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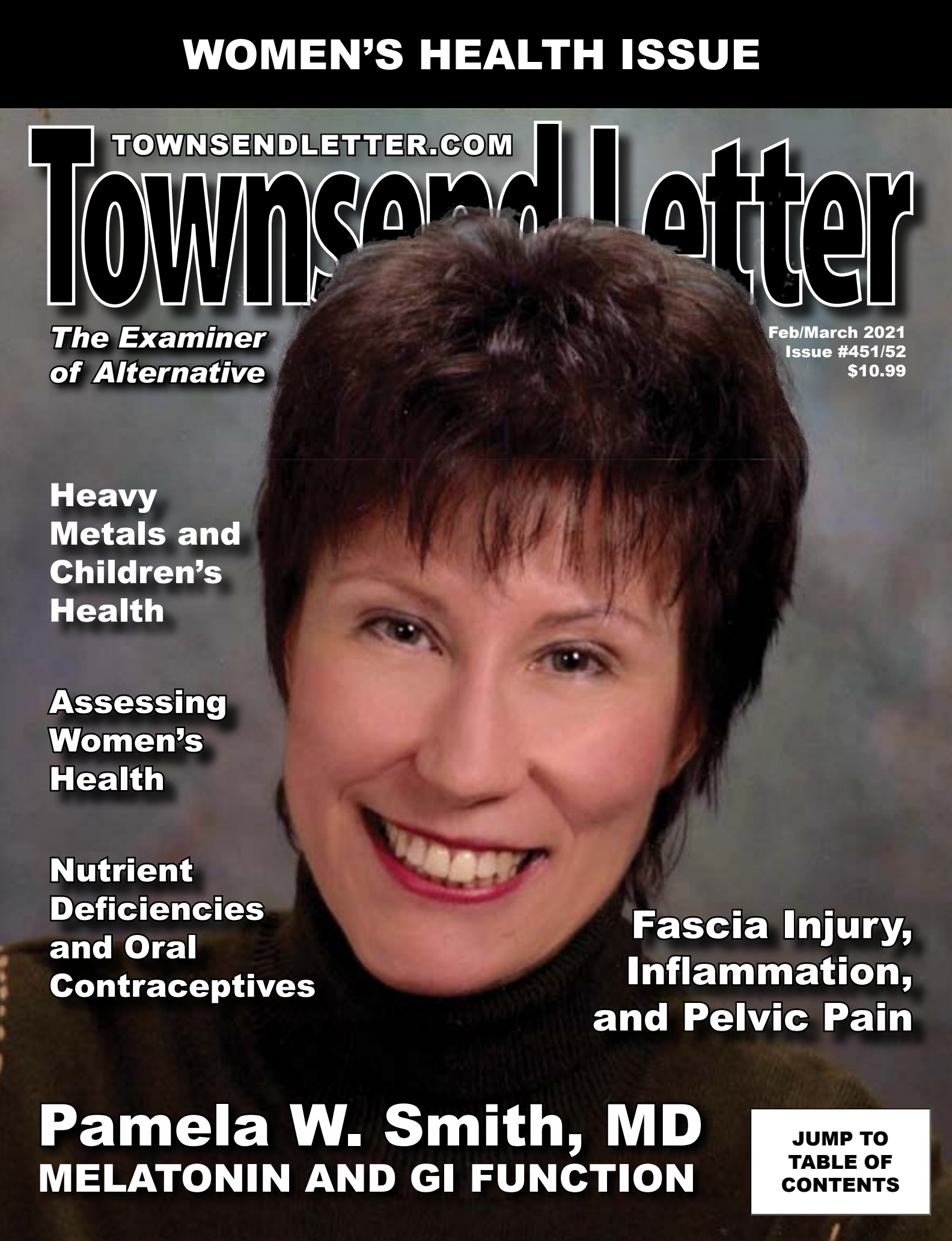

Heavy Metals and Children's Health

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MELATONIN AND GI FUNCTION

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From the Publisher

More Musings on the COVID-19 Pandemic

It's not plague, but the pandemic is real and testing our resilience. As I write this, the SARS-CoV-2 has mutated, according to genomic studies in the UK and South Africa; supposedly the B117 variant is purportedly more infectious. Simultaneously, the launch of the Pfizer and Moderna vaccines has begun in the UK and the US with great fanfare; the health professionals and nursing home patients have tolerated their injections quite well with very few developing major allergic reactions. And not in the least, intensive care units in California, the Mountain West, the South, and in the Great Lakes are filled to the rafters with COVID-19 patients; and more keep appearing in emergency rooms in respiratory distress. Whether a patient survives or not seems almost like a game of craps – betting against a seven roll is a fool's wager. Medicine wants only evidence-based medicine to be administered; so beyond oxygen and respirators and IV's, the mainstay treatment appears to be remdesivir, mono-clonal antibodies, and dexamethasone. But intravenous ascorbic acid remains unproven, so it is not evidence-based. Consequently, no one is receiving IV vitamin C as part of their treatment in the ICU.

For a treatment that would cost the hospital at most $50 daily, this is such a dereliction of duty, an appalling travesty that is undoubtedly costing thousands of patients their lives. Even if such treatment were to fail in 80% of patients (which I would bet it wouldn't), it is malpractice to deprive a treatment that is without adverse effect to 20+% of patients who are likely to die. Of course, we could enumerate here other treatment supports, including glutathione, vitamin D, vitamin A, and zinc, but intravenous ascorbic acid is the key omitted therapy. The irony of the situation is that it cannot be administered in the clinic setting by alternative practitioners who routinely infuse vitamin C because of the absence of on-site quarantine facilities. Of course, we can advocate for the public to use vitamin D and vitamin C as well as other nutraceutical support. In the interim, the rollout of vaccines will continue and presumably by the summer 50% of the population will have been injected. For those who opt not to be vaccinated, vitamin D and C supplementation should be routine even though public health authorities do not recommend their use. We can only hope that the B117 variant does not turn COVID-19 into a more devastating pandemic.

A Healing Virus?

As I have often marveled, *The New Yorker* is a wonderful source of medical information, particularly of the sort that readers of the *Townsend Letter* enjoy – cutting edge research illustrated with case reports that are ignored by mainstream media. In the December 21 issue, Nicola Twilley writes about the intriguing research of phage therapy that is now being investigated at the University of California-San Diego.[1] Using bacteriophage viruses to treat bacterial infections is not new; it has been used in Eastern Europe for over 80 years. In 2018 Steffanie Strathdee, an infectious disease epidemiologist, and Robert Schooley, a virologist, founded the first US phage therapy center, the Center for Innovative Phage Applications and Therapeutics (IPATH) at the UC-San Diego. Twilley details how Dr. Strathdee hunts for phages by first collecting sewage water, a source teeming with bacteriophage likely to be capable of infecting antibiotic-resistant bacteria such as Pseudomonas.

Bacteriophage are viruses that only infect bacteria; theoretically they are harmless to humans and other animals and plants. They infect bacteria in the same manner that COVID-19 infects human cells; once the virus enters the bacteria, it highjacks the bacteria's DNA, forcing a mass replication of phage DNA and leading to an explosion of viruses. When sufficient phage are produced within the bacteria, the bacteria "explodes" and dies. Estimates of the activity of phage are thought to be a trillion, trillion infections of bacteria taking place per second meaning half of all bacteria are killed every two days[1] Hence, bacteriophage play an extremely important role in controlling how bacteria function in our microbiome and body. A bacterial infection that has become septic, particularly one that is resistant to antibiotics, frequently is without recourse. If a phage were to be applied in such a circumstance, the MRSA or sepsis might be readily defeated without adverse effect or new resistance. However, finding the right bacteriophage for the specific bacteria causing the infection is a tricky business. Indeed, most phage viruses will not be able to infect the sick individual's disease-causing bacteria. Researchers at IPATH keep bacterial pathogens ➤

Letter from the Publisher

➤

– *E. coli*, Enterococcus, and Pseudomonas – available to test a phage's infectivity. Those phage found to be effective in infecting pathogenic bacteria are maintained and catalogued for phage treatment.

Twilley's article discusses how phage therapy worked out for several patients with very serious antibiotic-resistant bacterial infections. Not unexpectedly some experienced severe complications and did not make out well. Because phage commandeer bacterial DNA, it is possible that the bacteria may inadvertently become more virulent. Still in this pandemic time when everything we read and hear is about the need to control a virus, it is refreshing to be reminded that viruses play a critical role in maintaining control over bacterial organisms that threaten us with a multitude of infections.

Cover Story: Pamela Smith, MD, on Melatonin

For those of you who attend A4M (American Academy of Anti-Aging Medicine) conferences, Dr. Pam Smith is a familiar face. She is the founder of the Fellowship in Anti-Aging, Regenerative and Functional Medicine. Pam is frequently called upon to lecture about bio-identical hormones at the A4M national and international conferences. Currently she is the director of the Center for Personalized Medicine in Transverse, Michigan. Moreover, Dr. Smith also participates in academic work at the University of South Florida where she is co-director of the master's program in metabolic and nutritional medicine at the Morsani College of Medicine.

Anti-aging medicine was not always Smith's thing. After graduating from medical school, she was an ER doc. But at age 40 she suddenly found herself an insomniac; and despite evaluation by eleven physicians, she was not given any sensible explanation for her sleeplessness. Around this time when her health was endangered, she attended an A4M conference and was shocked to discover that salivary testing of her hormones revealed that her progesterone level was essentially nil. Following a prescription of progesterone, her insomnia resolved. This piqued Dr. Smith's interest, leading to her enrollment in an A4M fellowship. After passing the written exam, she needed to complete oral tests; but this required patient charts, which would not be available as an ER doc. So, she opened a small practice devoted to bio-identical hormone therapy. Dr. Smith thought the clinic would only be a temporary project, but she ultimately joined together with other practitioners knowledgeable in hormone therapy and anti-aging medicine. Today she is the director of her own clinic, the Center for Personalized Medicine.

Pam Smith is also not new to *Townsend Letter* readers: in 2015 she wrote about PCOS, in 2016 she discussed the importance of reverse T3, and in 2017 she examined treatment modalities for PMS.[2-4] Smith's books include *Vitamins: Hype or Hope* as well as *HRT: The Answers – A Concise Guide for Solving the Hormone Replacement Therapy Puzzle.* In this issue Smith explores the role of melatonin in our health – she informs us that it is not just something to use for insomnia.

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Letter from the Publisher

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Women's Health Featuring Dr. Tori Hudson

Townsend Letter readers are familiar with the writing of Tori Hudson, ND, who has penned her Women's Health Update column for 30 years. Dr. Hudson is currently serving as a clinical professor at the National University of Naturopathic Medicine (NUNM), Southwest College of Naturopathic Medicine, and Bastyr University. She is medical director of her clinic, A Woman's Time in Portland, Oregon. Hudson is the director of product research and education for Vitanica. She is the recipient of numerous awards in naturopathic medicine, including the 1999 Naturopathic Physician of the Year Award, and in 2012 was inducted in the NUNM Hall of Fame. Hudson's writing includes being the author of the *Women's Encyclopedia of Natural Medicine* (2008). She has been featured annually in the February/March issue of the *Townsend Letter* focusing on women's health.

In this issue's "Women's Health Favorites from 2020," Dr. Hudson examines naturopathic approaches to managing bacterial vaginosis. While docs and patients frequently misdiagnose this vaginal infection, the fishy odor, grey or greenish discharge, and alkaline pH of the vagina distinguish BV from candidiasis. For many women the problem is that, despite symptomatic relief with initial treatment, BV recurs frequently. For those who are looking for alternatives to metronidazole, Hudson provides natural medicine protocols both for acute and chronic recurring bacterial vaginosis.

Because Dr. Hudson's clinic focuses on women's health issues, this issue's article on "Testing Updates" provides a must read for gynecologic practices. It turns out that asking the patient about when she had her last period is not the best way to determine the onset of menopause – and measuring FSH levels is not much better. But there is another hormone test that more sensitively predicts the onset of menopause. Hypothyroidism is a relatively easy diagnosis – but not necessarily in pregnant women. Hudson points out that diagnosing subclinical hypothyroidism during pregnancy is critical as it may make a major difference in fetal development. This issue's tour de force is testing and diagnosis of patients with HPV and cervical dysplasia. The days of doing a Pap smear and referring the patient for a hysterectomy have long passed. Hudson reviews the strategic risk management in a patient having positive HPV genotype testing and high-grade squamous intraepithelial lesion cytology. For those who would like additional information about Dr. Hudson's recommendations for natural treatment of cervicitis, read "Sample treatment plans for HPV and abnormal Pap smears" in the Feb/March, 2017 issue available at www.townsendletter.com.

Jonathan Collin, MD

1. Twilley, N. A Healing Virus? *The New Yorker*. Dec. 21, 2020; 32-37. https://www.newyorker.com/magazine/2020/12/21/when-a-virus-is-the-cure?utm_source=onsite-share&utm_medium=email&utm_campaign=onsite-share&utm_brand=the-new-yorker
2. Smith, P. PCOS: A common endocrine disorder. *Townsend Letter*. 2015; 381, 61-66.
3. Smith, P. The importance of reverse T3. *Townsend Letter*. 2016; 396, 89-90.
4. Smith, P. Treatment modalities for PMS. *Townsend Letter*. 2017; 405, 36-39.

◆

Maintaining a Healthy Weight All Year Long, Every Year

Many people find themselves struggling with weight gain as a result of pandemic restrictions, inactivity, lack of sleep, and stress eating. It's clear that an extra 10, 15, or more pounds can be dangerous to physiological health, but an unhealthy microbiome precipitated by unhealthy eating habits can also compromise psychological health. ***Resiliency of the gut-brain axis is more important than ever before.*** Serotonin and dopamine production by the gut microbiota is critical to mental balance and to keeping anxiety and depression in-check. Long term imbalance within the microbiome (more bad bacteria than good bacteria) becomes a vicious cycle and compounds existing mental health and immune challenges

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Shorts

briefed by Jule Klotter
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CA Medical Board vs Integrative Doctor

Kenneth P. Stoller, MD, faced charges of incompetence and negligence before the Medical Board of California (MBC) during a four-day hearing in September 2020. Dr. Stoller is a pediatrician with expertise in integrative/functional medicine and hyperbaric oxygen therapy. MBC charged that he wrote ten 'inappropriate' medical vaccine exemption letters for children. The children had family histories and genetic variations that put them at risk for suffering adverse effects if they adhere to the CDC vaccination schedule.

California Senate Bill 277 (SB 277), which passed into law in 2016, eliminated personal belief and religious exemptions to vaccination. It requires children attending schools and day care centers to be vaccinated for diseases now on the CDC schedule and "[a]ny other disease deemed appropriate by the [public health] department, taking into consideration the recommendations of the Advisory Committee on Immunization Practices of the United States Department of Health and Human Services, the American Academy of Pediatrics, and the American Academy of Family Physicians." In other words, children will be required to get any vaccines added to the schedule in the future, as well. SB 277 retained medical exemptions, written by a licensed physician. The physician's written statement needed to include "…the specific nature and probable duration of the medical condition or circumstances, including, but not limited to, family medical history, for which the physician does not recommend immunization…."

Under the belief that they were adhering to the law, integrative physicians wrote medical exemptions for children who had experienced adverse reactions to previous vaccination or whose family history and genetics indicated risks. Disturbed by the number of medical exemptions, Senator Richard Pan, the physician who had spearheaded SB 277, pushed through Senate Bill 276 in 2019. SB 276 set up a government bureaucracy to oversee school vaccination rates and the number of medical exemptions written. Any physician who writes more than five exemptions in a year will undergo a review.

Moreover, only CDC, ACIP, or AAP criteria or other standard-of-care guidelines are to be used for medical exemption. According to CDC's Advisory Committee on Immunization Practices (ACIP), a severe allergic reaction (e.g., anaphylaxis) after a dose or component of a vaccine contraindicates further doses of that vaccine. Less severe reactions and family history are not viewed as reasons for exemption. While the California Department of Public Health (https://www.cdph.ca.gov/) claims that medical exemptions are permitted, the reality is that few doctors are willing to face bureaucratic review and medical board sanction.

Attorney Richard Jaffe, Esq., author of *Galileo's Lawyer*, represented Stoller at the September hearing. Jaffe argued "…that SB 277 created a statutory standard of care and allowed physicians to write ME's beyond ACIP guidelines, and the standards used by Ken and other like-minded physicians are within a minority view standard of care permissible under California law (Bus. And Prof. Code 2234.1)." California Senate Bill 1691, passed in September 2004, permits physicians to practice alternative medicine with informed consent. In addition to Stoller's own testimony, the defense presented two exhibits in support of integrative practice: "Best Practices for California Physicians Providing Complementary Health Care Methods" by Greg Glaser, Esq., who is the general counsel for Physicians for Informed Consent (PIC) and the national director of the Coalition for Informed Consent, and "Best Practices for Physicians Recommending a Medical Exemption to Vaccination," from a March 2019 PIC workshop, presented by Glaser and Toni Bark, MD. Also, for the defense, Kelly Sutton, MD, a board-certified internist with training in pediatrics and functional medicine, testified about the differences between conventional medicine and integrative medicine and about the importance of patient-centered risk assessment for immune health. Oddly (or maybe not), the medical board had filed an accusation against Sutton one week before her testimony, charging that she wrote medical exemptions that did not meet ACIP guidelines

The medical board's expert witness, Dean Blumberg, MD of UC Davis, asserted that "there can only be one standard of care (CDC guidelines)…." Stoller's views on informed consent and vaccine risk are far more nuanced – as he explains in his excellent article "The Denial of Adverse Event Risk Following Immunization and the Loss of Informed Consent – A Perspective" (available at www.townsendletter.com).

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Shorts

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Administrative Law Judge Juliet E. Cox, who presided over the hearing, submitted her proposed decision to MBC on December 8, 2020. A board panel will review her decision. The results should be available by late January 2021, or sooner if the Board releases a decision. (Jaffe posts updates on his blog: https://rickjaffeesq.com/) Stoller may have his license revoked with five years' probation if the judge finds significant departure from standard of care; or, if the judge thinks Stoller met the standard of care created by SB 277, she may recommend a letter of reprimand. In either case, the medical exemptions that Dr. Stoller wrote would no longer be honored by schools. If the judge exonerates Dr. Stoller, the board could ignore her decision and decide the case itself…after conducting another hearing. Physicians in California have the right to appeal board decisions, first to a superior court judge then to the Court of Appeals. Rick Jaffe has four more clients awaiting MBC hearings for writing medical exemptions.

Bolen T. Ken Stoller MD – California Medical Board "Vaccine Medical Exemption" Case Ended Yesterday. BolenReport.com

Jaffe R. Dr. Ken Stoller's Medical Board hearing is over (almost) so what's next? September 26, 2020. www.rickjaffeesq.com.

Jaffe R. Status Report on the Ken Stoller Medical Board Case (and other similar cases). November 29, 2020. www.rickjaffeesq.com

Jaffe R. Stoller Decision Watch in Progress. December 17, 2020. www.rickjaffeesq.com

Miller MC. The trial of Dr. Ken Stoller: Must-Read on the urgent issue of vaccine exemptions. September 30, 2020. www.markcrispinmiller.com

Physicians for Informed Consent Provides Key Information in Medical Board of California Hearing, Aims to Protect Patients at Risk of Vaccine Side Effects. PRWeb. October 2, 2020.

Zeolite Clinoptilolite

Zeolite is one of the supplements I've seen on the web that is supposed to promote detoxification. Zeolite, a microporous natural mineral found in areas with past or present volcanic activity, mainly consists of alumino-silicates, SiO4 and AlO4 structures connected by shared oxygen atoms. Zeolites come in many forms. Research has focused on zeolite clinoptilolite, which is being used in industry and animal agriculture. Clinoptilolite has a silicon (Si) to aluminum (Al) ratio greater than 4.0, which makes it stable in acid and unlikely to result in aluminum absorption by the body. Silicon-rich mineral water and silicic acid are known to remove Al from the body.

A 2018 scientific literature review of clinoptilolite, by Sandra K. Pavelić et al, reports that the mineral supports the GI microbiome, donates beneficial trace minerals (e.g., sodium, magnesium, calcium, potassium), and has antioxidant effects in addition to aiding detoxification. Animal studies form the bulk of this research; comparatively few human clinical trials have been conducted. Clinoptilolite has been added to animal feed for years because of its ability to adsorb ammonia; consumption reduces the amount of ammonia in animal waste. Animal experiments have found that clinoptilolite adsorbs other harmful substances in the digestive tract, including mycotoxins, heavy metals (e.g., lead), and organophosphates.

Feed supplementation has also produced other benefits. Studies with broiler chickens showed that clinoptilolite supplementation improved GI health and flora – and it may help humans, as well. The Cuban Drug Quality Control Agency, according to the authors, has approved a clinoptilolite supplement (Enterex®), which was "highly efficient in ameliorating diarrhea symptoms in several clinical studies on humans with acute diarrhea of different etiologies." Clinoptilolite also increases the activity of glutathione peroxidase, catalase, total SOD, and the total antioxidant capacity. A mouse study showed that EDTA and clinoptilolite supplementation protected the brain from lead toxicity by "inducing antioxidant mechanisms and greater activity levels of catalase, SOD, glutathione peroxidases, and glutathione."

The European Food Safety Authority (EFSA) Panel on Additives and Products or Substances Used in Animal Feed (2013) said that zeolite clinoptilolite was non-toxic in animal feed at doses of 10,000 mg/kg. Clinoptilolite appears to adsorb toxic substances and heavy metals only; there is no evidence that it affects trace mineral or micronutrient levels. Clinoptilolite and the toxins that it captures are excreted via the intestine.

Like any natural product, zeolite's source, composition (i.e., trace mineral content), and processing (mining, cleaning, sieving, dehydration, milling, etc) may enhance or decrease its benefits. Pavelić et al say, "In the future, it would be highly helpful to gather scientific data on the direct relationship between specific clinoptilolite material properties and sources with positive or negative effects and mechanisms of action *in vivo*."

Mastinu A, et al. Zeolite Clinoptilolite: Therapeutic Virtues of an Ancient Mineral. *Molecules.* April 17, 2019.

Pavelić SK, et al. Critical Review on Zeolite Clinoptilolite Safety and Medical Applications *in vivo. Frontiers in Pharmacology.* Nobember 2018;9:article 1350.

Dr. Paul Thomas and Informed Choice

Five days after the November/December 2020 publication of "Relative Incidence of Office Visits and Cumulative Rates of Billed Diagnoses Along the Axis of Vaccination" in the *International Journal of Environmental Research and Public Health*, the Oregon Medical Board called an emergency meeting and revoked the medical license of Paul Thomas, MD, one of the article's authors. Dr. Thomas, a pediatrician and addiction expert, has an integrative practice in Portland, Oregon, that employs seven health care providers and serves over 10,000 patients.

According to the board, it can temporarily suspend a license without a hearing when the board has evidence that a licensee's continued practice constitutes an immediate danger to the public. Among its explanation for the emergency suspension, the board cites eight patients who did not receive CDC recommended vaccines. The document also cited Dr. Thomas' use of an alternative vaccination schedule. In addition to the suspension of his medical license, Oregon Health Plan and Providence Health Plans terminated insurance contracts with Integrative Pediatrics (his practice) and all its providers; and Oregon Health Authority removed Integrative Pediatrics' Vaccines for Children program, preventing the disadvantaged from having access to free vaccines.

Thomas first attracted the board's attention in 2018, two years after the publication of his book, *The Vaccine-Friendly Plan*. As he explained in an interview with Spiro Skouras, parents of his patients are given information to make informed choices – information such as risks from getting a disease vs. risks from the correlating vaccine, how the illness can be treated, and signs of adverse reactions. His plan also aims to reduce exposure to aluminum by spacing aluminum-containing vaccines out and using aluminum-free vaccines when available. Aluminum is a known neurotoxin found in several childhood vaccines in the CDC schedule.

The 2020 study that Thomas co-authored with James Lyons-Weiler analyzed data from patients *born into his practice* between June 1, 2008 and January 27, 2019, and who had a first visit before 60 days of life and a last visit after 60 days (n=3324); 561 received

no vaccines, and 2763 received between 1 to 40 vaccines: "The variation in vaccination was the outcome of the final decisions on the part of the patients after consulting with their physicians in the practice."

Data for the study came from all billing and medical records; patients were "de-identified" by trained brokers. In addition to factors like breastfeeding, family history (particularly autoimmunity), gender, and age, the authors looked at vaccination in relation to incidence of diagnoses and average total incidence of billed office visits per outcome (Relative Incidence of Office Visit (RIOV)), as a measure of diagnosis severity. (Wellness visits, which were encouraged for all patients, acted as a control.) In all, 10 analyses were conducted on the data.

Overall, the unvaccinated group was very healthy. Adjusted numbers showed that the vaccinated group had more office visits for several diagnoses, including breathing issues, otitis media, eczema, and particularly respiratory infections and anemia. The authors wrote, "Our finding of a robust signal of anemia deserves follow up: aluminum is known to bind to transferrin and, in so doing, may interfere with the proper deposition of iron in the bones of children. Iron deficiency can also contribute to febrile seizures, a known side effect of some vaccines." The number of neurodevelopment conditions in the study's 3324 children was low: "Autism, at a study-wide rate of 8 per 1000, is far lower than the national rate (18.5-21 per 1000). Speech, learning, and social delays were found to have different full-cohort practice-wide incidences of 0.023, 0.002, and 0.009, respectively." None of the children in the unvaccinated group had attention deficit hyperactivity syndrome (ADHD).

As expected, the incidence of vaccine-targeted illness among the unvaccinated children was higher than the incidence in the vaccinated. Nine children in the unvaccinated group were diagnosed with pertussis, compared to one in the vaccinated group. Two in the unvaccinated group were diagnosed with rotavirus, compared to none in the vaccinated group, and 23 in the unvaccinated group were diagnosed with varicella (chickenpox) compared to six in the vaccinated group. Total: 34 cases of vaccine-targeted illness in 561 unvaccinated children and 7 diagnosed illness in the 2763 vaccinated children. The authors state: "It is important to note that zero deaths have been attributed to any vaccine-targeted diagnosis in this practice over the study period."

The authors intend to use the raw data for this study in a second one that will compare health outcomes associated with live vs. non-live vaccines, aluminum-containing vaccines vs. aluminum-free vaccines, and the impact of individual vaccines on specific health risks. They write: "Our society should work to identify safer vaccine schedules and safer adjuvants and to reduce autoimmunity risk by removing unsafe…peptide sequences from pathogens or human cell line remnants in vaccines that match human proteins in sequence or structure from any tissue…."

Kennedy RF, Jr. Join Me in Supporting Dr. Paul Thomas, A Hero Defending Children's Health. December 2, 2020. https://childrenshealthdefense.org/defender/support-dr-paul-thomas/
Lyons-Weiler J, Thomas P. Relative Incidence of Office Visits and Cumulative Rates of Billed Diagnoses Along the Axis of Vaccination. *Inter J Environ Research and Public Health.* November 22, 2020.
Oregon Medical Board. Order of Emergency Suspension – Paul Norman Thomas, MD. https://omb.oregon.gov/clients/ormb/OrderDocuments/e579dd35-7e1b-471f-a69a-3a800317ed4c.pdf
Skouras S. Dr. Paul Thomas Targeted by Medical Board and Media After landmark Vaccine Study – Interview. December 20, 2020. www.bitchute.com

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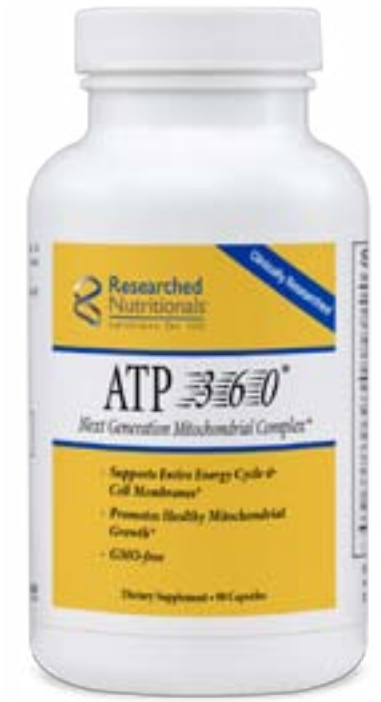

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Literature Review & Commentary

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

D-Mannose Prevents Urinary Tract Infections

A meta-analysis was conducted on three studies that examined whether D-mannose reduces recurrences of urinary tract infections (UTIs) in adult women with recurrent UTIs. One study was a randomized controlled trial, one was a randomized cross-over trial, and one was a prospective cohort study. The pooled relative risk of UTI recurrence comparing D-mannose with placebo was 0.23 (95% confidence interval [CI], 0.14-0.37), indicating a significant 77% reduction in risk. The pooled relative risk comparing D-mannose with prophylactic antibiotics was 0.39 (95% CI, 0.12-1.25), indicating a statistically nonsignificant 61% decrease in risk compared with antibiotics. D-Mannose was generally well tolerated, although a few participants experienced diarrhea.

Comment: About 25 years ago, Dr. Jonathan Wright began using D-mannose (a sugar structurally similar to glucose) to prevent and treat urinary tract infections. The use of D-mannose was based on *in vitro* evidence that it prevents uropathogenic *Escherichia coli* from adhering to the epithelial cells of the genitourinary tract. In Wright's experience, this treatment has an efficacy rate of 85-90%. In addition to being an effective treatment for UTIs, he found that D-mannose can prevent post-intercourse UTIs and is also effective for prophylaxis in women who are prone to recurrent UTIs. Because of the writings and teachings of Dr. Wright, D-mannose is now widely used by practitioners of integrative medicine.

Many people reading this column already know about the benefits of D-mannose, although there has been less interest in the mainstream medical community. The main reason I am reviewing this meta-analysis is to point out that it was published in the *American Journal of Obstetrics and Gynecology*, a high-impact journal that is read by many conventional practitioners. The publication of this article raises the hope that D-mannose, which is a safe, effective, and inexpensive treatment, will eventually become the standard of care for preventing and treating UTIs caused by *E. coli*.

Lenger SM, et al. D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020;223:265.e1-265.e13.

Can DHEA Help Prevent Osteoporosis?

A meta-analysis was conducted on four randomized double-blind trials (including a total of 295 women and 290 men over age 55 years) that examined the effect of dehydroepiandrosterone (DHEA) supplementation for one year on bone mineral density (BMD). In women, compared with placebo, DHEA significantly increased mean serum concentrations of testosterone and estradiol. Compared with placebo, DHEA significantly increased mean BMD of the lumbar spine, total hip, and trochanter, and nonsignificantly increased BMD of the femoral neck. In men, compared with placebo, DHEA significantly increased the mean estradiol concentration, but had no significant effect on testosterone levels. In men, DHEA had no significant effect on BMD at any site, and there was no clear trend for or against DHEA.

Comment: DHEA levels decline with age, and it has been suggested that this decline contributes to various age-related health conditions. The results of this study demonstrate that DHEA can help prevent bone loss in postmenopausal women but not in middle-aged and elderly men. In addition, DHEA supplementation increased the concentration of estradiol (one of the 3 main forms of estrogen produced in the body) in both men and women. In contrast, DHEA increased testosterone levels only in women. DHEA is apparently converted in part to estrogen and testosterone in both men and women, so it is not clear why DHEA supplementation did not increase testosterone levels in men. In many clinical trials, the dosage of DHEA was 50 mg per day, which appears to be a supraphysiological dose. Long-term administration of excessive amounts of DHEA has the ➤

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theoretical potential to promote the development of hormone-dependent cancers, such as breast, ovarian, and endometrial cancer. Circumstantial evidence suggests that a physiological dose for DHEA-replacement therapy is in the range of 5-10 mg per day in women and 10-20 mg per day in men. It has been my practice to consider DHEA supplementation for patients whose serum DHEA level (measured as DHEA-sulfate) is below or near the bottom of the normal range for young adults of the same sex. Using that approach, I have seen physiological doses of DHEA improve BMD, as well as various problems such fatigue, depression, menopausal symptoms, and age-related decline in memory and muscle mass.

Jankowski CM, et al. Sex-specific effects of DHEA on bone mineral density and body composition: A pooled analysis of four clinical trials. *Clin Endocrinol (Oxf)*. 2019;90:293-300.

