, and disease scores. In the five other men without testosterone treatment, no improvement was noted and all patients died within less than three months after transplant.[98]

In HIV infection, testosterone may also have a protective role. In one study, 30 percent of men infected with HIV had severe testosterone deficiency with low total serum testosterone levels below 2800 pg/mL (200 ng/dL) or low serum free testosterone levels (levels below 65 pg/mL).[99] In another observational study, 37% of women with HIV had testosterone insufficiency. These female HIV patients with testosterone insufficiency suffered from significantly more fatigue and tended to report lower sexual desire, physical activity, and physical function as well as more stress feelings and more severe depression.[100]

In COVID-19, testosterone may protect men against severe acute respiratory syndrome (SARS). An Italian study showed that in men with severe COVID-19 and pneumonia who developed SARS, the testosterone level was on the average three times lower than in men without SARS. A serum total testosterone level below 1450 pg/mL or 5 nmol/L, which is approximately 50% lower than the lower reference limit of young men, is particularly worrisome. Men with this low level had a 23 times higher risk of needing to be transferred to the intensive care unit, a sign of major aggravation of the infection. Their mortality was about 30 times higher than for men with testosterone levels above 5 nmol per liter (144.21 ng/dl) or 1450 g per mol.[101]

Conclusion

Correcting hormone deficiencies may prevent many patients from getting viral infections and may save the lives of people with viral infections, including COVID-19. Hormone therapy works through several mechanisms. First, many hormones strengthen our first immune barrier consisting of the skin and mucosa, making these areas more efficient in rejecting or eliminating pathogens. Second, hormones can stimulate not only the production but also the efficacy of white blood cells, including neutrophils, macrophages, and T- and B-lymphocytes, to attack and destroy intruders. Physicians can become considerably more efficient in protecting their patients against COVID-19 and other viral infections by diagnosing and treating hormone deficiencies in their patients in time.

Additional Information

You can learn more on hormone and nutritional therapies on www.hertoghemedicalschool.eu.

For scientific evidence, you can visit www.intlhormonesociety.org; there you will find scientific data and information on hormone research.

For more information you can contact isabel@hertoghe.eu.

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References and article are available online at www.townsendletter.com.

Born in Antwerp, Belgium, Dr. Hertoghe practices his medicine in his clinic in Brussels. With his sister, Dr. Thérèse Hertoghe, they proudly represent the fourth successive generation of physicians working with hormonal treatments – and this since 1892 (after Eugène Hertoghe, former vice president of the Royal Academy of Medicine in Belgium, and Luc and Jacques Hertoghe, endocrinologists). Dr. Thierry Hertoghe devotes his life to the promotion of a better, patient-oriented, and evidence-based medicine.

Author of numerous books, Dr. Thierry Hertoghe also travels a lot to take part in numerous conferences and congresses throughout the world. He co-organizes many of these specialized gatherings and holds important positions in several international and national medical organizations (which usually tend to fight against aging). He is the president of the International Hormone Society (over 2500 physicians), and of the World Society of Anti-Aging Medicine (over 7000 physicians), as well as the supervisor of two important postacademic trainings for doctors.

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COVID-19
An Orthomolecular View

by Dr. Efrain Olszewer

Clinical Director of CMP
(Center for Preventative Medicine)

As an independent organization we decided to evaluate different approaches in the prophylaxis and prevention of COVID-19.

Different levels of prevention and control of COVID-19 show that it is possible to take measures to control the evolution of the disease.

After 14 months of living with the pandemic induced by the presence of COVID-19, several approaches and procedures were used in order to control the evolution of the disease, all under the concept of evidence-based medicine, where biochemical and pharmacological reasons were the basis of fundamentals, remembering that the treatment in general aims to improve the patient's response to the aggression of the infection, as well as the response to the second phase involving the inflammatory concept.

This review aims to show that many behaviors that seem contradictory may have a place in the prophylaxis as well as in the treatment of patients with COVID-19 and should be analyzed to deal with the current situation, as well as for us to prepare for similar situations in the coming future.

Two hundred eighty-two patients diagnosed with positive rt-PCR COVID-19 were analyzed during this period, either in person or by telemedicine[1]: 36 patients from Bolivia, 26 from Peru, 18 from Ecuador, 3 from Argentina, 2 from Chile, 4 from Paraguay, and 193 from Brazil. Of the total, 206 (73%) were men and 76 (27%) were women.

Three patients (0.5%) ultimately died from the disease, but help was requested by two of them during the final phase of the patient's treatment. One obese muscular patient with high comorbidity was treated in the severe phase of intubation and responded favorably to the classic treatment associated with intravenous vitamin C in antioxidant doses, and was discharged after two months of hospitalization, refusing to be monitored, having high levels of dimer, and did not take anticoagulants. The patient had a fatal myocardial infarction two months after leaving the hospital.

Twelve (4.5%) patients were hospitalized; no patient was intubated.

Two hundred twenty-six (80%) patients with little symptoms (low-grade fever, pain, minimal discomfort, eventual anosmia) were treated symptomatically with analgesics and antipyretics.

Forty-two (15%) patients with severe symptomatology, (fever, pain, malaise, cough, shortness of breath and pulmonary impairment above 25%, increased ferritin, and D-dimer, along with elevated CRP) took immediate treatment that included[2-4] hydroxychloroquine,[5] azithromycin,[6] prednisone,[7]and 14 anticoagulants and two all of the above combined with colchicine.[6]

Intravenous vitamin C with pro-oxidative properties was administered in the first five days and with antioxidant properties if necessary; during the inflammatory phase after the 5th day of clinical evolution, we used vitamin C as an antioxidant in lower doses, below 10 grams a day. Of this total, 12 patients were maintained on anticoagulants for an average of two months until reaching an adequate level of D-dimer, two other patients maintained the modulation of inflammation, and regulation of thromboxane synthetase via omega-3 based on the amount of resolvins and protectins produced by omega-3 administration.[8,9]

Protocols for Doctors and Health Professionals

The protocols are based on the principles of hydroxychloroquine interference in hemoglobin iron competing effect with COVID-19 increasing ferritin in lab tests, a pharmacological mechanism already known in the prophylaxis of patients traveling to malaria-prone regions, where administering the medication for five days provides protection for a 60-day period, as it is a delayed-action immunomodulator in the control of pro-inflammatory cytokines. During a virtual meeting it was suggested that everyone who considers themselves to be at risk – either due to the day-to-day contact with infected patients or due to diseases associated with taking a protocol in hydroxychloroquine – the usual dose of 400 mg daily for five days each month, associated with the treatment to restore the immune function of T lymphocytes and B lymphocytes, was

administered. Aside from this, the following were also given[10]: 1 gram of vitamin C every 12 hours; vitamin D (50,000 UI per month)[11]; zinc, 50 mg per day, combined with copper after a month of administration equivalent to 3 mg[12,13]; and beta glucan, 100 mg a day.

Of 103 colleagues initially included in the study, which concluded in December 2020, 83 patients (80.5%) were continually treated with the hydroxychloroquine, presenting no case of COVID-19 within this group of patients (physicians). We have no concrete information about the group that did not take it continuously, as they were separated from the study group.

Patients in Continuous Use of Hydroxychloroquine with Collagenopathy Treatment. We are continually and routinely monitoring 23 patients with collagen disorders up to the present day, in continuous use of 400 mg hydroxychloroquine. None of these subjects presented complications with their ophthalmological evaluation performed every 12 to 18 months. Without needing to suspend the medication, 16 of these patients maintained social isolation, seven kept distance, and none of them developed the viral disease during the entire follow-up period. These patients continue with their usual treatment, and immune stimulus supplementation was not included.

Until today, after four decades of use of chloroquine in the form of hydroxychloroquine, we have never had the need for a cardiological evaluation, only ophthalmological, where we have seen a less than 1% incidence of maculopathy, a much higher number if we use chloroquine diphosphate.

Hydroxychloroquine is a slow cytokine immunomodulator that controls inflammation through modulation of IL-1, IL-6 and TNF-alpha.[8,14]

Vitamin C and COVID-19

Several studies have been published in China regarding the use of vitamin C in supportive treatment in patients with COVID-19, with the purpose of controlling the viral evolution, by activating the respiratory burst system where macrophages release pseudopods that carry the virus and inhibit by the myeloperoxidase enzyme, by converting ascorbate to ascorbate peroxide as respiratory burst usually do. In these cases, the doses used were above 35 grams (400-500 mg/kilo body weight) in intravenous infusion. However, in the inflammatory phase, much smaller doses (below 10 grams) were recommended to control oxidative stress via the release of pro inflammatory cytokines. In general, a portable glucometer can be used to identify pro and antioxidant levels when using intravenous vitamin C, since the vitamin C molecule is equal to glucose and the glucometer cannot differentiate it from hexose.[15,16]

Conclusions

The experience in closed circuit and without a large universe of patients has shown that it is totally possible to control the evolution of the disease once it has begun its process, considering the violent evolution of the disease in the last 14 months with a high number of infected population and proportional deaths worldwide. Despite not having an expressly significant number of patients involved, the results are gratifying to the point that it is time to discuss science and protocols in the different stages of the disease, to define the proper pathway for the use of drugs or nutrients for the benefit of patients, eliminating clarifications and guesswork.

Note: This is a work of guidance and does not aim to be a model of treatment, but rather to open the possibility of scientific discussions, which allow us to offer possibilities to patients in a time of difficulty with changes, pre-, during, and post-COVID.

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Insulin Resistance

by Pamela W. Smith, MD, MPH, MS©

Description

More than 80% of the population in the US who are adults have blood glucose levels that are too high.[1] If an individual has a fasting blood sugar (FBS) that is high-normal (over 85 mg/dL), the risk of the person dying of cardiovascular disease is increased by 40%.[2] Furthermore, having a FBS high-normal (over 85 mg/dL) increases the patient's risk of vascular death.[3] Likewise, high-normal levels of FBS may account for a 6% to 10% decrease in the volume of the hippocampus and amygdala.[4] Consequently, insulin resistance is a risk factor for cognitive decline. Also, the Honolulu-Asia Aging Study showed that the effect of hyperinsulinemia on the risk of dementia was independent of diabetes, and blood glucose.[5] Insulin resistance occurs when insulin is present but it does not work as effectively in the body as it should. Consequently, levels start to rise to help the body compensate for less than effective insulin function. Symptoms of insulin resistance include the following[6]: fuzzy brain, infertility, irregular menstrual cycles, irritability, loose bowel movements alternating with constipation, water retention, and weight gain.

The following are some of the common causes of insulin resistance:

- Genetic susceptibility,
- Eating processed foods,
- Increased stress,
- Excessive caffeine intake,
- Abuse of alcohol,
- Nicotine,
- Excessive dieting,
- Oral contraceptives,
- Lack of exercise,
- Decreased estrogen in women,
- Increased testosterone in men (over-dosage of testosterone replacement or due to elevated DHEA level),
- Increased testosterone in women (due to PCOS or elevated DHEA level),
- Decreased testosterone in men,
- Excessive progesterone in women (over-dosage that is prescribed),
- Insomnia,
- Elevated DHEA levels in men or women, and
- Hypothyroidism.

Conventional Therapies

Conventional therapies for insulin resistance are centered around exercise and a low glycemic index eating program. If the patient is overweight, then weight reduction is beneficial. If these methods are not successful, then a medication may be started such as metformin.

Personalized Medicine Therapies[7-10]

Exercise is important. Lack of exercise is a risk factor for the development of insulin resistance and diabetes in susceptible individuals. A suggested exercise program is one hour, four times a week. If the patient has not been exercising and they are over the age of 40, then they should see their health care provider and have an ECG done before starting an exercise program.

A healthy diet is paramount to control insulin resistance starting with a low glycemic index (GI) eating program.[11] The GI ranks carbohydrates and carbohydrate-containing foods on a scale from 0 to 100 according to the speed with which they enter the bloodstream and raise glucose levels. Foods high on the list increase blood sugar and cause insulin to elevate. Also, high glycemic index foods increase the production of epinephrine and norepinephrine, which decrease insulin sensitivity.[12] A study showed that insulin secretion was lower in people who were on a low glycemic index program for only two weeks.[13] Furthermore, the glycemic index is affected by the size of the particles into which the food breaks down. Therefore, the more processed the food or the longer it is cooked, the higher its glycemic index.

The best carbohydrates that curb insulin are broccoli, lentils, and chickpeas.[14] Likewise, whole vs. refined grains have been shown to decrease the incidence of diabetes.[15-17] In addition, the fat content of a food has an effect on its glycemic index. The fat slows down the absorption and therefore lowers its glycemic index. Consequently, the right balance of saturated to polyunsaturated to monounsaturated fats is important both for the prevention and treatment of insulin resistance and diabetes.

Moreover, the optimal eating program to prevent and treat insulin resistance should be high in fiber. Low fiber intake has been shown in multiple studies to be a risk factor for the development of diabetes.[18-20] Specifically, soluble fiber has been shown to also lower insulin levels.[21-22] Getting enough protein in the diet is a key component for glycemic control. The protein content of the food also decreases the absorption of sugars and consequently decreases its glycemic load. If an individual is overweight, weight loss is very beneficial.

Good sleep hygiene is also important for overall health as well as glucose control. If a person does not sleep at least six and one-half hours a night and/or does not get restorative sleep, then insulin levels may rise and lead to insulin resistance.

Moreover, there are many nutritional supplements that help regulate blood sugar. The sooner they are started the better. Once the patient's blood sugar is above 90 mg/dL, the patient is headed toward insulin resistance and eventual diabetes. Why wait? Start these personalized medicine therapies suggested above along with some of the following nutrients and/or botanical therapies. Bergamot, which is a polyphenol, is also extremely helpful for many individuals.

Nutritional Supplements

Chromium is needed for carbohydrate and lipid metabolism. Elevated glucose, insulin, cholesterol, and triglycerides as well as decreased HDL can all be improved with chromium

supplementation. It also increases insulin sensitivity by improving insulin binding to the cells by increasing the number of insulin receptors.[23,24] Dosage: 600 micrograms twice a day with normal kidney function.

Alpha lipoic acid (ALA) is both fat and water soluble and is a broad-spectrum antioxidant. ALA also functions as a co-enzyme in carbohydrate metabolism. It increases the number or activation of glucose transporters (GLUTs).[25] GLUTs are involved in regulating tissue-specific glucose uptake and metabolism in the liver, skeletal muscle, and adipose tissue to ensure homeostatic control of blood glucose levels. Reduced glucose transport activity results in poor use of energy substrates and is associated with insulin resistance and type 2 diabetes. Furthermore, alpha lipoic acid slows the development of diabetic neuropathy (nerve damage due to diabetes) and can be an effective therapy for diabetic neuropathy in conjunction with lowering blood sugar and other nutrients.[26] Dose: 300-400 mg a day.

Magnesium is involved in the activation of over 300 enzymes in the body. In addition, magnesium functions as an essential cofactor in glucose oxidation. It also modulates glucose transport across cell membranes. Magnesium deficiency is associated with insulin resistance.[27-29] Dose: 400-600 mg a day. Magnesium glycinate or magnesium threonate are particularly well absorbed forms of this mineral.

Vanadium has been shown to improve insulin sensitivity.[30-32] Dose: 10-50 micrograms a day. Exacerbation of bipolar disorder may be a side effect in higher doses. Consequently, 50 micrograms a day is the highest suggested dose.

Vitamin D is really a pro-hormone and not a vitamin. Low vitamin D levels are associated with insulin resistance and beta-cell dysfunction. One study revealed that metformin improves insulin sensitivity by 13% and a higher vitamin D status in the study correlated with a 60% improvement in insulin sensitivity.[33] In another trial, using 1,332 IU a day, for 30 days in 10 women with diabetes, vitamin D supplementation improved insulin sensitivity by 21%.[34]

Omega-3-fatty acids, such as EPA/DHA, have a beneficial effect on plasma insulin and lipid concentrations in animals.[35] Furthermore, omega-3-fatty acids have many functions in the body with the most important being a fabulous anti-inflammatory agent. Dose: 2,000 mg daily.

Conjugated linoleic acid (CLA) is the only naturally occurring trans-fat. Animal studies have shown CLA to normalize impaired glucose tolerance and improve hyperinsulinemia. Dosage: 1,000 mg a day.[36, 37]

Biotin deficiency results in an impairment of glucose utilization. A study in lab animals showed that biotin improved glucose handling without increasing insulin secretion.[38] The best way to improve biotin production by the body is for an individual to have a healthy gastrointestinal tract. Dose: 2-5 mg a day.

Vitamin E deficient individuals are more likely to develop type 2 diabetes. Likewise, vitamin E improves glucose tolerance and reduces glycosylation.[39-41]

L-Carnitine is an amino acid that is an antioxidant. It influences free fatty acid and glucose oxidation. It may improve diabetic neuropathy.[42,43] Dosage: 1,000-2,000 mg a day with normal renal function. Intestinal bacteria produce the precursor of trimethylamine-N-oxide (TMAO), trimethylamine (TMA), from carnitine, choline, or choline-containing compounds. Therefore, measure TMAO levels before supplementing with L-carnitine. If TMAO levels are high, then carnitine and choline should not be taken.

L-Carnosine is a nutrient that is a combination of two amino acids, beta-alanine and histidine. It is an antioxidant, and it aids the body by preventing glycation.[44] Carnosine is found in the brain, skeletal muscles, heart, and the lens of the eye. Dosage: 1,000 mg a day with normal renal function.

L-Taurine is an amino acid. It requires zinc to help it function properly. Taurine has a positive effect on insulin sensitivity and helps to control blood glucose.[45-48] Stress depletes the body of taurine! Dosage: 1,000-2,000 mg a day with normal renal function.

L-Arginine helps insulin sensitivity.[49] Use with caution in individuals with heart valves that are not functioning optimally. Dosage: 1,000 mg a day with normal renal function.

Botanical Supplements[50,51]

Berberine (*Berberis vulgaris*) has been shown to help lower blood sugar. It also may regulate insulin receptor transcription.[52] Dose: 200-500 mg two to three times a day. This botanical can cause uterine contractions; therefore, it is not to be used in pregnancy. The most common possible side effect is GI upset.

Ginseng species contains triterpenoid glycosides that lower blood sugar by regulating hepatic glucose uptake, glycogen synthesis, and insulin release. Ginseng (*Panax quinquefolius*—American ginseng) has been shown to reduce post-prandial glycemia in both type 2 diabetics and non-diabetics.[53] In an eight-week trial, it decreased fasting blood glucose and HgA1C.[54] Dose: Panax ginseng: 100-400 mg of extract standardized to 4% ginsenosides.[55]

Fenugreek seed (*Trigonella foenum graecum*) has a hypoglycemic effect due to its high soluble fiber content, which decreases the rate of gastric emptying and delays the absorption of glucose from the small intestine.[56-59] It also lowers cholesterol and triglycerides. There may be a cross-reaction if an individual is allergic to chickpeas.[60] Possible side effects include diarrhea, flatulence, and dizziness.[61-63] Furthermore, fenugreek preparations can contain coumarin derivatives and consequently could increase bleeding in a person with a blood dyscrasia or someone that is taking a blood thinning medication.[64] Since fenugreek is high in fiber, minerals and medications should be taken separately from fenugreek-containing products. Likewise, in one study, fenugreek

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Nutritional Supplements

- Chromium
- Alpha lipoic acid
- Magnesium
- Vanadium
- Vitamin D
- EPA/DHA
- Conjugated linoleic acid (CLA)
- Biotin
- Vitamin E
- L-carnitine
- L-carnosine
- L-taurine
- L-arginine

Botanical Supplements

- Berberine
- Ginseng
- Fenugreek
- Bitter melon
- Psyllium (fiber)
- Aloe vera
- Nopal
- Gymnema sylvestre
- Bilberry
- Cinnamon
- Green tea
- Olive leaf extract (500 mg BID)
- Green coffee bean extract
- Pycnogenol
- Ivy gourd
- Clove extract
- Maqui berry

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lowered potassium in a small group of people. Therefore, fenugreek may precipitate hypokalemia (low potassium levels) when used in combination with some laxatives or medications that lower potassium.[65] Also, decreases in the serum level of T3 and in the T3/T4 ratio, as well as an increase in the level of T4 have occurred in animals give fenugreek. Therefore, thyroid studies are suggested for individuals taking fenugreek.[66]

Bitter melon (*Momordica charantia*) is a tropical fruit widely used in Asia, Africa, and South America. It is also called bitter gourd. The precise mechanism of action is unknown. Hypothesized actions include the following: increased insulin secretion, increased glucose oxidation, and decreased hepatic gluconeogenesis.[67-70] Active components of bitter melon are charantin, vicine, and polypeptide-p (an insulin-like protein). Interestingly, a study on charantin found it to be a more potent hypoglycemic agent than tolbutamide.

Aloe vera in a single-blind, placebo-controlled trial of diabetics over two weeks showed improved blood sugar control.[71]

Nopal (*Optunia streptacantha*) is also called prickly pear cactus. It is high in fiber and pectin. Studies have shown its hypoglycemic (blood sugar lowering) effect.[72,73]

Gymnema sylvestre is an herb endemic to India. The common name is gurmar, which means "sugar-destroying." It has been shown in clinical trials to lower blood sugar.[74-76]

Cinnamon, cloves, bay leaves all have insulin-like or insulin-potentiating action in vitro.[77,78] Therefore, spicing up your life can help control/improve insulin resistance. Possible side effects of cinnamon include the following: GI upset, stomatitis, and perioral dermatitis.

Green tea in a study revealed that it contains insulin-enhancing activity through its predominant active ingredient of epigallocatechin gallate (EGCG).[79] EGCG was also shown to be a possible therapeutic agent for the prevention of diabetes mellitus progression. Another study showed that EGCG protected cytokine-induced B-cell damage, which is partly mediated by suppression of inducible nitric oxide synthase (iNOS) activity.[80]

Olive leaf extract contain oleuropein, which has been shown to lower blood sugar. It slows the digestion of starches into simple sugars and slows the absorption of simple sugars from the intestine. Furthermore, it Increases the uptake of glucose into tissues from the blood and lowers fasting insulin levels.[81-83] In animal trials, diabetic rats were given olive leaf extract. They had a significant reduction in their blood sugar and cholesterol.[84-85] In human trials, a study using 500 mg of olive leaf extract a day significantly lowered HGBA1C.[86] Another human trial revealed that olive leaf extract improved insulin sensitivity significantly in overweight middle-aged men.[87]

Green coffee bean extract has been shown to work like metformin in lowering blood sugar. It lowers after-meal glucose surges. One study showed that green coffee bean extract that was standardized reduced after-meal glucose by about one-third.[88]

Pycnogenol (*Pinus maritima)* is a standardized extract of French maritime pine bark. A study conducted on type II diabetics who were given 125 mg of Pycnogenol a day vs. placebo: individuals in the treatment group had lower HgBA1C, lower blood pressure, and lower LDL than before the study began.[89]

Ivy gourd (*Coccinia indica*) is an herb in the cucumber family. It helps insulin by its effects on lipoprotein lipase, glucose-6-phosphatase, and other glycolytic enzymes.[90] Two studies have shown that ivy gourd had significant glucose-lowering effects.[91-92] Dose: dried leaves or extracts at doses equivalent to 15 grams daily with meals. Ivy gourd has no known side effects.

Clove extract in a medical trial significantly lowered after-meal blood sugar levels. Dose: 250 mg before a meal with the most starches or sugars.[93]

Maqui berry extract has been shown to lower postprandial blood sugar and insulin. It also showed promise to lower HgA1C.[94,95]

Polyphenol: Bergamot

Bergamot juice is a polyphenol. There are a variety of phytochemicals that have been found in bergamot, including brutieridin and melitidin as well as other flavonoids, and flavones O-glucosides and C-glucosides. Bergamot has several main modes of action. Bergamot works directly on the insulin receptor, thus effectively lowering blood sugar.[96] In addition, bergamot blocks cholesterol absorption in the gut, like the plant sterols found in avocado, which is the major reason it is important to take bergamot before meals, i.e., to block the absorption of cholesterol and other fats following the ingestion of a meal.[97] Consequently, bergamot lowers total cholesterol, LDL cholesterol, and triglycerides. It also has been shown to raise HDL.[98,99] This polyphenol also works to block the rate-limiting step in cholesterol production known as the HMG CoA reductase enzyme, which is the enzyme that is blocked by statin drugs. However, bergamot works at a different site on this enzyme, and therefore it does not appear to affect muscles and the liver in the same way that statin drugs may. In addition, bergamot has anti-inflammatory action and is an antioxidant. 100 Dose: 800 mg twice a day.

Conclusion

As you have seen, it is important to treat insulin resistance early in the course of the disease. A conventional and personalized medicine approach to insulin resistance has a lot to offer so that every patient, hopefully, will be able to control insulin production and prevent type 2 diabetes. ◆

References and article are available online at www.townsendletter.com.

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Emerging from the Psychedelic Dark Ages – A Brief History of Psychedelics in the West, the War on Drugs, and Today's Psychedelic Renaissance

by Erica Zelfand, ND

The Psychedelic Renaissance is here, with powerful medicines like psilocybin, lysergic acid diethylamide-25 (LSD), and 3,4-Methylenedioxymethamphetamine (MDMA) back *en vogue*. But how did we get here? (Hold onto your seats, cosmonauts; we're going on a trip.)

The Debut of Psychedelics in the West

The history of psychedelic medicines is perhaps as old as humanity, with evidence of the shamanic use of mushrooms dating as far back as 5000 BCE in Algeria. The *soma* drink mentioned in the Indian *Rig Veda* between 1500 and 1200 BCE was likely a brew of psilocybin-containing mushrooms and honey. Mushroom-shaped statues from 1500 BCE are evidence of the medicine's sacred use in Central America.[1-4]

Psychedelic roots have also imbued elements of our modern-day practices, with the red-and-white color scheme of the *Amanita muscaria* mushroom reflected in Santa Claus' suit. The early shamans of Siberia were thought to use the mushroom to engender mystical visions and "fly" in the realms of psychedelic insight. Rather than eating the mushrooms directly and risk being poisoned, however, the healers likely collected and drank the urine of reindeer that had consumed the mushroom – hence the Christmas trope of the flying reindeer.[5,6]

Despite the long, rich history of entheogenic use around the globe, however, the so-called developed world was rather late to the proverbial party. It was not until 1941 that the Harvard-trained ethnobotanist Richard Evans Schultes published his doctoral thesis on the identity of two hallucinogenic plants of Oaxaca, Mexico. His paper on the mushroom *teonanácatl* (*Psilocybe mexicana*) and the morning glory species *ololiuqui* (*Turbina corymbosa*) was groundbreaking yet largely ignored at the time, perhaps on account of the eruption of World War II in 1939.[7]

It would not be until at least 1957 that Americans would take an interest in psychedelic mushrooms, when Maria Sabina became the first Mexican modern-day *curandera* to serve *los hongos* (mushrooms) to a Westerner. Her client, the American amateur mycologist R. Gordon Wasson, husband of Dr. Valentina Pavlova Wasson, published a photo essay in *Life* magazine in 1957 describing his experience with the so-called "magic mushrooms" – and the rest, as they say, is history. It is rumored that the Beatles, Bob Dylan, and a host of other *gringos* (both famous and not) flocked to Sabina's home village of Huatla de Jimenez, Oaxaca, to consume *los hongos* (this author being one such adventurer, though decades later than the celebrities).[8-11]

1965 Acid Test Flyer

But back to the late 1930s, when Schultes' papers were published and the world was rattled by the war, across the ocean, a Swiss chemist by the name of Albert Hofmann was working with

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various derivatives of ergot in hopes of developing a new cardiovascular drug. In the fall of 1938, Hofmann synthesized the twenty-fifth derivative of ergot, lysergic acid diethylamide-25 (LSD-25, or simply LSD). Initially dismissive of the derivative's value, Hofmann forgot about it for five years. Inspired perhaps by intuition, Hoffman revisited the molecule in 1943, intentionally ingesting what he believed to be a miniscule amount of the substance. Hofmann then rode his bicycle home in the throes of what is now understood to be the world's first-known "acid trip," and which to this day is celebrated annually on April 19th as "Bicycle Day."[12]

Although the psychedelic trip Hofmann experienced was more terrifying than glorious, it was clear he had stumbled upon a powerful compound. LSD-25 was branded "Delysid," and Sandoz Laboratories began an international crowd-sourcing project to research commercial applications for the drug. Between 1949 and 1966, Sandoz Laboratories provided researchers (and clinicians willing to take notes) virtually unlimited quantities of the drug in exchange for their observations and insights.[13,14,15]

Between 1953 and 1973, the United States federal government too took interest in LSD-25. Four million dollars were spent funding 116 studies on the drug in research involving 1,700 subjects. Those numbers do not include the Central Intelligence Agency (CIA)'s classified research, done under the code name MK-Ultra. With the country engaged in the Vietnam War (November 1, 1955 – April 30, 1975), MK-Ultra focused on how LSD-25 could be used for mind control or otherwise weaponized. Some of the MK-Ultra studies were illegal; others downright unethical.[16-18]

One MK-Ultra research subject was Ken Kesey, who in 1960 was paid to take LSD-25 in a study. Kesey's novel *One Flew Over the Cuckoo's Nest* was published two years later, in 1962. (The novel, Kesey explained, was less a book about mental illness than a story of how society pushes away those who do not conform.) In 1964, Kesey banded together with his friend Neal Cassady and their entourage of "Merry Pranksters" to introduce thousands of people to LSD-25 at "Acid Test" parties, which were often graced by the music of the Grateful Dead. Their Day-Glo painted *Furthur* bus is to this day an icon of the Hippie Generation.[19,20,21]

The psychologist Timothy Leary, PhD, was also among those experimenting with psychedelics. After reading Wasson's *Life* article, the Harvard University professor traveled to Mexico in 1960 to try the psilocybin-containing mushrooms for himself. With the approval of the psychology department's chair, Leary and his associate professor Richard Alpert, PhD, founded the Harvard Psilocybin Project. The two professors then administered psilocybin – and later LSD-25 – to hundreds of people in studies that often lacked a control group. Their research was criticized not only for its party-like atmosphere, but also for the researchers' tendency to take drugs themselves alongside their subjects, some of whom were undergraduate students at Harvard. In 1963, both men were fired from Harvard University, but it was too late: the psychedelic movement had escaped the lab. Leary continued his work with psychedelics; Alpert went to India and returned as the spiritual teacher Ram Dass. In 1971 Ram Dass authored *Be Here Now*, a book on yoga, meditation, and spirituality that some have described as the Bible of the Hippie Generation.[22,23,24]

Unsurprisingly (at least in retrospect), turning thousands of young people on to powerful psycho-active substances did not always yield sunny outcomes. By the mid-1960s American emergency rooms were regularly visited by distressed and bewildered folks complaining of "bad trips" – an phenomenon that turned much of the medical community off of psychedelics altogether.

Nineteen sixty-seven (1967) marked the Summer of Love in the United States, with approximately 100,000 people converging in San Francisco. Two summers later, in 1969, the Woodstock Music Festival took place, at which half a million people gathered for "three days of peace and music" (plus sex and drugs). In November of that same year, growing opposition to the Vietnam War climaxed in the largest antiwar demonstration in United States history.[25,26]

The War on Drugs

Despite the US government's initial enthusiasm for researching psychedelic compounds, the merits of the drugs were ultimately dismissed with Nixon administration's Controlled Substances Act of 1970. It has been suggested that Nixon's anti-drug stance had less to do with a legitimate concern for public safety than with a disdain for certain demographics – namely Blacks and anti-war hippies.[27]

John Daniel Ehrlichman, counsel and assistant to the President for domestic affairs during the Nixon years, once summarized it like this:

> The Nixon White House… had two enemies: the antiwar left and black people. You understand what I'm saying? We knew we couldn't make it illegal to be either against the war or blacks, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did.[28]

Nixon – who was himself no stranger to alcohol or prescription drugs – once described Leary as "the most dangerous man in America."[29,30]

The 1970 Controlled Substances Act created five schedules used to classify drugs based on their abuse potential, accepted medical use in the USA, safety, and potential for addiction.[31] Drugs placed in Schedule I became illegal overnight,

Amanita muscaria

categorized as having a high potential for abuse and no accepted medical use. Medicines categorized as Schedule I drugs to this day include LSD-25, cannabis, and heroin.[32]

The term "War on Drugs" was popularized by the media after a press conference on June 18, 1971, in which Nixon referred to drug abuse as "public enemy number one." In 1973, the Drug Enforcement Administration (DEA) was created.[33,34]

During the presidency of Ronald Reagan (1980 – 1988) MDMA, the active constituent of the street drugs "Molly" and "Ecstasy," was added to Schedule I, despite the fact that the drug had shown promise as an powerful adjuvant to psychotherapy.[35]

History of MDMA

3,4-Methylenedioxymethamphetamine (or MDMA) was first synthesized from an extract of sassafras by Anton Kollisch, a German chemist working for Merck. On December 24, 1912, Merck filed two patents on the molecule under the name "methylsafrylaminc."[36]

Although both Merck and the United States Army experimented with the molecule – mainly in the 1950s – it was not until the mid-1970s that MDMA's psychotherapeutic potential was first glimpsed. In search of an alternative to 3,4-methylenedioxy-amphetamine (MDA), which was made illegal in 1970 by the CSA, the American chemist Alexander T. Shulgin began tinkering in his laboratory. Shulgin re-synthesized MDMA and, in 1978, co-published a paper with David Nichols on the molecule's psychoactive properties. Appreciative of the benign, heart-opening, and non-hallucinatory properties of MDMA, Shuglin referred to the drug as his "low-cal martini" and passed it on to psychotherapists like Leo Zeff, PhD (AKA "The Secret Chief"), and Shulgin's own wife, Anne, a Jungian psychologist who is celebrated to this day as the matriarch of the psychedelic movement. The use of MDMA spread to other therapists, who used the substance with their clients as a therapeutic "lubricant," especially within the context of couples' therapy.[37-39]

Like many consciousness-enhancing substances, MDMA held value not only therapeutically, but also recreationally: in the 1980s MDMA (or "Ecstasy") became popular in the techno dance cultures of the United States and United Kingdom.

At the same time, the crack cocaine epidemic was ravaging inner cities of the USA, and the Reagan Administration was keen to respond. Nancy Reagan launched her Just Say No campaign, and the Drug Abuse Resistance Education (DARE) program was launched.[40,41] (Curiously, a meta-analysis from 2004 concluded "that D.A.R.E. is ineffective," and a 2009 meta-analysis of 20 controlled studies revealed that those who attended the DARE program were just as likely to abuse drugs as those who had no intervention.[42,43])

In 1985, MDMA was added to Schedule I, in a move perhaps akin to throwing away the proverbial baby with the bathwater (the baby being MDMA; the bathwater crack cocaine). The American psychotherapist Rick Doblin, PhD, sued the DEA in an attempt to block the total criminalization of MDMA. Many witnesses testified in support of the molecule, including psychiatrists who spoke of the drug's compelling therapeutic applications. Doblin won: DEA law judge Francis Young ruled that MDMA should be classified as a drug with a moderate to low potential for physical and psychological dependence, available prescription-only – and ergo placed in Schedule III. (Other drugs in Schedule III include acetaminophen with codeine, testosterone, and ketamine.[44]) Young's recommendation was rejected by the head of the DEA, however, and MDMA was categorized as a Schedule I drug.[45,46]

In 1986, Doblin created the Multidisciplinary Association for Psychedelic Studies (MAPS), an organization that has since fought to encourage more research on MDMA and other psychedelic compounds.[47]

Nineteen eighty-six (1986) also marks the year in which the Anti-Drug Abuse Act was passed. The law, which was signed by Reagan, substantially increased the number of drug offenses (including those related to cannabis) with mandatory minimum sentencing. This zero-tolerance policy directly contributed to an increase in nonviolent drug arrests and higher rates of incarceration in America. The Act instituted a five-year minimum sentence – without parole – for those convicted of possessing either five grams of crack cocaine (a drug more commonly used by poor Americans, in particular Blacks) or 500 grams of powder cocaine (an expensive preparation more commonly used by affluent Caucasians). This penalty disparity of 100:1 has been criticized as inherently racist. Regardless of the intention, the Anti-Drug Abuse Act certainly affected the Black community more adversely than the White: Prior to the enactment of the Act, African Americans were subject to 11% higher federal sentences for drug possession/sales than Whites; by 1990, that rate swelled to 49%.[48]

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Summary of the DEA Drug Schedule. Compiled using information from https://www.dea.gov/drug-information/drug-scheduling

DEA	Explanation	Examples
Schedule I	No currently accepted medical use. High potential for abuse.	Heroin, Cannabis, LSD, MDMA, Peyote
Schedule II	High potential for abuse. Use potentially leading to severe psychological or physical dependence. Considered dangerous	<15 mg hydrocodone per dosage unit (Vicodin), Methamphetamine, Methadone, Oxycodone, Cocaine, Adderall, Ritalin
Schedule III	Moderate to low potential for physical and psychological dependence.	<90 mg codeine per dose (Tylenol w/ codeine), ketamine, anabolic steroids, testosterone
Schedule IV	Low potential for abuse. Low risk of dependence.	Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, Tramadol
Schedule V	Lower potential for abuse.	<200 mg codeine per 100 mL (Robitussin AC), Lomotil, Lyrica, Parepectolin

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The War on Drugs did not stop the personal and recreational use of psychedelic substances so much as it drove it underground. What the War did do, however, was thwart decades of research – research that the medical community desperately needed, given the alarming rate at which depression and other mental illnesses have been steadily climbing (even pre-pandemic).[49] The criminalization of psycho-spiritual medicines like psilocybin, LSD-25, and MDMA did to psychological research what kinking a hose does to the flow of water.[50]

Water Returns to the Well: The Psychedelic Renaissance

Due to the persistent efforts of groups like MAPS and the Beckley Foundation, the generous donations from private parties like Tim Ferris, the courage of clinicians and researchers willing to risk it all, and a robust awareness-raising campaign (sweeping from the Joe Rogan podcast to Michael Pollan's two most recent books), we are once again able to research these unique molecules and consider their therapeutic applications.