Vegan Diet During Pregnancy

A retrospective study was conducted on 1,419 Israeli women to examine the association between consumption of a vegan or vegetarian diet and pregnancy outcomes. A vegetarian diet was defined as consuming meat, poultry, or fish once a month or less and eggs and dairy products once a month or more. A vegan diet was defined as consuming meat, poultry, fish, dairy, or eggs once a month or less. One thousand fifty-two women consumed an omnivorous diet, 133 consumed a vegetarian diet, and 234 consumed a vegan diet. Compared with the infants of omnivores, the infants of vegans had a lower mean birth weight percentile (42.6 vs. 52.5; $p < 0.001$), and a higher risk of being small for gestational age (adjusted odds ratio = 1.74; $p = 0.03$). Similar trends were seen when comparing omnivorous and vegetarian diets, but the differences were less pronounced and were not statistically significant. Vegan and vegetarian diets were each significantly associated with a lower risk of excessive maternal weight gain during pregnancy.

Comment: The results of this study suggest that consuming a vegan diet during pregnancy may increase the risk of having a small-for-gestational age baby. Vegan diets often contain virtually no vitamin B12, and they may also be low in protein, iron, vitamin D, zinc, iodine, riboflavin, calcium, and selenium. However, consumption of a vegetarian or vegan diet may reduce the incidence of a number of chronic diseases, including cardiovascular disease, hypertension, gallbladder disease, kidney stones, diabetes, obesity, constipation, and some cancers. A vegan diet, properly planned with the help of a dietitian or nutritionist, and supplementing with vitamin B12 and other appropriate micronutrients might reduce or eliminate the increased risk of having a small-for-gestational age baby.

Kesary Y, et al. Maternal plant-based diet during gestation and pregnancy outcomes. *Arch Gynecol Obstet*. 2020;302:887-898.

Niacin for Mitochondrial Myopathy

Median concentrations of nicotinamide adenine dinucleotide (NAD) were significantly lower in muscle and blood in five patients with adult-onset mitochondrial myopathy

than in age- and sex-matched controls. Muscle concentrations of niacinamide were also significantly lower in patients than in controls. The patients were treated with 250 mg per day of niacin, which was increased progressively, as tolerated, to a maximum of 750-1,000 mg per day, for a total treatment period of 10 months. Niacin treatment increased the median muscle concentration of NAD by 1.3-fold after four months and by 2.3-fold after 10 months. Blood levels of NAD+ also increased. At 10 months, the NAD concentrations had reached those of healthy controls. Niacin supplementation was associated with increased muscle mass after four months and with increased muscle strength after 10 months.

Comment: NAD is a cofactor in the electron-transport chain, which plays a role in the mitochondrial energy production. In this study, patients with adult-onset mitochondrial myopathy were found to have low concentrations of NAD. Supplementation with niacin increased NAD levels, as well as increasing muscle mass and muscle strength. Niacinamide would also likely be effective since it can also increase NAD levels.

Pirinen E, et al. Niacin cures systemic NAD+ deficiency and improves muscle performance in adult-onset mitochondrial myopathy. *Cell Metab*. 2020;31:1078-1090.e5.

N-Acetylcysteine and *Helicobacter pylori*

Six hundred eighty Taiwanese patients with *Helicobacter pylori* infection were randomly assigned to receive, in open-label fashion, triple therapy (dexlansoprazole, amoxicillin, and clarithromycin) for 14 days, with or without 600 mg of N-acetylcysteine (NAC) twice a day for 14 days. *H. pylori* eradication was defined as a negative urea breath test at least six weeks after completion of treatment. Among the 95% of patients who adhered to the treatment, the eradication rate was 85.7% with NAC and 88.0% without NAC (p = 0.40).

Comment: In previous studies, NAC increased the eradication rate in patients receiving standard *H. pylori* eradication therapy. NAC was thought to work by degrading the biofilm produced by *H. pylori*, thereby allowing for greater penetration of the antibiotics. NAC did not increase the eradication rate in the present study. However, the rate was very high in both groups, so there was little room for NAC treatment to demonstrate a benefit. NAC may be most successful in patients in whom previous attempts at eradication had been unsuccessful. In a previous study, 40 patients who had had at least four unsuccessful attempts to eradicate *H. pylori* were randomly assigned to receive 600 mg of NAC once a day or no NAC (controls) for one week, followed by a culture-guided eradication regimen that included two antibiotics and a proton pump inhibitor. The eradication rate was significantly higher in the NAC group than in the control group (65% vs. 20%; p < 0.01). Biofilm disappeared in all patients in whom eradication was successful but persisted in patients in whom eradication was unsuccessful.[1]

Chen CC, et al. Comparison of the effect of clarithromycin triple therapy with or without N-acetylcysteine in the eradication of Helicobacter pylori: a randomized controlled trial. *Therap Adv Gastroenterol*. 2020;13:1756284820927306.

Riboflavin for Crohn's Disease

Seventy patients (mean age, 42 years) with Crohn's disease received 100 mg of riboflavin once a day for three weeks. At baseline, 70% of the patients were in remission, 18.6% had mild disease, and 11.5% had moderate disease. Thirty patients (71.4%) were receiving medications (mostly tumor necrosis factor inhibitors and/or thiopurines). Riboflavin supplementation was associated with a significant improvement in median disease activity (as determined by the Harvey-Bradshaw Index; p < 0.001). The median concentration of interleukin-2 (a biomarker of inflammation) decreased significantly.

Comment: Riboflavin has demonstrated an anti-inflammatory effect in animal models of Crohn's disease. The results of the present study suggest that riboflavin may also be beneficial in the treatment of humans with Crohn's disease. Controlled trials are needed to confirm the efficacy of this safe, low-cost therapy.

von Martels JZ, et al. Riboflavin supplementation in patients with Crohn's disease [the RISE-UP study]. *J Crohns Colitis*. 2020;14:595-607.

Vitamin D and Bone Health

The VITamin D and OmegA-3 TriaL (VITAL) was a double-blind, placebo-controlled trial of vitamin D (2,000 IU per day) and/or omega-3 fatty acids (1 g per day) in 25,871 US adult men and women. The present study included a subcohort of 771 participants (mean age, 63.8 years) from the original trial. The mean serum 25-hydroxyvitamin D (25[OH]D) level at baseline was 27.6 ng/ml. After two years of treatment, compared with placebo, vitamin D resulted in a nonsignificant trend toward a more favorable change in bone mineral density (BMD) of the spine (0.33% vs. 0.17%; p = 0.55) femoral neck (-0.27% vs. -0.68%; p = 0.16), and total hip (-0.76% vs. -0.95%; p = 0.23), but the opposite trend for whole body (-0.22% vs. -0.15%; p = 0.60). These changes did not vary according to baseline 25(OH)D levels. Among participants with a baseline free-25(OH)D level below the median, vitamin D supplementation resulted in a significant increase in BMD of the spine (0.75% vs. 0%; p = 0.043) and attenuation of loss of BMD of the total hip (-0.42% vs. -0.98%; p < 0.05).

Comment: This study found that vitamin D at a dose of 2,000 IU per day had little effect on BMD in middle-aged and elderly men and women whose mean baseline 25(OH)D level was 27.6 ng/ml. Vitamin D may be beneficial, however, for individuals with lower vitamin D status at baseline. Interestingly, a low baseline 25(OH)D level did not predict a positive response to vitamin D supplementation, whereas a low baseline free-25(OH)D level did predict a positive response to vitamin D. Since free-25(OH)D levels are not commonly measured, standard laboratory testing for vitamin D status may not be useful for predicting who in the general population is likely to benefit from vitamin D supplementation.

In previous studies, 800 IU per day of vitamin D slowed the rate of bone loss, whereas 400 IU per day was ineffective. In a 2019 study that I reviewed in the February/March 2020 issue of the *Townsend Letter*, bone loss was significantly greater in participants who received 4,000 IU per day of vitamin D than in those who received 400 IU per day.[2] When considered together, these findings suggest that there is a "therapeutic window" with respect to vitamin D and bone health, such that vitamin D is less effective when the dose is either too low or too high.

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Gaby's Literature Review

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Based on the available evidence, I have suggested that the optimal vitamin D dosage range for preventing bone loss may be 800-1,200 IU per day. If that is true, the unimpressive results seen in the present study might be explained by the use of an excessive dose of vitamin D.

LeBoff MS, et al. Effects of supplemental vitamin D on bone health outcomes in women and men in the VITamin D and OmegA-3 TriaL (VITAL). *J Bone Miner Res*. 2020;35:883-893.

Update on Suspected Iranian Research Fraud

I have written several times in the *Townsend Letter* over the past few years about the large number of nutrition studies coming from Iran and other countries that appear to be fraudulent. Of particular concern has been the work of Zatollah Asemi, an Iranian researcher who has published more than 170 randomized controlled trials over a period of about six years. As I reviewed Asemi's papers, I became increasingly skeptical about how outrageously prolific he was, and about the large number of highly implausible aspects of his research. In March 2018, I contacted a researcher in New Zealand who had a history of exposing fraudulent research. I informed him about Asemi, and he agreed that Asemi's papers had many of the hallmarks of fabricated research. The New Zealand research team was able to obtain a grant to investigate Asemi's studies. With a small amount of my input, a 115-page report was created in July 2019, which outlined hundreds of major problems in Asemi's body of 172 randomized controlled trials.

This report was sent to the editors of all 65 journals in which Asemi's papers had been published, as well as to the companies that published the journals (such as Elsevier and Wiley). These efforts had very little effect for more than a year, but in October 2020 a few journals began to notify their readers of an "expression of concern" regarding some of Asemi's papers. An expression of concern is typically an interim step before further investigation leads to a retraction of the paper by the journal editors. As of November 12, 2020 an expression of concern had been posted for eight papers. Around the same time, Retraction Watch, a website that keeps a record of retracted studies, reported that more than three dozen of Asemi's papers had been flagged because of concerns about the integrity of the data.[3]

Over the past few years, I have spent several hundred hours analyzing apparently fraudulent research and trying to blow the whistle on the perpetrators. Sometimes I get annoyed that I have to waste so much time trying to protect the medical literature from people who appear to be "challenged" in the conscience department. But I have to admit: it can also be a lot of fun pretending to be Sherlock Holmes.

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2. Burt LA, et al. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA*. 2019;322:736-745.
3. No author listed. Journals flag concerns in three dozen papers by nutrition researchers. Retraction Watch: https://retractionwatch.com/2020/11/10/journals-flag-concerns-in-three-dozen-papers-by-nutrition-researchers. Accessed November 11, 2020.

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Applied Metabolomics: Practice Ready for Prime Time?

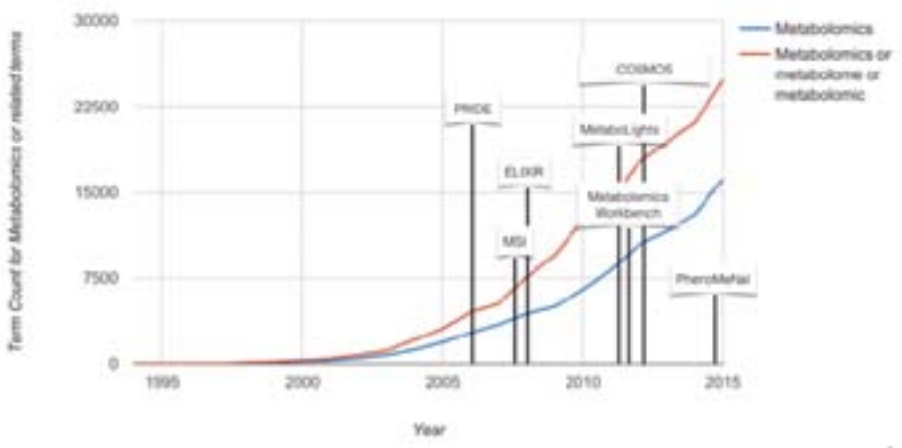
by Betsy Redmond, PhD, MMSc, RD[1] and David M. Brady, ND, DC, CCN, DACBN, IFMCP, FACN[2]

The term "metabolome" was first introduced in 1998. Metabolomics is the scientific study of chemical processes involving metabolites, and the metabolome represents the complete set of these metabolites.[1] A metabolomic fingerprint is the measure of metabolites to describe an individual's current metabolic status and has the ability to truly personalize healthcare. Metabolites can be impacted by past and current exposures, genetics, gut microbiome, diet, nutritional status, etc., and can aid in individualizing treatments and lifestyle recommendations. Functional medicine has long utilized urine organic acid testing to identify metabolites and impairments in key metabolic pathways. Conventional medicine clinicians are primarily familiar with organic acid testing for use in evaluating inborn errors of metabolism, such as maple syrup urine disease (MSUD) and phenylketonuria (PKU), or a few limited markers such as lactate, citrate, methylmalonic acid (MMA), and ketones. Though some claims made by functional medicine regarding organic acid testing have lacked support, metabolomics research is providing insight. Metabolomics allows the identification of key metabolites and pathways that can aid in discovery of associations with metabolic impairments or disease prediction, helping to refine functional medicine claims.[2,3] Establishing better biomarkers is especially exciting when combined with wearables that can monitor activity and physiology, along with knowledge of gut bacteria, genetic status, and nutrient intake. Complete knowledge of applied metabolomics and all its synergistic effects may take decades, though individuals can still identify biomarkers that could shed light on their individual function.

Many functional laboratories that are currently operating developed their organic acid test reports prior to the development of modern metabolomics. The majority of these laboratories originated in the 1990s, some as early as the 1970s, and their educational materials were developed well before the introduction and coming of age of metabolomics.[1]

Initially, laboratories offering organic acid testing relied on educational material primarily based on biochemical pathways with limited literature, or even a single supporting study. When specific markers were elevated, it was generally identified as a lack of nutrient cofactors and nutrient need. Markers also identified other issues such as increases in detoxification pathways or microbial activity. Several laboratories established proprietary nutrient algorithms that reviewed all the markers they believed could be impacted by a lack of a specific nutrient. The full algorithms are not generally available for review, though many of the nutrient claims appear to have limited literature support; yet functional and integrative medicine clinicians, as well as some nutritionists and health coaches, routinely make nutritional intervention recommendations based solely on this data. If a pathway is blocked due to an impaired enzyme and specific metabolites are elevated, it is extrapolated that those markers would also be elevated in a nutrient deficiency that requires the same nutrient. Though an insufficiency of nutrient cofactors ➤

Annual Count of Mentions of Metabolomics in Scientific Literature over Time



The future of metabolomics in ELIXIR. F1000 Research, (2020).[4]

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may certainly 'clog' pathways leading to elevated markers due to a decrease in enzyme function, it is often more complicated. A deficiency of a specific nutrient may not have the same metabolic impact as an impairment of a single enzyme. Research studies of metabolites from nutrient deficiencies are limited. Many laboratories have been slow to incorporate newer research and have shown reluctance to discontinue markers that have limited literature support.

An example is using elevated urine branch chain keto acids (BCKA) as a primary indicator for increased need of vitamins B1, B2, B3, B5, and lipoic acid. Biochemically it appears straightforward as each of the vitamins is needed for the BCKA enzyme function, though it has limited support in the literature, and there is only one human study that directly looks at B vitamin levels and intake in comparison to urine BCKA. The study found that supplementation of a B-complex (B1, B2, B3, B5, biotin, B12) supplement did lower urine BCKA levels, though it could not differentiate individual vitamins.[5] The BCKA dehydrogenase enzyme is most sensitive to B1 levels, as noted in thiamin responsive MSUD.[6] Additionally, the level of urine BCKA's can also be impacted by other factors such as level of exercise, protein intake, fasting, inflammation, etc.[7] Corporate algorithms may not consider these factors.

Henry Nix's famous statement[8]: "Data does not equal information; information does not equal knowledge; and, most importantly of all, knowledge does not equal wisdom. We have

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Table 1. Selected Markers for B-Vitamin Assessments

Vitamin	Merck Manual[23]: B-Vitamin Deficiency	IOM 1998[24]: B-Vitamin Deficiency	Key Functional Medicine Claims: Impairment of B-Vitamin dependent pathways
Thiamin (Vitamin B1)	Favorable response to thiamin supplementation.	No currently available indicator, by itself, provides an adequate basis on which to estimate the thiamin requirement. Combined erythrocyte transketolase enzyme activity, urinary thiamin excretion, and other findings.	Urine: • BCKA5,[25] (BCAA Catabolism) • Lactate[26] • Alpha-ketoglutarate • Pyruvate.[7,25,27]
Riboflavin (Vitamin B2)	Urinary excretion of riboflavin.	RBC glutathione reductase enzyme activity coefficient and urinary riboflavin excretion.	Glutathione need[7,28-30] Urine Pyroglutamate Urine Alpha-hydroxybutyrate Urine Ethylmalonate[7,31] (Impaired Beta-oxidation) Urine BCKA[5] (BCAA Catabolism)
Niacin (Vitamin B3)	Urinary excretion of N1-methyl-nicotinamide (NMN) is decreased; < 0.8 mg/day (< 5.8 mcmol/day) suggests a niacin deficiency.	Urinary excretion of niacin metabolites, N1-methyl-nicotinamide and its 2-pyridone derivative (2-YP).	Urine • BCKA[5] (BCAA Catabolism) • Pyruvate • Isocitrate Urinary excretion of niacin metabolites N1methyl-nicotinamide[32]
Vitamin (Vitamin B6)	Diagnosis of vitamin B6 deficiency is usually clinical. There is no single accepted laboratory test of vitamin B6 status; measurement of serum pyridoxal phosphate is most common.	Plasma 5′-pyridoxal phosphate.	Urine: (Tryptophan Catabolism) • Xanthurenic acid[33,34] • 4-Pyridoxic acid • Kynurenic acid • Anthranilic acid
Vitamin (Vitamin B12)	Complete blood count (CBC) and vitamin B12 and folate levels. Sometimes Methylmalonic acid (MMA) levels or Schilling test	Amount needed for the maintenance of hematological status and normal serum vitamin B12 values.	Urine MMA[35] Hematological status
Folate (Vitamin B9)	Complete blood count and serum vitamin B12 and folate levels.	RBC folate in conjunction with plasma homocysteine and folate concentrations.	Urine • FIGLU (formiminoglutamate)[36] (Histidine catabolism) • MMA Plasma Homocysteine[37]
Biotin (Vitamin B7)	Isolated deficiency of biotin virtually never occurs.	Intake data.	Urine: • β-Hydroxyisovaleric acid[38-40]

Branched Chain Keto Acids (BCKA): alpha-Ketoisovaleric acid + 3-Methyl-2-oxovaleric acid + alpha-Ketoisocaproic acid

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Metabolomics

➤ *continued from page 20*

oceans of data, rivers of information, small puddles of knowledge, and the odd drop of wisdom."

Early metabolomics research conclusions often had limited explanations of why individual metabolites or associated pathways were impacted. Clinicians aware of functional assessments are likely more familiar with many of the metabolites and proposed explanations, though many have not been well researched in a clinical setting. Newer metabolomics research helps to bring clarity to evaluating metabolites, their associated pathways, how they respond in specific disease states or nutrient deficiencies, and proposed treatments. In order to have a broader acceptance, functionally focused laboratories will need to be more transparent in how conclusions were made, such as the literature support for each recommendation, the specimen type used, and populations targeted. Ideally laboratories would partner with research institutions to better refine and support current assumptions. Patients have partially been attracted to functional medicine because of dissatisfaction with conventional medicine, which many patients feel has been slower to incorporate newer research into practice. However, the flip side of this may be the danger in functional and integrative medicine models of practice in relying too heavily on some of this functional testing data in its current state, with its limited literature and evidence support, as a primary, or even sole determinant of interventional and therapeutic strategy. The old saying "Keep your minds open, but not so open as to allow your brains to fall out" should be aptly remembered as we engage in the practice of functional and integrative medicine.

Moving from Organic Acid Testing to Applied Metabolomics

Metabolomics research has primarily looked at the metabolites of disease by identifying which metabolites are more common in a specific disease compared to controls. Though much of the early research utilized plasma markers, urine metabolomics has gained ground in the last several years, as urine is easy to collect and as a waste product represents metabolic breakdown. The Urine Metabolome Database was developed to house a full list of urine metabolites and has been folded into the Human Metabolome Database (https://hmdb.ca/). Research has focused on identifying key urine metabolomic markers and pathways that are able to discriminate disease states from controls in a range of conditions, including autism spectrum disorders (ASD), kidney disease, glucose homeostasis, non-alcoholic steatohepatitis (NASH), cancer cachexia, and others.[9-15] Newer research is starting to establish how these markers may identify an earlier stage of disease development and the associated pathways. For example, plasma alpha-hydroxybutyrate levels have been found elevated years prior to a diagnosis of diabetes and is known to be a key marker of glutathione status.[16] Metabolomics may also support clinicians targeting treatments by discriminating responders from non-responders or assessing the impact of a particular recommendation like exercise or supplementation.[17-20] Kim et al found urine glycine and phenylacetylglycine levels aided in discriminating responders from non-responders of antioxidant supplementation's impact on erythrocyte GSH:GSSG ratio (reduced to oxidized glutathione).[17] Research is starting to identify patterns of disease and connecting systems. An example of applied metabolomics in practice is utilizing data such as the Copenhagen Inter99 study. Subjects were drawn randomly from the Civil Registration System. Measurements were available for 4,117 subjects who participated in both baseline urine metabolomics

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assessment and a five-year follow-up examination. Researchers found several higher baseline markers to be associated with a greater risk of elevated hemoglobin A1c (HbA1c) and insulin resistance (IR) five years later. These included 1-methylnicotinamide, alanine, creatinine, and lactic acid. Though not diagnostic, the markers may help to identify areas of concern long before an issue arises, allowing patients the opportunity to focus on lifestyle and dietary strategies that may provide some level of risk reduction.[15] 1-Methylnicotinamide has been associated with increased rates of diabetes, cirrhosis, and cancers, suggestive of increased *nicotinamide N-methyltransferase (*NNMT) activity.[15] Perturbations in the glycolysis pathway have been reflected by increased lactate, pyruvate, and alanine.[21]

> Targeted Metabolomics methods have already identified new molecular markers and metabolomic signatures of cardiovascular disease risk (including branched-chain amino acids, select unsaturated lipid species, and trimethylamine-*N*-oxide), thus in effect linking diverse exposures such as those from dietary intake and the microbiota with cardiometabolic traits.[22]
>
> --Scientific State from the American Heart Association 2017

Research is also working to identify metabolomic markers that can objectively assess nutrient status, food intake, and the biological effects of foods. As noted, an issue of concern has been the recommendation of nutrients based on urine testing. Overall, many nutrients lack an ideal or consensus biomarker for deficiency diagnosis. Evaluation of organic acids primarily highlights that there may be a nutrient need or other issue impacting a metabolic pathway. Though not generally diagnostic, functional medicine testing may identify areas of concern. All laboratory assessments should be evaluated in the context of a full medical history and exam, and other contributing factors.

Applied Metabolomics Going Forward

While conventional medicine has largely ignored urine metabolites outside of serious inborn errors of metabolism (i.e., PKU, MSUD, etc.) or a few single markers, functional medicine or integrative nutrition has certainly been ahead of the curve in its excitement and interest in using metabolomics, specifically urine organic acids. Functional medicine has laid significant groundwork for providing a format for applying metabolomics, though it has not fully kept up with current research and accepted standards. Applied Metabolomics, as it currently stands, offers patients insight and additional information on their metabolic status. Though certainly, some criticism may be that it lacks clinically applied evidence, it is important to remember that in functional medicine it is primarily being used to adjust lifestyle, exercise, diet, or guide supplementation of nutrients or botanicals, and not to determine the use of interventions that carry with them a significant risk of harm, such as pharmaceutical agents. Patients have control over these extrinsic factors, making changes personalized and participatory. At the same time, clinicians and integrative and functional medicine organizations should be transparent in identifying the support, or lack thereof, for the information they are presenting to justify their suggested treatment plans. Support of a single study cannot override consensus science.

Another exciting advancement in the utilization of metabolomics data is the evolution of machine learning and artificial intelligence informatics platforms. As metabolome databases become more robust and standardized, the use of advanced analytical technology will likely allow for more comprehensive pattern analysis and clinical contextualization of the data set generated when a metabolomics test is performed, providing more evidence-based recommendations based on the subject's data and, ultimately, more impactful and efficacious therapeutic interventional options for the treating clinician to consider.

Metabolomics is improving our understanding of physiology, what is normal, what is normal for each individual, and what may identify impairments. It can characterize key markers in specific processes and pathways, physiology, impact of diet and microbiome metabolism, etc., all helping to identify a client's individual metabolism and better personalize treatments. While conventional medicine has primarily looked at laboratory markers that provide a diagnosis, functional medicine has looked at a broader picture of function. Metabolomics offers a pathway to move forward in the quest for truly precise and personalized medicine.

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

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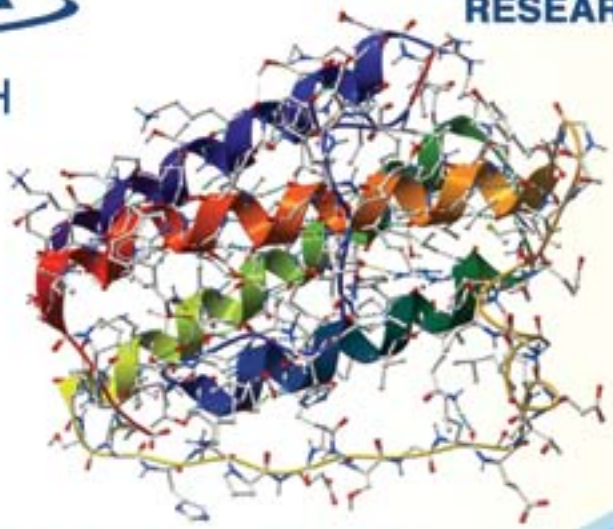

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Scientific Basis for a Novel Combination of Cell Signaling Factors to Decrease Autonomic Over-Expression and Rebalance Dysfunctional Cell-Signaling Pathways to Attenuate Symptoms Associated with PTSD

– A Four-Month Pre-Clinical Study –

by Paul E. Opheim, MIM, MA; Ann B. McCombs DO, DABHM, DNM; and Robert F. Waters, PhD

Unabridged, full annotated paper with references is available at http://www.townsendletter.com.

Abstract

This pre-clinical study sought to see if a complex of cell signaling factors (**CSFs**) could safely and effectively address the disrupted signaling pathways that give rise to the symptoms of PTSD. This study is the first of its kind to use an *isoenergetic cell signaling*™ formula composed of select CSFs prepared to non-molecular vibrational (isopathic) levels to address PTSD. Over a four-month period, a diverse group of 11 veterans with PTSD took the formula three times a day. A monthly Self-Assessment of Symptoms Questionnaire (**SASQ**) containing 91 questions was completed by each participant and their partners (only 3 were partnered at the time). After Paired t-Test biostatistical analysis using IBM SPSS (R) V 27 software was completed, 55 questions demonstrated statistically significant improvement ($p< 0.05$), and another 10 demonstrated trending statistical significance ($p< 0.095$). Partner analysis of SASQ forms demonstrated a dramatic concurrence that the formula had worked with $p<0.001$, $p<0.001$ and $p<0.003$ values. These positive study results scientifically validated anecdotal formula reports received over the past eight years. In the words of one participant: "*The benefits I have received have been nothing short of 'miraculous*'."

Study Goal

In a November 2013 article reported by CNN: "*… Every day, 22 veterans take their own lives. That's a suicide every 65 minutes. As shocking as the number is, it may actually be higher….*" Our goal was to offer people with PTSD a solution to their clearly urgent needs as well as improve their quality of life.

The lack of clinically proven, long-term, efficacious pharmaceutical or psychotherapy PTSD protocols currently demands that diverse, scientifically based research be utilized to address this costly, deadly, personal and societal affliction. Starting in 1999, when we developed isopathic recombinant DNA growth hormone (GH) and veterans came to us for help, we saw demonstrable benefits with that CSF alone. Because GH inhibits the somatostatin hormone, which becomes dominant when the sympathetic nervous system (SNS) flight, fight or freeze survival mode is engaged, we saw that it remained elevated in those with PTSD. In recent years, additional PTSD-related CSFs and the complex relationship of their intersecting pathways have been described in the literature. With a greater understanding of genetics and the discovery of CSF isotopes, many pieces of this puzzle began to come together. It is from this research that our PTSD formula was developed.

PTSD Risk Factors

Genetic risk factors show that some individuals are more susceptible to PTSD. **Epigenetic** factors also increase susceptibility to PTSD. In addition, while **cultural factors** are more complex, they also contribute to a greater incidence of PTSD. In particular, three categories of **daily stressors** have a threshold-lowering, cumulative effect and increase susceptibility to developing PTSD. Frequency, duration, and degree of these stressors contribute to the degree of PTSD severity.

- Occupational Stressors – Supervisors, coworkers, job difficulties
- Social Stressors – Discrimination, harassment, abuse, family issues
- Environmental Stressors – Pollution, chemical noise, dangerous home or work settings

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Diagnosing PTSD

PTSD symptoms may include dissociation, depression, anxiety, fear, helplessness, obsession, and social phobia and cover three sets of response-related symptoms:

- Re-experiencing the traumatic event through intrusive memories, flashbacks and nightmares
- Avoidance or affective numbing to traumatic experiences
- Hyperarousal/hypervigilance

These symptoms adversely affect one's self-esteem, self-worth, as well as intimate and social relationships, resulting in decreased quality of life and increased suicidal ideation. Therefore, it is imperative to understand alterations in the underlying expression of relevant CSFs and their pathways that lead to PTSD.

Failure to Correct PTSD Can Lead to Future Physical and Cognitive Problems

Current Issues	Future, Related Issues
Higher blood pressure	Stroke, heart attack
Elevated blood sugar	Type II Diabetes / Peripheral neuropathy
Decreased endogenous opiates	Substance abuse / Addiction
Concussive episodes or TBI	CTE (chronic traumatic encephalopathy)
Stress – higher cortisol levels	Chronic inflammation / pain Weakened immune system
Higher epinephrine (adrenaline) levels	Dysfunctional HPA axis
Increased lymphocyte glucocorticoid receptors	Weakened immune system
Phobic anxieties	Cardiovascular issues
Depression	Dementia /Alzheimer's / Suicide

COVID-19 Pandemic and PTSD

Individuals with PTSD might be at risk for greater severity and complications from COVID-19 due to a compromised immune system, increased systemic inflammation, and circulatory disorders. Please read the researched coronavirus "white paper" on this subject at www.LepticaMedical.com for insights and our medicines to address COVID-19, especially for those who cannot or should not take vaccines.

Psychological Treatment-Based Therapies

Based on feedback from veterans, psychological therapies alone are woefully inadequate even when combined with pharmacological therapies, and a ***new*** **paradigm is needed without the danger of creating additional adverse symptoms.**

Understanding Inter-Related Brain Regions and Their Integrated Signaling Pathways Is Crucial

As we looked at the variety of CSFs (see sidebar) and their positive and negative roles in PTSD, we saw that just targeting single cell-signaling pathways by single molecules would not be effective. Interactions are simply too complex. A single-molecule monotherapy failure is demonstrated by the inability of anti-depressants and anxiolytics to achieve satisfactory corrective results. We saw that a paradigm involving non-molecular, vibrational cell-signaling medicine that we first developed in 1995 was what was needed—using specific CSFs to stimulate the body to "self-correct" by activating the appropriate cell receptor site responses that address PTSD.

Certain Brain Regions Experience Trauma-Related, Hormonal-Signaling *Hyper*activity

The mesolimbic system is a recognized center for PTSD action. Cognitive processing (including fear, reward, surprise, anxiety) activate differing pathways involving different brain areas. The hippocampus and amygdala are key structures having reciprocal interactions with the basal forebrain (BF). During trauma-related cognition processes, the hippocampus and para-hippocampal gyrus, dorsal anterior cingulate and ventral prefrontal areas, inferior frontal gyrus and ventral-medial PFC show greater activity. The amygdala and insula show hyperactive responses to trauma-related emotional information in PTSD.

Certain Brain Regions Experience Trauma-Related, Hormonal-Signaling *Hypo*activity

There is reduced activity in the dorsolateral and dorsomedial PFC, as well as the hippocampus, with PTSD. The result of dysfunctional processing of cognitive inputs can lead to problems with the following:

- Memory processing
- Sustained attention
- Memory recall
- Stimulus overload
- Mental clarity
- Forgetfulness

The Axis Imbalance Hypothesis: Cell Signaling Imbalances Underlie PTSD Symptoms

Alterations in hormonal axes are implicated in PTSD, especially those relating to the autonomic / SNS (fight or flight or freeze survival mode) nervous system. CSFs are all involved in overlapping pathways and axes. People with PTSD have been found to exhibit alterations in hypothalamic-pituitary-adrenal (HPA) axis function. They also display an inability to suppress fear or feel safe, and this was found to significantly correlate with both cortisol and adrenocorticotropic hormone (ACTH).