After a lull of decades, in 1998, researchers led by Franz X. Vollenweider, PhD, at the University of Zurich published the first post-Drug War study on psilocybin,[51,52] effectively cracking the seal on a new generation of psychedelic research. Since then, Vollenweider has authored or co-authored over 90 studies on psychedelic compounds.[53]

In 2000, researchers at Johns Hopkins University obtained regulatory approval to research the effects of psychedelics in healthy volunteers. Psilocybin studies were followed by research focused on LSD-25.[54] Research into ayahuasca, MDMA, and other entheogenic substances quickly followed: Scientifically robust studies on psychedelics are now easy to find in PubMed. Most of the current studies are funded by non-profit organizations like Johns Hopkins' Center for Psychedelic and Consciousness Research (CPCR), the Centre for Psychedelic Research at the Imperial College of London, the Beckley Foundation, and MAPS. A newcomer to the effort is the Center for Neuroscience of Psychedelics at Massachusetts General Hospital, the original teaching hospital of Harvard Medical School.

What was once a choked garden hose is now a steady stream of science.

Psychedelic compounds have been shown to effectively help with a variety of ailments, including depression,[55,56,57] treatment-resistant PTSD,[58] social anxiety in those on the autism spectrum,[59] eating disorders,[60] obsessive-compulsive disorder (OCD),[61] anxiety in those with terminal illness,[62] and Parkinson's disease.[63] Psychedelics have also shown promise in the treatment of various drug addictions,[64] including nicotine,[65] opioids,[66] alcohol,[67] methamphetamine,[68] and crack cocaine addictions.[69] (Note: the references peppering this paragraph are far from an exhaustive list of indications or studies.)

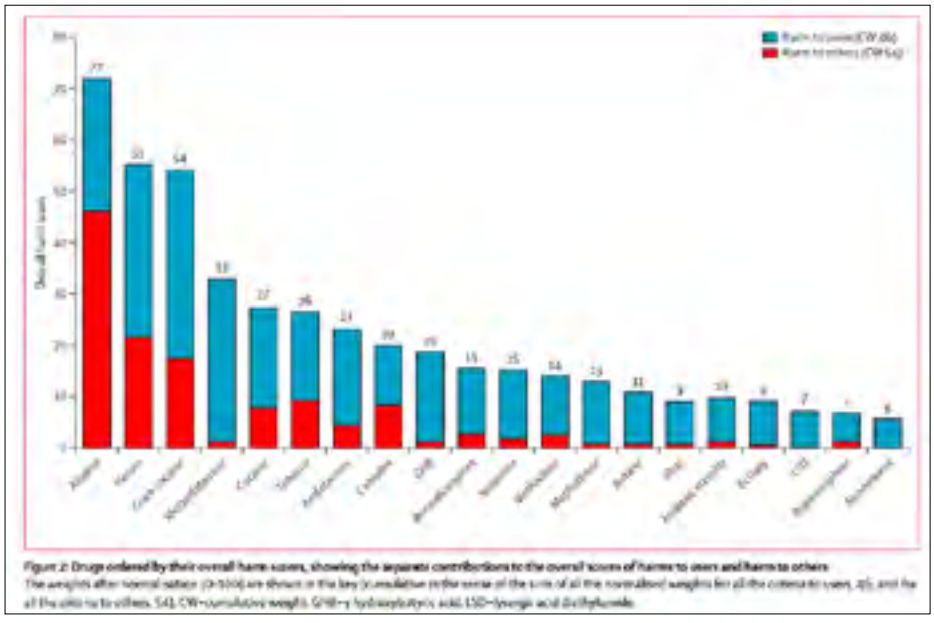

Image from Nutt DJ, King LA, Phillips LD. Drug harms in the UK: a multicriteria decision analysis. *Lancet*. November 6, 2010:376(9752);1558-65. Used with permission.

Dr. Z with Maria Sabina mural in Sabina home in Huatla de Jimenez, Oaxaca, Mexico

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The research has also shown that these once villainized compounds are not nearly as dangerous as once believed. In fact, a 2020 German analysis ranking the risk of harm associated with various drugs ranked methamphetamine, heroin, alcohol, and cocaine as the most harmful drugs. At the opposite end of the graph, non-steroidal anti-inflammatory drugs (NSAIDs) and triptans were found to be the least likely to cause harm. Psychedelics and cannabis fell somewhere in the middle.[70]

A similar analysis out of the United Kingdom ranked various "recreational" substances in order of most to least harmful, including both risk to the user and risk to others.[71] The authors ranked alcohol as the most harmful drug, with heroin and crack cocaine in second and third place, respectively. The least harmful drugs on the ranked scale were ecstasy, LSD, and mushrooms.[72]

Psilocybin (the active constituent in "magic mushrooms") has been granted breakthrough therapy status twice by the United States Food and Drug Administration (FDA) – first in 2018 for the treatment of treatment-resistant depression, and again in 2019 for the treatment of major depressive disorder.[73] Cities around the country are voting to decriminalize the psychedelics, and in 2021 the state of Oregon not only decriminalized the possession of all "recreational" drugs in small quantities, but also legalized psilocybin-assisted therapy, being the first state in the USA to do so.[74]

Bicycle Day themes LSD blotter paper

The legalization of MDMA at the federal level is perhaps soon to follow.[75] In January 2020, the FDA approved an expanded access program for MDMA-assisted psychotherapy, allowing 50 patients with post-traumatic stress disorder (PTSD) to legally access treatment outside of Phase 3 clinical trials. The purpose of the Expanded Access program (which is also called "Compassionate Use") is to allow people living with a serious or life-threatening condition to access potentially helpful investigational therapies.[76] A similar program was approved in Israel in 2019.[77]

The secret is out: psychedelic substances are medicines.

The Psychedelic Dark Ages are behind us. ◆

References and article are available online at www.townsendletter.com.

Photobiomodulation as a Treatment Modality for COVID-19 Sequelae

by Peter Newsom, MD

Introduction

The short-term effects of COVID-19 on public health have been well documented. However, COVID-19 has also become increasingly associated with various long-term cognitive and behavioral difficulties, which are often chronic and may be permanent. Patients experiencing these challenges are referred to colloquially as "long-haulers."[1]

The most common cognitive and behavioral difficulties encountered by long-haulers include "brain fog" (an inability to think clearly or concentrate)[2] and chronic exhaustion. The latter is similar to chronic fatigue syndrome,[3] and is often referred to in the literature as myalgic encephalitis/chronic fatigue syndrome (ME/CFS).[4,5] The foregoing challenges manifest themselves in 10% to 60% of all COVID-19 infections[6] and may occur even in mild or even completely asymptomatic infections.[6] Other neurological symptoms encountered with long-haulers include a feeling of disorientation or confusion, an inability to feel fully awake, mood swings, and patterns of irritability or emotional lability.[7]

Patients recovering from a COVID-19 illness may exhibit permanent brain damage in various forms. This damage may manifest itself as large, radiographically visible lesions (such as ischemic infarcts), intracranial hemorrhages, venous thromboembolism, MS plaque aggravation, diffuse leukoencephalopathic changes, supratentorial deep and subcortical white matter changes, and punctate microhemorrhages.[8-10] In many of these cases, the neurologic deficits may be considerable, and may result in significant and permanent neurological and psychiatric morbidities or disabilities.[11]

In this paper, we identify some of the possible physiological origins of the cognitive and behavioral difficulties encountered by long-haulers and propose a low-risk treatment modality that may help to ameliorate them. This treatment modality, known as photobiomodulation (PBM), is ideally accompanied by synchronized sound and augmented with a technique known as gamma flicker. PBM may provide an effective form of treatment for the long-term symptoms experienced by long-haulers that have proven resistant to other treatment modalities.

Brain Physiology

The potential of PBM in treating the long-term symptoms associated with COVID-19 may be appreciated within the context of brain physiology and a few of the anatomical aspects of virally induced brain trauma.

Many of the routine cognitive functions performed by humans on a daily basis require the simultaneous participation of multiple, widely separated locations of the cerebral cortex known as cortical lobules. These lobules interact with each other via a series of long tracts of nerve fibers known as white matter.[12] White matter allows the cortical lobules to coordinate their activities in carefully regulated degrees of coherence, at times requiring higher degrees of coherence, and at other times requiring lower degrees of coherence.[13,14] Ultimately, the ability of cortical lobules to work together with the proper degree of coherence allows the human brain to perform many of the higher functioning tasks that are necessary and commonplace in daily life.[15]

For example, the act of reading requires the coordinated functioning of multiple lobules located in the visual cortex areas and in both prefrontal cortical areas, and further requires the participation of lobules located in the left temporal areas that are associated with the understanding of human speech.[16,17] These disparate lobules are linked by long tracts of white matter and must interact with each other in the requisite manner, and with the necessary degree of coherence, to make reading possible.[18,19] In this respect, these long tracts of white matter may be thought of conceptually as part of the circuitry of the brain. However, the brain is a biological machine and all of its components are living matter. Hence, unlike the inert circuitry found in common electrical devices, the tracts of white matter within the brain form a circuitry that is pulsing with life and is actively working.

How the "Weak Link in the Chain" Can Have Consequences

In order to perform common cognitive functions such as reading, it is necessary for disparate lobules within the brain to be working properly and at their normal, incredibly high rates of speed. Since these lobules must operate in concert, all of the long fiber tracts of white matter extending between them must be functioning properly.[20,21] If any link in this fragile chain is compromised, then the associated cognitive functions may become difficult or impossible to perform.[22] Hence, the aphorism that "A chain is only as strong as its weakest link" is applicable when considering the consequences of physiological trauma to the brain, such

as those accompanying a COVID-19 infection.[12]

It will be appreciated from the foregoing that the loss of any discrete cognitive ability as a sequelae to a COVID-19 infection does not require that the entire brain be affected. Rather, a decrease in function can result from any area of impaired functionality. This impairment may arise from disruptions occurring in cortical lobules necessary to the circuit, or from damage to any part of the white matter linking these lobules. Moreover, any of these injuries may prove to be permanent or temporary.

We now have a simple picture to begin with in assessing the long-term effects of a COVID-19 infection. Namely, after the infection resolves, the brain may have suffered damage that manifests itself as one or more neurological symptoms. This damage may occur broadly across wide swaths of the cortex as well as in the deeper parenchyma.[23-25] It may also present as smaller areas of injury peppered across the brain,[26,27] or as a single small area of injury[27,28] that happens to be present in a critical cortical area[29] or a critical long tract connecting cortical areas essential to the function in question.

It was recently noted that the MRI of COVID-19 brains showed white matter "littered with tiny lesions."[27] These lesions were posited as a possible cause of neurological problems encountered in COVID-19 patients, including memory lapses, difficulty in concentrating or finding words, or stuttering. In brief, any injury anywhere in the circuit can cause impaired function.

Latent Viruses and Their Impact on the Brain

Different temporal patterns of neurologic injury may result from viral infections. In many types of viral infections, delayed "post viral syndromes" occur,[30] such as those encountered after infection with influenza, mononucleosis, measles, and hepatitis B. This phenomenon is observed in post-COVID-19 patients as well.[5] In some viral infections, delayed syndromes only occur long after the acute illness has ended. In the case of chickenpox, for example, the virus remains in the body in an inactive form (possibly for decades) after the initial infection, during which time the body appears completely normal. At some later point in time, the virus reemerges to wreak havoc in the form of shingles.[31]

The Impact of COVID-19 on Our Immune System and the Brain

Viral infections affect the brain via different pathophysiological pathways.[32,33] In some cases, the virus itself does not actually reach the brain, but nonetheless induces brain pathology. In fact, until recently, many viruses were not thought capable of penetrating the brain tissue itself. This belief was premised on the supposed existence of the so-called blood brain barrier (BBB), a special type of vasculature that segregates the brain from the circulatory system.[34]

The BBB is a unique structural characteristic encountered in the arteries supplying oxygen and nutrients to the brain. Within these arteries, endothelial cells (cells which may be anatomically ➤

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envisioned as tiny bricks that form the tubular walls of the brain's arteries) are attached to each other by "tight junctions." These tight junctions may be visualized as a dense or impenetrable "mortar" between the bricks. Together, the endothelial cells and tight junctions form a wall, which is theoretically impenetrable to the virus.[35,36]

In some viral infections, the virus is believed to remain entirely blood-born, a condition known as viremia.[37] In these infections, the virus appears not to actually enter the brain parenchyma itself but can nevertheless cause defects of a cognitive nature. These defects may arise, for example, from the body's immune response to the virus or from virulence factors associated with the virus.[38]

One new piece of this pattern may be found in recent research regarding the immune system, whose immunoglobulins and cytokines are also usually unable to get through the BBB.[39,40] According to this research, these complex molecules are able to attach to endothelial cell wall receptors located on the intravascular side of the endothelial cells.[41,42] This appears to then trigger subsequent immune signaling cascades on the parenchymal side (that is, the outside) of those same endothelial cells, thereby allowing these molecules to direct immune events in the brain tissue outside of the bloodstream.[43] These immune events then include the microglia, which are the brain's own immune cells.[44] This suggests a possible mechanism by which viruses in the bloodstream may be able to communicate with, and influence, the brain's immune system.

Virally induced damage to the brain can also vary temporally, resulting in temporary or long-term brain dysfunction. In the case of herpetic viral cerebritis known to occasionally affect pregnancy, diffuse damage may occur to the cortex, resulting in long-term scarring.[45] One consequence of this could be seizures which may be temporary, long-term, or permanent. The scarring and other damage resulting from these infections can also lead to the acute or delayed onset of a variety of psychiatric or cognitive disorders, which themselves may be long-term or permanent.

References and article are available online at www.townsendletter.com.

How Is the Brain Affected by a Viral Attack?

The brain is protected by both humoral and cellular immunity.[46] This is due to the presence in the brain of its own dedicated immune system, as well as the presence of immune cells and cytokines that arrive at the brain via the blood supply from other parts of the body (such as, for example, the spleen and thymus).[47] However, viruses have developed multiple workarounds to these measures, resulting in various forms of possible injury to the brain. Recent work[27,48] has demonstrated the ability of COVID-19 infections to penetrate into the brain parenchyma, and other work has shown its ability to enter the brain in mice. Others have shown that, in some cases, SARS-CoV-2 can enter the nervous system by crossing the neural–mucosal interface in olfactory mucosa, after which it follows neuro-anatomical structures and penetrates defined neuroanatomical areas, including the primary respiratory and cardiovascular control centers in the medulla oblongata.[49] However, even if the SARS-COV-2 virus does not enter the human brain, viruses in general are known to cause damage to the brain by virtue of the immune response they unleash.[50] In some instances, viral infections are known to trigger a massive release of immune molecules (including cytokines and chemokines, as well as other inflammatory markers), thus resulting in a particularly powerful immune reaction within the body and brain known as a cytokine storm.[51] Cytokine storms can result in further impairment of BBB function, ultimately resulting in injury to critical brain cells such as neurons and astrocytes.[52] Cytokine storms can also result in the activation of microglia (the brain's immune cells), possibly leading to further neuroinflammation and neuronal death.[53] The effect of the SARS-COV-2 virus on the body may be further understood from the perspective of the body's immune response, which includes the innate immune system and the adaptive immune system.[53] The innate immune system functions as a "ready to fire" system, standing by at all times during healthy homeostasis, and ready to repel infections within minutes of the body sensing the presence of any pathogens. The body, in general, and the brain, in particular, have the ability to recognize a wide variety of pathogens, and are also equipped with a store of premade immune biochemicals and immune cells with which to attack them.

The adaptive immune system works in cooperation with, and closely on the heels of, the innate immune system. The adaptive immune system takes a much longer time to attack, often requiring a week or more of preparation before fully responding. During this preparatory period, the adaptive immune system learns to recognize the invading pathogens, ostensibly by cutting them into molecular pieces and chemically recognizing (and subsequently chemically attacking) these molecular pieces and parts.

What Is Known About Our Immune System's Ability to Respond to COVID-19?

As previously noted, viruses have developed multiple workarounds for infecting the body, and these workarounds can result in various forms of injury to the brain parenchyma. First, the COVID-19 infection may be able to penetrate into human brain parenchyma. Second, certain deleterious side effects on the brain resulting from the body's overall immune response to COVID-19 infections have been noted.[54] It appears that the SARS-COV-2 virus has developed some very powerful abilities to disable or weaken the initial innate immune response (the first line of the human immune response), thus causing it to work inadequately.[55] Consequently, the virus is able to replicate within the body in the absence of some of the usual early checks on viral replication. This allows the virus to quickly flood the body with a high viral load.[56] As a result, the viral invaders may only come under full attack much later in the immune response when the adaptive immune system finally begins producing specific antibodies. Given the advanced state of the infection at this point in the process, the resulting immune response may need to be much stronger and more overwhelming to accommodate the greatly increased viral load. This situation may account for the dramatic escalation of the immune response and the resulting cytokine storm often observed in severe COVID-19 infections.[57] A recent article posits that Covid-induced blood flow changes may contribute to

brain fog via damage to capillaries, then resulting in decreased O2 delivery to the parenchyma. Thus, capillary damage and persistent inflammation may contribute to these long-haul syndromes, even long after the acute illness is over, resulting in problems with memory, as well as anxiety and depression. It is also a possibility that the decreased O2 delivery plus increased inflammatory markers could also lead to decreases in serotonin, resulting in mood as well as cognitive changes.[54]

The term "cytokines," as mentioned above, refers to a group of complex protein molecules that serve as signaling molecules to orchestrate the immune response to an infection. These cytokines are not precise in their ability to target exactly where the immune response will actually occur. Rather, the immune attack assumes more of a shotgun approach, and while many of the invading virus particles are hopefully attacked by the indiscriminate fire, significant damage may also be done to the body's own tissues present at the scene. This fact would then presumably result in all the more extensive damage to nonviral bystander cells in the event of any overwhelming generalized immune response, such as a cytokine storm.[58]

The foregoing results in significant injury to healthy body tissues and entails the death of some of the body's own healthy cells. The resulting battle scene leaves behind a significant amount of debris in the form of destroyed virus particles and human cellular debris. If the COVID-19 infection is sufficiently severe, the immune system's efforts to repair the areas of damaged tissue may leave long-term or permanent scarring in the form of tissue that is now quite possibly less elastic and less able to function *physiologically* in all the ways the previously normal brain parenchyma would have functioned. In addition, any damage to the capillaries supplying the brain could presumably further impair physiological function, whether by causing tissue hypoxia or by decreasing the body's ability to deliver other essential factors needed for healing.[59]

It will be appreciated from the foregoing that, regardless of whether or not the SARS-COV-2 virus actually enters the brain parenchyma during a COVID-19 infection, damage to the brain can theoretically occur simply due to the immune response unleashed by the body's immune response to the virus. In instances where viral infection appears to trigger a massive release of immune molecules, the resulting cytokine storm can further compromise the BBB.[60] The compromised BBB may then result in increased leakage of these same cytokines into the brain.[39] This may lead to further injury of critical brain cells such as neurons and astrocytes and microglia, as well as the activation of microglia. The extent to which these events ultimately lead to neuroinflammation and neuronal death will vary from case to case.[61]

Large segments of the population could well be described as significantly light *deprived.*

After the acute immune response to the virus has concluded, the body attempts to return to a normal, pre-COVID-19 state, a process referred to in physiology as homeostasis.[62] However, especially in the case of events activating the body's immune and inflammatory systems, this resolution is sometimes incomplete.[63] This may be due to the fact that cytokine signals that might promote strong immune responses or resolution of those immune processes in other areas of the body may have to go through very different mechanisms when it comes to the brain. Moreover, the brain also has its own set of immune cells specialized for the brain (microglia). These cells live within the brain parenchyma. When they become activated, they take part in the killing of bacterial or viral invaders and in the subsequent cleanup.[64,65] However, many aspects of the immune processes that occur within the brain are still poorly understood.

The brain is also known to be generally less able to clean up certain kinds of debris than is the rest of the body. A good example of this is observed when there is bleeding within the brain. When this happens, the hemoglobin protein molecules that leak into the brain parenchyma can be effectively removed and reabsorbed.[66] However, the iron content of hemoglobin is not as effectively resorbed, and instead, the iron content of the exsanguinated blood can remain in the form of clumps (called hemosiderin or hemosiderin crystals or particles), which then can remain in the brain far longer than the nonferrous protein portion of the hemoglobin molecule.[67,68] These hemosiderin deposits, which have been associated with the pathogenesis of SARS-CoV-2,[69] can be an indicator of diffuse axonal injury.[53] The amount and location of hemosiderin can be correlated with such neuropsychological deficits as difficulty with memory and also speed-of-processing tasks.[53] Although small, these particles and the axonal injury that accompanies them can disrupt the function of the (frequently extremely small and very finely tuned) neuronal fibers in long tracks.[70] Originally, these fibers are precisely grouped together in neuronal tracts and are able to efficiently allow information to move around the brain. However, even minute deposits of hemosiderin crystals or diffuse axonal injury can result in disruption of these fibers and therefore also their respective nerve tracts, resulting in significant impairment of higher cognitive abilities.[70,71] As previously noted, any weakening in any part of the chain of any brain circuit can have very significant consequences in terms of the disabilities a patient may suffer as a result of an injury.

How Can We Imagine or Conceptualize an Attack on the Brain Resulting from COVID-19?

As previously noted, once the SARS-COV-2 virus has been allowed to replicate unimpeded for a longer period of time than usual, the resulting viral load may induce an increased immune response. This response may be overwhelming and may reach the level of a "cytokine storm." Immune responses of this type may result in extensive diffuse or localized damage across a few or many areas of the brain. The foregoing results in significant amounts of cellular and viral debris, which gives rise to a final resolution that may include various patterns of brain scarring.

As previously noted, the weakening of any small link in the chain of any brain circuit can disrupt the entire function of the circuit, especially in tasks requiring large separate networks of neuronal groups spread across the brain. While ➤

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neurons existing in a given area of the brain *prior* to any neuronal depletion or thinning in the neuronal ranks due to the COVID-19 infection were presumably perfectly able to carry out their part in whatever large brain network they may have been part of, it may not take much cell destruction, scarring, or capillary injury, or hemosiderin crystals to disrupt or even completely disable the entire circuit. As an example of how sensitive the brain could be to such injury, any remaining neurons in any injured part of the circuit (if there are any) may now be unable to handle the (now increased) load of information processing required for the function of the circuit.

Significant scarring and neuronal loss are likely results of a severe COVID-19 infection,[72] leading to areas of brain with depleted energy reserves. Neurons are very high energy consumers. Although the brain only accounts for a few percent of our total weight (from 1% to 3% for most adults), it accounts for 20% to 30% of the body's total energy consumption.[71] Neurons are incredibly energy-hungry, in part because they contain a large number of mitochondria.[73] Mitochondria are the ATP generating organs of all cells. In many parts of the body such as adipose tissue, there are comparatively few mitochondria in a given cell. In the average neuron, by contrast, there may be tens of thousands of mitochondria,[74] due no doubt to the inherent metabolic needs of the other organelles contained within that neuron, as well as their various functions within that neuron. The presence of such a large number of mitochondria in typical neurons therefore reflects the underlying fact that the neuron is an energy-hungry type of cell and is evidence of that fact.[75] (This fact also has therapeutic implications, which will be described later in this paper.)

In light of the foregoing, it is conceivable that, when parts of a nerve tract have been partially or completely impaired, the strain on the remaining still functional (or partially functional) neurons may be high enough to quickly deplete them of their ATP stores. This may result in diffuse patterns of neuronal exhaustion, due to the presence of groups of depleted or injured neurons that are thereafter unable to keep up with the processing demands that had previously been spread across a much larger number of healthy cells. These patterns of repetitive neuronal exhaustion could then occur for months, or possibly indefinitely.

Interestingly, this pattern may well account for a symptom pattern that chronic fatigue sufferers often refer to,[76] in which they describe waking up in the morning with enough energy to concentrate or perform some simple task for, say, an hour, and then suddenly feel so depleted that they are then unable to get out of bed for the rest of the day. Such a temporal pattern of exhaustion could be explained by isolated yet critical areas of brain injury (very possibly in the reticular activating system (RAS), for example, an area responsible for maintaining a normal state of being and feeling awake) developing significant ATP depletion[77] upon comparatively brief exertion. This depletion can then only be repaired quite slowly (by, for example, sleeping through the night), during which downtime the ATP stores in the affected neurons can slowly be regenerated[77] – resulting in a repeat of this pattern the following morning.

The foregoing underscores the importance of the concept of the weak link in the chain: a small percentage of damaged or destroyed neurons in one localized area may be enough to render that entire circuit incapable of functioning at all or functioning as it used to, even though it may be a circuit essential to a key activity such as feeling fully awake. This may also include a number of particular circuits necessary for tasks demanding lots of concentration, the very sort of task many suffers from COVID-19 brain fog now complain of being no longer able to carry out, or of being able to carry out for only a short period of time before becoming exhausted.[78]

The foregoing presents a very rough picture of brain parenchyma that has been injured, either in small, localized areas or in a more diffuse pattern. The end result includes a significant amount of scar tissue spread or peppered across brain areas wherein a smaller group of neurons are now required to do the work previously shared by a larger number. This situation results in work that was previously accomplished quite well now being performed poorly or possibly intermittently, followed by periods of incomplete or complete dysfunction. Moreover, the smaller number of overworked neurons performing the task repeatedly tire out (partially or completely) until they can recharge their mitochondrial batteries.

As a further complication, the brain's immune system may also be significantly depleted or exhausted from the heavy task of cleaning up all the cellular and viral debris scattered throughout the injured parts of the brain. This may render the brain more prone to reinfections or to entirely new infections with other pathogens. Furthermore, the microglia, the brain's own specialized immune cells, may themselves also be exhausted, injured or decreased in number, due to the ability of the Covid infection, or the body's reaction to the virus, to attack microglia just as it is able to attack neurons.

Possible Therapeutic Ramifications

We believe that photobiomodulation (PBM) is a modality that should be considered for cases of post COVID-19 cognitive impairment for the following reasons.

PBM with red and near infrared (NIR) light (600 to 700 nm, and 760 to 940 nm respectively) has been shown to have various beneficial effects[79,80]:

- Increase synapse formation,[81]
- Increase BDNF (brain derived neurotrophic factor),[82]
- Increase glucose metabolism,[83]
- Increase antioxidant levels,[80]
- Decrease inflammation,[84]
- Decrease edema.[85]

PBM has been shown to increase brain circulation through the creation of new arterial blood vessel growth, a known effect of red and near infrared wavelengths.[86]

PBM has also been shown to interact directly with the mitochondria and to help generate ATP and increase mitochondrial membrane potential, O2 consumption, and ATP production, all of which promotes energy generation and mitochondrial metabolic health for the efficient transport of energy within cells.[87]

PBM with a 40hz (Gamma) synchronized light and sound has also been shown to possibly increase microglial activity, specifically improving phagocytosis of parenchymal debris.[88]

PBM with Gamma flicker has also been shown to facilitate the replacement and/or resumption of neuronal functions in 5xFAD mice.[89]

PBM has also been shown to help address chronic fatigue in other non-COVID-19 settings.[90]

It is notable that, whereas severe COVID-19 brain injuries (such as, for example, large CVAs or intracranial bleeds) might be marginally helped by PBM,[91] in our opinion, these may not be the cases that are likely to be helped the most by PBM. Instead, we believe that the cases more likely to be most dramatically helped by PBM may well be those cases wherein the brain pathology arising from the COVID-19 infection is diffuse and quite possibly radiologically normal and pathologically microscopic in nature, and yet still able to cause significant and long-lasting symptoms. Furthermore, there is currently no treatment available for these syndromes, short of waiting and hoping for the best.

Given the severity of post COVID-19 brain fog or COVID-19 induced chronic fatigue, patients experiencing these conditions risk the development of further issues (such as, for example, the development of clinical depression or substance abuse) in the absence of any ameliorative treatment. We believe that PBM may make a dramatic difference in a considerable number of these long-term cases, both by bringing about at least temporarily improved brain function and its accompanying symptomatic relief, as well as the hope such temporary improvement could well provide.

Possibly one of the most significant capabilities of PBM, with respect to its suitability of treating post COVID-19 brain fog or other sorts of cognitive impairment, is its ability, specifically when using the wavelengths in red and near-infrared range, to penetrate the brain to a depth of up to 50 mm.[92] This factor allows the light to hit a substantial portion of the cortical lobule neurons, as well as neurons making up long tract fibers of many important brain circuits. Furthermore, PBM not only reaches these tissues but also interacts with them in an amazing way by directly causing physiologic changes within the mitochondria, such as increasing the production of ATP.

Mitochondria contain important intracellular organelles known as *cytochromes*, which have the ability to absorb visible light energy in the red and near infrared wavelengths, and to use the absorbed energy to help generate ATP.[93] Light, especially in the red and near-infrared wavelengths, appears capable of activating cytochrome C oxidase in ways previously well described by others.[79] This ATP can be thought of as the little packets of electrochemical energy that serve as molecular energy currency in many areas of cellular metabolism. Red and near infrared light are also known to decrease inflammation.[79] A new component of photobiomodulation is 40 Hz gamma synchronized light and sound.

Photobiomodulation

Human brains are known to create a constant stream of endogenous EEG waves over the entire cortex. The frequencies of these waves range from 1 Hz delta waves (during sleep) to well over 40 Hz (so-called 'gamma' waves).[94] However, these higher frequency gamma waves also appear to decrease in extent during aging.[95] The consequences of this

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are still being investigated, but they may well contribute to the onset of one or more forms of senile dementia.

Recent research conducted by Singer et al[88,96] explored the ability of the combination of PBM delivered with 40 Hz flicker and synchronized sound to affect the function of microglia cells which, as previously noted, comprise the immune cells of the brain. That research featured genetically altered 5xFAD mice, which are known to develop Aβ plaques and phosphorylated tau tangles at a very accelerated rate similar to that seen in humans with Alzheimer's disease (AD). For reasons that remain unclear, it appears from this research that the microglia of these 5xFAD mice prematurely cease their regular function of cleaning up the brain parenchyma. It was thus speculated that this might be one reasons that AD brains become increasingly less able to function normally. In these experiments, Singer decided to expose these mice to externally produced light and sound. The light was flickered at a frequency of 40 Hz (in the so-called "gamma" frequency range), and the sound was pulsed at the same frequency in a synchronized fashion. When the mice were exposed to these stimuli, the results were astounding. For reasons that are still to be elucidated, the rodent microglia began functioning again, appearing to resume cleaning up the brain, reduce levels of Aβ plaques, and demonstrating other changes suggestive of improved microglial functioning.

A similar, preliminary study was then conducted on human subjects who had minimal cognitive impairment (MCI). In this study,[97] the subjects were equipped with special goggles and earphones that exposed them to 40 Hz gamma light and sound for sessions lasting an hour a day. The study appears to show that synchronized light and sound flickering at 40 Hz is capable of changing cytokine levels in the human body. The significance of these changes in cytokine levels has yet to be elucidated in any detail. However, treatment with 40 Hz gamma light and sound also appears possibly to have improved a number of cognitive symptoms in the test subjects, thus underscoring the potential that light and sound therapy may have for improving cognitive function in humans. Of course, these results are preliminary and need to be replicated.

Other light therapy benefits have been clinically proven to help significant brain disorders.

At present, large segments of the human population could well be described as significantly light *deprived*. The degree to which this light deprivation can cause real decreases in brain functioning has become increasingly clear in the past two decades. These effects are seen, for one example, in cases of seasonal affective disorder (SAD). In cases of SAD, the body can be described as lacking the blue wavelengths found in outdoor light for the winter months once days become short.[16] This lack of blue light if pronounced enough can result in depression and other brain disorders which may advance to the level of severe depression and psychosis, and which sometimes has even culminated in suicide. This is just one example of how profoundly prolonged inadequate light can affect the brain. Light treatment of the sufferers of SAD with blue wavelengths has been found to be extremely effective in the prevention or amelioration of SAD.[98] In many cases, exposure to light therapy for 20 minutes every morning is found to be effective in preventing the onset of SAD.[99]

PBM has also been shown to ameliorate various forms of brain injury. This may occur as a result of supplying neurons with an additional source of energy, or by furnishing microglia with some of the energy needed to continue or complete the tasks of cleaning up debris in the brain after significant injuries. Furthermore, PBM is essentially risk-free if applied within the constraints that make its usage safe and predictable. These constraints include staying within the safety limits of any given device with respect to light intensity and treatment duration and avoiding the use of this treatment in certain patient populations (such as patients who are bipolar or subject to epileptic seizures or other patients who have demonstrated other negative reactions to light therapy).

Conclusion

Based on what is already known about the effects of a COVID-19 infection on the brain, it appears more and more likely that once the Covid virus is cleared from the body, there will likely be damage left behind in the brain parenchyma, often in the form of inflammation, but possibly also including areas of regional hypoxia where the brain vasculature has been injured or destroyed. In some cases, the damage will be sufficient to cause the patient to develop cognitive symptoms. Although the damage will likely vary from case to case, the resulting inflammation and any viral and nonviral debris will need to be cleared away and resorbed to whatever extent the microglia can do so.

It appears that resolution of a COVID-19 infection may then result in significant impairment in functioning, which may manifest as brain fog, chronic fatigue, and a large number of other neurocognitive syndromes. These long-term effects have been observed following the full spectrum of COVID-19 patients, from those who are largely asymptomatic during the acute phase, to those with severe acute phase COVID-19 presentations.

It is quite possible that a percentage of these cases mild or asymptomatic cases will prove to be radiologically 'within normal limits,' or to have minimal and diffuse findings that may not even be radiologically detectable. It is also quite conceivable that, in those instances where post COVID-19 brain fog and/or chronic fatigue are the principal findings, PBM may well prove to be therapeutic due to a number of reasons as discussed above.

PBM (and more specifically, PBM with 40 Hz synchronized light and sound) is a very low risk therapeutic modality that shows a great promise at possibly being able to offer help with a significant and growing public health problem. We owe these patients a trial with any therapy that can provide a significant chance of symptom alleviation, which has little if any risk, and which is affordable.

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Peter Newsom, MD, has been board certified in emergency medicine, adult psychiatry, child adolescent psychiatry, brain injury medicine, and integrative holistic medicine. Additionally, Dr. Newsom has taught courses in Mind Body Medicine at Northwestern Medical School and is BCIA Certified in Neurofeedback. He is currently in private practice in the San Franisco Bay Area and is a board member of Reversal Solutions, Inc.

References and article are available online at www.townsendletter.com.

HYPERCOAGULATION

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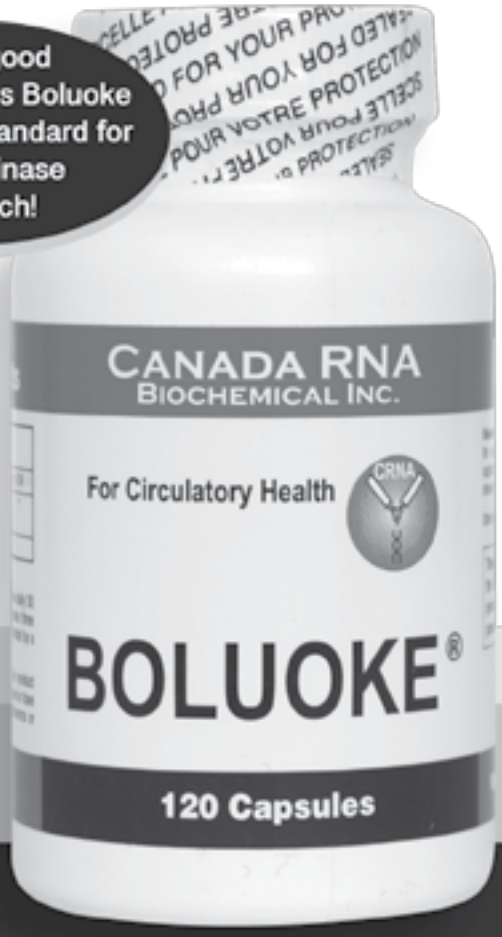

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Cadmium: Where This Menacing Metal Hides Out and How to Protect Yourself

by Jill Carnahan, MD

Air to breathe, water to drink, and food to eat; these are the basic necessities for us to sustain life. But what happens when these life-giving resources also contain something much more sinister?

The truth is, we live in an increasingly toxic world – and oftentimes these harmful toxins can be found lurking in the very resources we rely on. One such toxin that's been garnering more attention lately is a heavy metal known as *cadmium*.

Today we're going to dive into exactly what cadmium is, where it's found, and why it poses a threat to our long-term health. And most importantly, we'll cover how you can protect yourself from this menacing metal.

What Is Cadmium?

Cadmium is a soft, malleable, heavy metal found naturally in the earth's crust and is typically found bonded with other elements like oxygen, chlorine, or sulfur. Cadmium is not mined, but rather, it's obtained as a by-product of smelting other metals like copper, zinc, and lead. This recovered cadmium isn't wasted though, it's utilized in a wide array of products, including the following[1]:

- Rechargeable batteries
- Corrosion-protection coating for iron and steel
- Alloys
- Coatings (electroplating)
- Solar cells
- Plastic stabilizers
- Pigments
- Neutron absorber in nuclear reactors
- Cigarettes

But these products aren't the only place you'll find cadmium lurking.