Pre-Clinical Study

Primary Goals

- Quantify a significant improvement in the quality of life for veterans with PTSD
- Statistically prove an *isoenergetic cell signaling*™ PTSD formula is highly efficacious
- Demonstrate a significant reduction in suicidal ideation

Secondary Goal

- Reduce the need for pharmaceutical drugs prescribed for anxiety and depression

Study Design

- There was intentionally no placebo group. We firmly believe it is unconscionable and unnecessary for anyone with PTSD to be in a control group.
- In the initial interview, we ascertained each participant's degree of PTSD with a SASQ baseline.

- We worked with the Warrior Healing Center (WHC) in Sierra Vista, Arizona. We are indebted to the CEO (Dr Tim Kirk) as well as each veteran/veteran partner's participation in this study, including the veteran donor who helped fund the study.
- Through consulting with Dr McCombs, Dr. Kirk and two other veteran providers at the WHC, an SASQ of 91 entries was developed to serve as an assessment for this study.

Formula Challenge – Creating an Integrated Cell Signaling Formula

An accurate PTSD diagnosis is a composite of symptoms. From them, it is possible to identify the affected pathways, brain regions, and involved CSFs. To understand what elicits the symptoms associated with PTSD and effectively resolve this affliction by correcting multiple signaling dysfunctions, it was first necessary to understand the neuroendocrine mechanisms associated with the psychological and behavioral issues of PTSD. Following this methodology, we determined which CSFs could be causative, resultative or both, which are over- and under-expressed, and which are major CSFs. The result was ➤

Brief List of Cell Signaling Factors with Therapeutic Potential for PTSD

CSFs play a significant role on molecular pathways, which drive cell function. Some initiate cell-signaling pathways, some are involved in pathway progression, and others are expressed as a result of the pathway's actions. Their mechanisms include neuroprotective, neuroregenerative, pro-inflammatory and anti-inflammatory functions. Some CSFs also do *multiple* functions, depending on whether they are over- or under-expressed and what influences they receive from other CSFs. *With symptom progression during PTSD, the expression and ratios of these CSFs vary*.

Research has demonstrated that **the following important CSFs are involved in PTSD**. It is beyond the scope of this article to present a comprehensive list and explanation detailing their interactions. Instead, some of their *most relevant* functions are listed.

ACTH **Adrenocorticotropin Hormone**
ACTH plays a prominent role in the stress response which is associated with the HPA axis. Persons with PTSD have been found to exhibit alterations in HPA axis function.

ALLO **Allopregnanolone**
ALLO has an effect on GABA neurotransmitters, which is thought to give them antidepressant, anxiolytic and sleep-promoting benefits. ALLO exerts its antidepressant role through pathways associated with the limbic system, likely acting on all the main brain sites responsible for the balance that promotes depressive/anti-depressive regulation. *Social isolation has consistently been associated with a significant decrease in allopregnanolone*.

BDNF **Brain-derived Neurotrophic Factor**
BDNF is a crucial mediator of neuronal plasticity, which regulates synaptic composition, neuronal maturation, neurotransmitter release, survival and excitability in the adult nervous system. Pre-clinical studies suggest a role of the hippocampal BDNF system in fear extinction. The role of BDNF in mood disorders is also associated with anxious/depressed patients. Chronically impaired BDNF signaling implicates a progression from depression and PTSD disorders to dementia and Alzheimer's.

FGF-2 **Fibroblast Growth Factor-2**
FGF-2 is involved in brain development and regeneration through its effects on molecular signaling cascades involved in learning and memory. FGF-2 has been shown to facilitate long-term extinction of fear and reduce stress-precipitated relapse in rats.

GAL **Galanin**
Galanin receptors are expressed in the frontal cortex and hippocampus and is shown to be down-regulated by stress and trauma. Galanin is co-expressed with and modulates noradrenaline and serotonin systems, which are both expressed in depression.

GH **Growth Hormone**
During the heightened meso-limbic response with PTSD, the release of SST inhibits GH release which, depending on severity or duration, can result in a prolonged imbalance. Evidence of the influence of NPY and SST on GH is suggested by GH acting on NPY neurons in the hypothalamic arcuate nucleus (ARC) and SST neurons in the periventricular nucleus (PeV) through influencing the GH receptor also found on these neurons.

IGF-1 **Insulin-like Growth Factor-1**
Chronic stress can increase anxiety-like behavior and imbalance HPA axis functioning. IGF-1 attenuates spatial learning deficits, promotes mental clarity, short-term memory and reduces HPA axis dysfunction.

LEP **Leptin**
The leptin receptor is highly expressed in many brain regions that regulate synaptic plasticity. Deprivation of rapid eye movement (REMD) impairs cue and contextual fear memory and negatively affects pre- and post-synaptic functions of the thalamus–lateral amygdala pathway. Leptin treatment reversed REMD-induced memory deficits. Its neuroregenerative abilities are important for the establishment of hypothalamic, hippocampal and cortical pathways. Leptin also directly modulates the anxiety and dopaminergic pathways.

NPY **Neuropeptide Y**
NPY is positively associated with PTSD severity. NPY receptors are highly expressed in the cortex, hippocampus and amygdala – regions associated with mood disorders, stress responses and memory processing. Studies show NPY receptors mediate some aspects of depression-like disorders, anxiety and stress responses, fear learning and memory, blood pressure control and sympathetic activity. NPY feeds back to leptin which – in turn – stimulates BDNF. NPY is known to inhibit GH secretion via SST.

OXT **Oxytocin**
OXT promotes behaviors of self-confidence, social interactions and positive social memories. The presence of emotional trauma (ET) and PTSD is strongly associated with reductions in endogenous OXT. OXT reduces the stress hormones ACTH and cortisol.

STT **Somatostatin**
STT concentrations in PTSD patients are higher than those of control subjects. It is vitally important to note that on the STT-GH-GHRH-IGF1 axis, STT inhibits GH secretion.

TNF-α **Tumor Necrosis Factor alpha**
TNF-α, IL-1β and IL-6 are commonly overexpressed with low-grade systemic inflammation and have elevated expression with PTSD.

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a complex *isoenergetic cell signaling*™ formula designed to stimulate, inhibit, and ultimately rebalance these CSFs to see if the PTSD symptoms could be resolved.

Formula Goals

- Offer immediate, safe and effective relief, especially to eliminate suicidal ideation
- Be extremely affordable
- Be available for veterans and first responders to use without the "stigma" of PTSD in one's medical record
- As a prophylactic, initiate cell-signaling corrections *immediately* after a trauma occurs to avoid the "slippery slope" of developing or worsening PTSD
- Experience quality-of-life improvements starting the first week and observe a steady progression
- Be safe for children who are exposed to traumatic events
- Avoid adverse side effects
- Be available as a non-prescription medicine [The PTSD formula, like all our *isoenergetic cell signaling*™ medicines, meets FDA mandates that medicines prepared in a sequential kinetic fashion by succussion (homeopathic medicines) must be both effective and safe.]
- By its nature complement and enhance the efficacy of other PTSD therapies.

The PTSD Formula

Based on our earlier research, we believed that the same approach that had worked so well for the past 25 years (*isoenergetic cell signaling*™ formulas) could be employed to address PTSD. They are *not pharmaceutical drugs*, nor are they *traditional* homeopathic remedies. They incorporate scientific research, as well as safe and accurate sequential kinetic preparation. Through the addition of neuro-energetic cell-signaling frequencies, they truly represent **a different class of medicine**. They are derived from recombinant DNA human proteins (polypeptides) acquired from established FDA-approved laboratories that also produce bio-identical hormones. Because the bio-electrical energy of these *pure* molecules is *identical* to what the body itself naturally produces, it *recognizes* these molecules as "self."

Unlike **pharmacological drugs** (*derivatives* of molecules or *synthetic* creations and *not identical to what the body produces)*, our medicinal formulas do *not* come with the potential for adverse side effects, nor must they undergo Phase I, II and III clinical trials to establish sufficient safety and efficacy. Another very important difference from monotherapy pharmacological drugs is **our formulas are composed of *multiple* CSFs at *specific* signaling frequencies**, allowing them to respond promptly *and* simultaneously to *multiple* cell-signaling pathways. The PTSD formula used in this pre-clinical study was derived from recombinant DNA human CSFs.

Study Participant Selection/Exclusion

A spectrum of qualified veterans participated in this study. The goal was to match a complex cell-signaling formula with a diverse population of veterans to see if a small, formalized study would validate what had already been observed and demonstrated anecdotally with veterans over many years. Twelve veterans were invited to participate in this pre-clinical study, and 11 of them completed it.

The following conditions were exclusion factors due to potential for non-compliance or conflicting interactions of cell-signaling pathways: current alcohol or opioid addiction or being in treatment programs. Additional immunocompromised conditions were also declared on the Consent to Participate form as having the potential to be affected by the formula.

Self-Assessment of Symptoms Questionnaire (SASQ)

Clusters of symptoms were expanded upon in the study's SASQ, which was first developed in 2008. The 91 entries were grouped into 11 categories:

- Quality of Life 5
- Physical Constitution 8
- Oral 1
- Musculoskeletal 2
- Abdominal/GI 5
- Respiratory 5
- Neurological 8
- Sleep 6
- Skin 1
- Social Interactions 18
- Psychological 33

CSF Formula Application

Each participant was given one 2-oz bottle with a spray nozzle. For the first 5 days, they took 3 sprays under the tongue twice daily: (AM) upon rising and (PM) in the late afternoon. Starting the 6th day, they took it an additional time: (EV) nearing bedtime. Each participant used a *Chart Your Use* form to assist with compliance.

Study Results

Cross-supporting Entries: Of the 91 entries on the SASQ, 55 showed statistical significance ($p < .05$) and 10 demonstrated trending significance ($p < .095$). We grouped these 65 entries into 5 categories, because the cell-signaling pathways demonstrate the inter-related "cross-talk" of the CSFs. These re-grouped entries validate the efficacy of this formula.

- *Physically-compromising symptoms due to anxiety, stress, and tension*

Food cravings when stressed	.015	
Ignore pain/insensitive to pain	.016	
Shortness of breath	.019	
Headaches	.020	
Overall stress level	.021	
Teeth grinding / jaw tightness	.024	
Burning/cramping or gas	.026	
Diarrhea or constipation	.039	
Anxiety/panic attacks at home	.044	
Chest tightness or pain	.051	trending
Muscle tension or tightness	.055	trending
Nausea or vomiting	.061	trending
"Black outs" or suddenly feel disoriented to time or place	.083	trending

- *Social interactions*
  - Feelings of being betrayed.....005
  - Don't like people to invade my personal space.....006
  - Frequent difficulties with people I live with 007
  - Prefer to be alone 011
  - Mistrust or distrust of authority figures 013
  - Anxiety/panic attacks in public.....014
  - Difficulty sharing my feelings with other.....018
  - Don't like to be touched or held.....020
  - Feel your pet "gets" you better than people do 022
  - Prone to feelings of "road rage" 024
  - "Stress sweat" (social situations).....032
  - Uncomfortable in crowds .....083 trending*
  - Trouble initiating social interactions.....089 trending

* voluntary comments after March 2020 mention the COVID-19 pandemic as a contributing factor to crowd aversion

- *Sense of personal self*
  - Frequently feel sad 00
  - Frequently feel depressed 000
  - Feelings of helplessness.....001
  - Feelings of hopelessness ("why even bother?") 001
  - Feel emotionally numb..... .002
  - Feel rejected 002
  - Low self-esteem.....004
  - Currently feeling a sense of peace or calm.....004
  - Lack of self-compassion 007
  - Unsure about my future 010
  - Thoughts of suicide.....018
  - Self-loathing 020
  - Currently feeling positive or optimistic (in general) .024
  - Feelings of "survival guilt" .....069 trending

- *Behavior, mental state, mood swings, and emotional control*
  - Extreme mood swings 001
  - Inability to concentrate.....002
  - Often feel fearful / anxious/scared.....002
  - Adverse reaction to common sounds 002
  - Repetitive behaviors 003
  - Unexplained feelings of anger 003
  - Flashbacks triggered by sounds or smells.....003
  - Unexpected or unexplainable irritability towards others ("for no reason").....003
  - Exaggerated "startle" response 005
  - Internal struggle with intrusive thoughts which may or may not result in loss of impulse control..005
  - Constant feeling of being "on guard" hypervigilant..007
  - Sudden, irrational, unprovoked violent behavior 010
  - Prefer to sit with my back against the wall.....014
  - Difficulty remembering things.....018
  - Feelings of frustration.....021
  - Dizziness 026
  - Frequently argue with myself out loud.....030
  - Confusion.....088 trending
  - Unanticipated response to laugh or cry.....092 trending

- *Sleep*
  - Recurring dreams / nightmares.....002
  - Unpleasant dreams / nightmares 011
  - Night sweats or cold sweats 018
  - Unable to go to sleep (insomnia).....061 trending
  - Late night TV watching .....077 trending

PTSD

Discussion of Study Findings

PTSD is a disruption of inter-related cell-signaling pathways. To understand these brain processes, it is essential to understand the intra- and intercellular mechanisms that allow circuits to process, store, retrieve, and edit behaviorally relevant information. This formula was created to address the following pathways and CSFs which (1) initiate (2) drive and (3) result from activation of these pathways.

- Anxiolytic
- Depressiolytic
- Dopaminergic
- Neurogenic
- Sleep-Wake

Study Limitations

- Low "n" Number
- Manual Data Collection
- Duration
- Empathy Fatigue
- COVID-19

This Study Did Not Assess:

- Co-morbid issues
- Depression, anxiety, and PTSD relationships
- Duration and severity of trauma on recovery duration and improvement
- Influence of lapsed time between the PTSD trauma occurrence(s) and the study
- Gender differences
- Life circumstances pre-PTSD trauma(s) and threshold of PTSD susceptibility
- Combination of exercise and PTSD formula on recovery

Definitive Benefits Demonstrated. The PTSD formula conclusively demonstrated the efficacy and safety of a complex *isoenergetic cell signaling™* formula in significantly reducing a majority of the symptoms associated with PTSD, including suicidal thoughts.

What Comes Next

The extraordinary validation of the benefits of the PTSD formula demonstrated the need for immediate use in patient protocols and for an expanded, nationwide study.

Conflict of Interest

The primary author is the founder and CEO of Leptica Research, LLC and formulator of the PTSD formula used in this study.

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Unabridged, full annotated paper with references is available at http://www.townsendletter.com.

On the cover

Melatonin: More Than Just the Hormone That Regulates Sleep

by Pamela W. Smith, MD, MPH, MS©

Melatonin is a hormone produced in the pineal gland, retina, GI tract, and white blood cells that is associated with sleep. In addition, there are melatonin receptors expressed all over the body, for example, in the intestines, fat tissue, kidneys, liver, lungs, adrenals, and other organs. The amount of melatonin the body, produces decreases as one ages and depends on the activity of an enzyme called serotonin-N-acetyltransferase (NAT). The body's production of NAT, on the other hand, depends on its storage of vitamin B6.

Functions of Melatonin[1-5]

- Affects the release of sex hormones
- Aids the immune system
- Acts as an antioxidant
- Blocks estrogen from binding to receptor sites
- Decreases cortisol levels that are elevated
- Helps balance the stress response
- Helps prevent cancer and treat some cancers
- Improves mood
- Improves sleep quality
- Stimulates the parathyroid gland
- Stimulates the production of growth hormone
- Is cardioprotective
- Decreases platelet stickiness (decreases the risk of heart disease)
- Promotes healthy cholesterol levels
- Regulates skin pigmentation
- Relieves jet lag
- Dilates and contracts blood vessels
- Inhibits the release of prolactin, follicle stimulating hormone (FSH), and luteinizing hormone (LH)
- Inhibits the release of insulin from beta cells in the pancreas
- Protects skin cells against UV damage

Signs and Symptoms of Melatonin Deficiency

- Insomnia
- Fatigue
- Anxiety
- Early morning awakening
- Interrupted sleep
- Stress
- Increased risk of cancer
- Seasonal affective disorder
- Immunological disorders
- Heart disease
- Compromised immune system

Causes of Melatonin Deficiency

There are many etiologies of melatonin deficiency. Perhaps the most common cause of melatonin deficiency in today's world is electromagnetic fields. Other causes include the following:

- Acetaminophen
- Alcohol abuse
- Medications: alprazolam, atenolol, benserazide, bepridil, clonidine, dexamethasone, diazepam, diltiazem, felodipine, flunitrazepam, fluoxetine, isradipine, luzindole, metoprolol, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, prazosin, propranolol, reserpine, ronidazole (this list is not exhaustive)
- Tobacco
- High glycemic index foods
- Aspirin/indomethacin/ibuprofen
- Caffeine abuse
- Vitamin B12 deficiency

Therapeutic Benefits

The therapeutic benefits of melatonin are numerous. Melatonin is a hormone that does more than regulate the sleep cycle.

Hypertension. Melatonin has been shown to decrease blood pressure in patients with hypertension.[6-7] In fact, a study revealed that evening controlled-release melatonin, 2 mg for one month, significantly reduced nocturnal systolic blood pressure in patients with nocturnal hypertension.[8]

Heart Health. Patients with coronary artery disease tend to have low nocturnal serum melatonin levels. In addition, patients who developed adverse effects post myocardial infarction were shown to have lower nocturnal melatonin levels than patients without adverse effects. Melatonin is cardioprotective due to its vasodilator actions and free radical scavenger properties, and it also inhibits oxidation of LDL-C.[9-10] Likewise, melatonin has been shown to reduce hypoxia and prevent reoxygenation-induced damage in patients with cardiac ischemia and ischemic stroke.[11]

The MARIA study was a prospective, randomized, double-blind, placebo-controlled trial that used IV melatonin in patients following an acute MI that were having angioplasty. It decreased CRP and IL-6, two major markers of inflammation. Melatonin also attenuated tissue damage from reperfusion, decreased V tach and V fib after reperfusion, and reduced cellular and molecular damage from ischemia.[12] Another study revealed that there is an inverse correlation between melatonin levels and CRP levels after acute MI.[13] Moreover, melatonin has been shown to protect cardiac myocyte mitochondria after doxorubicin use.[14]

Insulin Regulation and Obesity. Melatonin is necessary for the proper synthesis, secretion, and action of insulin. In addition, melatonin acts by regulating GLUT4 expression, via its G-protein-coupled membrane receptors, the phosphorylation of the insulin receptor, and its intracellular substrates that mobilize the insulin-signaling pathway. Furthermore, melatonin is responsible for the establishment of adequate energy balance by regulating energy flow and expenditure through the activation of brown adipose tissue and participating in the browning process of white adipose tissue. Likewise, melatonin is a powerful chronobiotic, meaning that it helps regulate the body's internal clock. Consequently, the reduction in melatonin production that may occur with aging, shift work, or illuminated environments during the night commonly induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian changes that commonly lead to weight gain.[15] A study using laboratory animals showed that melatonin supplementation daily at middle age decreased abdominal fat and lowered plasma insulin to youthful levels.[16] A low melatonin level is a frequently overlooked cause for an individual's inability to effectively lose weight.

Neurodegenerative Disorders. Studies have shown that low melatonin levels are associated with an increased risk of developing neurodegenerative diseases.[17-20]

Alzheimer's Disease. Some of the symptoms of low melatonin levels are also common to patients with Alzheimer's disease: disruption of the circadian rhythm of the body, mood changes, and delirium.[21-22] One medical trial showed that melatonin levels in the cerebrospinal fluid (CSF) in patients over the age of 80 were one-half the level of younger, healthier patients. Individuals in this study with Alzheimer's disease had even lower levels, only 20% of the amount observed in young healthy people.[23] Fortunately, numerous studies have shown that supplementing with melatonin helps to protect against Alzheimer's disease.[24-30] In addition, in animal and human trials a benefit in melatonin replacement in patients with early Alzheimer's disease was seen, even before it was clinically evident.[31-32] In fact, when melatonin was replaced early, the participants did not show pathological changes nor have symptoms of cognitive decline.[33] In addition, melatonin supplementation has been shown to decrease the damage caused by amyloid beta proteins and tau proteins.[34-38] Moreover, medical trials revealed that using melatonin in patients with Alzheimer's disease that they had better sleep patterns, less sundowning, and slower progression of cognitive loss.[39] Likewise, melatonin has also been shown to guard against the harmful effects of aluminum, which has been shown to cause oxidative changes in the brain that are similar to those seen in Alzheimer's disease.[40-41]

Mild Cognitive Impairment. Mild cognitive impairment (MCI) is impairment that precedes actual dementia.[42] In fact, 12% of people with MCI proceed to develop dementia each year.[43] Studies have shown that people who supplemented with melatonin (3-24 mg daily) for 15-60 months did much better on cognitive tests.[44-46]

Longevity. Lab trials have shown that melatonin replacement increases SIRT1, which is a longevity protein. SIRT1 is also activated by caloric restriction.[47]

Parkinson's Disease. Melatonin replacement has been shown to decrease the risk of developing Parkinson's disease.[48-50] In fact, animal trials have shown that melatonin can prevent and to some extent may even help reverse the motor and behavior changes that are associated with this disease process.[51-53]

In Parkinson's disease there is an accumulation of a protein called alpha-synuclein.[54] Melatonin supplementation also attacks alpha-synuclein and makes it more available to be removed by the body.[55-56] In addition, a lab study showed that melatonin can reverse the inflammatory changes that occur in Parkinson's disease.[57] Moreover, an animal trial also showed that melatonin helps to restore the normal activity of a key enzyme that is involved in the synthesis of dopamine.[58-59] Furthermore, in lab studies melatonin supplementation was shown to increase the survival of dopamine-producing cells.[60-62] Consequently, more research needs to be done concerning melatonin's use in Parkinson's disease.

Cerebral Vascular Accident (CVA). If the patient has a low melatonin level, they have an increased risk of developing

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a stroke. The odds rise more than 2% for every 1 pg/mL decline in melatonin.[63] In fact, in individuals with a calcified pineal gland, the risk of developing a CVA is increased by 35%.[64] Moreover, melatonin supplementation has been shown to shrink the size of an infarct area in a patient with acute CVA. This may be due to melatonin's ability to

Melatonin is an effective therapy for many disease processes.

neutralize free radical production.[65-70] Melatonin may also decrease the risk of CVA by significantly lowering cholesterol and also decreasing blood pressure.[71] Furthermore, melatonin supplementation in lab animals decreased the damage after stroke and decreased seizure occurrence.[72] In addition, melatonin has been shown to increase plasticity of neurons after CVA.[73] Likewise, in animal studies, melatonin reduced the damage caused by stroke by decreasing the activation of "protein-melting" enzymes.[74-75] Melatonin has also been shown to tighten the blood-brain barrier, reduce tissue swelling, and prevent hemorrhagic transformation in animal trials with experimentally induced stroke.[76-79]

Closed Head Injury (CHI)/Traumatic Brain Injury (TBI). Supplementation with melatonin has been shown to minimize the brain swelling and dysfunction that occurs after a closed head injury.[80-85] Melatonin supplementation has also been shown to help protect the brain in the case of traumatic brain injury.[86-87] Likewise, studies employing lab animals have shown that giving melatonin after a TBI had the following results: maintained the integrity of the blood-brain barrier, prevented dangerous brain swelling in the hours and days after injury, and shrank the size of the bruised and injured tissue.[88] Melatonin, likewise, reduced the mortality rate after burst aneurysm in laboratory studies.[89-90]

Sleep Hygiene. Melatonin has long been known to be beneficial for sleep. Melatonin has been shown to synchronize the circadian rhythms and improve the onset, duration, and quality of sleep. The good news is that exogenous melatonin supplementation is well tolerated and has no obvious short- or long-term adverse effects when used in small doses to improve sleep hygiene.[91-92]

Pre-Op Anxiety. When compared to placebo, melatonin given as premedication (tablets or sublingually) can reduce preoperative anxiety in adults. In fact, melatonin may be equally as effective as the standard treatment with midazolam in reducing preoperative anxiety. The effect of melatonin on postoperative anxiety in adults is mixed but suggests an overall attenuation of the effect compared to preoperatively.[93]

COVID-19. Melatonin is now being used as an adjuvant treatment for COVID-19 since it has been shown to limit virus-related diseases. It has also been demonstrated to be protective against acute lung injury and adult respiratory distress syndrome caused by viruses and other pathogens due to its anti-inflammatory and anti-oxidative effects.[94-96] Unfortunately, COVID-19 tends to take a more severe course in individuals with chronic metabolic diseases such as obesity, diabetes mellitus, and hypertension. Since COVID-19 complications frequently involve severe inflammation and oxidative stress in this population, melatonin is being suggested as an add-on therapy for patients that are diabetic and overweight.[97]

Cancer. Many studies have shown that melatonin is an effective therapy for breast cancer as an adjunct to traditional care.[98-102] It has also been shown to be effective for the prevention and reduction of some of the side effects of chemotherapy and radiation including mouth ulcers, dry mouth, weight loss, nerve pain, weakness, and thrombocytopenia (low platelet count).[103] Moreover, melatonin has been used as a therapy for other cancer forms such as brain, lung, prostate, head and neck, and gastrointestinal cancer.[104]

Immune Builder. Melatonin has been shown to be a major regulator of the immune system. Consequently, disease states affecting a wide range of organ systems have been reported as benefiting from melatonin administration.[105-106]

Gastrointestinal Diseases. The enterochromaffin cells of the gastrointestinal tract secrete 400 times as much melatonin as the pineal gland. Consequently, it is not surprising that numerous studies have found that melatonin plays an important role in GI functioning. As previously mentioned, melatonin is a powerful antioxidant that resists oxidative stress due to its capacity to directly scavenge reactive species, increase the activities of antioxidant enzymes, and to stimulate the innate immune response through its direct and indirect actions. In the gastrointestinal tract, the activities of melatonin are mediated by melatonin receptors, serotonin, and cholecystokinin B receptors, as well as, via receptor-independent processes.[107-109]

Melatonin and the GI Tract

Let us now examine the use of melatonin in several disease processes of the GI tract. The prevalence of gastroesophageal reflux disease (GERD) is increasing with individuals experiencing symptoms such as heartburn, regurgitation, dysphagia, coughing, hoarseness, or chest pain. Fortunately, melatonin has been shown to have inhibitory activities on gastric acid secretion and nitric oxide biosynthesis. Nitric oxide has an important role in transient lower esophageal sphincter relaxation, which is a major etiology of reflux in people with this disease process. A study revealed that a combination of melatonin, l-tryptophan, vitamin B6, folic acid, vitamin B12, methionine and betaine was beneficial for patients with GERD. In addition, the other components of the formula exhibit anti-inflammatory and analgesic effects. All patients that took the combination of nutrients and melatonin reported a complete regression of symptoms after 40 days of treatment. However, only

65.7% of the omeprazole reported regression of symptoms in the same period.[110] Numerous other studies have also revealed that melatonin has a role in the improvement of gastro-esophageal reflux disease when used alone or in combination with omeprazole.[111-112]

In addition, melatonin can protect the GI mucosa from ulceration by its antioxidant action, stimulation of the immune system, limitation of gastric mucosal injury, and promoting epithelial regeneration. Melatonin can also reduce the secretion of pepsin and hydrochloric acid and influence the activity of the myoelectric complexes of the gut via its action in the central nervous system.[113-116] This hormone furthermore attenuates acute gastric lesions and accelerates ulcer healing via its interaction with melatonin receptors due to an enhancement of the gastric microcirculation.[117]

Similarly, melatonin is a promising therapeutic agent for irritable bowel syndrome (IBS) with activities independent of its effects on sleep, anxiety, or depression due to its important role in gastrointestinal physiology. It regulates gastrointestinal motility, has local anti-inflammatory reaction, as well as moderates visceral sensation. Studies have consistently showed improvement in abdominal pain; some trials even revealed improvement in quality of life in these individuals.[118-121] In fact, studies have regularly publicized that alteration of the circadian rhythm is associated with the development of digestive pathologies that are linked to dysmotility or changes in microbiota composition in irritable bowel syndrome and similar conditions.[122-123]

Moreover, disruption of circadian physiology, due to sleep disturbance or shift work, may result in various gastrointestinal diseases, such as irritable bowel syndrome, gastroesophageal reflux disease, or peptic ulcer disease. In addition, circadian disruption accelerates aging and promotes tumorigenesis in the liver and GI tract. Furthermore, identification of the role that melatonin plays in the regulation of circadian rhythm allows researchers and clinicians to approach gastrointestinal diseases from a chronobiological perspective. Recently, it has been postulated that disruption of circadian regulation may lead to obesity by shifting food intake schedules.[124-125] Likewise, a study suggests that sensing of bacteria through toll-like receptor 4 (TLR4) and regulation of bacteria through altered goblet cells and antimicrobial peptides is involved in the anti-colitic effects of melatonin. Consequently, melatonin may have use in therapeutics for inflammatory bowel disease.[126]

Lastly, foods that are high in melatonin (phytomelatonin) have recently been shown to be considered important in preventing diseases of the liver. Currently, more studies are needed to examine the potential beneficial effects of

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supplemental melatonin, and foods rich in melatonin, in liver diseases and to better clarify the molecular mechanisms of action.[127]

Other Sources of Melatonin

The following are common foods that contain the most melatonin.

- Tart cherries
- Corn
- Peanuts
- Oats
- Tomatoes
- Broccoli
- Strawberries
- Black olives/green olives
- Red grapes
- Walnuts
- Rice
- Barley
- Asparagus
- Black tea/green tea
- Pomegranate
- Brussels sprouts
- Cucumber
- Mushrooms

Side Effects and Contraindications

Melatonin is an immune stimulator. Therefore, it should be used with caution in patients that have an autoimmune disease and individuals who are pregnant, breastfeeding, taking steroids, or who have a mental illness, leukemia, or lymphoma.

Signs and Symptoms of Elevated Levels

- Daytime sleepiness/fatigue
- Depression
- Headaches
- Increase in cortisol
- Intense dreaming/nightmares
- Suppression of serotonin

The most common reason that a person has an elevated level of melatonin is that they take too large a dose or take melatonin and they do not need it. Likewise, an individual may also have high levels of melatonin if they eat too many foods that contain melatonin. Some medications such as clorgiline, desipramine, fluvoxamine, thorazine, tranylcypromine, and others may also raise melatonin levels as can St. John's wort supplementation. The herb Vitex agnus-castus (chaste tree) can also elevate melatonin levels. If melatonin levels are high, serotonin levels tend to decline. Therefore, it is very important to measure melatonin levels, by salivary testing, if taking more than one mg of melatonin at night.

Melatonin Dosing Schedules

Generally, women are more sensitive to melatonin than men if melatonin is being suggested for insomnia. Some women may need only a very low dose, and hence the melatonin may need to be compounded. In addition, medical studies have also suggested that as patients age, they may need less melatonin for insomnia.[128-130] As previously mentioned, large doses of melatonin are used to treat breast cancer and other cancers. Likewise, very large doses of melatonin are now being employed as co-therapies for COVID-19.[131] Measuring melatonin levels by salivary testing, before and after implementing melatonin therapy, for patients who are not hospitalized for COVID is recommended. For patients who are hospitalized for COVID, no testing methods have yet been standardized.

The following are common dosage ranges for patients. Changes in dosing may need to be employed depending on the results of follow-up salivary testing.