Where Is Cadmium Found?

Cadmium is naturally present in small quantities in the air, water, and soil. But thanks to modern industrial practices, cadmium levels in the environment are steadily rising. And because cadmium is capable of binding to other particles, it spreads far and wide. You can potentially be exposed to cadmium in a number of ways[2,3]:

- Occupational exposure: If you work in certain industries, you're much more likely to come into contact with elevated levels of cadmium. The highest-risk occupations include fields like manufacturing, construction, mining, welding, painting, and landfill operations/ waste collection.
- Living near high-cadmium areas: Living near certain industrial sites can also significantly increase your cadmium exposure. Areas located near landfills, recycling plants, mines, smelters, or manufacturing plants can have increased cadmium pollution.
- Smoking cigarettes: Cigarette smoke contains cadmium, and smokers are estimated to receive a daily dose of cadmium that's *double* that of non-smokers.
- Exposure to contaminated air: Even if you don't live near a high-cadmium area, cadmium particles can still make their way into the air you breathe and directly into your lungs.
- Exposure to contaminated water and food: Cadmium can bind to other elements in the air, soil, and water. From there, it can sneak its way into water sources, including your drinking water. It can also be absorbed and stored by plants – which can eventually make their way onto your plate.

Phosphate fertilizers contain cadmium as a trace impurity, and over time, cadmium can accumulate in soil with repeated application of these fertilizers. From there, it can sneak its way into water sources, including your drinking water. It can also be absorbed and stored by plants – which can eventually make their way onto your plate.

Grazing animals can consume significantly elevated levels of cadmium if fed forage grown in soils that have been repeatedly exposed to phosphate fertilizers. This cadmium can accumulate in the animal's kidneys and liver and eventually be passed on to you. Some shellfish and crustaceans can also contain higher levels of naturally occurring cadmium.

While our bodies are well equipped to deal with the minuscule amounts of cadmium naturally found in our environment, amplified exposure to this element can have serious consequences for your health.

Cadmium Poisoning Symptoms

Coming into contact with a large, concentrated dose of cadmium can result in acute poisoning symptoms – chills, fever, muscle pain. If ingested, cadmium poisoning can severely irritate the stomach, causing vomiting and diarrhea. And if inhaled, cadmium can cause permanent damage to your lungs and can even lead to death.

Acute cadmium poisoning is rare though, and typically only occurs in high-risk industries. The more common threat when it comes to cadmium is long-term exposure.

Cadmium Health Effects

Over time cadmium can accumulate in your body, slowly deteriorating your cells' ability to function properly. Cadmium is considered a highly toxic element and exposure has been linked to the following conditions.[4,5,6]

Kidney Damage. The kidneys are where cadmium predominantly accumulates and begins exerting its toxic effects. Cadmium exposure can slowly chip away at your kidneys' ability to function by diminishing the glomerular filtration rate – or how well your kidneys filter your blood. This can cause proteinuria (increased protein excreted in your urine), increase the frequency of kidney stone formation, and even lead to nephrotoxicity – or the destruction of your kidney cells.

Reproductive and Developmental Damage. Cadmium has the potential to cause reproductive and developmental harm. Cadmium has been found to

- Decrease sperm count, increase immature sperm forms, and negatively affect sperm quality;
- Decrease testosterone levels, diminish libido, and negatively impact fertility;
- Increase risk of ovarian hemorrhage and necrosis;
- Increase risk of low birth weights and spontaneous abortions.

Cadmium exposure can also impact fetal development during pregnancy – interfering with fetal metabolism, neurological development, and skeletal formation.

Skeletal Damage. Cadmium can cause bone demineralization and inhibit the synthesis of other bone-forming compounds like c-proteinases and collagen. This can result in skeletal issues like osteoporosis, osteomalacia, skeletal deformities, and bone pain.

In extreme cases, cadmium can cause a condition known as *Itai-Itai* – a massive disruption of bone mineralization that results in significant pain and skeletal distortion.

Cardiovascular Damage. Cadmium may inhibit vascular relaxation, which can result in hypertension (high blood pressure). It also stimulates the production of cytokines and other inflammatory molecules that trigger endothelial damage – resulting in the formation of plaque in blood vessels. This plaque formation increases the risk of peripheral arterial disease and heart problems.

Cancer. As you can see, this calamitous compound can have some nasty side effects, but can cadmium cause cancer? The answer is yes – *cadmium is a known human carcinogen.*

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Cadmium exposure has been identified as a carcinogen for the following cancers: lung, prostate, kidney, liver, bladder, stomach, and breast.

With such serious and widespread health effects, you're probably curious exactly how cadmium can cause so much damage. Let's take a little deeper look at exactly how cadmium exerts its toxic effects on the human body.

Over time cadmium can accumulate in your body, slowly deteriorating your cells' ability to function properly.

How Cadmium Exerts Its Toxic Effects

Once cadmium makes its way into your body, it goes straight to work wreaking havoc on a cellular level. You see, cadmium disrupts a number of crucial cellular processes, including the following[7]:

- Hindering cell proliferation and differentiation while promoting cellular apoptosis (cellular death),
- Interfering with DNA repair while promoting DNA damage,
- Generating damaging free radicals that cause oxidative stress,
- Depleting and blocking cellular antioxidants,
- Enhancing the growth of abnormal and cancerous cells.

Cadmium toxicity can be insidious; this toxic element slowly chips away at your health on a microscopic level. With such sneaky and serious implications, you're probably wondering what you can do to protect yourself from cadmium.

Can You Remove Cadmium from the Body?

Wondering how to remove cadmium from your body? Detoxing from cadmium requires an all-encompassing approach – an approach that helps you reduce the amount of cadmium and other toxins coming in, while simultaneously boosting your body's natural detoxification abilities. Here's what I recommend:

- *Invest in quality water:* Because cadmium and other toxins are readily found floating around in water sources, investing in a high-quality water filtration system is one of the best ways to minimize the amount of toxins you're ingesting on a daily basis. Look for water purification systems that have lab test results proving they remove dangerous contaminants like cadmium. Two of the best filtration systems on the market that I trust are Berkey water filters and Clearly Filtered water filters.
- *Eat a healthy, well-rounded diet:* Eating a diet that focuses on whole foods – like fresh produce, high-quality proteins, and healthy fats – will help ensure you're getting all of your essential vitamins and minerals which are crucial for detoxing. And it can also be helpful to add in some extra supplements to help fill in any nutritional gaps. Supplements like glutathione, vitamin C, and vitamin D are particularly helpful in supporting your immune system in detoxing.
- *Show your gut some love:* Your gut is crucial when it comes to keeping potentially harmful toxins from sneaking their way into the rest of your body. You see, your digestive tract is designed to be sealed up tight – only allowing certain molecules into your bloodstream. So it's essential to keep your gut healthy and strong. Some of the best ways to show your gut some love is to incorporate gut-healing supplements like probiotics, Gut Immune, and collagen.
- *Be mindful of your overall toxic burden:* Our never-ending exposure to things like EMFs, indoor air pollution, and other harmful compounds can overload our bodies with toxins. Taking steps to reduce your overall toxic burden will help your body be better equipped to handle the toxins we simply can't avoid.
- *Boost your natural detoxification abilities:* Your body has natural detoxification pathways to help eliminate harmful compounds from your body. Give your body the tools it needs to fully support and enhance these natural detoxing processes by integrating tools like PEMF therapy, infrared saunas, and detox binders.

While these steps may be simple, they're powerfully effective and can go a long way in protecting you from the harmful effects of cadmium and other toxins.

How Concerned Should I Be When It Comes to Cadmium?

The truth is we live in an increasingly toxic world. And the risks that come with prolonged and/or elevated exposure to cadmium and other harmful toxins are very real. And while there may not be much we can necessarily do to avoid the fact that our world is becoming more toxic, the good news is, you are not at the mercy of your environment.

When it comes to your health and well-being, you are in the driver's seat. You have control over your day-to-day choices that have a monumental impact on your health. That's why I'm dedicated to arming you with the tools you need to defend and preserve your health for years to come.

So if you enjoyed this article and are looking for more ways to prioritize your health, head over and check out my blog (https://www.jillcarnahan.com/). It's chock-full of resources just like this. And if you're ready to take it to the next level, you can sign up for my newsletter.

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In Memoriam:

John Diamond, MD

August 9, 1934 – April 25, 2021

John Diamond, MD, DPM, FRANZCP, MRCPsych, FIAPM, DIBAK

For almost half a century John Diamond, MD, who passed away in April at the age of 86, was a pioneer in the field of holistic medicine. The best-selling author of thirty-five books, his approach to healing is brilliant and original, an inspirational blend of the medical, cultural, and spiritual; and it offers a veritable cornucopia to anyone seriously interested in healthy living and healing.

Diamond was born in Sydney, Australia, in 1934 and began his career in psychiatry, graduating from Sydney University Medical School in 1957, winning the psychiatry prize, and receiving his diploma in psychological medicine in 1962 from Melbourne University. He was a Fellow of the Royal Australian and New Zealand College of Psychiatry, a Foundation Member of the Royal College of Psychiatrists (UK), a Diplomate of the International Board of Applied Kinesiology, and a Fellow and past President of the International Academy of Preventive Medicine (USA). He was also an honorary board member of the Price-Pottenger Nutrition Foundation and their Japanese sister organization the Koushika Foundaton. He held numerous senior clinical and university teaching appointments in clinical psychiatry, the basic sciences and the humanities, and lectured extensively throughout the world.

Throughout the 1960s Diamond worked in private practice in Melbourne, and as a psychiatrist for various organizations, including the Victorian Department of Mental Hygiene, the Repatriation Department in the State of Victoria, the German consulate, and the Royal Australian Air Force. A career highlight at this time was a series of groundbreaking interviews he did with an Australian politician called Jim Cairns, later to be Deputy Prime Minister. The interviews, set up by Monash University in Melbourne, were designed to explore the psychological motivations of politicians and are regarded as highly innovative and revealing.

In 1971 he moved to the US, which was to be his base for the rest of his life, apart from a four-year residence in the UK in the 1990s. In America, he initially worked as a psychiatrist for the Legal Aid Society, an adolescent drug-abuse program at Mount Sinai Hospital in New York, and at Beth Israel hospital. Throughout his career as a psychiatrist, he was always proud that unlike many of his colleagues, he never had a suicide or even a suicide attempt from any of his patients. This was because he spent so much time and care with them.

However, in 1974, growing increasingly disenchanted with the confines of mainstream medicine, he became actively involved in alternative medicine. The catalyst, according to Diamond, was reading Lyall Watson's book *Supernature*, which had recently been published, and which was given to him by a doctor friend. As he handed him the book, the friend said "This book will change your life" – and it certainly did. A door opened, and Diamond's career dramatically transformed as he enthusiastically embraced a holistic approach, studying at first with Warren Levin, MD**,** who became a life-long friend.

Diamond set up an innovative holistic private practice in New York, using an approach that effortlessly combined complementary and mainstream medicine, the humanities, applied kinesiology, acupuncture, creativity and the arts, and spirituality. Part of his genius was his ability to draw on a vast array of resources, which he effortlessly navigated to suit the needs of a patient or a particular situation. He was able to do this because he saw each modality as part of a unified whole. In an age of specialisms, his mind was exceptionally holistic.

During his long career Diamond created a powerful body of work that is unique in successfully fusing the physical, psychological and spiritual aspects of healing into an integrated whole. Beginning in the 1970s and continuing right up until his passing, he actively explored a vast array of different modalities, embracing fields as diverse as acupuncture, Alexander Technique, chakras, color therapy, cranial-sacral therapy, creativity, crystals, herbs, dentistry, homeopathy, kinesiology, meditation, nutrition, and osteopathy. With all these, and many more, he managed not only to grasp their essence but to incorporate them seamlessly into his own system. The result is an approach to health and healing that is unrivalled in its scope, depth and holistic outlook, and places him far ahead of his time.

The essence of his work is the concept of what Diamond termed Life Energy. Life Energy is the innate healing force in all living things, what Hippocrates called the *Vis Medicatrix Naturae*, the healing power of nature, and the equivalent of *Qi* in Chinese medicine (and, of course, so many other traditional systems have had parallel concepts: the Egyptians, *Ka;* the Hindus, *Prana*; the Hawaiians*, mana*; and so on). Life Energy enters our body with

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the breath, flows through the acupuncture system and vitalizes the organs and tissues, and Diamond saw it as the fundamental driving force behind all health. When it is low, we are stressed and prone to illness, and when it is high, we are unstressed and healthy. And when it is at its highest, we feel truly loved and are able to fully embrace our lives. The only true healing comes by raising our Life Energy, and he therefore placed it at the center of his system.

Dr. Diamond's understanding of the importance of Life Energy dated back many years. Newly qualified as a doctor, he began work in the neurosurgery department of a large hospital. In the ward, there were two young men who had both been seriously injured in motorcycle accidents. They acquired the same hospital infection at the same time and both were treated with the same course of antibiotics. And yet within a week, one was cured and the other was dead. When Diamond asked his supervisor the reason, he was simply told that some patients have it and some don't – but couldn't tell him what the *it* was. Diamond observed that the patient who survived fully embraced life, while the other just turned his face to the wall. He realized that this *It,* seemed to be more important than anything else and later named it Life Energy, which formed the bedrock of his distinctive approach to health and treatment.

One of Diamond's key insights about a person's Life Energy was that it is constantly affected by everything they encounter in their life. Every facial expression, every thought we have, every piece of music we listen to, the food we eat, the supplements we take, every color we perceive and every shape, in fact, any interaction with our environment in any way. It all has its effect – however subtly and unconsciously – upon us. Each stimulus will either raise or lower our Life Energy.

Being aware of the effects of these stimuli is an important first step in being able to control them and thus to optimize one's Life Energy. This was the basis of Diamond's best-selling *Your Body Doesn't Lie* from 1979. For example, he showed how even a tiny amount of refined sugar placed on the tongue will lower a person's Life Energy. An equally small portion of raw, unrefined honey, on the other hand, will not.[1] In the course of his career he researched the effects of literally hundreds of thousands of such factors on Life Energy. A major discovery Diamond presented in *Your Body Doesn't Lie* is the importance of the thymus gland. At that time, the standard teaching was that the thymus gland had no function at all in the adult, a delusion fostered by the fact that during autopsy the thymus was usually found to be quite small and atrophied. Diamond argued that the thymus gland was affected by stress, was extremely important in regulating the immune system, and monitored and regulated energy flow in the meridian system. For this he was widely ridiculed by mainstream medicine. It was as a result of his suggestion to Royal Lee that Standard Process produced a thymus supplement. His latest wish was to talk with his colleagues about the Life Energy problems with supplements and how certain excipients often harm the healing aspect of the main ingredients.

Coming out of Diamond's research on Life Energy was work that was equally important: his discovery of the link between the acupuncture meridians and the emotions. Diamond spent nearly fifty years researching this link, delineating the major positive and negative emotions associated with each acupuncture meridian. In doing this, he effectively established the foundation for psychosomatic medicine – the acupuncture system as the communicating link between the emotions and the organs and muscles. Every disease, every bodily imbalance, every muscle problem – and even every gesture – will have an emotional component which can be accurately determined by its mediation through the meridian system. This approach opened many new lines of treatment, shows the role the unconscious plays in disease (both mental and physical), and was the basis for his classic book, *Life Energy: Using the Meridians to Unlock the Hidden Power of Your Emotions*.[2] That book was also groundbreaking in that it seems to be the first time that these basic emotions had been accurately defined (while there is some mention of them in the early Chinese acupuncture writings, they are not systematically defined, nor are they precisely translated to be readily applicable for our culture). Diamond showed that dictionary definitions of emotions are confusing, and often referenced in terms of one another. For example "sad" is defined as "unhappy," and vice versa: however, neither entry will actually define the state. The clue to their underlying meaning was to be found in the etymology of the words. Diamond had been involved in etymology at that time for nearly thirty years and was able to use his experience in the field to define the emotions exactly, distinguish clearly between them, and relate them specifically to each of the acupuncture meridians.

Diamond named his work with the meridians and the emotions *The Acupuncture Emotional System* (AES). Over time Diamond further developed the AES, finding precise emotional states, both positive and negative, relating not just generally to a meridian, but to a specific point on that meridian. He discovered over two hundred such states, which he called *syndromes*. The AES as a whole offers a new, comprehensive map of human psychology and the emotions and their relationship to the meridian system. No less significantly it amounts to a precisely delineated model of how the health of the mind affects that of the body, and vice versa.

One of Diamond's most distinctive traits as a healer was to nurture the positive in a patient wherever possible. He argued that orthodox medicine focuses too much on what is wrong with a patient, at the expense of what is right: a person's strengths are so often the thing that really gives them the motivation for truly embracing life and achieving full health. With everyone who came to him, he encouraged the activity which could most help their Life Energy, sometimes with near miraculous results.

Many years ago, a man in his forties consulted with Diamond. He had once been a dentist but was now very sick with advanced ALS and on disability for life. He had a pronounced foot drop, lived alone, drank, smoked, and spent his time just watching TV. In terms of conventional medicine, he was told that there was little that could be done for him, and a large prestigious hospital gave him just six months to live. Diamond only had a day to try and help him. What was he to do? He had known and worked with many dentists and knew that so many of them are at heart frustrated sculptors – they love to make bridges and appliances out of gold and silver and porcelain. In his office Diamond had him do some modeling with plasticine, and he became greatly enthused by it, making many exquisite little animals while singing the entire time. His Life Energy was transformed, and suddenly he had a reason to live. When he shook hands upon leaving, Diamond knew a change

had occurred in this man and hoped he would continue to heal.

The man returned home and enrolled in a pottery class. He called Diamond about six months later: his foot drop and all symptoms had disappeared, and he was feeling fine. He had stopped smoking and drinking, and later he married. In short, his life turned around. A few years later he contacted Diamond again to say his symptoms had returned. When Diamond asked him if he was still doing the pottery, the man said he had given it up. So, Diamond encouraged him to take it up again, and the symptoms again disappeared. This man dedicated himself to going around the US talking to ALS patients and how they could help themselves. He lived on into his late seventies, every year writing a card to thank Diamond.

This story also illustrates a central part of Diamond's approach: his use of the healing power of human creativity. There was surely no medical doctor who used that power with his patients more consistently and with greater effect. In a passage in his book *Facets of a Diamond* – perhaps the best introduction to his approach to healing – he tells us why. He regarded creativity as "The Power within [the patient] that alone can cure him. This is his innate ability to make, at every moment, the best choice for health and love and life… Every act of Creativity actuates the will to be well and enhances the Life Energy."[3]

One of the areas of creativity he explored the most was music. Diamond deeply loved music and intuited its therapeutic power: "Of all the physical modalities, music most activates the Life Energy and uplifts the soul. Only pure love can do more," he wrote at the beginning of his groundbreaking four-volume *Life Energy in Music* series.[4] As a young doctor, he experienced the healing power of music first-hand. Working in the back wards of a mental hospital in Melbourne with seemingly incurable, long-term patients, he arranged for a piano to be donated – and the results were remarkable. A woman with schizophrenia who had been in the hospital for many years, seemingly quite uneducated, found her way to the instrument and began playing. Diamond realized to his surprise – no-one had any idea that she could even play – that it was a part of a Beethoven sonata, played very slowly. Over the next few days she played all thirty-two of Beethoven's sonatas from memory. And then she went home and never came back.[5] This happened with other patients as well, with Diamond getting more releases from the "incurable" patients than the other doctors from the "good" patients.

Inspired by many similar experiences, Diamond began systematically investigating music in all its aspects: which styles, which performers, which composers, which instruments, which acoustics would raise the Life Energy and which would not. This research into music is a revelation, delineating in unprecedented detail its therapeutic power.

As well as music, he also was deeply involved in investigating the Life Energy of other art forms, among them painting, photography, drama, literature, and poetry. He used his research in his clinical work with his patients, and he wrote books about his findings – *Art for Healing: Guided Painting Then and Now*[6] and *Beyond the Obvious: Photography for Healing*[7] are two examples – and presented many seminars on different aspects of creativity. More important, Diamond actually himself did these things himself. He was deeply involved in developing an approach to therapeutic photography which he termed Life Energy Photography – and painting, Life Energy Art, which resulted in works made with the explicit intention of raising the Life Energy of the viewer. He created innumerable such images in both media, especially in the last twenty years of his life, exhibiting internationally, and setting up a permanent gallery devoted to his work, the Life Energy Art Gallery in Mount Kisco, New York.

As should be clear by now, Diamond's output was prodigious. The thirty-five books that were published in his lifetime cover a remarkable range, each in its way highlighting a different aspect of his work, and between them offering a glimpse of the totality of his vision. He also wrote literally thousands of papers, a sampling of which are available on his website, and he recorded innumerable seminars given to students and professional practitioners, which are now starting to be released publicly for the first time. His writings and seminars show a brilliant, endlessly creative mind constantly trying out new ideas and exploring old ones in ever greater depth.

One of the most inspiring features of Diamond's work as a whole is its spiritual dimension. This was a natural part of his approach, because true healing, he argued, was a synergy between body, mind, and spirit. For him, spirituality began with the love of the mother, which he called *Matrophilia,* noting that it is "the most basic, the deepest feeling within each of us since our own beginning."[8] He regarded the maternal relationship to be at the very essence of health and Life Energy, and believed that our life's suffering was ultimately caused by the fact that, often unconsciously, we do not feel fully loved by her. The true purpose of healing was directly or indirectly to reconnect us with that love, which always exists at a deep level. In later years, his spirituality broadened and became more overt. He increasingly researched the existence of a Spirit World, and at his death was working on a book on the subject, *A Doctor in Two Worlds: The Guided Life of a Healer*, scheduled for publication in 2022.

Diamond was an exceptional personality: a powerful communicator, deeply compassionate and humanitarian in his outlook, open-minded and open-hearted, a brilliant therapist, gifted with a fount of ideas and insights that poured forth in abundance throughout his whole life. Despite all this, he was remarkably modest, which is perhaps one of the reasons his work is not as widely known as it should be. One of his favorite affirmations was: "I enthusiastically, passionately, whole-heartedly and gratefully Embrace all of my life." That was indeed how he lived, and if there is anyone to whom the overworked word "genius" could be meaningfully applied, it was surely he.

For more on John Diamond's life and work, visit www.DrJohnDiamond.com.

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Ask Dr. J

by Jim Cross, ND, LAc
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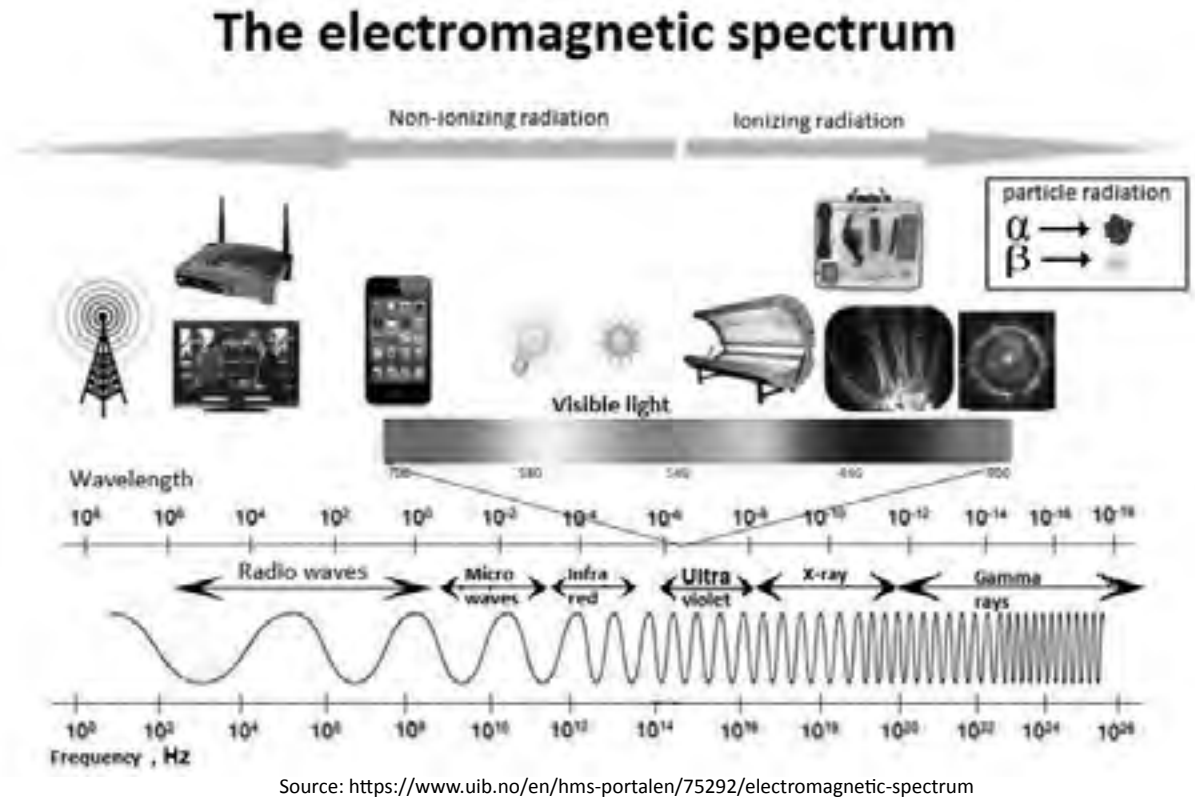
The Tipping Point

With regards to acute viral illnesses, I think all of us have had that specific point in time where we became excessively cold, lost sleep for several nights, or had a cold wind hit us hard at our C7/T1 area and presto we developed a cough or a cold or a fever. What happened? I am going to call it the tipping point. We had been eating non-food for several days, staying up late studying for finals all week, or not covering up our neck area in a strong, cold wind. Due to these nefarious activities, our bodies were on the brink of tipping into an acute viral illness. Then one of the above situations hit us and, since we were at this critical state, a small bump in our daily bodily ride triggered the internal transition to an acute illness.

I believe the same scenario applies to chronic illnesses like cancer/heart disease/autoimmune disease. A dysfunctional internal milieu has been percolating for an indeterminate amount of time that is not externally decipherable by the individual. Suddenly, a dramatic symptom appears, such as being terribly short of breath on a minor exertion. Now, this person is diagnosed with severe coronary artery disease. Some situations, such as the death of a relative or shoveling excessive snow in the first snowstorm of the winter, served as the tipping point for the disease to be transformed into an entity that is now apparent to the individual and their doctor.



Source: https://www.uib.no/en/hms-portalen/75292/electromagnetic-spectrum

What factor(s) had led to the tipping point? Readers of the *Townsend Letter* will recognize multiple possibilities: chemicals in our food/water/environment, chronic life stresses, suboptimal genetics, etc. What I want to focus on as a factor that will cause a slow, cellular degeneration is chronic exposure to non-ionizing electromagnetic radiation/EMR.

In the picture on page 76 ionizing radiation exists above the frequency of 10^{15} waves per second but at a relatively short wavelength of about 10^{-5} to 10^{-12} meters. This part of the EMS is acutely dangerous to all life on earth (except for probably cockroaches & bacteria) and will immediately kill or seriously injure life upon exposure.

Non-ionizing radiation/NIR, on the other hand, is the antithesis of ionizing radiation in terms of exhibiting a longer wavelength (about 10^{-5} to 10^{3} meters) and a much shorter frequency (below 10^{14} waves per second). Many people believe that chronic exposure to non-ionizing radiation also can have a negative effect on our bodies. In Sweden, for e.g., they moved high power lines away from schools. In Europe, trains run on electricity. Switzerland retires their train engineers at 50, or many will develop heart disease**.** *Cross Currents* by Robert Becker, MD, is a wonderful synopsis of the negative effects of non-ionizing radiation on various parts of our bodies. **One important caveat to remember**: Every one of our 100 trillion cells is a battery, and electromagnetic smog is having potentially negative effects on those batteries called our cells. Our organs are composed of cells, and it is the cells that actually do the work of our organs. If the cells aren't healthy, the organs will not be also.

Let us look at a couple quick areas where NIR has adversely affected life on earth. It appears that almost every US citizen, except for me, owns and uses a cell phone. The US Food and Drug Administration initiated a study on radio frequency radiation/RFR for a National Toxicology Program/NTP study because of the widespread public use of cell phones and the limited knowledge related to potential health effects from long-term exposure. They only, however, studied 2G and 3G wireless radiation, which operate within a range of frequencies from about 700 – 2700 megahertz, in a two-year toxicology study on rats, which was published as technical reports in November 2018.[1]

The NTP study found that high exposure to radiofrequency radiation used by cell phones was associated with:

- Clear evidence of an association with tumors in the hearts of male rats. The tumors were malignant schwannomas**.**
- Some evidence of an association with tumors in the brains of male rats. The tumors were malignant gliomas**.**
- Some evidence of an association with tumors in the adrenal glands of male rats. The tumors were benign, malignant, or complex combined pheochromocytoma.

A follow-up to the study, from October 2019, found DNA damage in THREE regions of the brain, the liver, and in blood cells that were removed from rats at an earlier timepoint from the ongoing two-year toxicology study.[1] As we already know, unrepaired DNA damage can eventually lead to tumors. Most people will say that this only occurred in rats, but wireless radiation still triggered DNA damage and potentially deadly tumors in living mammalian beings.

Another potential long-term source of NIR is electric heat cables that have been installed in ceilings as a more efficient means of heating an entire room. This type of heating source can engender large EMF fields in the entire room of up to 10 milligauss, which is much higher than the 1 milligauss ceiling that most researchers say should be the maximum long-term exposure level. In this study, Nancy Wertheimer determined that the miscarriage rate among pregnant women living in such homes was significantly higher than that of pregnant women living in homes not heated in this manner.[2]

Truthfully, EMR is an entity that is odorless, tasteless, and invisible. If you search PubMed for negative effects of EMR, you will literally unearth hundreds of articles targeting their negative effects on multiple organ systems. It appears that unwise use of EMR in our public domain has produced environmental changes of unparalleled proportions with grave consequences for the health and well-being of all life on earth. Unfortunately, it is more than likely too late to eliminate EMR. Wise people can access multiple books and websites to learn how to mitigate their negative effects on our bodies. Here are a few websites for you to unleash your search. I receive no financial compensation from any of them:

- https://emfexperts.wildapricot.org/
- https://www.electricsense.com/
- https://greenbankobservatory.org/
- https://www.emf-portal.org/en

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Environmental Medicine Update

by Marianne Marchese, ND
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Are You Testing Your Patients for Arsenic?

Introduction

Arsenic is a metal that is present in our food, air, and water. It is an element and a naturally occurring mineral found in the environment. Arsenic persists in the environment because it does not break down easily. Arsenic exists in two main forms: inorganic and organic. Organic arsenic is the main form found in foods while inorganic arsenic is present in soil and groundwater. Inorganic arsenic is more hazardous to human health than organic arsenic. Of course, toxicity is dependent on the dose of the exposure, absorption, and elimination from the body.[1] Inorganic arsenic used to be produced in the US by being heated in smelters, which produced a fine dust in the air. This form of arsenic was made as a preservative for wood and although no longer made in the US, it is still imported from other countries. In the past, arsenic used to be in pesticides used in agriculture, and it still permeates the soil and groundwater. Some organic arsenic compounds are used as additives in animal feed.[1] Arsenic has been used as alloy additives; in electronic devices, such as smartphones; in veterinary medicines; pigment production; in glass manufacturing; as bronzing or decolorizing agents; in textile printing; in tanning; and many other uses.[2] Inorganic arsenic is naturally occurring and is released into the air by volcanoes, the weathering of arsenic-containing minerals and ores, and commercial and industrial processes. Arsenic cannot be destroyed in the environment; it persists forever accumulating in water and food. This is how people are exposed to arsenic, which can have adverse health effects.

Food

Grains, produce, fish, especially shellfish, are the main sources of organic arsenic exposure via food. Arsenic found in fish and shellfish exists primarily as two forms of organic arsenic that are essentially nontoxic.[2] Rice is a significant source of arsenic exposure, and it is estimated that a half cup of rice equals drinking a litter of water containing 10 ug/L of arsenic.[3] Rice simply absorbs arsenic from the groundwater in which it is grown. The form of arsenic in rice is also organic arsenic and is rapidly cleared from the body and considered harmless. Shrimp and tuna are significant sources of dietary exposure as well. It does not matter if the tuna is wild caught, packed in water verses oil, or deemed low in mercury. It still may contain organic arsenic. Organic arsenic from food has a very short half-life, is metabolized, and eliminated quickly from the body, and determined to be harmless to human health.

Water

Groundwater is the most common source of exposure of inorganic arsenic in the US. Inorganic arsenic can get into rivers, lakes, or an underground water by dissolving in rain or snow. It also gets into the water through the discharge of industrial wastes and agriculture run-off. Inorganic arsenic in groundwater is generally about 1 ug/L but may exceed 1,000 ug/L in contaminated areas or where arsenic levels in soil are high. Groundwater is more likely to contain high levels of arsenic than surface water.[2]

The Environmental Protection Agency (EPA) regulates public drinking water under the Safe Drinking Water Act, which was enacted in 1974. It requires the EPA to set standards for contaminants through the National Primary Drinking Water Regulations, which minimizes risk for contaminants. Standards fall into two categories: the maximum contaminant level (MCL), which is enforceable by law and is less stringent, and the maximum contaminant level goal (MCLG), which is only a guideline. These two numbers can vary significantly. The federally mandated MCLG for arsenic is 0 ug/L; however, the MCL is 10 ug/L.

It was only in 2006 that the EPA set the limit for municipal water supply to the current level of 10 ug/L. The level used to be set at 50 ug/L. Suddenly dropping the level from 50

ug/L to 10 ug/L put the burden on cities to figure out how to remove arsenic from the drinking water. Many areas of the US still exceed the 10 ug/L level.[3] Some areas of the US contain high natural levels of arsenic in rock, and this can lead to high levels of arsenic in the water. Due to geographical variations, people will not know if the water they are drinking contains high levels of arsenic unless they test their home water.

In 2011 the United States Geological Survey published results of a study on arsenic in the drinking water. They sampled wells in parts of aquifers used for drinking water in the US and found that 7 percent of the wells sampled contained arsenic at a concentration that exceeded the MCL of 10 ug/L. The greatest concern was in the Southwest**,** where concentrations of arsenic exceeded the MCL in about 16 percent of drinking-water wells sampled.[4] In the Southwest basin-fill aquifers**,** arsenic concentrations in drinking-water wells exceeded the MCL more than twice as frequently as in drinking-water wells nationwide.

But at what level in the water does arsenic start to pose a risk to health. Is the EPA maximum contaminant level at 10 ug/L low enough to keep us safe? Some environmental organizations and recent published studies say the level needs to be lowered and arsenic basically removed from the drinking water to prevent adverse health effects. Other studies conclude that the level set at 10 ug/L is adequate. Currently the EPA is considering lowering the MCL from 10 ug/L to 5ug/L to reduce cancer risk, specifically bladder and lung cancer.[5]

Health

Both the Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry list arsenic as a cancer-causing compound. Human studies suggests that exposure to inorganic arsenic by inhalation may result in lung cancer, and exposure by ingestion may result in nonmelanoma skin cancer, bladder, kidney, liver, and lung cancers. Arsenic is absorbed in the GI tract, distributed throughout the body, and reduced to arsenite to be methylated. Methylation is the main way in which arsenic is metabolized by the body. Inorganic arsenic (including arsenate and arsenite) is methylated into monomethylated and dimethylated compounds (MMA, DMA) in the liver. These metabolites are then excreted through the kidney together with unmethylated inorganic arsenic.[6] It appears that an individual's ability to methylate and eliminate arsenic plays a role in disease development.

A 2017 study tried to examine the differences in arsenic methylated metabolites and risk of disease. It found that inorganic arsenic exposure was associated to cancer risk in persons with higher percentage of MMA metabolites and lower percent of DMA metabolites. The same was true for cardiovascular diseases and carotid atherosclerosis. For diabetes, however, lower MMA% and higher DMA% was associated with higher risk of diabetes and metabolic syndrome.[6] Methylation of arsenic occurs primarily in the liver and individual genetic differences in metabolism called single nucleotide polymorphisms, SNPs, affect arsenic break down.[3] There are several labs that can test for methylation SNPs in the body to help determine one's ability to break down arsenic.

Most studies linking arsenic to adverse health effects show exposure from groundwater, not food, is the main culprit. Cancer, COPD, cardiovascular disease, diabetes, pre-diabetes, and decreased cognitive function are linked to inorganic arsenic in the water.[3] A study published in 2017 found that arsenic levels in the drinking water below the 10 ppb standard is linked to prostate cancer.[7] Other studies did not come to the same conclusion. Perhaps the determining factor of the health effects at levels in the water below 10 ug/L is genetic variations in arsenic metabolism and length of low-dose, chronic exposure. Regardless, since many people are unknowingly exposed to arsenic in their drinking water, it is important to test not only home drinking water for arsenic but to test patients for elevated arsenic in the urine.

Arsenic Levels in the Body

The Center for Disease Controls' National Health and Nutrition Examination Survey (NHANES) samples a large segment of the US population monitoring for various chemicals through blood and urine testing. Arsenic is best tested for via urine sample (either a 24-hour collection or a random sample). Most samples do not differentiate organic arsenic from inorganic arsenic. However, some commercial labs can specify arsenic in the urine upon request. To eliminate organic arsenic from a urine sample leaving mostly inorganic arsenic, it is important to have patients avoid all seafood, chicken, and rice three to four days before urine collection. Reference ranges vary from lab to lab. NHANES lists a urine arsenic above 55 ug/L as in the 95th percentile. Any level above 55 ug/L would be considered elevated.