- Females under the age of 55: 0.25 to 1 mg, 30-60 minutes before bedtime
- Males under the age of 55: 1-3 mg, 30-60 minutes before bedtime
- Patients over the age of 55: In middle-age to older adults, the use of the lowest possible dose of immediate-release melatonin to best mimic the normal physiological circadian rhythm of melatonin and to avoid supra-physiological levels is suggested: 0.25 mg to 1 mg, 30-60 minutes before bedtime is commonly an adequate dose. Doses above 5 mg are not initially suggested for insomnia in patients over the age of 55.
- Cancer therapies: 12-20 mg, 30-60 minutes before bedtime
- COVID-19 as an adjunct therapy to other treatments:[132]
  - Patients with comorbidities: 3 to 10 mg, 30-60 minutes before bedtime
  - Health care workers with direct contact with COVID patients: 20 to 40 mg, 30-60 minutes before bedtime
  - Mildly symptomatic patients admitted on the hospital floor: 50 mg BID for 7 days
  - Patients admitted to the ICU: 200 mg BID for 7 days
  - **Review the medical literature before beginning therapy to check the newest recommendations since COVID-19 treatments are changing on a regular basis.**

Conclusion

Melatonin is a wonderful hormone that has so many functions in the body aside from regulating sleep. As you have seen, it has been shown to be an effective therapy for many disease processes along with a beneficial method to build the immune system. ◆

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

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The Pill Problem: Oral Contraceptives Deplete More Nutrients Than Any Other Class of Drugs

by Ross Pelton, RPh, PhD, CCN

I am the author of *The Drug-Induced Nutrient Depletion Handbook.*[1] During the process of writing that book, I was astounded to learn that oral contraceptives deplete more nutrients than any other class of drugs. This knowledge motivated me to write *The Pill Problem*, which teaches women how to protect themselves from the side effects of oral contraceptives.[2]

Oral contraceptives commonly cause nutrient depletions, resulting in health problems that can be prevented by taking nutritional supplements.

The purpose of this article is to summarize the nutrient depletions caused by oral contraceptives and the potential health risks associated with these nutrient depletions. I will not be making dosage recommendations. I believe practitioners should make these decisions on a case-by-case basis due to individual differences in genetics, diet, lifestyle and health history.

Although *The Pill Problem* was published in 2013, I was not successful in getting national publicity or wide spread distribution (I wasn't born with a gene for marketing). However, I still strongly believe this information is critically important for women and I am grateful for the opportunity to summarize this information in an article for the *Townsend Letter*.

History of "The Pill"

On May 9, 1960, the Food and Drug Administration approved Enovid as the first oral contraceptive (OC) for use in the United States. This ushered in a new era of sexual freedom for women who could now enjoy spontaneous sex without the fear of becoming pregnant. It is estimated that over 100 million women utilize oral contraceptives worldwide.[3]

A survey conducted between 2015-2017 reported that 25.9% (9.7 million) women in the US between the ages of 15-44 were using oral contraceptives, which made "the pill" the most commonly used form of contraception during those years.[4] However, various studies report that from 46 to 60% of women who begin using oral contraceptives discontinue using them within the first six months due to side effects.[5,6]

Oral Contraceptive Nutrient Depletions

Oral contraceptives deplete vitamins B1, B2, B3, B6, B12, folic acid, vitamin C, vitamin E, magnesium (Mg), selenium, zinc, tyrosine, DHEA, and coenzyme Q10.[7] Fourteen nutrients are being depleted in the bodies of approximately 10 million women in the US and over 100 million women worldwide.

There are other factors contributing to nutrient depletion(s). Factory farming practices such as lack of crop rotation, use of artificial fertilizers, use of pesticides and herbicides, and loss of topsoil each contribute to destruction of the microbiome in the soil and declining levels of nutrients in the crops being grown. In a manner similar to the way probiotic bacteria in the human gut microbiome regulate digestion of food and absorption of nutrients, bacteria break down organic matter in the soil and regulate the delivery of nutrients to growing plants. Multiple studies have reported alarming declines in the nutritional content of our agricultural food supply since the end of World War II. Many foods currently have 20 to 30% lower levels of many vitamins and minerals compared to 70 years ago.[8,9]

I believe the massive widespread use of highly toxic pesticides and herbicides on agricultural food crops, residential lawns and gardens, golf courses and city parks (to name a few) is one of the greatest sins in the history of humanity. We are killing off the microbiome in the soil, lakes, streams and oceans on planet earth, which is creating nutrient depletion problems for all living things. A majority of people also consume diets that consist of highly processed fats and carbohydrates, large amounts of refined sugar, and are dangerously low in fiber content.

Polypharmacy: America's Other Big Drug Problem

Americans take far more drugs than any other country.[10] According to data from the 1999-2006 National Health and Nutrition Examination Survey (NHANES), 47% of non-pregnant women between ages 15-44 take prescription drugs, and

about half take two or more prescription drugs daily.[11] Thus, in addition to oral contraceptive nutrient depletions, multiple other factors can cause nutrient depletions, which increases the risks for developing a wide range of health problems.

Difficult to Detect

When an individual has a side effect to a new drug their physician has prescribed, symptoms such as nausea, vomiting, diarrhea, or a skin rash usually happen within 24-48 hours. However, many of the health problems associated with drug-induced nutrient depletions develop gradually over time. Since they do not initially cause noticeable symptoms, women are often not aware of a developing health problem.

Here's an example: Consider a woman who has been taking oral contraceptives for 10 years, without any noticeable problems. However, over the past six months, she has been increasingly noticing that she is tired all the time. She struggles to get up in the morning; or by mid-afternoon, she is feeling so exhausted that she can hardly function. Oral contraceptives deplete folic acid, vitamin B12, coenzyme Q10, and magnesium. Each of these nutrients is critically important for energy production. A depletion of any one of these nutrients can cause tiredness, weakness, lethargy and/or anemia over time. However, this woman probably doesn't realize that the medication she has been taking for years has been causing nutrient depletions that are now causing health problems.

Overview of Health Risks

The nutrient depletions mentioned above can increase the risk of depression, sleep disorders, anemia, low energy, migraine headaches, heart attacks, strokes, blood clots, diabetes, a weakened immune system, giving birth to an infant with birth defects, and colon and breast cancer. I am not suggesting that women should stop taking birth control pills. My goal is to educate women and healthcare professionals about the fact that oral contraceptives commonly cause nutrient depletions and that the resulting health problems can frequently be prevented or corrected by taking the appropriate nutritional supplements. After each health problem, I will list the oral contraceptive nutrient depletions associated with the problem.

Fatigue (Mg, CoQ10, Folate, and Selenium): Numerous studies report that twice as many women suffer from fatigue as men.[12] Studies also report that fatigue occurs most frequently in people between the ages of 15 to 34, which is the age range that women are more likely to be taking oral contraceptives.[13] The OC-depleted nutrients associated with fatigue are below.

- Magnesium (Mg) and coenzyme Q10 (CoQ10) are both required for the production of cellular energy in the form of mitochondrial ATP.
- Folic acid and vitamin B12 are required for production of red blood cells. Depletion can cause anemia, tiredness, and fatigue
- Selenium (selenoproteins/deiodinases enzymes) is required for the production of thyroxine (T4) and conversion of T4 into its bioactive metabolite triiodothyronine. Fatigue is just one of many symptoms associated with low levels of thyroid hormones.

Blood clots (Mg, B6, B12, Folate): Magnesium, which functions as a mild anticoagulant, is depleted by oral contraceptives.[14] Hence, magnesium deficiency increases thrombotic risks, which explains why women taking oral contraceptives have a greater risk of developing blood clots.[15]

Physicians frequently encourage women to take calcium supplements to help prevent osteoporosis. Calcium is involved in several steps in the blood coagulation process so excess calcium can promote clotting. At the same time, birth control pills deplete magnesium, which increases risks for clot formation. Increased calcium, along with magnesium depletion create a wider gap between the normal calcium/magnesium balance, which can create a "double-whammy" for increased risk of forming blood clots.[16]

Vitamins B6, B12, and folate are required to metabolize homocysteine; and decades ago, elevated homocysteine was found to be a major risk factor for the initiation of thrombosis/blood clots.[17]

Birth defects (Folate): Folate deficiency has been recognized as an "imminent health hazard" and is the primary cause of a worldwide epidemic of birth defects.[18] Many studies document that folate is significantly depleted by oral contraceptives, and it is strongly recommended that women supplement with folate before and during early pregnancy.[19]

It is important to emphasize that folate and folic acid are not the same. Folate occurs naturally in foods. However, folic acid is a man-made supplement that is structurally different from folate. Whereas folate is totally safe to take, several studies have reported people taking high-dose folic acid supplementation have higher rates of cancer. For example, results from a six-year trial in Norway revealed that people taking high-dose folic acid had a higher incidence of cancer and were 43% more likely to die from cancer.[20] In a 10-year trial, women who took folic acid supplements had 20-30% increased risk of developing breast cancer.[21] Encourage your patients to supplement with natural folate, not synthetic folic acid.

Atherosclerosis (Vit. B6, B12, Vit. C, Folate): The B-vitamins, vitamin B6, vitamin B12 and folate are required for the metabolism of homocysteine, and elevated homocysteine is a major risk factor for cardiovascular disease from plaque build-up and clogged arteries.[22]

Low levels of vitamin C also increase the risk of atherosclerosis as evidenced by increased free radical damage, increased levels of oxidized LDL-cholesterol, and accelerated plaque build-up.[23]

Hypertension (Mg, CoQ10): Magnesium, a natural muscle relaxant, helps relax blood vessels and lower blood pressure. Women taking oral contraceptives have substantially lower levels of serum magnesium compared to nonusers.[24]

Coenzyme Q10 levels are lower in women using oral contraceptives, and blood pressure is higher in individuals with low levels of CoQ10.[25] Supplementation with CoQ10 is a very

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effective natural therapy to lower elevated blood pressure.[26]

Oral contraceptives cause a slight elevation of blood pressure in most women. A condition referred to as *Oral Contraceptive Hypertension* occurs in about 5% of OC users. These blood pressure elevations are generally reversible within a few months after stopping.[27]

Heart attacks (Mg): Magnesium regulates heart rhythm, and it also functions as nature's natural muscle relaxant. Every year, many people with relatively healthy hearts experience a serious heart attack; and in about 50% of these cases, the heart attack causes sudden death.[28] Many Americans are deficient in magnesium and taking adequate magnesium supplementation on a daily basis provides strong protection against heart attacks.

Cancer (Selenium, Folate): Selenium is a powerful antioxidant, and selenium and selenium-dependent enzymes play critical roles in detoxification. Women using oral contraceptives have been found to have lower levels of selenium compared to nonusers, and low selenium levels are associated with greater risks of breast cancer and colon cancer.[29,30]

Low folate levels cause abnormalities during cellular division, which are associated with numerous types of cancer, such as cervix, colon, lung, and esophagus.[31]

Osteoporosis (Mg): Calcium and magnesium play critical roles in the regulation of bone metabolism, and the calcium/magnesium balance is critical for bone health. Many women take calcium supplements, which increase serum calcium levels while oral contraceptives lower magnesium levels. This is a double dilemma for bone health. The body attempts to normalize the calcium/magnesium ratio by leaching magnesium out of the bones, which actually weakens bone structure and can accelerate the development of osteoporosis.[32]

Weak immune system (Vitamins C, E, Selenium, Zinc, Coenzyme Q10): Antioxidant nutrients play critical roles in the regulation of immune function, and each of the oral contraceptive-depleted nutrients listed above function as antioxidants. Additionally, vitamin C, selenium, and zinc provide anti-viral protection, which is critical for immune health.[33] A deficiency of any one of these nutrients will weaken the immune system.

Women taking OCs had vitamin C levels that were 30% to 42% lower than women not taking OCs.[34] Also, plasma levels of vitamin E,[35] selenium,[36] and zinc[37] are significantly lower in women taking oral contraceptives.

Depression (Vitamin B6, Folate, Vitamin B12, Tyrosine): In a meta-analysis, the incidence of depression in women taking oral contraceptives who reported depression ranged from 16% to 56%.[38] In a study comparing women taking oral contraceptives with non-users, women taking birth control pills had depression rating scores that were almost two times higher than women who were non-users.[39]

Vitamin B6 is required for the synthesis of serotonin. Tyrosine is the precursor for the synthesis of the neurotransmitter norepinephrine. Disrupting these pathways increases the risk of depression.[40]

Elevated homocysteine is associated with depression. Since B6, B12 and folate are required for homocysteine metabolism, a deficiency of any of these B-vitamins could contribute to elevated homocysteine and depression.[41]

Sleep disorders (Vitamin B6): Vitamin B6 is required for the conversion of tryptophan into serotonin, which then gets converted into melatonin. Melatonin is the chemical produced in our brains that triggers sleep. Sleep problems are one of the most common health issues for women. Approximately 25% of women in America suffer from insomnia.[42] Hence, a deficiency of vitamin B6 inhibits the synthesis of serotonin, which can lead to depression; and it also inhibits the synthesis of melatonin, which can cause sleep disorders.

Vaginal yeast infections (Probiotics): Oral contraceptives alter the acid/base balance in the intestinal tract, which favors the growth of candida. In addition to a number of OTC treatments, there is emerging evidence that some strains of probiotic bacteria specifically promote a healthy vaginal microbiome.[43]

Migraine headaches (Riboflavin, Magnesium, CoQ10): Studies show that high-dose riboflavin can help prevent or treat migraine headaches although the mechanism is not clear.[44]

Brain imaging studies reveal that brain magnesium levels are low during migraine attacks.[45] Other theories include magnesium's role as a muscle relaxent and its role in ATP production.[46] Coenzyme Q10's role in migraines appears to also be related to mitochondrial energy metabolism.[47]

Fluid retention/weight gain (Not due to nutrient depletions): Most women will retain some excess fluid, which results in weight gain when they begin taking OCs because synthetic estrogens alter several hormonal systems that regulate fluid in the body. Hormones altered are arginine vasopressin (AVP), atrial natriuretic peptide (ANP), renin and

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Website, Blog, and full bio at https://www.naturalpharmacist.net/

aldosterone. This causes slight retention of sodium and fluid, resulting in a new "set point."[48]

Sexual side effects (Not due to nutrient depletions): Oral contraceptives lower a woman's sex drive, which is one of the most common reasons that women discontinue taking the "pill." Common sexual side effects associated with oral contraceptives include the following:

1. Decreased desire for sex,
2. Greater difficulty becoming aroused,
3. Vaginal dryness resulting in painful sex,
4. Difficulty or inability to achieve orgasm.

These sexual side effects are caused by hormone imbalances that result from ingesting the synthetic, chemically altered hormones in oral contraceptives. The unnatural hormones react differently with cell receptors. This alters signals that are sent to genes, which causes negative effects on a woman's sexual hormones and on other physiological processes.

Oral contraceptive-induced sex hormonal imbalances include the following: 1) Testosterone levels are lower in women taking OCs.[49] 2) Dehydroepiandrosterone (DHEA) is the precursor for testosterone production. Women taking oral contraceptives have lower circulating levels of DHEA.[50] 3) Sex hormone binding globulin (SHBG) is a protein that binds to sex hormones so they can be transported throughout the body. When testosterone is bound to SHBG, the testosterone is not free to function at the cellular level. Women taking oral contraceptives have been found to have levels of sex hormone-binding globulin **four times higher** than the level of SHBG in women who had never taken oral contraceptives.[51] This dramatically lowers the amount of free testosterone available to act at the cellular level, which decreases sex drive and the ability to achieve an orgasm.

A disturbing long-term problem: Blood samples from women who had discontinued taking oral contraceptives for six months revealed levels of SHBG that were still two times higher than the levels in women who had never used oral contraceptives. This means that even after women stop taking oral contraceptives, they may experience long-term sexual dysfunction.[51]

Increased free radical damage/ accelerated aging (Vitamin C, E, Selenium, Zinc, Coenzyme Q10): Depleting levels of antioxidants in the body can result in increased levels of free radical damage throughout the body, which accelerates biological aging. ◆

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

Pelvic Pain – Is It Really Pudendal Neuralgia?

by Hal S. Blatman, MD

Introduction

Pelvic pain has many causes that can be tested and diagnosed using well-known instruments and methods. Many of these cases are then easily and successfully treated. This article is not about these open-and-shut cases; it is for the people who continue to suffer, as well as the healthcare personnel trying to help them.

There are many men, women, and children with disabling and unrelenting pain despite continued efforts to find and treat the sources of their issues. For these people, there are options for surgery, ongoing therapies, and various medications that may or may not mitigate chronic and life-shaping pain.

To complicate matters, healthcare providers are taught that our diagnostic technology accurately determines what is causing pain in the body. So, when testing does not discover a cause, we are often taught that a person has "made up pain"; that it is "all in their head." And yet, I have never examined a person with pelvic pain who had no relevant markers that could be improved.

I first discovered my own pelvic pain when activities that had once been easy, like tennis and exercising at the gym, became difficult. Suddenly, reaching sideways to hit the ball, or doing a seated leg press, caused a strain to my groin, hamstring, adductor and gluteal muscles all at once. A week later I still had not slept through the night without waking up when changing positions.

Every facet of life can be affected by pelvic pain. It's not just bowel, bladder, and sexual function, but ambulation, sitting, and quality of sleep. I feel grateful that I knew about and had access to the effective treatments described in this article, and I think all the time about those who don't.

Some Common Treatments

Finding the physical source of pain is synonymous with finding the places where our biology and engineering have structurally failed. Unfortunately, we have been taught to perform our investigation with laboratory equipment and imaging studies, such as MRI, EMG, and CT scan, which lead us toward therapies that do not work.

I have seen many people, especially women, wearing pelvic braces based on the understanding that their sacro-iliac (S-I) joint is their major issue. They are generally able to maintain function with a variety of pelvic floor therapies, adjustments, injections, and bracing, but they live with pain.

Alternately, when our sophisticated diagnostic imaging cannot find an obvious cause for a patient's pain, we blame it on a nerve and call it *pudendal neuralgia*. Many patients who call our center ask whether I treat pudendal neuralgia, and do not even consider the possibility that their pain may have little to do with their pudendal nerve. To their credit, the doctors on their care team have all agreed that neuralgia is the issue, and that they must seek treatment that interrupts the nerve's signal by drug, ablation, or surgery. In my experience, pelvic pain is rarely due to a pudendal nerve injury, and surgical options for treatment should rarely be considered.

Lyrica has become a popular pain medication for pelvic complaints, but it reduces pain by making our nerves "numb." Not being able to feel is quite different from reducing pain by healing. And higher doses often make patients more forgetful and sleepy, as other parts of the nervous system are adversely affected. Any medication that reduces a patient's ability to sense injury and pain can more easily allow further aggravation.

Unfortunately, it is a rare provider that will give you a comprehensive physical examination (pelvic, thigh, abdominal, and gluteal), not merely to poke you and ask about tenderness, but to understand underlying fascia texture changes that occur from injury. Your pelvic floor therapist may have helped you find some relief, but they cannot provide the level of fascia reconstruction needed to hold your body together and get you out of pain.

Of the myriad techniques that have arisen to alleviate suffering (therapies, braces, and tools to address the mind, spirit, energy fields, emotions, biochemistry, and biology of those in pain), the treatment theories and activities that are most effective are the ones that have a significant effect on the biology of our fascia.

Fascia

Fascia refers to the assimilation of collagen, elastin, fibronectin, hyaluronic acid and other components that hold our bodies together. Facial tissue is made by fibroblast cells, and it surrounds every muscle cell and fiber, and the entire muscle; it attaches,

weaves, and anchors muscles to the fascia that covers our bones, and keeps our organs, nerves, and blood vessels in their place. Collagen fibers, of which there are many forms, provide strength to ligaments and tendons.

Fascial tissue is affected by everything we eat, see, hear, think, touch, and do. My article about fascia and pain in the November 2018 issue of this magazine describes how a lifetime of fascia injuries transcribe to chronic pain, which can be resolved by *unkinking* the fascia trigger points (also called myofascial trigger points) and restoring the areas where fascia anchors and holds a person's biology together. In a similar vein, what we can find from examining the fascia can explain many of the intricacies we hear as people describe their pain symptoms.

Once you understand this paradigm, you will view your patient and their anatomy through a different lens, which you can then tune to other body systems, and use to treat localized pain in a whole new way. In this article, we are looking through the lens of the Blatman Pain Paradigm with the specialized knowledge of how it applies to the pelvic region.

Fascia is a totally different "animal" (compared to spine, disc, and nerve) when considering any particular origin of pain. Most importantly, lifetime injuries to fascia are the underlying cause for almost all pain in our bodies.

Roughly 80% of the information coming to our brain from our periphery originates from free interstitial nerve endings within the strands of collagen and ground substance that make up our fascia, which primarily measure shear forces (friction) and pressure. They are part of the autonomic sensory nervous system, and the signals they transmit can become neuropathic pain. Sidenote: While it is good for academics and researchers to learn about the difference between nociceptive and neuropathic pain, the reality is that they cannot be distinguished by clinician or patient, and the distinction is not relevant for determination of cause, decisions about medication, or any other part of treatment. Pain from trigger points is autonomic afferent pain, and as such it is all neuropathic.

With equal importance, it should be recognized that inflammatory food and environmental toxins, however minimal the exposure, can induce an immune-fascia body-wide reaction that adds pressure to these nerve endings and "lights up" these areas of injury, sometimes for several weeks. High quality bodywork and treatment will not be as effective if a patient is eating food that is inflammatory to their immune system and fascia. (While it is important to identify and heal old injuries, merely decreasing or no longer ingesting inflammatory foods can reduce a total pain burden by more than 50% within 4-6 weeks.)

Pelvic pain symptoms and conditions, as seen through the lens of the Blatman Pain Paradigm, vary widely. Many of them are actually recognized and thought to be discrete conditions or diseases. They include the following:

- Painful burning urination
- Interstitial cystitis
- Painful sex
- S-I joint pain
- Penis pain
- Clitoral pain
- Prostatitis
- Psychogenic pain
- Fibroids
- Endometriosis
- Vaginal pain
- Rectal pain
- Vulvodynia
- Pudendal neuralgia

History of Injury

History-taking is important with special reference to injury involving tail bone, pelvis, thighs, and hips. There are usually multiple injuries resulting from a lifetime of impact and repetitive strain to these tissues, including from childhood gymnastics, falls, soccer, cycling, and running. Specific injuries are not always remembered and may have been insidious. Next, it is incredibly important to define the specific locations of symptoms. Verbal descriptions are rarely sufficient to help and require too much time for accuracy. Much better is the pain diagram that the patient shades by color according to numbness/tingling (yellow), cramping (green), burning (red), and pain (blue). You can expect to see highlighted, to various degrees, the inner thighs (most consistent, fig 1), lower abdomen, buttocks, coccyx, and rectum.

Lifetime injuries to fascia are the underlying cause for almost all pain in our bodies.

Physical Examination and the Blatman Pain Paradigm

Finding the most important fascia-based sources of chronic pain requires physical examination by touch. I believe there are two main goals for this kind of a physical examination.

1. To learn what the injured body has to tell that the person has not been able to adequately sense or express.
2. To make sure that what the examiner feels on their side of a person's skin very closely matches what the person feels on their side.

In other words, the examiner needs to be able to independently determine trigger point and injured enthesis of fascia by texture during palpation. Actual tenderness and report of sensitivity should be mainly confirmatory to the examiner. This specific technique of examination leads to a mapping of injured tissue according to the Blatman Rules for Pain *CSI*.

The Blatman 5 Rules of *CSI* for finding fascia injury and healing from pain:

1. You cannot believe the pain comes from where you feel it.
2. You cannot believe what the pain feels like.
3. You can only believe that where you are specifically tender, mm by mm, indicates where your fascia is kinked and tied in a knot, or where your fascia anchors, holds you together and is injured. ➤

➤

4. The places where you are specifically most tender represent the fascia kinks (myofascial trigger points) and injured areas of anchoring (fascia enthesis) that produce most of your worst pain.
5. As soon as you unkink the fascia, and repair how you hold together, the pain you used to have will go away.

This approach seems to work most of the time, no matter how long a person has suffered from chronic pain. And no matter what the suspected or even 'proven' diagnosis, there is virtually always a myofascial component to the symptoms. Most of the time, just treating this 'component' will have profound effects. And this approach should always be done before an irreversible procedure. Often surgery causes additional injury that makes recovery more difficult.

Physical examination of fascia by texture is the single most important technique in both diagnosis and treatment. Understanding the texture of injury allows a physician to know where someone is tender, and even the degree of tenderness, independently of the patient's response.

With pelvic pain, the most significant injuries are usually between the knees and belly button. Examine all the fascia of the thighs, pelvic floor, gluteals, and lower abdomen for specific differences in texture and tenderness. Most likely the proximal adductor and hamstring muscle fibers will be very tight, stuck together, and tender. Palpate also the enthesis (attachment) of these muscles where they meet the femur, pubic bones, ischial tuberosities (sit bones), and more. For the most part, a tender enthesis is an injured enthesis, and those that are more tender are usually also more injured.

You can feel your own body to become familiar with how tight and tender the muscles of your inner and posterior thighs are. Touch your pubic bone in the front below your abdomen and then follow the bone along the inside of your thigh toward your sit bone. (Fig. 2) Any tenderness along these bones likely reflects the degree of injury to the fascia anchors of adductor, hamstring, and pelvic floor muscles. And if these areas of anchor are not strong enough for the muscles that pull against them, then every time you use these muscles the fascia kinks may cause enough pain to shut you down. This includes bowel and bladder relief, walking, and other activities requiring use of thigh, gluteal and pelvic muscles.

These same textures and tenderness to touch can be identified all over the body. The textures of muscle, ligament, tendon, and enthesis vary with degrees of health and injury. The challenge is to learn to understand the texture of injury and the pain patterns from injured fascia.

When examining a patient with pelvic pain, expect to find tight and tender proximal inner thigh muscles and tendons. Both adductors and hamstrings can be involved. Look also to palpate the lower pelvic rim, all around the ischial tuberosity, and all that flows from the thigh muscles. This then needs to be repeated for gluteal and abdominal muscles. Inner thigh muscles are almost always involved in causing anyone's pelvic pain. Indeed, they are often the driving force for the worst pain. Gluteal muscles are also almost always involved. It is generally important to examine all the hip and thigh related muscles that participate in locomotion.

Now apply rule 4 from above: the places that are specifically most tender reflect the injuries through a lifetime that are causing most of the person's pain. Treatment should direct healing efforts to these areas of injured tissue. Primary goals include unkinking the knots of muscle and fascia and restoring integrity to injured entheses. As these areas become less tender, more and more of the pain will go away. Keep in mind that the pain always comes from an *orchestra* of fascia injury and failed repair. When the tubas quiet, it is easier to hear the viola, and pain may seem to *move*.

Figure 1. All patients color a pain diagram every visit using a color code. Intensity/ severity are generally indicated by darkening.

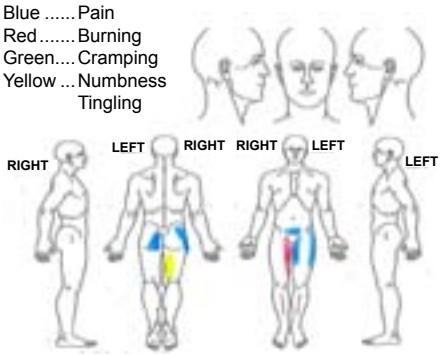
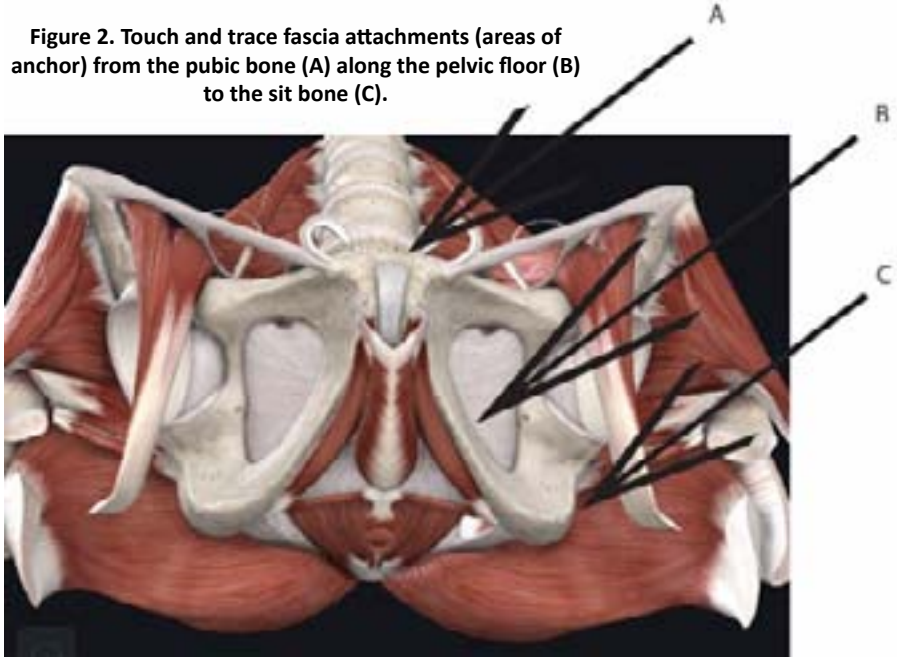


Figure 2. Touch and trace fascia attachments (areas of anchor) from the pubic bone (A) along the pelvic floor (B) to the sit bone (C).



Your treatment must unglue the stuck fibers and repair the injured muscle/fascia anchors. More important, **as long as these areas of tissue remain tender, pain cannot be solely attributed to neuralgia, endometriosis, or even interstitial cystitis.** There is still work to be done to reduce the myofascial component of the pain pattern.

Treatment of Pelvic Pain

It is not difficult to find tight and tender muscles and fascia. What is difficult is making people realize that **none of the tenderness is benign or unimportant**, and all of it must be decreased enough for pain to improve.

Stretching can be helpful, but most of what patients are taught are variations of pulling on the ends of the muscles. If you are trying to get a non-slip knot out of a shoelace, do you pull on the ends? Well, it does not work well for muscle and fascia either.

Real stretch and unkinking of fascia is done from the inside by a needle, or from the outside using the skin as a handle, as taught by Ada Rolf as fascia stripping. For these techniques to be most effective, there are three requirements:

1. Enough pressure on the tissue to be useful
2. Enough friction so the skin becomes the handle for the fascia underneath
3. Slow enough movement that the fascia has time to unkink as you go

Pain that is coming from this fascia will be different (usually improved) as soon as the tissue changes with your stripping. And the more the fascia is released, the more the pain will go away. If the fascia re-tightens, however, pain will come back. There are basically three reasons pain points come back after the muscles and fascia are released and unkinked.

1. The enthesis is still kinked and cannot support the muscle staying more laminar.
2. The enthesis is not strong enough to support what the muscle has to do and slips again.
3. Food is too inflammatory to the immune system, and the fascia 'glues' itself back together.

Of these, often the most important factor inhibiting recovery is food that is inflammatory to a particular person's immune system. Of all the diet suggestions for pelvic pain, this list of foods are most important to avoid:

- Wheat
- Sugar
- Potato
- Juice
- Artificial sweeteners
- Hydrogenated fake fat
- Dairy from cow
- Many people also need to avoid fruit, due to epigenetic changes, and our inability to metabolize natural sugar from fruit.

Decreasing inflammatory food will hopefully provide a concomitant decrease in pain. However, if a person wants to feel really good, they have to completely eliminate inflammatory foods from their diet. This conversation is about setting off an immune system reaction; and when a person is sensitive to bee stings, it only takes one to kill.

Interstitial cystitis is often treated with repeated rounds of – and sometimes chronic – antibiotics. There may be bacteria identified, but predominantly the treatment is based on symptoms related to painful urination. The typical person-with-pain diagram (see Figure 1) had a history of this scenario for three years before seeing us. Initial treatment was directed to her diet, inner thighs, and buttocks. Much of her pain reduced, until circumstances required increased physical exertion and ingestion of flour and sugar. Before contacting her other doctor and requesting antibiotics, she redoubled her efforts with regards to dietary changes and performing prescribed exercises and was able to decrease her 'bladder' symptoms.

Chronic prostatitis is another pain condition generally treated with repeated antibiotics. Fortunately, it is generally a very similar scenario for treatment of pelvic and rectal pain in men as is described for women. Injuries are often similar, as are areas of tenderness.

As long as the fascia of thighs, pelvis, gluteals, and abdomen is kinked and tender, it is still likely to be the cause of pain. But keep in mind, "healing to perfection" is not necessary. All that is needed is for your injuries to no longer be a blip on your pain radar.