The World Health Organization states a 24-hour urine level <50 ug/L is acceptable. Mayo Clinic has a tighter reference range of <35 ug/L for a either a 24-hour urine or random urine collection. Lab Corp reference range for either a random or 24-hour collection states <50 ug/L is normal. Lab Corp can differentiate inorganic arsenic in the sample from organic arsenic and states inorganic arsenic <19 is acceptable. Quest Diagnostic reference range for a random urine arsenic test is <35 ug/L and a 24-hour urine range of <80 ug/L.

Different labs have different reference ranges for what is an acceptable level of arsenic in the body. In general, a random level above 35 ug/L and 24-hour level above 50 ug/L would be a cause for concern. If a patient's urine arsenic is elevated and they avoided food sources of arsenic three to four days before the urine collection, then the home water should be tested. Drinking water is the most common source of exposure. Unless they have reverse osmosis water filtration for both cooking and drinking water there is a chance that their water is the source of exposure.

Case Example

Early 2020 a 36-year-old female presented with joint pain in her hands, hair shedding in the shower, body pain all over that comes and goes, and fatigue. March 2019: her primary care provider ran blood work showing negative ANA and normal CBC, CMP, lipid, ESR, CRP, Lyme disease, EBV, CMV, and TSH.

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Later her vitamin D, B12 and iron were tested and normal. She was referred to a rheumatologist who repeated labs May 2019 and did an x-ray of her hands. The x-ray was normal, rheumatoid factor negative and again the ANA was negative. The rheumatologist said the joint and muscle pain was from overuse and prescribed ibuprofen. She changed her mattress, pillow, started stretching, and got a sit-stand desk. She came to see me because she had been taking ibuprofen for six months and felt like her symptoms still flared up every now and then. She specifically wanted heavy metal testing.

At the initial appointment she complained of hair shedding, muscle and joint pain that comes and goes with no pattern, and she had fatigue. She was on no medications as she had stopped the ibuprofen. She took vitamin-D3 (4,000 IU a day), a fish oil (1,500 mg a day) and B-complex. She had no other health concerns or issues. Repeat TSH, CBC, CMP and thyroid antibodies were all negative.

An environmental exposure history revealed no exposure at work to metals, solvents, or pesticides. Her hobbies are exercising and piano. She does not any eat fish and tries to eat organic fruits and vegetables and mostly eats a plant-based diet. She is gluten free and eats very little cow milk products. Her protein sources are organic soy products, eggs, some cow milk products, and occasional wild game that her husband hunts. She has a very healthy and balanced organic diet. She does not use any personal care products with parabens, phthalates or BPA and minimizes chemical exposure in general. She grew up in Tucson Arizona, on city water, and was not near agriculture or a golf course. She drinks refrigerator filtered water at home for the past 10 years, which eliminates lead according to the label. She has lived in Phoenix Arizona, in the same house for the past eight years with no water leaks or remodel done. She wanted heavy metal testing. We did a random first morning urine metal test and blood lead and mercury. The blood lead was <2 and blood mercury <3, which are normal. The results of the urine metal test show the arsenic level in a random sample was 93 ug/g, which was above the reference range.

Identifying the source of exposure was the top priority. As already mentioned, she did not eat any fish and very minimal rice and chicken. She drank and cooked with water from the refrigerator filter, which is not reverse osmosis. Reverse osmosis filtration removes arsenic from water. So she tested her home water for arsenic. She used an Arizona Department of Health certified commercial drinking water laboratory. The level came back at 10.9 ppb only 0.9 ppb above the EPA maximum contaminant level. Although this is not a significantly elevated level, we do not know how long this level of arsenic has been in her water nor do we know if she has any SNPs of methylation metabolism pathways. She was not interested in SNP testing.

The treatment plan consisted of installing a reverse osmosis water filtration system for both drinking and cooking water. For four months she took N-acetylcysteine (600 mg twice a day) and a liver phase one and phase two supplement providing co-factors for metabolism and methyl donors. The cofactor support product contained vitamin A, vitamin D3, vitamin K1, vitamin B-1, vitamin B-2, vitamin B-3, vitamin B-5, vitamin B-6, vitamin B-12 (as methylcobalamine), vitamin C, vitamin E, biotin, folate (5-methyl-tetrahydrofolate), calcium, chromium, copper, iodine, magnesium, manganese, molybdenum, potassium, selenium, zinc, choline, inositol, boron, vanadium, green tea extract, and turmeric.

Six months after starting treatment, she felt remarkedly better. She had energy, her hair stopped shedding and joint pain resolved. We retested her random urine arsenic level six months after starting treatment and using reverse osmosis water with a commercial lab to utilize her insurance. The level dropped from 93 ug/g to 31 mcg/g. (note that mcg and ug are the same).

Summary

Arsenic is a metal that is present in our food, air, and water. Organic arsenic is the main form found in foods while inorganic arsenic is present in soil and groundwater. Inorganic arsenic is more hazardous to human health than organic arsenic. Arsenic can have adverse health effects on humans with cancer being the number one consequence of high-dose, acute exposure or low-dose, chronic exposure. Other milder and more subtle health effects occur over time as well. The case example demonstrates a need for health care providers to think outside the box. Consider blood and urine metal testing as a screening tool when other labs are normal and the patient's symptoms cannot be explained. Since water is a common source of exposure, testing the home drinking water can help identify if arsenic is present. Arsenic is cleared from the body through methylation processes, which is why methyl support and antioxidants along with avoiding the source of exposure is helpful for eliminating arsenic from the body.

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CALENDAR

SEPTEMBER 24-26: 8th INTERNATIONAL CONGRESS ON COMPLEMENTARY & ALTERNATIVE MEDICINE in Montreal, Canada. CONTACT: https://complementarymedicine.conferenceseries.com/

SEPTEMBER 24-26: ADVANCED INTEGRATIVE ONCOLOGY in Scottsdale, Arizona, and live online. CMEs available. CONTACT: Sharon Phillips, phone 954-540-1896; Email: sharon@aampconferences.com; https://aampconferences.com/

SEPTEMBER 29-OCTOBER 3: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE (ICIM) FALL MEETING – Vaccines and Immunology: Truth and Fiction in Fort Worth, Texas. CONTACT: https://icimed.com/

OCTOBER 1: THE ACADEMY OF INTEGRATIVE HEALTH AND MEDICINE (AIHM) INTERNATIONAL FELLOWSHIP IN INTEGRATIVE HEALTH & MEDICINE begins its next session. Scholarships available for this 1000-hour hybrid program for clinicians who aim to become leaders in integrative health and medicine. CONTACT: https://aihm.org/

OCTOBER 1-3: THE BIOREGULATORY MEDICINE INSTITUTE (BRMI) presents Optimizing Clinical Skills and Knowledge in Scottsdale, Arizona. Featured Guest - Dr. Ralf Oettmeier of Switzerland's Alpstein Clinic. CONTACT: https://www.biologicalmedicineinstitute.com/upcoming-events

OCTOBER 1-3: MID-ATLANTIC NATUROPATHIC CONTINUING EDUCATION CONFERENCE online. CONTACT: https://www.njanp.org/2021conference

OCTOBER 1-3: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – Cardiometabolic UK 2021 livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modulesapm-cardiometabolic-uk-2021/

OCTOBER 14-17: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE FALL CONFERENCE – Immunity, Inflammation, and Autoimmunity in San Diego, California. CONTACT: http://aaemconference.com/

OCTOBER 14-17: 16th ANNUAL CARDIOMETABOLIC HEALTH CONGRESS in National Harbor, Maryland. CONTACT: https://www.cardiometabolichealth.org/2021/cmhc-16th-annual.html

OCTOBER 14-17: ACADEMY OF INTEGRATIVE HEALTH & MEDICINE VIRTUAL CONFERENCE online. CONTACT: https://aihm.org/conference/

OCTOBER 20: BUILDING LIFETIME IMMUNITY PROFESSIONAL CERTIFICATE TRAINING in San Antonio, Texas, with Cornell Richard Nerl, MD. Sponsored by Children's Future Foundation. CONTACT: 442-234-3263; Lifetimeimmunity.com

OCTOBER 22-24: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – Restoring Gastrointestinal Equilibrium livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modulesapm-gi-2021/

OCTOBER 29-30: 12th ANNUAL BIOMARKERS AND CLINICAL RESEARCH CONGRESS in Vancouver, Canada. CONTACT: https://biomarkers.conferenceseries.com/

OCTOBER 29-30: 8th INTERNATIONAL CONFERENCE ON NATURAL, TRADITIONAL, & ALTERNATIVE MEDICINE in Vancouver, British Columbia, Canada. CONTACT: https://naturalmedicine.conferenceseries.com/

NOVEMBER 5-6: NEW HAMPSHIRE ASSOCIATION OF NATUROPATHIC DOCTORS (NHAND) 2021 ANNUAL CONFERENCE: Science, Spirit & Clinical Pearls. In-person and Livestream. CONTACT: conference@nhand.org; https://www.nhand.org/annual-conference/

NOVEMBER 5-7: 21st ANNUAL CONFERENCE OF THE WESTON A. PRICE FOUNDATION – Staying Healthy in a Toxic World in Allen Texas (near Dallas). CONTACT: https://www.wisetraditions.org/

NOVEMBER 6-7: CHILD & ADOLESCENT PSYCHIATRY REDEFINED – An Online Symposium. Six renowned clinical experts in integrative and functional medicine share cutting-edge research and evidence-based treatment protocols for ADHD, autism, PANDAS, pediatric depression, eating disorders, and more. CONTACT: to https://www.psychiatryredefined.org/child-adolescent-psychiatry-symposium/.

NOVEMBER 19-21: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – ENVIRONMENTAL HEALTH 2021 livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modulesapm-environmental-health-formerly-detox-2021/

NOVEMBER 29-30: FUNCTIONAL FOOD AND ADVANCED NUTRITION 2021 online. CONTACT: https://nutritionalscience.nutritionalconference.com/

DECEMBER 6-7: 5th INTERNATIONAL CONFERENCE ON PROBIOTICS, PREBIOTICS, SYNBIOTICS, & GUT NUTRITION in Vancouver, British Columbia, Canada. CONTACT: https://probiotika.conferenceseries.com/

DECEMBER 9-12: A4M/MMI 29th ANNUAL WORLD CONFERENCE – Unmasking the Hidden Epidemic in Las Vegas, Nevada. CONTACT: https://www.a4m.com/29th-annual-world-congress.html

DECEMBER 22: 13th INTERNATIONAL CONFERENCE ON PREDICTIVE, PREVENTIVE, AND PERSONALIZED MEDICINE & MOLECULAR DIAGNOSTICS online. CONTACT: https://personalizedmedicine.conferenceseries.com/

JANUARY 21-23, 2022: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – Cardiometabolic livestream online. CONTACT: https://www.ifm.org/learning-center/functional-mfunctional-medicine-advanced-practice-modulesapm-cardiometabolic-2022/

FEBRUARY 25-27: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – The Many Faces of Immune Dysregulation and Inflammation livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modulesapm-immune-2022/

FEBRUARY 26-MARCH 2: NATIONAL CONFERENCE ON WILDERNESS MEDICINE in Big Sky Ski Resort, Montana. CONTACT: https://wilderness-medicine.com/cme-conferences/ski-big-sky-montana/

MARCH 21-22: 21st INTERNATIONAL CONFERENCE ON DIABETES, NUTRITION, OBESITY, AND EATING DISORDERS online CONTACT: https://nutrition-eatingdisorders.annualcongress.com/

APRIL 8-10: ENVIRONMENTAL HEALTH SYMPOSIUM (EHS) ANNUAL CONFERENCE – Clinical Applications in Environmental Medicine in Tucson, Arizona. CMEs available. CONTACT: 855-347-4477; www.environmentalhealthsymposium.com / email Info@environmentalhealthsymposium.com

APRIL 22-24: JOINT AMERICAN HOMEOPATHIC CONFERENCE in Reston, Virginia and virtual online. CONTACT: https://www.homeopathycenter.org/

APRIL 29-30: 12th WORLD CONGRESS ON DRUG ADDICTION AND REHABILITATION THERAPY in Las Vegas, Nevada. CONTACT: https://addiction.healthconferences.org/

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Classified Advertising

Pediatric Pearls

by Michelle Perro, MD

Tinnitus in a Young Musician

Dealing with the vast array of issues that have arisen caring for children occurring from the innumerable changes in our society over the decades has had its challenges. The need for flexibility, creativity, and keeping up with the literature has been made evident during the present pandemic. It has been even more taxing to manage the new crop of health-related dilemmas brought on by this situation. Despite the pandemic-induced mayhem, for those of us committed to the well-being of children, we put on our wizards' caps, take out our wands, and get to work.

Chad is an 18-year-old male that I've known since birth. He is an outstanding musician and was just accepted into a prestigious music college. One of the requirements for entry was the SARS CoV-2 vaccine, and Chad got his first vaccine as directed. The following day, the mom contacted me that her son developed severe tinnitus in his right ear. He was distraught since the ringing interfered with his music practice. She wondered if it was caused by the vaccine since he didn't have any of the other exposures she investigated. Neurologic sequelae from the injection are reported in the Pfizer study. I acknowledged it was the likely culprit and decided to try and quell his inflammatory response with our usual integrative tools. The mom attempted to report it to VAERS but was unsuccessful in doing so.[1]

A two-fold dilemma had quickly surfaced from Chad's case: how to treat side effects from the experimental vaccination, and whether children/young adults should be vaccinated. Although there are reports on how to treat COVID infections integratively, there is less information reported on treating vaccine reactions.[2] Additionally, there are now more issues arising from side effects from the vaccine than from the actual disease. Published statements are now available from physicians stating, for example, "…{A}t the very least, based on current evidence, it's entirely plausible to assume the answer is yes: That risks of COVID vaccination outweigh potential benefits of the vaccine for college age students."[3] While the literature describes that the vaccines are immunologically effective, are the costs to young people with essentially no risk of morbidity and mortality worth it? A recent publication from the journal *Vaccines* declares, "…We should rethink the policy."[4]

Back to our young man…

Considering what we know about SARS CoV-2 and how it manifests in COVID-19 disease, I extrapolated and focused my treatment to quell the vaccine reaction based on the disease itself and several common practices for immune support in our repertory:

- Boost key nutrients to support immune function.
- Decrease neurologic/systemic inflammation; rebalance immune resilience while decreasing the proinflammatory state.
- Assist with detoxification.

The treatment protocol in part was derived from published therapeutic responses to the virus itself.[5] The assumption was if the spike protein is what causes the cascade of the unregulated immune response and thrombotic phenomenon, then we could assume that the spike protein from the injection is the problem and could be approached in a similar fashion. Additionally, mainstream medical treatment for tinnitus is sparse with ineffective recommendations in general, and integrative approaches have much more to offer. I did refer Mom to the American Tinnitus Association for information to appease her own mounting anxiety.[6]

My job was made easier since this young man was a model patient: healthy and disciplined. He ate mostly organic food and exercised regularly. Having been raised on homeopathy, treatment with remedies was in his favor since historically he responded very well to homeopathics. I had worked out his constitutional remedy in the past, which was *Kali carbonicum*. Luck was with us since that remedy is also noted for treating tinnitus.

I began a treatment course of vitamins C and D3/K2, quercetin, zinc, curcumin, N-acetyl cysteine (NAC), and *Kali carbonicum* 30c. He was already on a multivitamin with selenium/methyl B12/methyl folate, and probiotics. His symptoms disappeared by the next day, and I advised Chad and Mom not to receive the second vaccine. I was about to restore my faith in happy endings until I received a call four weeks later. Mom went ahead and got Chad the second shot. The tinnitus returned almost immediately, and the simple treatment plan re-administered was not effective the second time around.

I had an immediate call out to the Gods to grant me internal calmness. Fear clearly has produced cognitive dissonance in reasonable parents. Despite an explanation of nearly a zero risk of dying from COVID-19 and the ability to obtain a waiver for schools, parents are proceeding in vaccinating their children despite evidence-based advice against vaccination from their

long-term practitioners, even when their children are manifesting serious sequelae from a first injection. Clearly, the media mafia has succeeded in taking its hold and has been amplifying parental anxiety. While tinnitus is not regarded in the same level of severity as other issues being reported from the Pfizer vaccine, such as Guillain-Barre[7] and stroke,[8] this is still a brain issue with inflammation occurring between the auditory nerve and the brain (as well as a known association with hearing loss). Think about this…do we want to be inciting inflammation in any part of the brain?

What is profoundly concerning is that it is known that mRNA vaccines have also been linked to other serious health disorders such as myocarditis which began appearing soon after the roll out of the vaccine on pediatric subjects. The mRNA in the vaccines has been engineered to produce spike proteins at an even greater rate than the virus as well as resist degradation.[9] This alteration of the vaccine spike protein allows it to remain attached to ACE2 receptors, which in effect disables their function in the membrane.[10] Despite the known side effects as reported by Pfizer of both cardiac and neurologic sequelae of the experimental gene therapy and the avalanche of cases of untoward vaccine effects being reported, Dr. Yvonne Maldonado, chair of the American Academy of Pediatrics on Infectious Diseases stated, "…there is no recommended change to vaccination of adolescents 12 and older."[11]

Once Was Not Enough

This was a difficult situation for me as a practitioner. I recalled and pondered over infrequent cases of Munchausen syndrome by proxy that I've treated over the decades and other forms of child abuse and the present similarities I was noting. While these analogies may seem extreme, I posit that injecting children with an experimental therapy for a disease with essentially no mortality or morbidity mounted to blatant **pediacide**.[10] Yet, I had this young man, full of musical promise suffering in front of me. Where is Dumbledore when you need him?

Some of my best advice is don't forget homeopathic remedies when treating vaccine side effects.[12] My go-tos are *Thuja*, *Silicea*, and *Ledum*. I gave Chad *Thuja* 200c for several days. But, the days of giving a single remedy for a vaccine reaction are long over. In addition to the previously outlined protocol, I also prescribed Chad ivermectin, 12 mg daily for five days, to theoretically bind the spike protein, and lumbrokinase as an anti-thromobolytic.[13] Although this is a modified recommended prophylaxis and treatment for COVID-19, I did not find any studies in the literature to support their usage in vaccine reactions. Because of the high safety record of both of these medications, I proceeded. To my delight and relief, his tinnitus cleared within 48 hours.

The obvious question is whether resolution would have occurred eventually on its own? What role did his combination treatment protocol play? I cannot say if indeed he would have cleared spontaneously, but the fact that he had a return of auditory symptoms rapidly and more aggressively with the second shot led me to believe a quick or any resolution is dubious at best. I couldn't reckon not doing everything I could to clear this potentially life-altering condition in a promising musician.