Conclusion

Pain does not occur without cause. And often the cause is latent, repeated wear, tear and injury. Pelvic pain in men and women can usually be attributed to years of micro-tears in the muscles and fascia of the thighs, abdomen, and pelvis. Pain is not intractable and does not come from nerves, so we should not be killing nerves and ablating tissue to relieve pain. We should be reducing body-wide inflammation and striving to identify and heal the fascia injuries that accrue over a lifetime. Coping skills are useful, but the best treatment for chronic pain is to make it go away. ◆

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Women and Lyme: Creating Protocols that Honor the Rhythm of Female Hormones and Their Influence on the Immune System

by Ginger Nash, ND, and Christine Schaffner, ND

Women are more likely than men to suffer with certain chronic illnesses. Many of these are the things that we treat daily in medical practice – anxiety and depression, chronic fatigue, headaches, gallbladder disease, arthritis, osteoporosis, and autoimmune diseases just to give a few examples. Epidemiological and clinical studies have determined that in almost all cases of "gender gap" in various conditions, the gap is connected to a mix of biological and social factors.

A woman's immune system shifts throughout her monthly menstrual cycle.

Worsmer and Shapiro found that "patients with chronic Lyme disease differ with regard to gender from those with either *B. burgdorferi* infection or post-Lyme disease syndrome. This finding suggests that illnesses with a female preponderance, such as fibromyalgia, chronic fatigue syndrome, or depression, may be misdiagnosed as chronic Lyme disease."

The goal of this article is to explore treating women with chronic illness, namely those that have been diagnosed with Lyme disease, by pulsing therapeutic strategies depending on the phase of their menstrual cycle. In some cases, we also consider treatments in accordance with a woman's phase of life. For example, perimenopausal and menopausal women are in a different hormonal rhythm than those that are still menstruating on a monthly basis.

A woman's physiology is deeply connected and impacted by the fluctuation of hormones throughout the monthly rhythm of their menstrual cycle. Women who are in the midst of perimenopause or who have entered menopause experience a shift in their hormonal rhythm that also impacts their physiology.

We have observed clinically that many women who struggle with Lyme disease and its common co-infections experience symptoms that include insomnia, depression, anxiety, brain fog, fatigue, chronic digestive issues, dysautonomia, mast cell activation syndrome, POTs, air hunger, interstitial cystitis, and more.

Women with chronic illness, including those namely who struggle with Lyme disease, often experience signs and symptoms related to estrogen dominance. This may include ovarian cysts, fibroids, menorrhagia, PMS, and painful periods. Another observation is that these women often experience a flare of symptoms one week prior to menstruation. We have called this phenomenon, luteal phase flare (LPF).

The severity of the LPF is variable and dependent on a number of hormonal imbalances, but primarily lower progesterone and higher estrogenic activity. We know this can be related to anovulatory cycles, the estrogenizing effects of our environment, overall body burden of toxicants, and in some cases trauma. We also note that many women with chronic pathogen problems may have an earlier start to the perimenopausal transition. The entire hypothalamic-pituitary-ovarian (HPO) axis is sensitive to the effects of pathogen exposure.

Our approach in the treatment of chronic illness is to address the patient's terrain, remove toxicants and improve eliminations via the gut, liver, and kidneys. We focus on the extracellular matrix and address the lymphatic system as well since it is essential for removal of many toxicants and permeates the whole body, including the central nervous system and brain.

We know from basic physiology that a woman's immune system shifts throughout her monthly menstrual cycle. During the follicular phase, when estrogen is rising, there are higher levels of circulating antibodies and a heightened inflammatory response. Prior to ovulation and potential pregnancy, a woman's body is ready to fight foreign invaders so she can be healthy to conceive.

After ovulation, women enter the luteal phase when estrogen drops off and progesterone begins to rise. A women's immune system is downregulated by progesterone in order to prevent immune cells from attacking a fertilized egg and thereby prevent implantation. Immune suppression during this time can make women more susceptible to infection. Ovulating females are more prone to infections from yeast, bacteria, and viruses. On the other hand, immune suppression may play a role in other conditions so that women are less likely to suffer with things like asthma symptoms during this time.

In the late luteal phase, typically one week prior to menstruation, women with chronic illness may experience negative or worsening of symptoms due to the rise of prostaglandins as the uterine lining prepares to shed. The complexity of immune recognition means that certain susceptibilities are present in the late luteal phase, and the reactivity of certain inflammatory pathways are occurring at the same time.

This is especially concerning for women with chronic pain and those women suspected of having endometriosis. There is a lack of coordinated immune response that leads to unchecked inflammation and a heightened sensitivity to pain. In some women, there is also a susceptibility to autoimmune processes. The same underlying issues are involved in an ongoing immune response to a past infection, like Borrelia or many other pathogens. We know there is an overlap with the symptom picture in women diagnosed with Lyme – chronic pain, fatigue, digestive issues, brain fog, and mood challenges. Root causes such as inflammation, stress, gut microbiome dysbiosis, and nutrient deficiencies must be addressed in both scenarios to help women heal.

As noted, women with Lyme tend to have an increase in symptoms the week before their menstrual cycle. Dr. Marylynn Barkley studied the relationship of female hormones on the rise and fall of Lyme disease symptoms.

She observed (data recorded over a two-year period) an intensification of night sweats in a cyclical pattern coinciding with the decline of ovarian hormones and onset of menses in women with Lyme. She also found that during this phase of the cycle, the immune recognition of Borrelia antigen in the urine (LUAT) was at a peak and that cytokines were found to be above normal. Night sweats are often correlated with immune activation.

Dr. Barkley identified this interval of increased immune activity several days before the onset of menses. She speculated that the increase in immune response leads to an increased die off of spirochetes during this period, which leads to the intensified symptomatology and the increased shedding of antigen.

Of note, the timing a woman gets a tick bite (or other route of exposure) may also affect likelihood of an infection or resistance to infection. Also, timing of Lyme test may be best three to four days prior to the period.

With this in mind, we propose adjusting support for various conditions dependent upon the time of the menstrual cycle or the life-stage of the woman: i.e. puberty, perimenopause, post-menopause.

For women that are still cycling monthly, we recommend various support for both halves of the roughly 28-day cycle. For example, supporting healthy estrogen metabolism by working with liver and gallbladder health is key in the follicular phase. In the luteal phase we shift focus to supporting healthy levels of progesterone and the delivery and sensitivity of tissues to progesterone. Some of this is accomplished by making sure a woman's lymphatic system is optimized, and there are many aspects of our work that intersect with lymph and the clarification of the extracellular matrix.

In addition, luteal phase flare support may include increased antimicrobial strategies to pair with the noted increased immune activity against spirochetes, addressing biofilm, immune modulation therapies, and enhanced elimination remedies, such as binders, to support a woman's immune system during this time.

Perimenopausal and menopausal women with chronic illness have different needs and different symptomatology. These women often experience anxiety, insomnia, brain fog, low libido, vaginal dryness, and weight gain in more dramatic fashion than simply transitioning through menopause alone. Recommended therapies may focus more on tonifying or nutrifying tissues and organ systems based on the individual's history, including past exposure to viral, bacterial, or fungal pathogens and how they responded to those events. This is where our understanding of miasm is very helpful.

Shifting treatment strategies each month also allows women to connect more deeply to their inner rhythms while further connecting to the outer rhythms in nature. ◆

Spectrum of Ill Health in Infants and Children from Environmental Pollution

by Paul K. L. Lam, MD

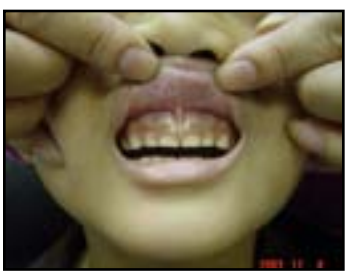
Over an eighteen-year period, the use of an innovative treatment paradigm for intractable ill-health in infants and children, through application of environmental medicine, has been rewarding. This has bridged the knowledge gap in conventional medicine about the rising global incidence of non-communicable diseases. This observation has also explained the paradox of poor health and neurobehavioral disturbance in exclusively breastfed, apparently healthy infants. In recent years, research has indicated the fast-degrading environment can cause a silent epidemic of neurodevelopmental brain drain in the next generation through trans-placental passage of toxic chemicals from asymptomatic pregnant mother to the fetus in utero.[1] An oxidative, nutritional approach to health and diseases has been shown useful in reversing toxin-related ill health. This observational research has unanimously demonstrated the link between toxin overload and chronic ill health.

Through the judicious application of toxin-eliminating chemicals and nutritional supplementation, numerous intractable diseases can be cured. Notable examples are autism, cerebral palsy, global developmental delay, severe eczema, tics, Asperger's syndrome, and stunted growth dated from in utero stage to early childhood. The logistics of testing this treatment paradigm in these diseases has defied the randomized placebo-controlled trial model of conventional medical practice. The role model of single pharmaceutical intervention in disease management would be futile to address the relentless rise in global non-communicable diseases.

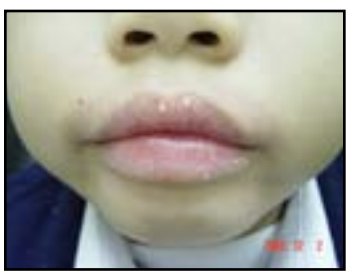
Several thousand toxin-overloaded pediatric patients have been treated over the last eighteen years based on this perspective. Their signs and symptoms are described as follows:

- *Intrauterine growth retardation*.
- *Unexplained low Apgar score* at birth.
- *Excessive jitteriness* in early infancy with frequent inconsolable crying bouts and fidgety sleep.
- *Feeding problems*: poor sucking, slow feeding, frequent regurgitation or vomiting, with either diarrhea or constipation and suboptimal weight gain.
- *Early eczema* starting in the first few weeks of life, frequently triggered by routine vaccination and progressively become intensive and resistant to conventional medical therapy.
- *Bruxism* (teeth grinding) at night during sleep. Severely toxic children would have bruxism during the daytime. This can start in infancy and affect the child for years with the front teeth flattened through physical grinding and often the gum shows a horizontal brownish discoloration. Another sign is dark teeth staining developed in infancy and early childhood.
- *Poor sleep*: frequent awakening at night with inconsolable crying bouts.
- *Frequent respiratory infections* and *allergic rhinitis* in infancy and early childhood, usually recurrent and poorly responsive to medication. Associated with recurrent wheezy attack, otitis media, sinusitis.
- *Adverse reactions to vaccinations.* These infants are more prone to developing high fever, skin rash, convulsion, and loss of developmental skills after vaccinations.

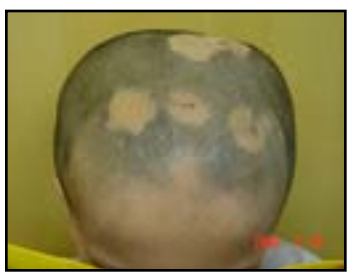
Toxic Metal Overload in Children



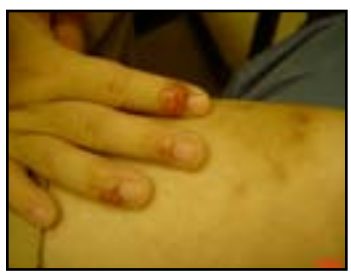
Gum showing brownish thick line and flattened teeth



Peri-oral eczema



Alopecia areata



Finger with intractable cellulitis

• *Food allergies*. Early food allergies to cow milk protein, egg and gluten often develop in these toxin-overloaded infants. IgG mediated food allergies occur as early as three months of age and usually severely allergic before one year old.

• *Neurodevelopmental delay* and neurobehavioral disturbances: In infancy: poor head control, delay in gross motor function and coordination. In childhood: delay in speech acquisition, dysarthria, dyslexia, learning disability, autistic features, Asperger's syndrome, tics, attention deficit and hyperactivity.

• *Endocrine disturbances*: Failure to grow at any age, from infancy to adolescence. Polyphagia and early obesity from overload of persistent organic pollutants affecting thyroid receptor sensitivity. Precocious puberty and short stature. Thyroid dysfunction from autoimmune diseases.

• *Immune disturbances*: Lack of protection from vaccinations due to lack of antibody production from organic pollutant overload. Toxin-loaded infants and children are more prone to diseases related to immune dysfunction: Kawasaki disease, Henoch-Schonlein purpura, autoimmune thyroiditis, and rheumatoid arthritis.

• *Hair and nails*: Hair in toxic-loaded infants or children would be dry and frail. Nails in toxic children would be thin, brittle, laden with whitish specks. Another sign is thickened pigmented dysplastic nails.

• *Lips* are dry with eczema, frequently accompanied by perioral involvement. Toddlers or children may show frequent ulcers within the mouth with slow healing. The tongue may present with persistent whitish coating due to candida infection.

• *Bizarre skin lesions* may appear in toddlers or children: generalized erythematous papulo-vesicular rash simulating chickenpox; palmar and plantar erythema with thickening of the skin, reminiscent of the "acrodynia" of the children in last century poisoned by mercury-ladened teething powder; indolent skin ulcers with weeping erythematous surface and peeling skin margins. (See images)

Assessment of Toxic Burden of Infants and Children

Conventional medicine stipulates the use of blood levels of heavy metals in assessing patient's toxicity.[2] However, blood levels of toxic metals show only recent exposure as the toxic metals would be deposited to various organs with partial excretion a few weeks after initial exposure. Hair analysis for toxic metals has been widely accepted and validated for epidemiological studies by the World Health Organization for indication of toxic metal exposures. A false negative result does occur in severely toxic patients, as the abnormal metabolism has compromised hair growth.

For assessment of symptomatic infants, the hair of the mother can be taken for toxic metal analysis as this reflected the toxic burden of the mother in the preceding three months. The provoked urine test where urine is collected and analyzed following administration of chelating medicine is a relatively accurate test in reflecting toxic load of the patient. The limitation of this test is that the levels of toxicities shown do not reflect the total toxic burden of the patient. In practice, serial provoked urine challenge test done a few months apart would show higher levels of toxic metals excreted with resolution of the ill health. This implies more ready release of toxic burden from the body's tissue with effective toxin-eliminating therapy.

For small infants, an indirect yet relatively reliable test to assess body's toxic burden is the urine porphyrins test. This is done by collecting early morning urine and saving the urine sample in a light-proof container. The amount of the various porphyrins would reflect the quantities of persistent organic pollutants, arsenic, lead, and mercury occurring as their metabolites. The most accurate assessment of body burden of toxins would be tissue biopsies of various organs. Obviously, this is impractical due to its invasiveness.

Management of Toxic Overloaded Patients

The medical history for affected infants begins with the mother. Mother may have a history of prolonged ingestion of Chinese herbal medicine, frequent fish meals, and/or presence of multiple dental amalgams. For nursing mothers, frequent consumption of fish soup is another risk factor. In Hong Kong, infants and children are frequently given daily fish meal.

After testing for presence of toxic metal overload, the treatment begins with the advice of strict abstinence of fish or seafood meals for a period of three to six months. Nutritional supplementation would be given to facilitate toxic elimination. Selenium, zinc, magnesium, omega 3 fatty acid, antioxidants (N-acetylcysteine, alpha lipoic acid), and probiotics comprise the treatment regimes. For more severely affected infants, home injection of vitamin B12 (methylcobalamin) given subcutaneously once every three days would expedite recovery. Notable examples are the infants with severe, whole-body eczema and neurodevelopmental handicap.

The younger these affected children are started on this therapeutic regime, the greater the chance of complete cure.

Duration of therapy would be variable depending on the severity of symptoms and magnitude of toxic overload. An average of three to six months would usually be required. Apart from resolution of the original symptoms, gratifying improvement of other health parameters would be frequently elicited: phenomenal catch-up growth of the head size, then of the body; increased appetite; improved temperament, mood, and learning ability are frequently observed.

For management of autistic or other neurodevelopmentally handicapped children, the use of intravenous nutrients (phosphatidylcholine, folinic acid, glutathione, vitamin C) or chelating agents have to be instituted in order to achieve cure within a reasonable time, say within one to two years. Contrary to the prejudice of conventional medical practitioners, intravenous chelation has been safe with no major adverse side effects in the author's practice. For successful cases, some autistic children

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not only have their autistic features eradicated, but they were also noted to have higher intelligence quotient upon successful treatment. Due to the plasticity of the infant's brain, the younger these affected children are started on this therapeutic regime, the greater the chance of complete cure.

Due to the inherent growth potential of infants and children, once the constraint of a chronic ill-health has been relieved, an accelerated growth would be observed with upward crossing of the growth percentile. In recent decades, idiopathic short stature has become more common and the administration of recombinant growth hormone has become an indication to address this problem. However, the cost and duration of treatment by this means are prohibitive, apart from the need for daily injection. Two cases worth reporting to illustrate this phenomenon.

Case 1. A 7-year-old boy has had idiopathic supraventricular ectopic for two years with no treatment deemed available. After he came to my attention, his hair mineral analysis identified toxic heavy metal overload. Oral nutritional supplements were given, and avoidance of seafood advised as management for toxic elimination. After six months, the boy's height and weight were noted to cross percentiles from the 10th to the 50th, apart from sustained remission of the cardiac arrhythmia.

Case 2. An intrauterine growth-retarded baby girl with birth weight 2.2 Kg at term delivery has recurrent vomiting and poor weight gain within the early weeks of life. The mother frequently ate fish and dried fish bellies (fish maw) during pregnancy. After oral supplementation of a potent antioxidant (alpha lipoic acid around 50 mg per day), the baby showed dramatic catch-up growth starting with the head circumference. It increased from 31.5 cm to 35 cm within a month's time. Her weight deficit resolved with catch-up gain within a three-month period.

As conventional medicine does not entertain the diagnosis of toxic pollutant overload, the mechanism underlying the idiopathic growth-stunted patients would remain elusive.

Below are illustrative cases of severe neurological handicap reversed through mercury detoxification.

Case 1. A boy, aged 2 years and 4 months, diagnosed with cerebral palsy came for assessment. He had no birth asphyxia, and developmental milestones were all delayed. He walked clumsily with a limping gait and a marked club foot on one side. He was nonverbal with few intelligent words. He showed poor eye contact and could not carry out verbal instruction. The result of his hair mineral analysis and urine porphyrins showed an overload of mercury, xenobiotic, and other toxic heavy metals.

He was advised to abstain from all seafood and freshwater fish. Nutritional supplementation was given, and injectional nutrients and detoxifying medications were given once every two weeks. Injectional medications included phosphatidylcholine, glutathione, and calcium EDTA. DMSA (dimercaptosuccinic acid) 75 mg suppositories were also given twice per week. The clinical progress was dramatic, as evident by marked improvement in his neurocognitive function after each injectional detoxifying therapy. There were no adverse side effects during the course of the three-month period of therapy.

Upon completion of the therapy, he could talk in sentences and answer questions intelligently; he became responsive socially and understood most commands. His gross motor function also improved with no more limping gait and improved coordination. His neurocognitive function has advanced within a brief period of three months to near-age-appropriate developmental milestones.

Case 2. A boy was diagnosed to have intrauterine stroke in early infancy. He was born at 36 weeks gestation by a 32-year-old mother as her first pregnancy. The antenatal and perinatal course were uneventful. The boy's limbs on the left side were noted to be completely paralyzed a few weeks after birth. CT brain scan showed a markedly shrunken brain on the contralateral side, up to one-third size compared to the normal half. The parents were told that this boy would likely have lifelong physical and mental handicaps, and the cause was an intrauterine stroke of unknown etiology.

The baby was first seen by the author at seven months of age with complete hemiplegia of the left side. He was noted to be hyperirritable and with no social response. His sleep had been fidgety with frequent crying bouts. The mother's hair was checked for minerals and showed an overload of mercury. The boy was treated continuously for 14 months with nutritional supplements. Mercury detoxification was started at 10 months of age by DMSA (dimercaptosuccinic acid) suppository. The boy responded favorably with resolution of the abnormal symptoms in the next few months. Subsequent provoked urine challenge revealed excretion of mercury. His sleep became peaceful with less interruption. Both physical and neurodevelopmental function improved, and catch-up growth occurred. His paralyzed limbs started to move, and his speech development slightly delayed.

At the age of 5, he was assessed to be appropriate in his neurodevelopmental function and could be relocated to a normal school. He did have a tight heel tendon on the left leg and later required a tendon release operation. The cause of this in utero cerebrovascular accident has never been explored. There are reports of adults with a higher risk of stroke being clustered in areas with excessive consumption of mercury-contaminated fish.

This case illustrated the potential plasticity of the infant's brain in repairing injuries if given the chance of early elimination of the deadly neurotoxin, mercury. Mercury might be the culprit in genesis of this disease from in utero transfer of the chemical from the asymptomatic mother who got

her overloaded mercury from daily fish consumption.

Rational Approach to Management and Prevention of Autistic Spectrum Disorder

In the recent decade, the incidence of autism has risen dramatically worldwide. Environmental factors have been blamed for this phenomenon, but practical means to reverse this trend have been elusive. As autism is usually diagnosed between two to three years old, there is a therapeutic window for regaining normal neurological function through toxic elimination, nutritional supplementation, and immune modulation. From the author's experience, the prognosis of radical cure from autism depends on the age of therapeutic intervention. The younger these children are started on this therapeutic regime, the higher the chance of cure, and the shorter would be the duration of therapy. The main reason is the inherent plasticity of the children's brain. The younger the patient is started on this therapy, the higher the potential of the brain to repair the toxic damage. Toddlers before three years of age presenting with delayed speech, impulsivity, and hyperactivity would be particularly responsive to this therapeutic regimen of detoxification and nutritional supplementation.

Almost all autistic children present with severe allergies, especially the IgG food allergies. The most frequently encountered allergic foods are cow milk proteins, wheat, and egg. This allergic tendency is partially responsible for the neurocognitive dysfunction of the autistic. The management to reverse the allergy is through food abstinence, administration of enzymes, probiotics, and the use of intravenous gamma globulin therapy.

Adjunct therapies to facilitate rehabilitation of these autistic children are hyperbaric oxygen and energy therapy. Acupuncture and neurofeedback are useful to expedite recovery.

Intravenous detoxification of the mother has been carried out to prevent autism from recurring. Ideally, the mother should undergo detoxification before contemplating pregnancy. In practice, this chance of detoxification is frequently overlooked. Dozens of pregnant women have been given intravenous nutritional and detoxification treatment with no adverse effects. In all of them, autism has been prevented, and most of the babies who have undergone intrauterine detoxification show advanced neurodevelopment and superb physical health. From the experience of treating pregnant women to prevent autism, another observation is the prevention of severe allergies of the fetus in utero. This is accomplished through provision of a nontoxic and nutritious intrauterine environment to the fetus. This phenomenon testifies to the fetal origin of adult diseases and the mechanism of epigenetics.[3] Further research on a larger scale would be imperative to restore the health of our next generation.

Conclusion

The increasing global population and industrialization in modern times have led to a fast degradation of the environment with pervasive pollutants. The continuing stockpile of these pollutants in the biological systems and its ultimate adverse effects to human health have been daunting. However, this alarming phenomenon has not been appreciated by the government and medical arena. The silent chemical brain drain, related to the ubiquitous environmental pollution, has been described by Dr. Philippe Grandjeans. The world is still skeptical of this entity; but from the author's perspective, this is authentic – and the trend would be fast worsening. Reformation of the healthcare paradigm with integration of nutritional and environmental detoxification would be imperative. The emerging science of epigenetics[3] and nutrigenomics would best be utilized to stem the relentless rise in incidence of non-communicable diseases. Epigenetics stands for the modification of genetic expression by manipulating environmental factors while nutrigenomics is the study of the effects of different food constituents on genetic expression. Nutrigenomics has the potential for preventing, mitigating, or treating chronic diseases. There are political hurdles in introducing this treatment paradigm into the healthcare system. The heavy reliance on pharmaceuticals with a vested financial interest of patented pharmaceuticals would impede the propagation of this innovative disease management plan. Nutriceuticals, even if effective in curing diseases, would not be published after formal research as they cannot be patented. Clinical metal toxicology is a specialty unfamiliar to most medical doctors, and its efficacious potential in abating most chronic diseases has never been appreciated as a useful tool.

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Testing Updates in Women's Health

by Tori Hudson, ND

Predicting Age of Menopause Onset

Current methods of predicting final menstrual period (FMP) are not very accurate. They can only predict final menstrual period to within four years. These methods include measuring menstrual bleeding patterns and follicle stimulating hormone (FSH). Measuring FSH indirectly measures ovarian reserve; but levels vary widely across the menstrual cycle, and even within a given day.

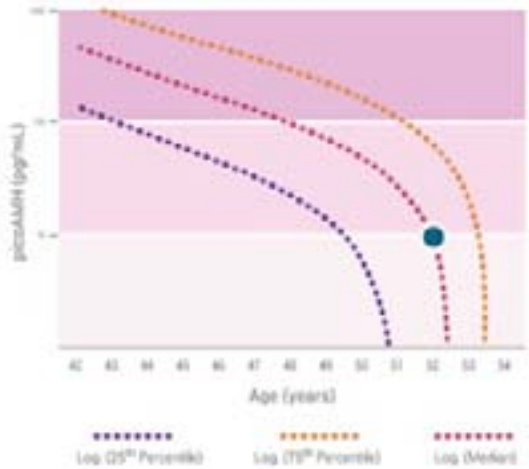
Anti-mullerian hormone (AMH), produced in the ovarian follicles, slowly but continuously decreases as the number of follicles declines. AMH generally stays stable and is also increasingly being used although previous tests have not been very precise; however, a new ultrasensitive AMH test that is providing a much lower detection limit is considered more accurate (1.85 pg/mL, compared with 50 to 100 pg/mL).

Lower serum AMH levels, high serum FSH levels, and low antral follicle count (AFC) are associated with the onset of menopause; but it is unclear which of these measures or combination of measures best predicts menopause. In the updated 2011 STRAW + 10 analysis of newer studies, the authors deemed cycle day 3 FSH levels greater than 25 IU/L characteristic of the late menopause transition and associated with onset of menopause within one to three years.

The 2013 analysis of the CARDIA women's study showed that an antral follicle count of 4 or lower independently predicted menopause within seven years.

In another study, Nair and colleagues showed that an AMH of less than 0.5 ng/dL was independently associated with natural menopause.

The AMH test is one of the most common hormones used in estimating a woman's fertility and is often used during fertility treatments like in-vitro fertilization (IVF). The level of AMH measured for that purpose (measured in ng/mL) is often 1000-fold higher than the levels measured by the ultrasensitive test in order to determine the time to final menstrual period.



AMH Conc. pg/mL	Menopausal Status	Time to final Menstrual Period (FMP)
>100	Pre Menopause	>5 Years to FMP
99.9-10	Peri Menopause	<5 Years to FMP
<10	Post Menopause	At FMP or Later

It took the SWAN study (Study of Women's Health Across the Nation), which followed the same women year after year from well before menopause until well after, to get the data necessary to be able to demonstrate the predictive value of AMH. Results showed that the ultrasensitive AMH test had significantly better accuracy for predicting final menstrual period within the next two years compared to FSH, as well as the next three years.

For women with an AMH <10 pg/mL, the probability of having a final menstrual period in the next 12 months ranged from 51% for those younger than 48 years to 79% for those aged 51 years or older.

If AMH <10 pg/mL, the probability of having a final menstrual period (FMP) in the next 12 months ranged from 51% for those <48 years old to 79% for those aged 51 years or older.

For 36% of samples, AMH levels were <10 pg/mL. The sensitivities for having a FMP with an AMH <10 pg/mL ranged from 71% for women younger than 48 years old to 82% for women aged 51 years or older. For these age groups, positive predictive values ranged from 51% to 79%.

For 38% of samples, AMH levels were >100 pg/mL: 65% for women younger than 48 and 27% for women aged 51 or older. The specifics for not having a FMP in the next 12 months ranged from 65% for women <48 years old to 27% for women 51 or older. For these aged groups, the negative predictive values ranged from 97% to 90%.

The level of AMH fluctuates much less over the course of menstruation than FSH, LH, estrogen, and progesterone, so

it won't change much based on which day you took this test. The chart (p. 48) shows typical changes in AMH levels with age.

Does Screening Mammography Reduce Breast Cancer Mortality??

According to this Australian study covering the last three decades, it looks like the answer is "no." Rather, it is adjuvant therapy for breast cancer patients that reduces mortality. Breast cancer screening's primary goal is to identify women with early breast cancers, stages I or II. The principle is based on the assertion that early detection and thus early treatment results in reduced incidence of advanced malignancies and thus, saves lives. The results of this study seriously challenge that paradigm. In addition, other studies in the last few years, have resulted in changes in screening guidelines as well as confusion and differences in recommendations amongst different organizations.

The current study assessed the relative influences of screening mammography and adjuvant therapy on breast cancer mortality trends by analyzing data from cancer registries and mammographic results for 76,630 women with invasive breast cancer in an Australian region that offers screening every two years for women ages 50-69 over a period from 1982 through 2013. In that age group, screening rates increased from 48% in 1994 to 57% in 2012. By 1999, they report that 74% of women with early stage breast cancers were receiving tamoxifen and the use of adjuvant chemotherapy was 72% for premenopausal women and 29% for postmenopausal women. In the time period of the study, breast cancer mortality fell from 32 per 100,000 in 1982 to 24 per 100,000 in 2013. Unfortunately, the incidence of advanced breast cancer rose from 12 per 100,000 in 1986 to 24 per 100,000 in 2013.

Commentary: It has been generally presumed for decades that screening mammography and early detection of breast cancer plays an essential role in the declining mortality of breast cancer. However, important studies in the US in 2012 (*NEJM* 2012 Nov 22; 367:1998, and *NEJM* 2012;367:1998) and in the Netherlands (*BMJ* 2017;359:j5224) actually found that the incidence of advanced breast cancer was stable or increased after screening mammography was introduced. The researchers of the current Australian study concluded that the reduced mortality from breast cancer in women in that region can be entirely due to the increased utilization of adjuvant therapy and that the increase in the incidence of advanced breast cancer rules out a direct association of mammography screening with a decline in mortality. They then proposed a radical shift in medical practice and that government-sponsored programs for screening mammography be discontinued.

This evolving story of the value of screening mammography and resulting guidelines will continue to slowly change based on a more individualized approach.

This evolving story of the value of screening mammography and resulting guidelines will continue to slowly change based on a more individualized approach, taking into account age and other distinguishing, known breast cancer risk factors such as first degree relative with a history of breast cancer, pregnancy/birthing history, hormone therapy, alcohol, exercise and weight history... and maybe eventually, even nutrition.

Burton R, Stevenson C. Assessment of breast cancer mortality trends associated with mammography mortality trends associated with mammographic screening and adjuvant therapy from 1986 to 2013 in the State of Victoria, Australia. JAMA NetwOpen 2020 June 1;3:e208249.

Diagnosis of Subclinical Hypothyroidism in Pregnancy

The threshold for diagnosing subclinical hypothyroidism in pregnancy during the first trimester is thought to be a thyroid stimulating hormone (TSH) value of >2.5 mIU/L (with a normal T4 level) by most organizations, although not all.

Investigators in Poland wanted to know if this approach and thus prescribing of prescription T4 was inaccurate. Baseline serum levels of free T4, free T3 and TSH every 30 minutes for a two-hour period during the morning time was conducted in 110 pregnant women, with an average gestation of 9.9 weeks, and 19 non-pregnant women of a similar age and body mass index.

TSH levels in the pregnant women averaged 1.6 mIU/L but varied by about 40%. The mean TSH levels and variation were similar in the pregnant vs the nonpregnant women. The number of pregnant women with a TSH >2.5 ranged from 12.7% (based on the lowest of 5 consecutive TSH measurements) to 20.9% (the highest of 5 consecutive measurements).

Commentary: While we do not know about the assays being used, the results are an important reminder that the secretion of TSH is pulsatile and using diagnostic cutoff values can be misleading. None the less, untreated hypothyroidism during the first and third trimester, in particular, is potentially harmful to the fetus and resulting child. I would refer people to clinical guidelines in managing subclinical hypothyroidism with special attention to the recurring need and timing of f/u TSH testing. In addition, low dose prescribing of T4 to pregnant women with suspected subclinical hypothyroid carries very little risk as long as testing and adjusting of dose is scrutinized. At the same time, it should be pointed out that thyrotoxicosis as well as subclinical hypothyroid during pregnancy can have adverse pregnancy outcomes and adverse effects on infants and children born to mothers with unmanaged or poorly managed thyroid disorders

Lewandowski K, et al. Subclinical thyroid dysfunction in the first trimester of pregnancy: Disease versus physiological (pulsatile) variation in TSH concentrations. Clin endocrinol (Oxf) 2020; May 19; e-pub.

Colposcopy and Cervical Pathology Guideline Changes

In 2019, the American Society for Colposcopy and Cervical Pathology (ASCCP) revised their prior guidelines moving from result-based to risk-based

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management recommendations for HPV and cervical dysplasia. Below is a summary of these changes as published in the Perkins, et al paper of April 2020. The purpose of the updated management guidelines are the following:

- Allow for a more complete and precise estimation of risk
- Provide more appropriate intervention for high-risk individuals
- Recommend less intervention for low-risk individuals
- Allow for additions of new risk modifiers, screening and management technologies in the future

The summary that I share here does not address primary natural treatment methods or adjunct natural treatment methods.

Essential Changes from Prior Management Guidelines

1. Recommendations are based on risk, not results.
   - Recommendations of colposcopy, treatment, or surveillance will be based on a patient's risk of CIN3+ determined by a combination of current results and past history (including unknown history). The same current test results may yield different management recommendations depending on the history of recent past test results.
2. Colposcopy can be deferred for certain patients.
   - Repeat HPV testing or co-testing at one year is recommended for patients with minor screening abnormalities indicating HPV infection with low risk of underlying CIN 3+ (e.g., HPV-positive, low-grade cytologic abnormalities after a documented negative screening HPV test or co-test).
3. Guidance for expedited treatment is expanded (i.e., treatment without colposcopic biopsy).
   - Expedited treatment was an option for patients with HSIL cytology in the 2012 guidelines; this guidance is now better defined.
   - For non-pregnant patients 25 years or older, expedited treatment, defined as treatment without preceding colposcopic biopsy demonstrating CIN 2+, is preferred when the immediate risk of CIN 3+ is ≥60%, and is acceptable for those with risks between 25% and 60%. Expedited treatment is preferred for nonpregnant patients 25 years or older with high-grade squamous intraepithelial lesion (HSIL) cytology and concurrent positive testing for HPV genotype 16 (HPV 16) (i.e., HPV 16–positive HSIL cytology) and never or rarely screened patients with HPV-positive HSIL cytology regardless of HPV genotype.
   - Shared decision-making should be used when considering expedited treatment, especially for patients with concerns about the potential impact of treatment on pregnancy outcomes.
4. Excisional treatment is preferred to ablative treatment for histologic HSIL (CIN 2 or CIN 3) in the United States. Excision is recommended for adenocarcinoma in situ (AIS).
5. Observation is preferred to treatment for CIN 1.
6. Histopathology reports based on Lower Anogenital Squamous Terminology (LAST)/World Health Organization (WHO) recommendations for reporting histologic HSIL should include CIN 2 or CIN 3 qualifiers, i.e., HSIL (CIN 2) and HSIL (CIN 3).
7. All positive primary HPV screening tests, regardless of genotype, should

Glossary and Definitions

Atypical glandular cells (AGC)

Atypical squamous cells of undetermined significance (ASC-US)

Atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H)

Cervical intraepithelial neoplasia (CIN)

CIN 2+: CIN 2, CIN 3, AIS, and cancer

CIN 3+: CIN 3, AIS, and cancer

Co-testing: screening or surveillance performed with the evaluation of both cytology and testing for HPV

Excisional treatment: procedure to remove transformation zone and produce tissue sample for histologic evaluation. Excisional treatment options may include lip electrosurgical excision procedure (LEEP), large loop excision of the transformation zone (LLETZ), laser cone biopsy, or cold knife conization.

High-grade squamous intraepithelial lesion or worse (HSIL)

Human papillomavirus (HPV). While there are over 100 varieties of HPV, those with oncogenic potential are of primary concern and at present include the following: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Low-grade squamous intraepithelial lesion (LSIL)

Negative for Intraepithelial lesion or malignancy (NILM)

Primary HPV testing: screening or surveillance performed with HPV testing only

Reflex testing: ASCCP defines reflex testing to mean "that laboratories should perform a specific additional triage test in the setting of a positive screening test to inform the next steps in management. For example, an ASC-US cytology should trigger a reflex HPV test. New for these guidelines, a positive primary HPV screening test should trigger both a reflex genotyping test (to determine the presence/absence of HPV 16/18 if that information is not included in the initial primary test result) and also a reflex cytology test to determine whether the patient would be a candidate for expedited management."

Surveillance: ASCCP defines surveillance as "repeat testing (HPV primary screening, co-testing, or cytology alone) that occurs at shorter intervals than those recommended for routine screening. For example, HPV primary testing or co-testing at intervals of less than 5 years, or cytology alone at intervals of less than 3 years."

have additional reflex triage testing performed from the same laboratory specimen (e.g., reflex cytology).
    - Additional testing from the same laboratory specimen is recommended because the findings may inform colposcopy practice. For example, those with HPV-16 positive HSIL cytology qualify for expedited treatment.
    - HPV 16 or 18 infections have the highest risk for CIN 3 and occult cancer, so additional evaluation (e.g., colposcopy with biopsy) is necessary even when cytology results are negative.
    - If HPV 16 or 18 testing is positive, and additional laboratory testing of the same sample is not feasible, the patient should proceed directly to colposcopy.
8. Continued surveillance with HPV testing or co-testing at three-year intervals for at least 25 years is recommended after treatment and initial post-treatment management of histologic HSIL, CIN 2, CIN 3, or AIS. Continued surveillance at three-year intervals beyond 25 years is acceptable for as long as the patient's life expectancy and ability to be screened are not significantly compromised by serious health issues.
    - The 2012 guidelines recommended return to five-year screening intervals and did not specify when screening should cease. New evidence indicates that risk remains elevated for at least 25 years, with no evidence that treated patients ever return to risk levels compatible with five-year intervals.
9. Surveillance with cytology alone is acceptable only if testing with HPV or co-testing is not feasible. Cytology is less sensitive than HPV testing for detection of precancer and is therefore recommended more often. Cytology is recommended at 6-month intervals when HPV testing or co-testing is recommended annually. Cytology is recommended annually when 3-year intervals are recommended for HPV or co-testing.
10. Human papillomavirus assays that are Food and Drug Administration (FDA)-approved for screening should be used for management according to their regulatory approval in the United States. (Note: all HPV testing in this document refers to testing for high-risk HPV types only).
    - For all management indications, HPV mRNA and HPV DNA tests without FDA approval for primary screening alone should only be used as a cotest with cytology, unless sufficient, rigorous data are available to support use of these particular tests in management.

Perkins, *et al*. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors, Journal of Lower Genital Tract Disease: April 2020 - Volume 24 - Issue 2 - p 102-131. doi:10.1097/LGT.0000000000000525

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She is a nationally recognized author, speaker, educator, researcher, and clinician. Dr. Hudson serves on several editorial boards, advisory panels and as a consultant to the natural products industry.

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Three New Scientific Theories to Explain Why Women Are More Susceptible to Autoimmune Disease Than Men

by Dr. Chad Larson, NMD, DC, CCN, CSCS

Advisor and Consultant on Clinical Consulting Team for Cyrex Laboratories

Although autoimmune disease (AD) affects both genders, women are at an overwhelming disadvantage. Of the approximate 8 percent of the population affected by AD, a whopping 78 percent of those cases are women (NCBI).[1] The National Institutes of Health has officially designated autoimmune disease as a major women's health issue.

High levels of estradiol can trigger the onset of autoimmune disease.

Autoimmunity in and of itself is very complicated with more than 80 diseases under its umbrella. The rate at which AD affects women over men is no exception to the complexity of understanding this group of diseases. Through recent studies, scientists have found evidence to support three significant theories to explain why women are so greatly affected by AD compared to men.

Testosterone levels protect men. According to researchers at the University of Gothenburg, there is a link between the male sex hormone testosterone and protection against autoimmune diseases.[2] Men are generally more protected than women, who only have one-tenth as much testosterone. Their study confirmed that this hormone reduces the number of B cells, a type of lymphocyte that releases harmful antibodies. Testosterone suppresses the protein BAFF, which makes the harmful B cells more viable. Therefore, women don't benefit from the same protection against these B cells.

These findings support those of a previous study showing the link between varying levels of BAFF and systemic lupus erythematosus (SLE), an autoimmune disease that affects nine women for every one man. Lupus is one of the most common autoimmune diseases among women.

Skin. Perhaps one of the most interesting findings was uncovered in a study at the University of Michigan three years ago. Researchers discovered that women carry more of a molecular switch, called VGLL3, in their skin than men do. In 2019, further research pointed to evidence showing that having too much VGLL3 in skin cells pushes the immune system into overdrive, leading to a "self-attacking" autoimmune response that can extend beyond the skin, also attacking internal organs.[3]

The same gene expression-level changes in skin cells with extra VGLL3 are also seen in autoimmune diseases such as lupus. It is still not known why women have more VGLL3 in their skin than men. However, men with lupus do show the same VGLL3 pathway activated as in women with lupus.

"The Pregnancy Compensation Hypothesis" and hormones. The idea behind this theory is that a woman's immune system evolves to support the heightened need for protection during pregnancy. According to Melissa Wilson, PhD, and senior author of a study conducted at Arizona State University, reduced pregnancy rates in today's modern, industrialized societies means women's immune systems don't have the reproductive challenges they are meant to stand up against.[4] These changes in the reproductive ecology of women makes them more susceptible to autoimmune disease because immune surveillance is heightened.

Furthermore, results from the study concluded that due to a more sedentary lifestyle in modern society, an overabundance of calories supports greater amounts of the female hormone estradiol. Maintaining such high levels of hormones can trigger the onset of autoimmune diseases. So not only do men get protection from AD with their higher levels of testosterone, but women have increased risk of AD due to higher levels of estradiol, thus widening the gap of AD in men versus women.

There is still so much to learn about autoimmune disorders, especially with the various types of diseases being categorized as autoimmune-related. Scientists do know that some of the highest risk factors of AD include genetics, environmental factors, lifestyle and even prior infection. But newer findings, especially those discussed here, suggest that simply being female puts you at higher risk for AD, with lupus seemingly at the top of the list.

Interestingly, a multitude of auto-immune diseases present some of the same early signs, including the following:

- Skin rashes, itchiness or flakiness
- Fatigue
- Rapid weight gain or loss
- Digestive tract issues
- Joint pain
- Swelling/Bloating
- Lack of focus
- Abdominal pain

If you or any women in your life suffer from any of these symptoms without an

identified, underlying cause, seeking the advice of a health care professional and medical testing should be considered. Cyrex Laboratories, a leader in advanced clinical testing, offers several screens for the detection of autoimmune-related reactivities. The Array 5 – Multiple Autoimmune Reactivity Screen™ is one of their comprehensive tests offered to measure predictive antibodies, some of which can appear up to 10 years before the clinical onset of disease. This groundbreaking test can help alert at-risk patients in time to stop the development of actual disease in some cases.

Preventative medicine is the best medicine, which is why symptoms should never be ignored. Taking control of your medical wellbeing through smart lifestyle practices, healthy eating, and regular physical exams can help you live your best life and prevent disease. Finally, it is important for women to understand how their bodies work, the unique health risks they are susceptible to, and protocols for optimal health.

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Guest Editorial | Guest Editorial | Guest Editorial

What Has US Medicine Got Against Vitamin C?

It is realized that most readers of the *Townsend Letter* will not find what is written here particularly new. But the title question is asked honestly. What follows just makes the necessity of asking the question even more obvious.

It was printed somewhere in the past that most medical physicians receive one to two hours of instruction on nutrition in medical school. Hopefully that has changed in more recent years, but it doesn't seem to show.

When studying "vitamins," it is emphasized that they are called that because they are essential for life. That is, the animal or person who does not receive any one vitamin, dies of the extreme deficiency.

There is a large body of knowledge on the conditions resulting from sub-optimal intakes of vitamins. Scurvy as a result of vitamin C deficiency is the famous example known to most persons. Perhaps the most important piece of information about vitamin C is under emphasized, as it is neglected by physicians and unconsidered by the general population.

That critical information is that humans are one of the very few mammals, along with only a couple of species of birds, that do not make their own vitamin C. It was once called a "fatal genetic flaw."

Vitamin C is used in human biochemistry in a variety of ways. Among them is its requirement for formation of the connective tissue that holds all our parts together. It is a necessary antioxidant. It is the agent that white blood cells use to kill engulfed bacteria. The Chinese have recently shown the world that intravenous vitamin C greatly aids survival in severe COVID-19 infection. Biochemical reasons for that shouldn't surprise anyone in medicine.

Pets and other animals in the US seem healthier than the human population. A likely reason is that if one's dog gets an infection, the dog's system makes more vitamin C and gets over it. The so-called superior brain of a human is supposed to remind us to take more vitamin C and frequently, so as to keep the level high until the problem is subdued. Somehow most persons don't understand this, and physicians rarely give the advice.

Which brings back the title question and the wonder how most physicians and most of the population manage to forget vitamin C. Historically it was used for many serious viral infections, and today intravenous vitamin C is used as adjunctive therapy for cancer in doses as much as 100 grams over three to four hours with proper evaluations beforehand. Any argument that it is dangerous is ridiculous. How many pharmaceuticals could be given at 100 grams without killing someone?

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Functional Diarrhea

by Julie Rhodes

Chronic diarrhea can be a severely debilitating condition and a common chief concern prompting patients to seek medical attention. The American College of Gastroenterology defines chronic diarrhea as loose or watery stool lasting longer than four weeks.[1] Persistent diarrhea lasts between two to four weeks, and diarrhea lasting less than two weeks is considered acute.[1] Acute and persistent diarrhea typically result from infection (eg, parasites, bacteria, and viral) or ingestion of osmotic substances and are both often self-limiting, whereas chronic diarrhea is more challenging to diagnose and persists unless therapy is initiated.[2-4] A broad differential diagnosis enables practitioners to avoid missing common etiologies; and the likelihood of identifying the root cause(s), whether structural, functional, or infectious, significantly increases when combined with a systematic history and clinical reasoning of physical exams and labs. However, diagnostic work-up and lab testing can become costly and complicated, increasing the risk of delayed or improper treatment. Chronic diarrhea can differ in etiology for pediatric, adult, and geriatric patient populations. Lab testing and treatment approaches should be chosen based on age, history, stool patterns, and characteristics of the disease process.[3] This essay aims to inform readers of the recommendations outlined in the most recent guidelines for diagnosing chronic diarrhea, review some unique etiologies of chronic diarrhea to have on the differential, and describe a few approaches to therapeutic intervention.

The American Gastroenterology Association (AGA) and the British Society of Gastroenterology (BSG) recently published guidelines to help clinicians choose appropriate investigative lab tests and treatment approaches when patients present with chronic diarrhea. The goal is to enable more primary care clinicians to better support patients with this chief concern, mitigate the financial strain of unnecessary testing, provide timely diagnosis and treatment, and reduce specialist burden.[5,6] Focusing the differential begins with a thorough interview, physical exam, and preliminary testing. Characteristic alarm features warranting colonoscopy or flexible sigmoidoscopy include diarrheal onset after age 50, melena or hematochezia, nocturnal pain, progressive abdominal pain, unexplained weight loss, and family history of colorectal cancer.[5] Asking patients to report the quality of their stool based on the Bristol Stool Form Scale, whether they notice blood, mucus, or undigested food, and the frequency of episodes will help the clinician characterize the stool pattern into infectious, inflammatory, fatty, or watery, with secretory or osmotic subtypes.[3] Inquiring about stool changes over time, and a dietary history, will also provide useful information for narrowing the differential and focusing testing.

The AGA and BSG are closely aligned in their recommendations for the clinical work-up of chronic diarrhea. Basic blood work for all patients should include CBC, electrolytes, glucose, liver function tests, thyroid function tests, and hematinics (B12, folate, ferritin).[7] When stool pattern implicates infection, *C. difficile* and *Giardia* are the two most common culprits that testing should target. Casting a wider net to identify other pathological species of parasites, protozoa, bacteria, viral agents, and helminths is dependent upon a patient's history of travel or immigration, and immunocompetency.[5,6] An inflammatory stool pattern warrants lab evaluation of fecal calprotectin (threshold value of 50 µg/g to optimize sensitivity for IBD diagnosis), fecal lactoferrin (threshold value of 4.0-7.25 µg/g to optimize sensitivity), as well as a celiac panel that includes IgG and IgA tissue transglutaminase, IgG or IgA deamidated gliadin, and total IgA (patients must be eating gluten for this test to be reliable).[5,6]

Chronic diarrhea may also be the consequence of an enzyme deficiency, bile salt malabsorption, certain medications, or unintentional chronic overuse of magnesium supplementation. Certain etiologies will present with specific stigmata, whereas some may be less obvious, and many may even overlap. Disaccharidase deficiency can be a congenital or acquired disorder of carbohydrate maldigestion, existing on a spectrum of enzymatic functionality of the various disaccharidases, mimicking IBS symptomatology of abdominal pain and osmotic diarrhea.[8,9] Disaccharidases include lactase, sucrase, palatinase (isomaltase), and maltase, all of which are brush border enzymes located in the duodenum and proximal jejunum, areas at higher risk of mucosal injury.[8,9] The challenge for clinicians is to figure out which enzyme(s) are not functioning and treat accordingly with diet and enzyme repletion.

Much of the data on congenital sucrase-isomaltase deficiency (CSID) is found in the pediatric literature. Seven different CSID phenotypes have been identified with lactase deficiency dominating in incidence (15-80%), followed by the overlap of lactase and sucrase deficiency, and pan-disaccharidase deficiency the second most common disaccharide deficiency

(8% incidence).[8,9] These studies add to the evidence in support of the underestimation of CSID in the general US population. The gold standard for diagnosis, the Dahlqvist method, entails quantitative measurement of liberated glucose from hydrolyzed discrete enzyme substrates on biopsied tissue that has been frozen immediately following removal to prevent enzyme degradation.[8,9] Stable isotope-labeled breath testing is a less invasive technique for diagnosing CSID, and includes carbon-13-labeled starch and carbon-13-labeled sucrose as substrates.[10] This form of testing has been shown to be effective for revealing overlapping disaccharidase deficiencies, informing clinicians in recommending the removal of one or multiple disaccharides from the diet and supplementing specific digestive enzymes for children or adults presenting with chronic diarrhea and abdominal pain.[10]

Pancreatic exocrine insufficiency (PEI) and bile acid diarrhea (BAD) are two additional conditions to keep on the radar when patients present with steatorrhea. These conditions have unique fingerprints that can be useful to differentiation them from each other and other possible causes of chronic diarrhea. PEI can be associated with a variety of conditions affecting the pancreas, including insulin-dependent and insulin-independent diabetes, celiac disease, chronic pancreatitis, pancreatic cancer, and surgical intervention at the pancreatic-gastrointestinal interface.[11] The typical presentation is characterized by abdominal pain, steatorrhea, flatulence, and bloating.[12] Patients with PEI often change their diet to reduce the experience of steatorrhea, masking the presence of this condition, which highlights the importance of asking about restrictive eating patterns and the consequences of eating without such caution.[12] Emulsification of fats begins in the upper gastrointestinal tract with mastication and gastric mixing of food with lingual and gastric lipases. Pancreatic enzymes are essential for proper fat digestions and include lipase, colipase, cholesterol esterase, and pancreatic bicarbonate. Fat maldigestion can be a result of inadequate production, insufficient secretion, limited activation, inactivity of these enzymes, or structural changes to the GI tract following surgery that can lead to asynchronization in enzymatic release and passage of nutrients (pancreaticocibal asynchrony).[12] Fecal elastase-1 and fecal chymotrypsin are noninvasive tests that are fairly inexpensive but may have limited diagnostic accuracy in patients that have undergone pancreatic surgery, which has an estimated prevalence of PEI ranging from 46-100%.[12] After recognizing the signs and symptoms, clinicians can either choose to run testing to confirm the presence of this condition, or treat empirically with trials of a few different types of pancreatic enzymes containing lipase, amylase, and protease. Plant-based enzymes, derived from the fungus Aspergillus, are active in a wide pH range (about 2-12) and can therefore act effectively for the patient with hypo- or hyper-chlorhydria when taken at the beginning of a meal. Animal-based enzymes are derived from pork pancreas and are active within a narrower range closer to a basic pH. Their metabolic action begins once the gastric contents enters the duodenum, therefore taking these at the end of a meal will maximize exposure to consumed food. It is important to note that enteric-coated, pork-based enzyme supplements may contain unwanted excipients, such as phthalates, polyethylene glycol, talc, carrageenan, and carnauba wax, which may be a concern for patients and practitioners. The type of enzyme and dosage should be adjusted to optimize supplement effectiveness and bring about symptomatic relief.

Bile acids (BAs) are underappreciated in their function within the cycle of fat digestion and absorption, but their biochemistry and "lifecycle" is fascinating and dependent upon the coordinated efforts of liver hepatocytes, the microbiome, and ileal enterocytes. Bile acids are synthesized within the liver from the conjugation of cholesterol with taurine or glycine to form the primary BAs chenodeoxycholic acid (CDCA) and cholic acid (CA).[13] Under normal conditions, BAs pass through the duct system that connects the liver and gallbladder to the duodenum via the sphincter of Oddi, where they accumulate to a critical concentration that enables the formation of micelles, which surround fatty acids and monoglycerides and facilitate transfer to enterocyte brush border membrane for absorption.[13] Once the BAs reach the terminal ileum, if all is well, they are 95% absorbed and taken up into enterohepatic circulation to return to the liver until their next adventure.[13] The co-regulatory relationship between the colonic microbiome and BA pool size and composition continues to be investigated, and has been suspected to play a role in the dysregulation of

Patients often change their diet to reduce the experience of steatorrhea, masking the presence of this condition, which highlights the importance of asking about restrictive eating patterns.

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the normal cycling of BAs through the digestive tract, contributing to the development and maintenance of BAD.[13]

The constellation of symptoms that patients experience when afflicted with BAD includes steatorrhea and watery diarrhea, fecal urgency due to accelerated transit time, and severe abdominal pain from the effects of BAs inducing colonic high amplitude propagated contractions.[13] BAD is classified based on causal factors, Type 1 is due to ileal dysfunction and impaired reabsorption commonly associated with Crohn's or ileal resection, Type 2 is idiopathic and absent of morphological abnormalities (BAM), Type 3 is caused by other GI disorders, such as SIBO, celiac or chronic pancreatitis, and Type 4 results from an excessive hepatic synthesis of BAs.[13] Testing for this condition may proceed with a trial of bile acid sequestrants or serology, including 7α-OH-4-cholesten-3-one (C4), serum FGF19, or selenium homotaurocholic acid test (SeHCAT. Not available in the US).[13,14] Serum C4 is a surrogate for hepatic BA synthesis rate, and an elevation in this measurement is indicative of BA malabsorption.[14] FGF19 is more of a screening tool for BAD and not yet fully validated for diagnostic purposes.[13] BAD and BAM are most frequently treated with bile acid sequestrants, rendering the choice of testing or empirical treatment up to the clinician and patient. Fat malabsorption can result in severe deficiencies of fat-soluble vitamins, contributing to a number of debilitating pathological conditions, which highlights the importance of recognizing these conditions and treating them accordingly.

Functional diarrhea is a diagnosis of exclusion when no objective underlying cause can be identified, which is rarely the case. The prevalence of functional diarrhea in the general population of resource-rich countries, including the US, is estimated to be anywhere from 1-5%, with more precise frequency being challenging to assess due to the lack of diagnostic distinction from IBS-D in epidemiological studies. Rome IV Diagnostic Criteria characterizes functional diarrhea as loose or watery stools in at least >25% of stools, without predominant abdominal pain or bloating, for at least six months, with active symptoms three months prior to diagnosis.[15] The consequences of not addressing this condition can be devastating to physiological homeostasis and include dehydration, nutrient deficiencies, and dysbiosis of the microbiome, all of which can lead to intestinal and systemic inflammation. The interaction of biological and psychosocial elements of altered motility, disruption in the gut-brain-immune system axis, ACEs and stress, genetics, and environment are suspected to factor into this condition's etiology and pathophysiology.[16–18] Dietary modification, psychotherapeutic intervention, various antidiarrheals, and when indicated digestive enzymes and bile acid sequestrant medications are standard of care treatments that provide a foundation for the adjunctive application of more targeted interventions.

Dysbiosis within the gut microbiome may be the cause and/or the consequence of diarrheal conditions, including SIBO, Crohn's, IBS-D, bile acid diarrhea, acute gastroenteritis, resistant *C. difficile*, and the use of antibiotics. Reducing populations of protective microbes such as *Bifidobacterium, Bacteroides, Lactobacillus, group D Streptococcus,* and *E. coli* can result in the proliferation of opportunistic pathogens to take their place, shifting the microbial-mucus-enterocyte interface towards increased permeability, activation of the local immune system, and a pro-inflammatory local and systemic state. Probiotics containing individual or combined strains of *Bifidobacterium breve Bb99, Bifidobacterium lactis B94, Lactobacillus rhamnosus GG, Lactobacillus acidophilus CL1285,* and *Saccharomyces boulardii* have been shown to rebalance the microbial ecosystem and modulate the microbiome-immune axis toward immune tolerance, reduced inflammation, and healthier stooling patterns.[19-21]

Diarrhea, dysbiosis, and reduced butyrate production have been linked to impaired intestinal mucosal integrity, poor nutrient absorption, and intestinal immune activation.[22–24] Butyrate, a short-chain fatty acid byproduct of microbial fermentation of dietary fiber, plays a crucial role in regulating colonocyte proliferation, gut barrier integrity, gastrointestinal motility, and modulation of local and systemic immune activity.[25–27] Butyrate levels can be elevated through

The Gary M. Weiner Memorial Scholarship in Integrative Gastroenterology

Gary Weiner, ND ('97), LAc ('05)

Gary Martin Weiner, ND, LAc, a graduate of the National University of Natural Medicine's naturopathic and classical Chinese medicine program, was a devoted and accomplished naturopathic physician. In 2001, alongside his wife, Ellen, he established Pearl Natural Health, an integrative naturopathic and Chinese medicine clinic in Portland, Oregon. Over the course of the past 22 years, his passion for medicine and his drive to help others only grew, expanding his contributions. He developed an integrative approach to treating his patients specializing in naturopathic gastroenterology and worked as a doctor and teacher to apply these principles for the benefit of his patients and peers. He was an esteemed member of the naturopathic community, a frequent speaker and writer on the treatment of inflammatory bowel disease, a beloved doctor to the many patients he inspired and helped, as well as a mentor to naturopathic students and residents.

The Gary M. Weiner Scholarship for Integrative Gastroenterology was established to promote the field of whole systems integrative gastroenterology and support a 4th, 5th, or 6th year naturopathic medical student who demonstrates academic excellence and dedication to the field of integrative gastroenterology.

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direct supplementation or the ingestion of non-starch polysaccharides (NSP).[24,28] NSPs are insoluble fibers that constitute fungi, seaweeds, and seeds, which may be a therapeutic strategy to enhance butyrate production, reduce diarrhea and constipation, and shift microbial populations within the gut by providing a source of nourishment for SCFA-producing bacteria. Advancements in natural product-based nanomedicine may improve the solubility, bio-availability, and localization to areas of the disrupted mucosal lining, enhancing NSP's therapeutic potential.[29]

Low-dose naltrexone (LDN) has a local and systemic impact on regulating inflammatory cytokines, therefore reducing inflammation within the GI and CNS compartments while also addressing the visceral hypersensitivity that may develop with chronic diarrhea.[30,31] LDN is similar in structure to endogenous endorphins and acts as a competitive opioid receptor antagonist.[30,31] By binding to Toll-like receptor 4, LDN sets off a signaling cascade that results in reduced TNF-α and IFN- α production.[30,31] LDN has shown effectiveness with few adverse side effects in treating IBD and other autoimmune conditions and may address the multi-system inflammatory effects of chronic diarrhea.[32] Therapeutic strategies that target the multi-factorial causes of functional GI conditions are essential as we continue realizing the interconnected nature of our psychophysiology and the microbes with which we have co-evolved.

Diarrhea is a symptom that may be part of a constellation of other objectively measurable physiological experiences, or the single distressing manifestation of a life severely impacted by covert stressors. Patients will seek care because they are experiencing embarrassment, anxiety, discomfort, or limitation of quality of life. A clear vision of the process for accumulating an accurate and informative history, practical physical exams, basic labs, and more specific ones when indicated is a set up for more effective diagnosis, management, and care coordination for patients presenting to primary care with chronic diarrhea.

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When not studying, she can be found hiking in the state parks scattered throughout the Pacific Northwest searching for fungi, snails, and birds, or snuggling up with her husband and three cats watching movies or documentaries.

COVID-19 Is Really Two Diseases – To Treat the Second One, You Have to Name It Correctly

by Daniel Cobb, DOM

COVID-19 starts out as an usually mild and rather benign viral infection. In conventional medicine, they either claim that "there is no treatment" or possibly use anti-viral pharmaceuticals. Then they wait for the virus to go away. Sometimes it works, and sometimes it doesn't in rather spectacular ways.

Those in the medical community have looked at the amputated limbs, the death count from fluid-filled lungs and blood clots, and they have set about trying to understand how a virus can cause all of this. Answers have been elusive. This is because the most damaging and deadly part of this syndrome is not caused by the viral infection. It is caused by the total depletion of blood levels of vitamin C.

The name of this second disease is "acute scurvy."

Scurvy in the Modern World

Most people think of scurvy as a disease of the past – before James Lind told the British Navy to keep limes on their ships. The common view is that, by the 19th century scurvy was nothing more that a subject in history books. But this is not true. Scurvy has always been with us. We are surrounded by scurvy without even knowing it, and the worst part of the COVID-19 crisis occurs because we simply can't believe that there is such a simple answer as taking vitamin C.

Vitamin C

In nutritional medicine, the definition of "vitamin C" varies. I want to be clear that my definition of vitamin C is L-ascorbic acid or any of the mineral ascorbates based upon L-ascorbic acid.

First I need to make a few points about vitamin C. Once vitamin C gets into the bloodstream, it has a half-life of about 30 minutes. It is gone in four hours.[1] The only place that vitamin C is stored in the body is the adrenal glands, and the amount that is stored there is mostly for use by the adrenal glands.[2]

Vitamin C has many uses in the body, but for the purposes of this article, I will highlight only three of them.

1. It fights infections. The white blood cells absorb the vitamin C, and as a result are able to spit hydrogen peroxide at the infecting microbes.[3]
2. Vitamin C is the body's number one antioxidant.[4] It neutralizes free radicals. Free radicals are atoms or molecules that are missing one or more electrons. They cause damage by stealing electrons from nearby atoms/molecules. This causes more free radicals. When vitamin C is acting as an antioxidant, it is neutralizing free radicals by donating one or two electrons without itself becoming a free radical.

   Free radicals are always being created in our bodies, but inflammation causes much higher levels of free radicals.[5] Infections cause inflammation. Therefore, a serious infection can generate troublesome levels of free radicals.
3. Vitamin C is used to create collagen fibers.[4] Vitamin C is not in the end product, but it is used to cross-link the fibers to make them much stronger and much more durable. Collagen fibers are, for example, found in skin, blood vessels, ligaments, tendons, cartilage, bones, and any tissue in the body that requires flexible strength.

Common Characteristics of a COVID-19 Infection

Many COVID-19 infections are of short duration and almost symptom-free.[7] However when this does not happen and the infection worsens, there are several common things that occur.

1. The most common dangerous symptom and cause of death is that the patient gets fluid in the lungs.[6] This limits the absorption of oxygen, and if this condition is not quickly reversed, it frequently results in death by the patient drowning in their own fluids.
2. The next most common dangerous symptom is diffuse blood clots.[8] At the beginning of the year, this was mostly found at an autopsy because it was an unexpected symptom, but now that it is more known in medical circles, it is more often found before death occurs. These blood clots are most often found in the small vessels. Of course, they can obstruct the flow of blood and cause serious problems anywhere they occur.
3. Most COVID-19 infections start off with a fever and the patient feeling a "just a bit" sick. They might think that they are going to have a mild case and be back to normal in a day or two. Many of these patients are better in a day or two, but not all of them. For those who do not recover quickly, there is very often a sudden worsening of their condition.[9]

How a COVID-19 Infection Affects Vitamin C Blood Levels

When you get a COVID-19 infection (or any infection for that matter), additional vitamin C is used to directly fight the

microbe. The worse the infection gets the more vitamin C is used for this purpose.

When you get a COVID-19 infection, there will be more inflammation in your body. This inflammation will generate more free radicals. Vitamin C will be used in greater amounts to neutralize these free radicals. As the infection gets worse, more and more vitamin C is used for this purpose.

Collagen and elastin fibers are constantly breaking down and being replaced. Vitamin C is being used in this process. The rate of usage of vitamin C for this purpose is not affected by the COVID-19 infection.