A few other sticky points emerged during Chad's treatment that veered away from my usual practice with young adults. Chad had reached the age where I would normally see patients on their own. This was difficult to do with this family, and Chad reluctantly went along with his mom's views. To be addressed in another visit! Other very concerning aspects in regard to this teen's case emerged, which can also be shared with other families in a similar predicament include the following:

- Providers are not educated regarding COVID vaccine reactions.
- Providers do not know how to recognize and treat vaccine reactions.
- Providers often do not report vaccine reactions to VAERS.
- When there are clear-cut vaccine reactions, they are shuttled to 'other' diagnoses.
- Parents trying to seek help for their vaccine-injured child may be 'gaslighted' or dismissed.[14]

Although there was an eventual 'happy ending', there are many features to this patient's case that were avoidable and could have led to a chronic condition. There is no way of knowing whether Chad would have gone on to be one of the long-standing sufferers from tinnitus, also taking into account mainstream medicine has little to offer this potentially persistent disorder. In sum, the unsubstantiated push to vaccinate children is not acceptable. Final thoughts: When in doubt, go back to the first rule of medicine: First, do no harm.

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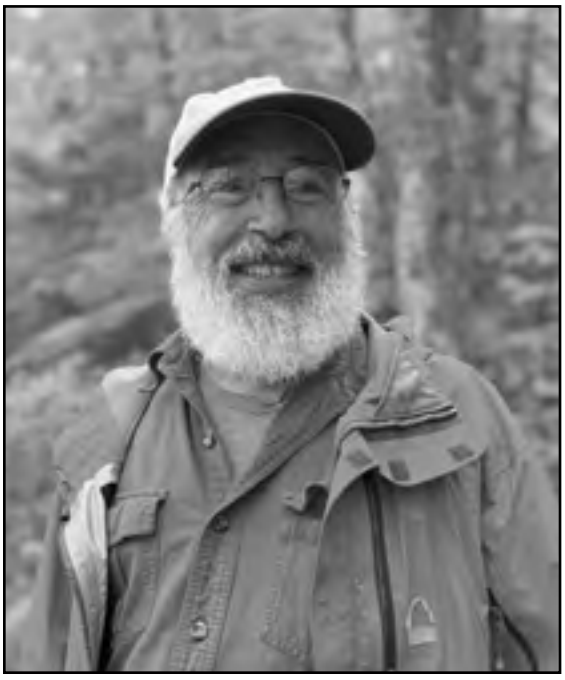

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Treating Periodontal Disease Delays Alzheimer's

Back in November 2020, a federal panel of medical experts refused to endorse a new drug for Alzheimer's disease, saying that the evidence wasn't persuasive enough. However, half a year later, in June 2021, the FDA went ahead and approved this same drug, aducanumab. Even if you pay little attention to pharmaceutical current events, you may have heard the uproar over this decision and how members of the expert committee have resigned as a result. Even if you aren't prone to believing conspiracy theories, it's hard not to wonder what motivated the FDA to make this choice that goes strongly against both expert opinions and common sense.

Treatment with aducanumab is expected to cost patients over $50,000 a year. In theory the drug will slow progression of Alzheimer's disease by clearing amyloid plaques from the brain. For years, the accepted theory has been that these plaques disrupt cognition. Prior drugs developed to clear amyloid plaque have not improved symptoms or slowed the disease and have not been approved by the FDA. Biogen, the company behind aducanumab, claims that the drug was useful in high doses for late-stage disease. Biogen reworked data from previously discounted studies in which the drug was ineffective to show slight possible improvements. "The average degree of improvement on a 0-18 point cognitive scale was just 0.39 points relative to placebo, far smaller than the 1 or 2 point threshold typically used to define a clinically important difference…"[1]

The commotion questioning why the FDA has taken this step to approve an expensive drug with considerable side effects while there are grave doubts whether it is helpful at all have obscured news coverage of several recent studies on Alzheimer's disease that really do deserve our attention. These studies question whether the amyloid plaque theory of AD is true and should have weakened enthusiasm for Biogen's drug further.

Let's back up to 2016 and recall a paper by Mark Ide et al published in March of that year on periodontitis and Alzheimer's disease.[2] Ide and colleagues at Guy's Hospital in London followed sixty non-smokers, who had not been treated for periodontitis in the prior six months and who had mild to moderate dementia. The goal was to see if there was an association between disease symptoms, chronic inflammation, and rate of cognitive decline. The study participants diagnosed with periodontitis at the start of the study declined more rapidly than those without this disease; periodontitis was associated with a six-fold increase in the rate of cognitive decline.

Ide's results supported a new theory that AD is an immune response to infection. Up to this point the association between periodontal disease and cognitive decline was known but the assumption was that it was a case of inverse causation, that AD caused periodontitis because people who can't remember things don't remember to brush their teeth.[3,4,5] Ide et al was the first study to correlate the rate of cognitive decline with poor dental health and suggested the association went the other way, that poor dental health causes mental decline.

In May 2016, Deepak Kumar and colleagues at Harvard suggested that the amyloid proteins, which are the hallmark sign of AD, serve an antimicrobial function protecting the brain against infection. Kumar suggested that some form of chronic infection triggers an over response by this defense system triggering excessive amounts of amyloid plaque to be generated. Amyloid-Beta might be made by the brain for a good reason. It helps fight infection; Kumar described amyloid as "... primary effector molecules of innate immunity, antimicrobial peptides (AMPs)."[6] When bacteria or viruses slip across the blood brain barrier, the brain generates amyloid-Beta to trap the invaders. Amyloid literally cages the bacteria, surrounding them in a matrix, preventing further invasion. The problem is that the plaque remains after the bacteria die, forming long lasting deposits. While Kumar demonstrated this process in Petri dishes, Mark Ide's periodontitis study was the first study involving humans to support this idea.

Over the last two years several significant studies have been published that lend further support to this idea that periodontal disease is causatively associated with AD. A significant study by May Beydoun and a team of researchers from the National Institute on Aging (NIA) was published in 2020. They examined

whether gum disease and infections with oral bacteria were linked to dementia diagnoses by using data from the third National Health and Nutrition Examination Surveys (NHANES III) that was linked with National Death Index and Medicare data. The team compared different age groups at baseline, with up to 26 years of follow-up, for more than 6,000 participants.

The NHANES participants had received a dental exam for signs of gum disease. In addition, the participants received blood tests for antibodies against causative bacteria. The team analyzed antibodies against 19 oral bacteria seeking an association with Alzheimer's, any kind of dementia, or death from Alzheimer's.

The data revealed that older adults with signs of gum disease and mouth infections were more likely to develop Alzheimer's disease in the future. Both Alzheimer's diagnoses and deaths were associated with antibodies against the oral bacterium *P. gingivalis,* which is the most common cause of periodontal disease.[7]

A second important study, one by Schwahn et al, looking at the association between these two diseases was published in May 2021.[8]

Schwahn's team simulated a controlled clinical trial by utilizing recently developed statistical models that allowed them to combine data from treated and untreated patients from two different population cohorts. They shuffled data from 409 untreated participants in the Study of Health in Pomerania (SHIP), a cohort recruited in 1997 to track the effect of dental disease on general health, together with data from 177 patients who underwent periodontal treatment in the Greifswald GANI-MED study. Magnetic resonance imaging (MRI) was used to stage onset of Alzheimer's disease. All patients were younger than 60 at the time of their MRI examination that occurred a mean of 7.3 years after periodontal treatment.

Treatment of periodontal disease years prior to AD onset was associated with a significant reduction in loss of brain matter. Brain atrophy in treated patients was lower, (-0.41; 95% CI: -0.70 to -0.12; P = .0051), a shift from the 50th to the 37th percentile of the outcome distribution.

While the FDA is defending their approval of an expensive drug that probably won't do patients any good, the theory of what causes AD is quietly shifting. The idea that treating the amyloid will cure the disease is now doubtful. This new hypothesis suggests chronic inflammation and microbial infection of the brain lead to Alzheimer's disease. Instead these bacteria, *P. gingivalis,* which have been detected in the brain tissue of AD patients, should be the target for disease prevention. While recent experiments in mice suggest that *P. gingivalis* has a causative role,[9] these studies by Schwahn et al have brought us to the point that we can talk about treating periodontal disease to prevent AD.

Proving that this association is causative in humans is a challenge. Both diseases, AD and periodontitis, have many risk factors in common, including age, obesity, smoking, diabetes, alcohol, depression, stress and education. Cognitive decline, as mentioned, raises risk for poor oral hygiene so people with AD tend to have more periodontal disease.[10,11] Sorting through this tangle of associations and relationships has made discerning causation difficult. The greatest challenge to clarifying the ➤

Curmudgeon's Corner

➤

relationship though is ethical. One cannot ethically withhold a medical intervention, in this case dental care, when doing so may cause disease, in this case Alzheimer's disease.

This ethical necessity has left us to rely on observational studies. That's why Schwahn's statistical manipulations have us paying attention; they simulate a clinical trial and may be as close as we get to a randomized clinical trial to test the hypothesis.

These findings strongly suggest that a timely intervention and treatment of periodontal disease may have a significant benefit in future years. It reinforces our understanding of whole-body medicine and reminds us that the etiology of disease may be complex and, in many circumstances, we need to act together with other healthcare providers. In this instance, actively getting our patients to see dentists and dental hygienists is good preventive medicine. Periodontal disease is caused by plaque formed by bacterial biofilms.

It may be more complicated. The chain of events that leads to AD may actually start in the gut with intestinal microbiota. An August 2016 paper hypothesized that gut dysbiosis increases intestinal permeability, which, in turn, increases blood brain barrier permeability that in turn bring more antigenic material to the brain and that this surge triggers the amyloid beta production.[12]

If the new hypothesis holds true, efforts to prevent AD should focus on preventing biofilm formation that develops into dental plaque rather than dissolving amyloid deposits. Our role as naturopathic doctors may be to suggest diets and supplements that decrease dental biofilm and to reduce periodontitis.[13]

While certain diets may reduce biofilm formation, they do not remove it. Biofilm adheres to the teeth tightly and cannot be rinsed away. Physical removal is required either with a toothbrush or those dental scraping tools that make me weak in the knees even thinking about them. Thus, no matter how compliant your patient is with diet and supplements, their good behaviors will not replace the need for dental treatment.

Rowinska and colleagues, in a comprehensive review of dental infections, suggest a diet that isn't that different from what we generally consider a healthy diet that avoids simple sugars and refined carbohydrates while emphasizing vegetables and fresh fruit, and that is high in antioxidants, essential fats, fiber and collagen.[14,15] As far as specific nutritional supplements, Rowinska suggests among other things, coenzyme Q-10, green tea, and quercetin.[16,17]

While reducing *P. gingivalis* exposure remains key to controlling periodontal disease, reducing stress may be nearly as important.[18,19] People with high levels of stress and poor coping skills have twice as many periodontal diseases as people with minimal stress and good coping skills. There is a relationship between cortisol levels and severity of periodontal disease. Oxidative stress may be just as important as emotional stress on degree of periodontal disease.[20] We were already aware that stress is associated with Alzheimer's disease. Americans living under high psychological distress are nearly twice as likely to die of AD than those with lower stress levels.[21]

This reminds me of a 2010 paper that reported that individuals who were primary caretakers of a spouse with Alzheimer's disease were at much higher risk to also suffer from eventual dementia.[22] The explanation tendered was this effect was due to stress. I recall wondering at the time whether it might be some sort of infectious etiology. The spousal risk was so high, about double or triple that of someone suffering from PTSD.

A Mediterranean diet and exercise may be helpful in preserving cognitive function.[23] The idea that such lifestyle interventions may also improve periodontal disease is quite plausible[24,25] and has been examined but not definitively proven. Consuming olive oil may lower risk of periodontitis.[26] What we offer as naturopathic doctors certainly may be helpful,[27] but alone does not appear sufficient.

Schwahn et al strengthens the argument that periodontal disease contributes to development of Alzheimer's disease and that early intervention to prevent periodontal disease can also decrease incidence of AD. A healthy diet, of course, helps, and certain supplements may be useful; but routine dental checkups and proper oral hygiene performed by the patient may be the foundation for prevention. ◆

References and article are available online at www.townsendletter.com.

➤ *continued from page 88*

negative as the overall visual field worsens. At baseline, the mean value for visual field mean deviation was -5.46 in the group that received placebo first and -4.51 in the group that received niacinamide first. A higher proportion of patients had an improvement of at least 1 dB from baseline in the visual field mean deviation after treatment with niacinamide than after placebo (27% vs. 16%) and a lower proportion had a worsening after treatment with niacinamide than after placebo (4% vs. 12%) (p = 0.02 for the overall effect of niacinamide vs. placebo). Thus, niacinamide treatment resulted in objective improvements in inner retinal function and an apparent improvement in visual field defects. The authors of this study suggested that the improvement in visual fields might have been more pronounced if the treatment period had been longer than 12 weeks.[3]

Coenzyme Q10

Like niacinamide, coenzyme Q10 (CoQ10) is a component of the electron-transport chain and, as such, plays a role in mitochondrial energy production. The concentration of CoQ10 in the human retina has been reported to decline with age,[4] and it is conceivable that this decline contributes to the development or progression of glaucoma. DBA/2J mice (the animal model for glaucoma) were fed a diet containing 1% CoQ10 or a control diet for six months. The dietary interventions were started before the animals had developed glaucoma. Compared with the control diet, the CoQ10 diet increased the survival of retinal ganglion cells by 29% and preserved the axons of the optic nerve head.[5] Based on these findings, clinical trials of CoQ10 in humans are warranted.

Magnesium

As a cofactor in ATP synthesis, magnesium is an essential component of mitochondrial energy production. Magnesium also has many other biochemical actions, including functioning as a vasodilator. Two uncontrolled trials examined the effect of magnesium supplementation in patients with primary open-angle glaucoma (n = 6) or normal-tension glaucoma (n = 19).[6,7] In one study, the dosage was 122 mg twice a day (as magnesium aspartate hydrochloride) for four weeks. In the other study, magnesium was given for one month, but it was not clear what the dosage was. In both studies visual field defects were said to improve. The improvement was of borderline statistical significance (p = 0.09) in one study, and the statistical significance was not specified in the other study. The authors of one of the studies speculated that the improvement was due to the vasodilatory effect of magnesium, which may have enhanced blood flow to the eyes. However, in the other study there was no increase in ocular blood flow despite the apparent improvement in visual field defects.

Conclusion

Basic-science research and preliminary trials in humans suggest that niacinamide, coenzyme Q10, and magnesium may be useful for preventing or treating glaucoma. Controlled trials of longer duration and with larger numbers of patients are needed to confirm the effectiveness of these nutrients. However, considering their relative safety when used in appropriate doses, it would seem reasonable to include niacinamide, coenzyme Q10, and magnesium as part of an overall treatment program for patients who have, or are at risk of developing, glaucoma. Riboflavin and iron also play a role in mitochondrial energy production, but I am not aware of any studies of these nutrients in relation to glaucoma.

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Preventing and Treating Glaucoma by Enhancing Mitochondrial Function

Glaucoma is one of the most common causes of visual impairment, affecting 70 million people worldwide. It is characterized by progressive degeneration of the optic nerve, which can lead to loss of peripheral vision and eventual blindness. At the cellular level, there is gradual dysfunction and loss of retinal ganglion cells and their axons, which make up the optic nerve. Most people with glaucoma have elevated intraocular pressure (IOP), and this elevation is a major factor in the development of optic nerve damage. Medications that lower elevated IOP are the mainstay of conventional therapy, and these medications frequently halt or slow the progression of glaucoma. However, some people develop glaucoma despite having normal IOP, and medical therapy that normalizes IOP does not always stop disease progression. Those observations suggest that factors other than increased IOP also contribute to the pathogenesis of glaucoma.

The retina is one of the most metabolically active tissues in the body and, as such, requires an ongoing supply of energy, which is obtained by mitochondrial production of adenosine triphosphate (ATP). The DBA/2J mouse is a genetic strain of mice that spontaneously develops glaucoma. This strain of mice is widely used in research as an animal model of age-related inherited glaucoma. In a study of DBA/2J mice, mitochondrial abnormalities were found in retinal ganglion cells before cellular degeneration was detectable.[1] That finding raises the possibility that impaired mitochondrial energy production renders retinal ganglion cells more susceptible to degeneration and more vulnerable to the adverse effects of increased IOP. If that is true, then supplementing with nutrients that play a role in mitochondrial energy production (such as niacinamide, coenzyme Q10, and magnesium) could be useful for preventing and treating glaucoma.

Niacinamide

In DBA/2J mice, decreased concentrations of nicotinamide adenine dinucleotide (NAD) were found in retinal ganglion cells before cellular degeneration was detectable. NAD is a component of the electron-transport chain, and a decreased NAD concentration could lead to impaired mitochondrial energy production. Niacinamide (vitamin B3) is a precursor to NAD, so adequate dietary intake of this vitamin is needed to maintain adequate retinal concentrations of NAD. Treatment of glaucoma-prone mice with a large dose of niacinamide (500 mg per kg of body weight per day) prevented the development of glaucoma without decreasing the elevated IOP.[1]

The potential relevance of this study to humans is suggested by a report that the mean plasma concentration of niacinamide was significantly lower by 30% in 34 patients with primary open-angle glaucoma (the most common form of glaucoma) than in age- and sex-matched controls.[2] In addition, the concentration of NAD in retinal cells declines with age, and older age is a risk factor for the development and progression of glaucoma.

In a double-blind trial, 57 patients with glaucoma whose IOP was well controlled were randomly assigned to receive niacinamide or placebo for 12 weeks, and then the alternate treatment for an additional 12 weeks. The dosage of niacinamide was 1.5 g per day (it was not specified whether this was in divided doses) for six weeks, followed by 1.5 g twice a day for six weeks. The primary outcome measure was the change in inner retinal function, as determined by photopic negative response (PhNR) parameters: saturated PhNR amplitude (Vmax) and ratio of PhNR/b-wave amplitude (Vmax ratio). Compared with placebo, niacinamide significantly improved both of these parameters ($p = 0.03$ for each). Visual field loss was assessed by measuring visual field mean deviation. Normal values for this parameter range from 0 dB to -2 dB, and values become more

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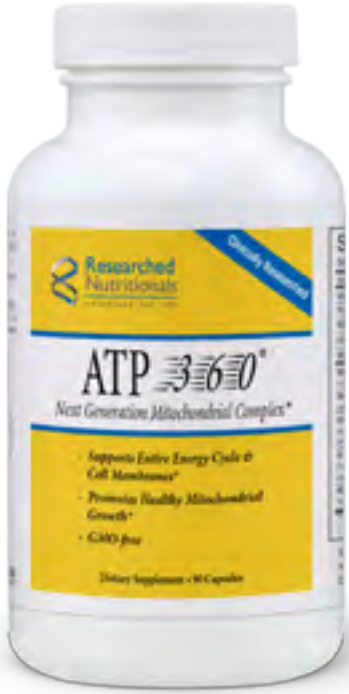

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