As long as the consumption of vitamin C remains at or close to the usage of vitamin C, then all Vitamin C functions will remain relatively "normal." However, as the infection continues, especially if the patient is not taking supplemental vitamin C, the requirements for vitamin C is likely to significantly exceed the supply. In this case, the blood levels of vitamin C will, for extended periods of time, be zero.

What Happens When Blood Levels of Vitamin C Are Zero?

The immune system will not be quite as effective in the absence of vitamin C. However, there are many other vitamins, minerals and plant-sourced molecules that are very useful in supporting the immune system. Your immune function will drop off a bit, but you will still be fighting the infection.

Your ability to neutralize free radicals will decrease in the absence of vitamin C. However, there are literally thousands of antioxidant molecules in a wide variety of foods. Your antioxidant capability will drop a bit, but you will still be neutralizing free radicals.

For the production of collagen fibers, there is no substitute for vitamin C. When vitamin C blood levels drop to zero, collagen fiber production drops to zero.[4]

In most cases, this is of little concern. Your skin might sag or wrinkle and your tendons and ligaments in your joints might not work as well if you tried to exercise. These problems are not life-threatening. However, there are two places in your body where collagen fiber production dropping to zero is life-threatening.

I will be making the case that the "significant downturn" that is common in COVID-19 patients directly follows when the vitamin C blood levels drop to zero. This is where we should acknowledge that there are two diseases in play. The first is the ongoing viral infection and the second is acute scurvy.

Collagen Fibers in the Alveolar Membrane

The alveoli are the location in the lungs at the end of the bronchioles. There is a very thin membrane around each of the alveoli.[10] This membrane has two purposes.

1. It is the location where gas exchange occurs. The CO2 needs to be passed from the body fluids to the lungs and the O2 needs to be passed from the lungs to the body fluids. This is via passive diffusion, and it needs to occur fast enough to keep us alive. To accomplish this, portions of this membrane need to be extremely thin.[10, 11]
2. This membrane needs to keep the body fluids on one side of the membrane and not let them into the air passages of the lungs. The only way to accomplish this with such a thin membrane is with the support of collagen fibers.[10]

Collagen fibers break down on a constant basis and need to be frequently replaced. Under normal circumstances, this is not a problem, but when the blood vitamin C levels drop to zero, this replacement stops. The alveolar membrane begins to weaken, and within a day or so becomes porous. Fluid starts to leak into the lungs, which inhibits the gas exchange.

This is the point at which ventilators become useful. They do get more oxygen into the blood, but they do not address the structural problem, which is the integrity of the alveolar membrane. In the absence of sufficient vitamin C, the membrane gets more porous, and in a few days, the patient drowns in their own fluids.

Collagen Fibers in Vascular Tissue

In a similar way, collagen fibers are important in the integrity of the walls of blood vessels. Their primary function is to keep the blood inside the blood vessel. The flexible strength of collagen fibers is a major part of this function.[12] These collagen fibers also need to be frequently replaced, and this is not normally a problem. However, when blood vitamin C levels drop to zero, the replacement of collagen fibers stops. The blood vessel walls become porous, and the result is bleeding. The normal response to bleeding is clotting.

COVID-19 patients are dying from connective tissue problems related to severe depletion of vitamin C levels.

The pathology of diffuse blood clots is that they impair blood circulation, oxygenation, the delivery of nutrients, tissue repair, and the removal of metabolic waste and CO2. Many COVID-19 deaths have resulted from these problems and their downstream effects.[8]

Current Medical Research on Blood Clots in COVID-19 Patients

Because the problem with diffuse blood clots in COVID-19 patients is a recently observed problem, it is only now getting the attention of medical researchers. There are research efforts going on across the globe. Most of these are still in process, but several have come out with preliminary results. The study results are that, yes, diffuse blood clots do commonly occur in severely ill COVID-19 patients. The recommendation is to use blood thinners to combat the blood clots.[13-15]

Of course blood thinners (anticoagulants) can address these blood clots, but when the cause of the blood clots tie back to bleeding caused by loss of integrity of the vascular walls, this constitutes a dangerous recommendation. The likely result would be a significant worsening of the bleeding and even more blood clots. From at least one source that I have found, this is exactly what is being observed.[16]

ARDS and DIC

My central premise in this article is that there are two stages in the progression of a COVID-19 disease scenario. The first stage is the plain infection. In the absence of multiple or severe underlying conditions (COPD, heart disease, etc.), it is unlikely to be life-threatening. The

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second stage is what happens when vitamin C blood levels start spending long periods at zero. What happens in the lungs and vascular tissue in this second stage has already been described as separate conditions. The fluid in the lung condition is named Acute Respiratory Distress Syndrome (ARDS).[6] The vascular tissue condition is named Disseminated Intravenous Coagulation (DIC).[17]

Because both of these conditions primarily occur in hospitals, they are not well known to the public; but hospital medical personnel are very familiar with them. There is an abundance of medical journal articles written on both of them. Looking through the available medical literature should easily confirm the correlation between DIC/ARDS and what happens in the advanced stages of COVID-19 disease.

The reason why DIC and ARDS are viewed as such mysterious and deadly diseases is a familiar problem. They should both be named "acute scurvy," but in an age where we believe that scurvy no longer exists, this has been difficult to do.

For background reading purposes, I want to direct you to my favorite two articles on DIC and ARDS. These are both found on the website of the Foundation for Alternative and Integrative Medicine. If you take the time to read them, you should read the DIC article first.

- DIC article link: https://www.faim.org/a-proposed-mechanism-for-disseminated-intravascular-coagulation.
- ARDS article link: https://www.faim.org/acute-respiratory-distress-syndrome-ards

Concluding Statement

COVID-19 is viewed as an infectious disease that has killed over 100,000 people in this country in the past few months. My purpose in writing this article is to point out that the infection, by itself, is killing only a small fraction of that total. What COVID-19 patients are dying from is connective tissue problems related to severe depletion of vitamin C levels. The key to reducing COVID-19 deaths is naming the disease correctly. If the second stage of COVID-19 were named "acute scurvy," then getting people to take 3 or 4 grams a day of vitamin C would be easy. With the current naming convention, vitamin C is viewed more as a distraction.

I have calculated the wholesale price of vitamin C recently based upon the retail purchase of vitamin C capsules from Swanson's Vitamins. For a gram dosage, the price comes out to be 4.3 cents. So, the material price in a hospital for the daily consumption of four grams ends up being just shy of 18 cents. I think it is rather surprising that, in most cases, you can provide more benefit to a severely ill COVID-19 patient with 18 cents worth of vitamin C that you can with a $50,000 ventilator.

Postscript

The COVID-19 infection stage can easily be prevented/treated/cured with the use of vitamin and minerals and a few other supplements. I like to use vitamins A, C, D, selenium, zinc, copper, iodine, and quercetin. Others may have different formulas that use herbs, homeopathic remedies, dietary recommendations, in addition to vitamins and minerals. All of these will also work. The COVID-19 infection is very easy to deal with through nutritional and alternative medicine. But that was not the subject for this article, so in a different document, I will address this other topic.

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Letters to the Editor

Correction: Selenium – Essential Comments on an Essential Nutrient

In my article "Adrenal Fatigue; Does it Exist?" which appeared in the *Townsend Letter* Issue #449 (December 2020), on page 40 there is an erroneous comment: "The only known enzyme function of selenium involves glutathione peroxidase." This comment is incomplete and misleading; it should have read: "Selenium is involved with the enzymes of thyroid metabolism, the enzymes of glutathione metabolism, and the enzymes of other multiple ancillary enzyme systems." The complexity and broad scope of this subject of selenium metabolism and its involvements is well beyond this allotted space.

For the reader who is interested in more on this broad and fascinating subject of selenium, it is suggested that he/she read the excellent review article: Fairweather-Tait SJ et al "Selenium in human health and disease." *Antioxidants and Redox Signaling.* vol 14 No. 7, 2011 (Mary Ann Liebert Inc, Publishers). Reader, please note that, in addition to the fine comprehensive text, this article's bibliography is a treasure trove of enlightenment gems.

Alfred V. Zamm, MD

Re: Testing for Magnesium Levels

I loved the adrenal fatigue article in the December 2020 issue. It emphasizes the importance of magnesium in optimal health. I was disappointed to see that the author, Dr. Alfred V. Zamm, mentioned that there was no way to easily check a patient's intracellular magnesium levels.

I have used the Exatest on my patients for many years now to tell me the levels of magnesium inside the cells. It would be an easy test any practitioner or their assistants can take in a few minutes.

This may be a test naturopaths or holistic practitioner can use to help patients obtain optimal health.

Blessings to you and the whole team.
Rev. Dr. Stephen A. Lawrence

Re: Gaby's December Editorial

Alan Gaby has done it again with his articulate and important editorial in the December 2020 *Townsend Letter.* Congratulations, Alan! Someday 20 or 30 years from now, people will look back, shake their heads, and wonder why doctors continued to not implement what you have been advocating for at least three decades.

I really suffer as I witness the continual malpractice occurring in American medicine because of the two points you eloquently make.

1. Allopathic mainstream medicine has such a long-standing (and uninformed) bias against nutritional therapies.
2. Allopathic mainstream medicine too often delivers substandard care by failing to embrace safe, effective, low-cost treatment options.

It reminds me of an experience I had in the 1990s when I was medical director at my hospital in Mankato, Minnesota. I had a "must-attend" meeting with the family physicians, pediatricians, and ENT doctors at our hospital. I presented to them three major studies from top-notch medical journals showing that a food-elimination diet (and especially dairy) could eliminate 80% of the need to place tubes in the ears of children with chronic serous otitis media. Tubes in the ears were a very common procedure done on at least a weekly basis in the winter.

Prior to that meeting with my colleagues, I had reviewed the history and physical of the previous 30 PE tube placement surgeries in our hospital. Not even ONE H & P had anything about food or food allergies in them. After my talk/seminar/lecture with those physicians involved in these cases, I waited a year and once again reviewed the PE tube placement surgeries in our hospital. Guess what? Once again, not even one H & P had anything about food allergies.

It was at that time that I began to feel sorry for all of us physicians. I believe that there is something in our seven or eight years of medical training that teaches us to not actually think for ourselves. Power corrupts and absolute power corrupts absolutely. We learn to take orders from our elders so we can make it through medica/osteopathic school and residency, but we then continue that same ingrained habit into our lifetime practices. Do what we were taught! Doing something a bit out of the box can be dangerous AND can get us in trouble.

So, swinging back to your article, Alan, we were all taught almost zero nutrition and zero low-cost, safe, natural treatments. Therefore, they do not exist! And that is so sad. Besides that, it is detrimental to our patients – and probably to us.

Bill Manahan

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Herbal Formulas for Migraines and Other Headaches

by Jill Stansbury, ND

The following excerpt is from Jill Stansbury's new book *Herbal Formularies for Health Professionals*, *Volume 4* (Chelsea Green Publishing, July 2020) and is reprinted with permission from the publisher.

Headaches are one of the most common medical complaints treated in general clinical practices and are a significant public health burden in terms of suffering, disrupted family interactions, and lost work and wages. Possible underlying causes of headaches include stress, hormonal influences, vascular inflammation, allergies, dysglycemia, exhaustion, chronic constipation and toxemia, and other phenomena. There are many formal classifications of headaches, and the research into the molecular mechanisms is too extensive to do justice to it in this text. It is the responsibility of the medical clinician to seek out the underlying cause to truly cure the condition and not just provide habitual pain relief. The triptans are the current "gold standard" pharmaceutical for migraine therapy but are effective in only 30 to 70 percent of users, depending on the criteria used to define success.

Triptans such as sumatriptan (Imitrex) are serotonin agonists that promote vasoconstriction to help correct excessive vasodilation but will elevate liver enzymes with regular use. Methysergide has been shown to cause fibrosis of retroperitoneal organs as a side effect. The nonsteroidal anti-inflammatory analgesics, such as aspirin, acetaminophen, and ibuprofen are relied on by the general public and readily available but are appropriate only for occasional use because of concerns of renal and hepatic damage with chronic use.

Acetaminophen, in fact, is a dangerous drug, despite its over-the-counter availability. These pain relievers may also worsen leaky gut and actually increase the occurrence of headaches in those with toxemia and allergic phenomena. Hence, the use of general vasodilating and salicylate herbs, as well as other specific herbs named in this chapter, may be the safest options for treating headaches, especially when combined with dietary, stress-relieving, detoxifying, and antiallergy approaches as specifically indicated.

Food allergies and exposure to mold and toxic environments may also result in chronic headaches. Anti-inflammatory diets and an investigation of work and living environments may be warranted in such cases. Chronic tension headaches are associated with sleep disturbances and sleep apnea, and efforts to improve sleep quality are important. A thorough history and intake can typically diagnose the specific type of headache and suggest the most appropriate herbal treatment.

Migraines are not hard to diagnose and in fact are impossible to miss as a result of the visual disturbance, acute intense onset, accompanying nausea and vomiting, and often a marked spot location or one-sidedness. A combination of addressing underlying contributors (stress, hormonal influences, vascular inflammation) and using specifically indicated herbs as listed at the end of this chapter will often alleviate chronic migraines and tension headaches.

Common Types and Causes of Headaches

Migraines. Such headaches are due to vascular phenomena characterized by a preceding aura, one-sidedness, and rapid onset with throbbing and disabling pain; often accompanied by nausea and vomiting.

Cluster headaches. These headaches are associated with trigeminal autonomic dysregulation. The symptoms of cluster headaches include severe unilateral orbital or supraorbital or temporal pain that is associated with lacrimation, nasal congestion and rhinorrhea, facial sweating, miosis, ptosis, and eyelid edema.

Hormonal headaches. Hormonal changes in relation to the menstrual cycle can cause headaches that occur in a cyclical pattern.

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Herbal Headache Formulas

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Vascular headaches. High blood pressure or blood reactivity can increase intercranial pressure. Allergic headaches: Histamine-driven inflammatory cytokines can lead to inflammation in the brain. Rebound headaches: Cessation of use of acetaminophen, triptan, ergotamine, and other pain relievers can lead to this type of headache. Sinus headaches: Allergies and sinus congestion cause pressure in the face.

Stress, muscle tension. Tightening muscles in the shoulders, neck, and scalp may induce headaches. Dysglycemia: Low blood sugar and fast blood sugar reactivity can frequently cause headaches. Exhaustion: Fatigue, stress, and overwork can often provoke a dull headache.

Chronic constipation. Dysbiosis, inability to eliminate waste, and increased abdominal pressure as a result of chronic constipation can result in headaches.

Toxemia. Constipation and exposure to environmental toxins can lead to oxidative stress and inflammation.

Altitude. Travel to unaccustomed high altitudes can trigger dull to intense headaches.

Drugs. Many drugs have headaches as a side effect.

Dehydration: Hangovers and other causes of dehydration frequently cause headaches in the forehead area.

Caffeine withdrawal. Many daily coffee drinkers experience headaches upon abstinence.

Cervical subluxation. Bony displacements in the cervical spine can cause occipital and other headaches.

Herbal Therapies for Headaches

There are similarities between herbal therapies for migraines and those for tension headaches, but migraine formulas may require more vascular anti-inflammatories and mast cell stabilizing herbs, while tension headaches require nervine herbs and muscle relaxants. Salicylate-containing herbs, including *Salix* species (willow) and *Actaea racemosa* (black cohosh) can be helpful acutely, but unless specifically indicated may do little to reduce chronic headaches. Thus, it may be helpful to use two separate formulas – one acute and one chronic – in some cases to take advantage of the anodyne effects of fast-acting palliative herbs, complemented with a deeper acting long-term formula or protocol to correct hormonal imbalance, improve vascular inflammation, treat stress, and improve sleep. Drugs that reduce sympathetic stimulation of the vascular smooth muscle are commonly used to reduce blood pressure but may also be useful for migraines and heart palpitations where reducing stress-induced vascular tension is helpful. Reserpine in *Rauvolfia serpentina* falls in this category, as do various pharmaceutical drugs known as beta-blockers, such as atenolol, propranolol, and metoprolol, which block adrenaline cascades. In addition to *Rauvolfia*, herbs in this category include *Lobelia inflata*, *Leonurus cardiaca*, and *Tilia cordata*. These may be key herbs in formulas for those with chronic headaches concomitant with stress, hypertension, and possible tachycardia and panic attacks. Additional herbs for headaches due to stress and tension are *Piper methysticum*, *Passiflora incarnata*, *Valeriana officinalis*, *Piscidia piscipula*, and *Actaea*.

Compress for Headaches

Hot or cold showers, ice packs, or heating pads may be comforting to those with head pain, and headwashes (washing the head with an herbal tea) are traditional remedies for headaches in some parts of the world. This compress formula may complement any of the tinctures in this section and help speed pain relief; it can be combined with a hydrotherapy technique if desired. A time-honored method of reducing vascular congestion to the head is to place ice on the back of the neck and immerse the feet in hot water to pull blood downward and relieve some of the pressure.

- *Capsicum frutescens* powder: 2 teaspoons
- *Gaultheria procumbens* essential oil: 10 to 30 drops

Pour 2 cups boiling water over the *Capsicum* (cayenne) powder and let stand 10 minutes. Strain through a coffee strainer to remove the particulate, which can burn the skin if used in the compress. Fold a soft cloth to roughly four- or five-inches square, and soak in the strained cayenne tea. Shake the drops of oil onto the compress and apply to the nape of the neck and leave in place 20 to 30 minutes. Be sure to keep the compress liquid out of the eyes. The therapy may be complemented by placing an ice pack over the compress and placing the feet in hot water.

Tincture for Migraine Prevention

Some people experience only one or two migraines per year, which makes it difficult to justify the use of a regular preventive agent. However, at times when a person is experiencing migraines several times per week, the use of the following herbs may reduce the frequency and severity of migraines.

- *Tanacetum parthenium*
- *Zingiber officinale*
- *Petasites hybridus*
- *Scutellaria baicalensis*

Combine in equal parts and take 1⁄2 to 1 teaspoon, three or more times a day for several months, reducing to once a day for another several months. If the use of the tincture is effective, it may be taken in a cyclical fashion, such as one month on, one or two months off.

Tincture for Acute Headaches

Actaea and *Salix* both contain salicylates, and while aspirin can irritate and ulcerate the digestive mucosa, herbs that contain salicylates have not been shown to do so. In this formula, these herbs are combined with *Piper*, a powerful muscle relaxant, and *Rauvolfia*, a powerful vasodilator, to cover the bases for the most common causes of acute headaches. This formula is fairly all-purpose for acute migraines, tension headaches, or simple pain relief, and thus is a useful choice while a case is being evaluated or blood tests are being run.

- *Actaea racemosa*: 7 ml
- *Piper methysticum*: 7 ml
- *Atropa belladonna*: 2 ml
- *Salix alba*: 7 ml
- *Rauvolfia serpentina*: 7 ml

Combine ingredients in a 1-ounce bottle. Take 1 dropperful of combined tincture every 5 to 15 minutes at the onset of an acute headache, reducing as pain abates. ◆

Dr. Jill Stansbury is a naturopathic physician with 30 years of clinical experience. In 2019, she was awarded Order of the University for Excellence in Herbal Medicine. Dr. Stansbury lives in Battle Ground, Washington, and is the medical director of Battle Ground Healing Arts. She also runs an herbal apothecary featuring many of her own custom formulas. She is the author of *Herbal Formularies for Health Professionals, Volumes 1-4* (Chelsea Green Publishing).

Ask Dr. J

by Jim Cross, ND, LAc
thias1020@yahoo.com

Playing with Fire: The Pathophysiologic Effects Of Pollution

Many humans love to play with fire. Such a pyromaniac started a monstrous fire three years ago that fortunately didn't burn down my lovely mountain home and retirement villa atop my garage. The human race is also playing with a different type of fire that is environmentally induced. The title to this month's article was also the subject of the American Academy of Environmental Medicine's/AAEM's October conference. AAEM agrees with me that humans are actively destroying our wonderful planet's ecosystem. Fortunately, they also attempt to educate their members more thoroughly on this large topic through their conferences, attempting to counteract society's detrimental environmental effects on their patients.

First, who exactly is the AAEM. This is directly from their website:

> The American Academy of Environmental Medicine was founded in 1965 and is an international association of physicians and other professionals interested in the clinical aspects of humans and their environment.
>
> The Academy is interested in expanding the knowledge of interactions between human individuals and their environment, as these may be demonstrated to be reflected in their total health. The AAEM provides research and education in the recognition, treatment and prevention of illnesses induced by exposures to biological and chemical agents encountered in air, food, and water.[1]

Next, why even be concerned with environmental pollution. Our politicians, especially our present president, don't appear to be. The following is from AAEM's promo for this conference: "According to the EPA, more than three and a half billion pounds of toxic chemicals are released each year directly into the environment. One to two billion pounds of pesticides are used each year in the United States alone. These chemicals are now ubiquitous in our air, water, food, home and workplaces."[2]

In 2015, environmentally induced diseases were responsible for 9 million premature deaths, that is 16% of all global death. Exposure to contaminated air, water, and soil kill more people than war, AIDS, hunger, or smoking.[2]

Environmental pollution has been associated with respiratory and immune system diseases, development or exacerbation of cardiovascular diseases, impairment of intellectual and motor skill development in children, recurrent infections, development of type 2 diabetes, brain degenerative disorders, the increase of some cancers, and greater all-cause mortality. The health implications of long-term exposure to low levels of these compounds are not well understood by the medical community. Environmental medicine physicians have a superior ability to help their patients reduce the harmful effects of environmental factors, and this ability should be shared and underscored in every healthcare practice. **Pollution is the world's largest environmental threat to health.**[2]

Joseph Hickey, MD

Gervasio A. Lamas, MD

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Effects Of Pollution

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With me, they are preaching to the choir. I graduated from the University of California Davis in 1975 with a degree in biology whose focus was ecology. I also helped start the campus recycling program and helped to dramatically expand the campus community food garden. Unfortunately, capitalism doesn't care a whit about people or their environment, only about maximizing profits. AAEM's group of physicians and other health care professionals are interested in educating their members in the various aspects of environmentally triggered illnesses and cost-effective ways to understand, diagnose, treat, and prevent these disorders. Their members can then return to their clinics and begin educating the public in general. Optimally, this will trigger a tsunami of environmental education that can begin to transform the way Americans actually contemplate their day-to-day effects on the environment and how their environment can positively or negatively affect them in return.

There were three days of educationally stimulating talks, so I will concentrate on the ones I found most interesting, which of course doesn't mean the ones I don't cover weren't. Apologies to the speakers I didn't cover.

The first talk on Friday, 23rd October, was "Environmental Contaminants and their Association with Chronic Infectious Diseases, Diagnostic Management and Treatment Difficulty" by Pilar Munoz-Calero, MD, who works and lives in Spain and has organized nine international congresses of environmental medicine there. She emphasized a very important point: The failures in the treatment of new pathologies appear to be the result of overemphasizing the actual symptoms but not paying special attention to the causes of these novel diseases.

She showed in her lecture that there is a direct relationship between environmental xenobiotics – such as heavy metals/volatile organic compounds/electromagnetic radiation/etc., which weaken the immune system tremendously – and various autoimmune diseases and allergies. These diseases and allergies weaken the human body to the point where it is more vulnerable to the effects of pathogenic microorganisms. This creates the internal terrain for chronic, subtle, infections like Epstein Barr and Lyme's to gain a foothold and eventually disable the individual. To effectively treat this type of patient, she says you must return to the original bodily insult and reduce the toxic load before beginning to try to eliminate the microorganisms. This is also the method by which Eric Gordon, MD, treats his chronic tick-borne disease patients.

Another talk that caught my eye was "Principles of Hormone Action Apply to Environmental Endocrine Disrupting Chemicals/EDC's" by Frederick vom Saal, PhD. He apparently was way ahead of his time, as he initially recognized problems with EDC's in the early 1990s. He composed a very thorough list of our daily exposures to EDC's and multiple examples in each category plus a list of steroidal and xenobiotic estrogens.

Dr. Saal had some very interesting conclusions. One important takeaway was that very small changes in hormones during embryonic development can have life-long consequences on the expression of genes. He cited evidence that early EDC exposure will result in epigenetic changes that can lead to metabolic alterations, which will segue into various adult chronic diseases. For me, this is probably the most important information regarding the environment: its effect on fetal development. Just think how hard it is to go from one cell to an approximately 30-foot long GI tract with its various accessory glands, a four-chambered heart where all the valves open and close in a coordinated fashion to effectively pump blood, etc. This is one of the real miracles in life. To damage someone before they even have a chance to draw a breath is tantamount to the worst mortal sin I was taught in Catholic school. Everybody deserves to exit their mother in as perfect a shape as possible!

Next up was "Reducing Risk of Cancer from Exposure To Smoke: An Action Plan For Firefighters, First Responders, Residents Exposed To Wildfire" by Louise Tolzmann, ND. I thought this was a very important talk because whole communities like Paradise, California, and Talent, Oregon, are being consumed by infernos of fire. It isn't just trees and bushes that are being incinerated. She displayed a comprehensive list of toxic substances emitted by these fires:

- Toxic Gases (CO2; CO; NOx; SOx; ozone)
- Solvents and Polycyclic Aromatic Hydrocarbons (benzene, styrene, toluene, PAHs)
- Toxic Metals (lead, arsenic, cadmium, copper, mercury)
- Herbicides and Pesticides
- Perfluoronated Compounds
- Plastics
- PCB's/Asbestos
- Over 100 different chemicals produced from incomplete combustion of organic matter (coal, oil, gas, garbage, trees).

The above is a veritable who's who of substances that you do not want to inhale, ingest, or have absorbed transdermally. In addition, there are ample amounts of extremely tiny particulate matter that become airborne, especially PM 2.5, which are particles less than 2.5 micrometers in diameter, and PM ultrafine, which are ultrafine or nanoparticles that are between 1 and 100 nanometers in size. These are the truly scary-sized molecules because they evade capture by the cilia in your larger airways and can then reach the end of your respiratory train line: the alveoli. Especially the ultrafine particles can cross the respiratory

membrane in the alveoli, enter the blood stream, and translocate to all organs and parts of our bodies. They have been linked to numerous pathological conditions but especially diabetes, cancer, cardiovascular disease, and low birth weight.

On a different note, Steve Tower, MD, presented "Arthroprosthetic Cobaltism: A Commonly Overlooked Iatrogenic Toxin." There was a phenomenal *House* episode several years ago where a woman with seemingly unrelated severe symptoms was finally diagnosed with cobalt poisoning from a joint replacement. My take on this is how many joint replacement patients have mild to moderate symptoms that are just being dismissed as normal aging or hypersensitivity? A good history will pick up history of a joint replacement. You wouldn't have to be as diligent as House to order testing to confirm mild to moderate cobalt poisoning or not.

Dr. Tower also seemed to have a review of studies proving the efficacy of chelation therapy at his fingertips. My recommendation was that he start hiring himself out as a professional witness to help other doctors whose medical boards were stymieing their use of chelation. I think he would be perfect!

Chelation was a popular topic on Saturday. One talk was "Toxic Metals, Health Effects and Use of Calcium EDTA and DMPS for Treatment" by Jeffrey A. Morrison, MD, CNS. The other was "How Treating the Elephant in the Room Became a Black Swan Event: Lead and Cardiovascular Disease" by Gervasio A. Lamas, MD.

Dr. Morrison submitted excellent material, including the information that lead (Pb), cadmium (Cd), and zinc (Zn) have higher binding constants than calcium and will therefore replace the calcium when they meet the calcium-EDTA complex. For me this is excellent info because my provocative urine heavy metal testing showed high lead. Calcium EDTA is a quick push, not like a very slow sodium EDTA one.

Dr. Lamas entered a great quote in slide #3 of his lecture: "If you say there is an elephant in the room, you mean that there is an obvious problem or difficult situation that people do not want to talk about (**but should**)." Next slide, he had a great picture of that elephant covered with proven, vasculotoxic metals: lead and cadmium. He also comes to these conclusions concerning Pb and Cd from journal articles:

- Lead is associated with hypertension, stroke, MI, and mortality. Its principal storage is in bone. Once in bone, the half-life is 30 years.
- Cadmium is associated with coronary artery disease, cerebrovascular disease, and particularly peripheral artery disease. Its principal storage is in kidneys, liver, and lungs. The half-life is 30 years.
- Strong mechanistic and experimental evidence exist supporting vasculotoxic effects of Pb and Cd.[3-5]

He then looked at other studies on chelation and heavy metals plus some incredible before and after chelation pictures of feet and toes with diabetic ulcers that made my wife leave the room. Finally, he asks the question, "Why has it taken so long?" – meaning so long to recognize the efficacy of chelation. His answer was a quote from Marlon Brando in the movie *Godfather*: "It's not personal, it's business."

Finally, at the Q & A session on Saturday afternoon, I had an extremely odd question posed to me: Dr. Cross, do you not believe in the Black Lives Matter Movement? I was slightly taken aback and initially came back with what I believe: all lives are important. Then my cognitive dexterity fortunately kicked in. I subsequently said that poor black lives don't matter, nor do poor Hispanic ones, or poor white ones, or poor red ones, or even poor green ones – if there happen to be Martians living somewhere disguised as humans living in poverty. St. John's Parish, west of New Orleans and predominantly black, had in 2019 the highest cancer risk from airborne pollutants in the US due to various chemical plants in the area brazenly releasing hazardous chemicals.[6] A similar story repeats itself around the US and the world. *Corporations mostly place their polluting factories closer to poor communities, which leads to the above scenario.* What these greedy people don't understand is that wind and water are the great equalizers. They may not be exposed to the same concentrations as places like St. John's Parish, but wind and water still bring the pollution eventually to their doorsteps.

Steve Tower, MD

So, let me end this article with an incredibly prescient quote from the indomitable Rachel Carson which, to me, terrifically conveys the elephant in the proverbial environmental room: "The human race is challenged more than ever before to demonstrate our mastery, not over nature, but of ourselves."[7]

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Pediatric Pearls

by Michelle Perro, MD

Pediatric Dermatology Cases: An Integrative Approach to Common Rashes

Dr. Google may have too much to offer the detective mom scanning websites and blogs for medical advice, often after the kids are in bed and after many hours have already been spent on their devices. While their regular traditional docs may offer up the usual menu of pharmaceuticals, many parents are seeking more 'natural' (my least favorite word in the integrative lexicon) therapeutics.

We are there to help with our more diverse treatment options. However, I don't throw the baby out with the bathwater (my favorite metaphor as you have probably guessed) and offer the least toxic, most effective, and hopefully somewhat affordable therapies based on pragmatism and common sense honed on the streets of my growing up on the Lower East Side. This approach is invaluable when it comes to the visible and often distressing issue of skin disorders. Who would have thought!

Rash Madness

The following cases have all presented over the past few months via Telemedicine.

Case 1. The Garcia family decided two new baby kittens would be just perfect companions for their three- and six-year olds during social isolation from COVID. They noted that the kittens had 'dry patches' on their skin which their own children were sharing and rubbing over their own faces. The three-year-old developed ring lesions with raised borders and central clearing on the neck and the six-year-old had a matching pair below her eye. Studies have shown that in 30-70% of households where a cat develops ringworm a minimum of one person acquires the infection.

This type of case would normally be a slam dunk; topical anti-fungals are quick, affordable and relatively non-toxic, such as clotrimazole. But the parents did not want pharmaceuticals. So, my easy fix became my Plan B, and I turned to Plan A, *Sepia* 30c two times a day for 14 days with 2 drops of tea tree oil in a carrier oil such as olive or coconut oil (with its own antifungal benefits work well), two times a day topically, with a few drops of vitamin E, carefully applied, since the location of the infection was near the eye. Allergic reactions can occur with potent essential oils as well as accidental introduction into the eye. The Garcia kids did great, although it did take almost three weeks to clear their tinea corporis infections. Their vet did prescribe clotrimazole along with diluted apple cider vinegar over the affected skin for the kittens. I was impressed!

Case 2. Josh is an active 16-year-old boy, bored during school closures from COVID, and spent a lot of time on his mountain bike. He was covered with an array of road rashes in various stages of healing from his biking adventures. One particular area on the shoulder was warm, erythematous, contained a few vesicles, some slight streaking towards his pectoral muscle and was painful with touch/showering. The mom was reluctant to bring him to the ER since he had a prior visit to the ER for road rash gone cellulitis which bought him two antibiotics (to cover for MRSA). My inclination was to begin cephalexin only since he wasn't at a high risk for MRSA, but mom preferred a non-pharmaceutical approach, if possible.

Having a low threshold for bringing in pharmaceutical antibiotics if needed, the following regimen was created for Josh: *Sulfur* 30c three times a day (a great cellulitis remedy), topical homeopathic calendula ointment two times a day to be washed off in between since it can get crusty (another skin ointment must-have for kids), organic reishi mushroom powder (https://medicinal-foods.com/shop/reishi-mushroom-powder-organic/), doubling the dose (which boosts white blood cells and has beta-glucans activity; can activate macrophages and natural killer cells), topical Argentyn 23 gel (https://www.argentyn23.com/argentyn-23-silver-first-aid-gel/) and probiotics. Now this may seem like quite a bit to do for a teen, but the family was willing to try this creative concoction in order to avoid oral pharmaceutical antibiotics. I was contemplating the addition of an herbal antibiotic formula if necessary as well (https://biocidin.com/products/biocidin-capsules).

Within 24 hours, Josh stated that the pain resolved and the erythema was decreased. The evidence of lymphangitic red streak had disappeared (which was one of my big concerns), and I didn't need to add anything to his treatment plan. Phew.

Case 3. Yasmin is a seven-year-old gal who loves hiking with her dog. After an afternoon of rolling down a hillside, Yasmin complained of a pruritic rash covering most of her legs and arms, in linear red streaks, with thickening of the skin, vesicular eruptions, and scattered weeping lesions. Within 24 hours, the rash covered most of her face as well and the parents were concerned that she had chicken pox.

Chicken pox was a good thought because of the vesicular component and extent of the rash, but the presentation of the rash wasn't in the right order, wrong time of year, lack of exposure, and no systemic illness. (The patient was unvaccinated for chicken pox.) Only 20% of us do not react to the allergic oils of poison oak (poison ivy for the East Coasters), and every practitioner has at some time treated this common affliction. The extreme pruritus will have most adult patients begging for a steroid prescription such as prednisone since antihistamines (diphenhydramine) are only modestly helpful.

As an integrative practitioner, I try to avoid steroid usage since we have so many other tools to employ and I am concerned regarding the immune suppressive effects. I recommended an organic oatmeal bath (which contain avenanthramides and phenols, both anti-inflammatory) which can help soothe the itching. I prefer colloidal oatmeal, but that may be hard to find. Grinding the oatmeal and adding it to the bath and soaking in tepid water for 15-20 minutes can bring immediate itch relief. When the oatmeal bath doesn't do the trick, apple cider vinegar can be dabbed on itchy lesions, more useful when the affected area isn't too large. Aloe vera gel topically is soothing and I heavily prescribe topical homeopathic cardiospermum tincture 10% (http://www.florasone.org) for patients all summer long for itchy maladies such as eczema flares, insect bites, and allergic reactions. Apply frequently since its antipruritic effects last just a few hours.

For the non-homeopaths, prescribing a combination remedy (https://www.hylands.com/products/hylands-poison-ivy-poison-oak-relief) may be the easiest way to go, administer every few hours and the dosing can be tapered as the child becomes less symptomatic. I use *Rhus tox* 30c preventatively for those individuals that are extremely allergic to the sumac family of plants. Once the rash is in full bloom, I find the common rhus tox remedy not to be too effective. Calendula ointment, again, is a useful adjunct to calm the inflamed skin as well. It took almost two weeks for this case to resolve, but the intensity of the itch was better within two to three days; and we avoided superinfection from scratching with a bit of ice cream medicine. I'm not too proud to offer an occasional bribe!

Case 4. Sofia is a two year old, who presented with a rash on her foot for several days. The rash was serpiginous, raised, non-pruritic and approximately 10 cm in length. The mom denied travel history or exposure to animals, nor were any other family members affected. Mom did bring Sofia to the park to play in the sand box on a regular basis and Sofia may have enjoyed an occasional mouthful of sand. (And according to Murphy's Law of Medicine, this patient was the last of the day. Smile.)

So, not your typical rash. For those practitioners that don't treat children or people that work with animals frequently, may not be familiar with the cutaneous larva migrans rash of *Toxocara canis* (or *T. catis*). Infection is caused by the larvae of ascarid roundworms of mammals when ingesting the infective eggs or undercooked meat of infected hosts. The eggs can hatch and larvae can circulate through the body. The damage is caused mechanically and by local reactions. Many kids may not have any symptoms, or they may range from mild to severe. In countries where this infection is prevalent, children are often not treated since infection may clear spontaneously when the larvae die.

Trying to calm the mom, who was freaking out, was harder than treating the infection, which is quite straightforward. In this case, because of the potential organ involvement and the mom's nervous system, I decided to use a pharmaceutical, thiabendazole (500mg/5ml), 250 mg two times a day for two days. Occasionally a second dose is recommended if active lesions are still present two days after the completion of the drug (which this patient did not require). However, the mom reported that Sofia had some mild diarrhea and gassy tummy starting before the rash began and increasing afterwards. I did several stool samples for ova and parasites to test for other potential uninvited guests and began the patient on homeopathic treatment for parasites (https://desbio.com/product/ver/) as well as probiotics. Her symptoms resolved completely within five days, and her stool tests did not reveal any co-infections.

The art and beauty of what we do lies within the experiential framework of our practices. There was a time 20 years ago when simple homeopathic remedies may have resolved a dermatologic issue. But our environment and our kids have changed requiring more complex therapies. Thus, when creating integrative treatment plans, I employ the judicious usage of pharmaceuticals, select various homeopathics to be administered both locally and systemically, protect and support the microbiota, and offer herbals/essential oils and whatever dietary interventions are required to eliminate a pathogen, calm a reactive immunologic response, and to regain the terrain. This strategy seems to work well, and most parents find comfort in an integrative approach. And it's fun. ◆

Environmental Medicine Update

by Marianne Marchese, ND
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Prenatal Environmental Exposures and Preconceptive Care

Introduction

Many women thinking of becoming pregnant are not aware of the impact environmental toxicants can have on their pregnancy and the health of their child. Toxicants from food, water, air and products can be passed in-utero and during lactation, affecting the health of the newborn child. Exposure to chemicals during these critical windows of development can affect the unborn child in various ways. Prenatal exposures can also affect the health of the pregnancy and pregnancy outcomes. It is imperative that physicians take an in-depth environmental history, offer testing for metals and other toxicants, educate woman on how to avoid exposures to chemicals, and guide them through a detoxification plan to remove chemicals from the body prior to conceiving.

Prenatal Exposure and Health Effects

Every day we eat, breath, drink, and put on our body, chemicals that can disrupt the hormonal, neurological and immune system. Many of these chemicals are lipophilic and easily cross the placental barrier. These chemicals not only affect the health of the child but also the health of the pregnancy. One example is the metal lead. There is a significant link between maternal blood lead levels and preeclampsia.[1,2] It is also known that maternal blood lead, at even low levels, can cause pre-term birth.[3] Health care providers and patients need to be aware that adverse pregnancy outcomes may occur at blood lead concentrations well below the current acceptable levels. Lead isn't the only chemical affecting pregnancy and the health of the newborn. Mercury from fish; PCBs from food, solvents from air pollution, and products used in the home; phthalates from plastics, food, and cosmetics; pesticides from food and air pollution; bisphenols from canned food, water bottles, and paper receipts; polyaromatic hydrocarbons from food and air pollution; and perfluorinated compounds from food and products, all play a role in prenatal health and outcomes.

In 2015, the International Federation of Gynecology and Obstetrics released an opinion documenting the links between prenatal exposure to environmental chemicals and adverse health outcomes on fertility and pregnancy, and neurodevelopment. The highlights include a link between the following chemicals and health conditions.[4]

- Decreased semen quality with PCBs;
- Miscarriage with solvents;
- Impaired fetal growth with pesticides;
- Miscarriage, low birth weight, and preterm delivery with air pollutants;
- Decreased birth weight, and congenital malformations with toluene;
- Shortened gestational age with phthalates;
- Low birth weight with PCBs;
- Reduced birth weight and fetal growth with perfluorinated compounds (PFCs);
- Impaired cognitive and neurodevelopment; increase in attention problems and ADHD, and reduction in working memory capabilities with pesticides and lead;
- Impaired neurodevelopment and reduction in executive function with phthalates and lead;
- Reduced cognitive performance, impaired neurodevelopment, and reduced psychomotor outcomes with methyl mercury;
- Reduced IQ, attention and executive function deficits with PCBs;
- Impaired neurodevelopment and reduction in attention with polybrominated diphenol ethers (PBDEs);
- Attention problems with polycyclic aromatic hydrocarbons (PAHs);
- Aggression and hyperactivity and reduction in executive functioning skills with BPA.

It is clear that exposure to toxic chemicals in food, water, air, and consumer products affects maternal and child health. Health care providers need to be on the front lines of educating women

about avoiding exposure to chemicals before they get pregnant. It starts with in-depth environmental history to identify possible sources of exposure and offering toxicant testing to look for elevated levels in the blood and urine. Since almost every person is exposed in some degree to low doses of toxicants every day, some of which are difficult to detect with testing, providers may consider treatments to help remove the chemicals from the body prior to conceiving. This is often referred to as preconceptive detoxification or cleansing.

Detoxification or Cleansing

There are various methods to help the body process exposure to environmental toxicants. These methods are often referred to as detoxification or a cleanse. In general, the four steps in detoxification treatment plans include mobilizing stored toxins, supporting liver metabolism, enhancing elimination from the body, and avoiding re-exposure to chemicals in the environment.[5-9]

Methods used to mobilize pesticides, solvents, and other fat-loving chemicals include caloric restriction, sauna therapy, and chelation for metals.

Methods used to support liver phase one and two metabolic pathways, often called biotransformation, include nutrients that provide cofactors for liver phase one and phase two enzyme pathways: vitamin A (from mixed carotenes), vitamin C, vitamins D and E, all of the B-vitamins, calcium and magnesium, zinc and copper, molybdenum, kelp and iodine, selenium, choline, green tea, turmeric. Also beneficial are herbs that support the liver such as burdock, taraxacum root, silymarin, beet root, and artichoke. For women a treatment plan may include addition nutrients to support hormone metabolism, such as DIM, calcium-d-glucarate, NAC, ALA, methyl B12, methyl folate.

Lastly the plan should include methods to enhance elimination of toxicant bi-products, such as castor oil packs and sauna therapy and bowel support with fiber, coffee enema, or colonics.[5-9] Of course, avoidance education is key to reducing exposure to toxicants. Next follows an example of how to take a patient through this process.

Case

A few years ago, a 33-year-old woman came for a preconception detoxification plan and help with uterine fibroids. She had moderate dysmenorrhea her entire life and recently discovered she had small fibroids. She was ready to start a family with her husband and get healthy. Six years prior to the appointment she had an umbilical endometrioma removed, it was 1.5 cm. It was assumed by the OB/GYN she had endometriosis due to the endometrioma and dysmenorrhea, but the patient did not want to undergo laparoscopy at that time because the dysmenorrhea was mild.

Her family history was significant for the fact she was an only child and her mother had difficulty with fertility, had two miscarriages, uterine fibroids, and dysmenorrhea. Her paternal grandmother had ovarian cancer and her maternal aunt had breast cancer. She was on no medication and took 1,500 mg a day of omega-3 fatty acid, 5,000 iu a day of vitamin D, and a B-complex. She ate very well – all organic, fish low in mercury – and had already removed cleaning and cosmetic products from her home deemed to contain toxicants. Her current labs were all normal and included CBC, CMP, Lipid, TSH, FT4, FT3, TPO AB, estradiol, testosterone, vitamin D, B12, iron, ESR, DHEA, cortisol and day 21 progesterone. A pelvic ultrasound showed two fibroids about 2 cm each.

An in-depth environmental history revealed she grew up in a major metropolitan city in Pennsylvania where there used to be a lot of industrial plants. She went to college in an area with numerous factories. Scorecard.org revealed that in the zip code where she grew up 3% of the homes had high lead and lots of industry polluting the air with solvents, sulfuric acid, nitrates, and propylene. There was one superfund site in her area, which from 1947 to 1963 disposed of waste contaminated with pentachlorophenol (PCP) in a well that drained into the ground water. In 2002, her county ranked among the dirtiest/worst 10% of all counties in the US in terms of cancer risk score (air and water releases) and the dirtiest/worst 10% of all counties in the US in terms of particulate matter (2.5). She had no toxic hobbies and as an adult did not live near industry or golf courses. She started filtering her water about 10 years prior with reverse osmosis and use a HEPA air filter eight years prior.

We decided to run blood and first morning urine metal tests and interpreted the results based on the NHANES data; her levels were below the 70%. She declined testing for other toxicants but did a test for liver phase one and two single nucleotide polymorphisms. The results showed a SNPs of phase one CYP 1A1 and CYP1B1 and heterozygous for phase two COMT, NAT2, and SOD2 pathways. It isn't clear if she was born with these alterations or they were induced later in life by exposure to toxicants. It is clear however that these changes make it difficult for the liver to bio-transform toxicants and hormones.

The patient's goal was to try and shrink the fibroids, and support her body to mobilize, metabolize, and eliminate toxicants from past and current exposures. Her plan included sauna therapy, which she managed to complete one session a week for eight weeks. She ate a healthy organic and toxicant-free diet, had four treatments of frequency specific microcurrent for uterine fibroids, and took three supplements. The supplements included one that provided cofactor support (ingredients listed above), an herbal product that had milk thistle, burdock root, dandelion root, beet root, and artichoke, and a third product with hormone metabolism support that contained methyl B12 and methylfolate, ALA, DIM, calcium-d-glucarate, and NAC. She was already using good water and air filtration at home and work and already taking vitamin D and fish oil. After eight weeks her dysmenorrhea resolved and never returned. The repeat pelvic ultrasound showed both uterine fibroids shrunk 1 cm each. She got pregnant easily eight months after completing the 8-week plan and she has three kids now. The dysmenorrhea never returned, and 3 years after the initial plan she had a pelvic MRI that showed the same two fibroids were still 1 cm each; there was no growth during the pregnancies.

Although this seems like a general plan, it can be applied to both women and men to help them prepare for a healthy pregnancy and pregnancy outcomes. Educating couple on avoiding exposures from food, products, air, and water is the first and very important step. An in-depth exposure history can guide the health care provider towards possible high dose exposure versus low dose daily exposure or exposure during critical windows of development such as in-utero and puberty. Toxicant testing can help determine best treatment options. If metals are present in the blood or urine, then chelation would be part of the treatment

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plan versus a general detoxification and cleanse to support liver biotransformation and elimination.

Summary

The endocrine, immune, and neurological effects of low dose chemical exposure from food, air, water, and products is well known and documented. It is also evident that prenatal exposure can affect the health of a pregnancy contributing to preeclampsia, low-birth-weight babies, and pre-term birth. Prenatal exposures can cross the placental barrier during this critical window of development affecting the health of offspring. Children's asthma, allergies, ADD, ADHD, hormonal and developmental problems can be linked to prenatal exposure to toxicants.[10,11] It is imperative that health care providers educate men and women on avoiding toxicants not only for their health but for the health of their offspring. An in-depth environmental history and toxicant testing can guide the practitioner towards possible exposures and help individualize a treatment plan. A treatment plan may include methods of mobilizing chemicals and supporting the liver's biotransformation process and eliminating chemicals from the body. Early intervention prior to a couple conceiving is the best form of preventative medicine. All health care providers should consider making environmental health part of health care.

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Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Moonlighting and Forest Bathing

There is a concept in Vedantic thought that life is divided into stages or "Ashramas." Youth and young adulthood are referred to as *Brahmacharya*, the period of life dedicated to learning. *Grihastha*, the second ashrama is the period of life dedicated to building a career, a family, accumulating wealth, and striving for earthly reward. *Vanaprastha* is the third ashrama*; Vanaprastha* is Sanskrit for 'retiring into the forest'. At this stage of life, people focus less on professional ambitions but turn toward a life devoted to spirituality, service, and wisdom. *Vanaprastha* is followed by *Sannyasa*, a life dedicated to enlightenment.

In June 2019, I handed over the keys to our office to two younger colleagues, one of whom had once worked for us as our office receptionist. I am writing this now almost six months later, a curmudgeon retired in the forest.

When we were in Portland in August for the AANP Conference, colleagues expressed surprise, shock, dismay, and perhaps a touch of envy that we'd chosen to do this. There is an assumption in our profession that we work until we die. Few among us have stashed away funds for retirement. The common response I hear from colleagues when queried about their 'plans' is that they hope to emulate Dr. Bastyr and practice until they die. While I'm all for optimism, this approach works better when you are young and idealistic enough to believe that naturopathic doctors will not succumb to the infirmities of aging. Such optimism is inversely proportional to age and the older one gets the less certain this sounds like a reliable plan.

My wife Rena Bloom and I took this Vedic concept of *Vanaprastha* literally and, shortly after the AANP conference finished, retreated to a cabin in the New England woods. It has been a change for us. Denver, where we spent the last 28 years, is high dry prairie made green only by water piped beneath the Continental Divide from the Western Slope. We lived in a lovely neighborhood in the center of the city. In contrast our forest property borders a pond as big as any lake in Colorado. We spend our days deep in the forest or by the water.

The first few days without internet were a challenge psychologically. I've never been caught up with social media and don't even have a Facebook page. I have a cellphone but rarely use it. Yet, it was apparent that I was going through withdrawal symptoms living in the cabin, itching to check my email, wanting to log onto PubMed to look something up. One could write a scholarly paper on the neurochemicals released in the brain when someone is using electronic media and contrast that with the chemicals behind addiction. Someone besides me.

It was startling how much of my mind was lost in that Cloud place and how pleasant it has been to let go of it. I still wonder about things. I make lists of stuff to search for next time we go into town to use WiFi at the library. Is there, I wonder, a study that delineates cancer risk in people by type of diabetes? In other words, does having type 1 autoimmune diabetes raise risk to the same degree as type 2 does? That question has been on my list for a month now.

I find myself pondering the loons on the pond. Why do these birds have such a heart-piercing call? Do they purposefully position themselves so their calls echo down the pond and back, or is that phenomenon just random chance? Has anyone written a translation of their different calls? They produce so many different distinct calls, surely, they must mean something. These sorts of questions have taken precedent.

There was a full moon early on during our forest stay, and we were excited about seeing the moonlight on the pond; but it was raining that evening, so we went to sleep disappointed. The weather cleared during the night and the moonlight shook me awake before the first whisper of dawn. Sitting pondside with a full moon, we tried to identify the many sounds of the night. The cones falling from pine and fir trees land gently in contrast to the acorns, which shoot through the foliage and thud into the ground. Newton's Law appears to hold true, and acorns do accelerate the further they fall. Perhaps it wasn't apples that triggered his

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observations? Acorns from the upper branches of tall trees do clearly hit the ground with more speed and force. As the season progresses and ripening acorns increase from single shots to volleys, I've taken to wearing a hard hat when the wind blows.

One can sit lakeside watching waves and imagine a growing perception of the wave patterns crossing the pond surface. There is the dominant wave coming from the far shoreline created by the wind. Then there are the secondary retreating waves bouncing off of our shore and traveling back to that far shore. With a twist of the mind one can see the momentary flat spots, where interference patterns, when two waves moving in opposite directions, cancel each other out. Don't think that any of this is symmetrical as we have a rocky shoreline of large boulders. In theory one should be able to read the patterns of these interacting waves and be able to visualize the shoreline's irregularities, to draw a picture; I wonder how long one will need to watch the waves until one can read the waves? Will it be like the FedEx arrow? One moment it is not there and then the mind clicks and that's all you can see?

Not seeing patients has been surprisingly easy. A load lifted from my heart. I had acquired the weight so gradually, becoming accustomed to bearing a list of cares as I built the practice year after year, I had forgotten what a burden of care and concern we carry on an ongoing basis – that is until the weight was removed. That's just the burden of patient care; retiring the monthly financial burden of keeping the doors open, that was a joyous occasion. So far this retirement thing is ok with me.

Our profession has a problem in store for it. I'm not the only one who has reached the end of my professional line; other colleagues, those who may be smarter, wiser, and more competent practitioners, will eventually follow my example. A generation of our colleagues will age out of practice soon. They are our most experienced and some would argue our most committed practitioners. These are the doctors who were called to the naturopathic profession when it hardly existed, the ones who went to Kansas, the ones who envisioned what this profession might someday become. These are the doctors who built the profession from nearly nothing, who fought for our licensing laws, who expanded our scopes, who founded our schools, who invented the supplements we sell, and who advanced the knowledge of our medicine. The way things stand now we are going to lose them; they will slide into retirement and slip away from us and no longer continue to contribute.

In recent decades, our profession was driven by the need to reestablish itself, to build itself up from near extinction. It is as if the profession itself has just emerged into its own *Grihastha* stage. Everything we have done and continue to focus on is about building up our young doctors and their opportunities. We need to get them out of school and help them build practices so they can pay off their loans and raise their families. In reality, our older doctors are now at the point in their lives where they have the most to offer back. They have honed their skills over the years in practice, they know what works and doesn't. Rather than let them sneak off into the forests we should be enlisting them to teach, to mentor, to provide the profession with the wisdom needed to provide direction in the future. We should be doing everything possible to keep them involved in their profession and offering them opportunities to serve.

I am reminded of a description David Brooks, the *New York Times* columnist, used in his 2015 book, *The Road to Character*, about this stage of life. He wrote many people experience a deep need to contribute and give back, using two terms apparently of his own invention. He distinguished that *Grihastha* stage from the *Vanaprastha* stage as the difference between "résumé virtues and eulogy virtues." Résumé virtues are the professional achievements that are linked to career success. They are the things we might write down in order to get ahead in life, successes used to compare ourselves to others and make us look better. Eulogy virtues are the opposite of competitive achievement. They are the accomplishments you hope people remember and recount at your funeral; they are how you want to be remembered.[1]

We are pretty much the first generation of modern naturopathic physicians. We do not have the institutions in place that other medical professions offer to retired practitioners, or from a different angle, do to make the most of them.

What are old people good for?

Awhile back, I noticed that I wasn't getting smarter. Some of our readers might say I've been writing dumb things for years. Among people who study career productivity the standard thinking is that success and productivity increase for the first 20 years after one begins a career. If you finished your naturopathic school at thirty, your competence peaked at fifty.[2] That puts my high point more than a decade ago. (As for my good friend Davis Lamson, best not to go there.)

People who make prize-winning scientific discoveries or develop key inventions generally do so in their late 30s. Chances of doing so go downhill from then on. The likelihood of producing a major innovation at age 70 is back down to what it was as a teenager.[3]

Poets peak in their early forties. Novelists peak a bit later; Martin Ortiz summarized data from the *New York Times* best seller lists and reported that authors are most likely to reach #1 on the list in their forties to fifties.[4] The chances of a seventy-year-old writing a best seller are low. Poets tend to produce half of their lifetime creative output by age 40. Historians are the exception; they do peak later; they don't reach their halfway mark until 60.

High-tech entrepreneurs peak even earlier. The *Harvard Business Review* reported in 2014 that the founders of tech enterprises valued at a billion dollars or more tend to cluster in the 20 to 34 age range.[5] For air traffic controllers, performance decline is so significant that they are forced to retire by 56. Professional decline begins earlier than most of us realize and without our notice. Professional decline, like entropy, appears to be a fundamental law in our universe.

My memory for numbers, facts, names and faces has faded perceptibly. Too much of what we need to do with patients requires the quick analytic capabilities of being able to see and comprehend the details of a problem quickly. It's not a take-home exam that we complete at our leisure.

The admonishment to 'quit while you're ahead' is not to be taken lightly. About 80 years ago, Raymond Cattell, a British psychologist, devised an interesting pair of descriptions to classify

the shifting ways we evaluate the world as we age. He said intelligence could either be fluid or crystallized. Fluid intelligence is the ability to reason, analyze, and solve novel problems, the sort of intelligence that innovators need. Crystallized intelligence is the ability to use knowledge gained in the past: the acquired library of experience, what we might call wisdom. Careers and occupations that rely on fluid intelligence peak early while those that rely on crystallized intelligence peak later.

For those in our profession, who are hoping to work late into life, we need to think about how best to transition away from work that relies on fluid intelligence toward the wisdom of crystallized intelligence and the strengths that persist later in life. Perhaps this is why we see older doctors starting to use the same general protocols over and over with the majority of their patients over time? Or perhaps less generously, some of our older colleagues appear to have fixed ideas and are drawn to dogmatic approaches to medicine.

College professors have perhaps the longest professional longevity of any profession. While their research productivity drops with age, the ability to impart knowledge seems to improve; the best teachers and mentors tend to be in their mid-60s or older. Is there a way that we might recruit retiring practitioners to volunteer at our schools or serve as mentors in a more organized manner? As it stands now it seems our associations have no interest in keeping retired colleagues as members. While they all provide substantial dues discounts to new doctors, there is no similar financial incentives for retired doctors to remain on membership roles.

If I were king of the forest, every organization in our profession would have a membership category for retired doctors that is as discounted as what we offer students. Those who have paid full membership dues for two decades or more would need not pay anything going forward to be members. To use the expression, "They have paid their dues." If we can discount conference registration fees for students, we should do the same for our retired colleagues. They don't need the CE hours anymore but will still come because they are part of the profession and want to contribute.

Asking them to pay full price when they no longer deduct business expenses from a limited income is rude. Most important, we need to open avenues for them to volunteer and contribute. Let's invite retired doctors to the schools and make it easy for them. Provide lodging for them to stay and volunteer. Think of those practices that took in student preceptors year after year; we owe those doctors more than gratitude; we owe them a channel where they can continue to coach students.

As a profession we need to make room for those of us who are graduating into the forest, those who care little for their résumés and who, if thinking about anything, are wondering who might write their eulogy. We need to create space for our most experienced practitioners to volunteer to teach, to lobby, to train, and to create visions of our future.

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CALENDAR

Please visit www.TownsendLetter.com for the complete calendar

FEBRUARY 4-6: AMERICAN CHIROPRACTIC ASSOCIATION ANNUAL MEETING AND CONFERENCE. Virtual online. CONTACT: https://www.acatoday.org/Education-Events/ACA-Engage-2021

FEBRUARY 27: PHARMACOLOGY UPDATE FOR NATUROPATHIC DOCTORS online. Early bird registration until January 20. CONTACT: http://www.collaborativeeducation.ca/

MARCH 5-7: FLORIDA HOMEOPATHIC SOCIETY ANNUAL CONFERENCE – Homeopathy & Traditional Chinese Medicine: Where the Modalities Meet with Hilery Dorrian, L.Ac, LCH in Orlando, Florida. CONTACT: www.floridahomeopathicsociety.org; cicamp7@gmail.com

MARCH 5-7: THE FORUM FOR INTEGRATIVE MEDICINE "Navigating Recovery in Complex Chronic Illness" online. CONTACT: forumforintegrativemedicine.org

MARCH 10-14: 68th CONGRESS OF THE INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE – Endocrine Ecosystem: Balanced Hormones and Reduced Toxicity for Patient Health and Happiness in Memphis, Tennessee. CONTACT: https://www.eventbrite.com/e/endocrine-ecosystem-balanced-hormones-and-reduced-toxicity-tickets-94725166523

MARCH 26: SOUTHWEST CONFERENCE ON BOTANICAL MEDICINE begins streaming online. Pre-conference intensive on managing the side effects of pharmaceuticals, plus 24 other lectures on botanical therapies for chronic disease, fungal infections, opiate use disorder, long-term COVID-19 syndrome, and more. 40 hours of continuing education for ND, DO, MD, RN, FNP, LAc and others. CONTACT: 541-482-3016 or www.botanicalmedicine.org

APRIL: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE SPRING MEETING – Mold, Mycotoxins, and Human Health online. CONTACT: http://aaemconference.com/

APRIL 14-17: ENVIRONMENTAL HEALTH SYMPOSIUM 2021 In Tucson, Arizona. Toxic metal effects, diagnosis, and treatment. Building immune resilience. CONTACT: https://www.environmentalhealthsymposium.com/about-ehs

APRIL 17-18: LOW-DOSE LITHIUM – The Mineral as Medicine online. This international, online symposium will review the evidence-based use of low-dose lithium for treatment of psychiatric and neurological disorders. CONTACT: www.LithiumSymposium.com.

APRIL 22-25: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING with Simon Yu, MD, in St. Louis, Missouri. Also, **AUGUST 26-29.** CONTACT: 314-432-7802; http://www.preventionandhealing.com/

APRIL 23-25: 16th ANNUAL JOINT HOMEOPATHIC CONFERENCE in Reston, Virginia. CONTACT: www.homeopathycenter.org

MAY 13-14: INFLAMMATORY BRAIN DISORDERS CONFERENCE online. CONTACT: https://www.neuroimmune.org/inflammatory-brain-disorders-conference/

MAY 21-23: ADVANCED INFECTIOUS DISEASE MANAGEMENT in Scottsdale, Arizona, and Live Online. CMEs available. CONTACT: Sharon Phillips, phone 954-540-1896; Email: sharon@aampconferences.com; https://aampconferences.com/

MAY 28-JUNE 1: 12th INTERNATIONAL CONGRESS ON AUTOIMMUNITY in Athens, Greece. Special session on diet and autoimmunity, chaired by Dr. Aristo Vojdani. CONTACT: https://autoimmunity.kenes.com/

JUNE 3-6: SASKATCHEWAN ASSOCATION OF NATUROPATHIC DOCTORS HEALING SKIES CONFERENCE in Saskatoon, Saskatchewan. CONTACT: http://www.sanp.ca/index.html

JUNE 4: MEDICINES FROM THE EARTH HERB SYMPOSIUM begins streaming online. Intensive: Targeting the Biological Terrain in Collaborative Oncology, plus over 25 other lectures. Over 40 hours of continuing education for ND, DO, MD, RN, FNP, LAc and others. Early bird ends March 3. CONTACT: 541-482-3016 or www.botanicalmedicine.org

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

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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.

Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Women's Health Favorites from 2020

More Ways to Reduce Breast Cancer Risk

There are two recent studies that I want to call attention to, that are relevant for our continued efforts to reduce the risk of breast cancer. The first addresses the issue of weight loss. In post-menopausal middle-aged women who lose weight and actually are successful in keeping it off, their risk of breast cancer is lower. Researchers studied over 180,000 women who were 50 years old or older and had their weight recorded three times over about 10 years. (wow – only 3 times!!!). The follow-up period for assessing invasive breast cancer started after the last weight measurement.

Over a period of eight years, more than 6,900 invasive breast cancers occurred. After the researchers adjusted for baseline body mass index, the use of hormone therapy or not, and other select issues, women who had lost 2.0-4.5 kg and were successful in keeping the pounds off, had a 13% lower risk for breast cancer compared to women who had no weight loss and had stable weight. In those who kept off 9 kg or more, had even better results with a 26% reduction in risk. (1 kg = 2.2 pounds). These benefits of weight loss and maintaining weight loss were strongest among overweight and obese women, meaning a body mass index of more than 25, and also among women with no history of using postmenopausal systemic hormone therapy.

Bottom line: If you are overweight and 50 or older, make every effort to lose weight, a minimum of 4.5-10 lbs. and maintain that weight loss – even better risk reduction if you achieve 20 lb. weight loss and maintain that.

Teras L, et al. Sustained weight loss and risk of breast cancer in women ≥50 years: a pooled analysis of prospective data. *JNCI: Journal of the National Cancer Institute,* 2019. (early release online)

The second study is likely more controversial as is common with environmental exposures and disease risk and incidence. In an observational study of approximately 47,000 women in the US, questionnaires about their use of hair care products was used to assess breast cancer risk. These women were followed over eight years. At entrance to the study, women did not have a history of breast cancer but did have at least one sister who had a breast cancer diagnosis. Over the course of follow-up, 2,800 breast cancers were reported and after analysis, any use of permanent hair dye in the prior year was associated with a 9% increase in breast cancer risk, which is considered statistically significant. The risk was even greater for black women in the US, with an increased risk of 45%. Hair straighteners were less risky but did have an increased risk if they were used at least every five to eight weeks.

We know from other research that the chemicals found in human hair dye have been shown to cause mammary gland tumors in rats when those animals are exposed to those same chemicals. We also know that some hair straighteners contain formaldehyde, which is a known carcinogen.

These results on hair dye and hair straighteners are a part of a larger study called the Sister Study. The Sister Study is an ongoing study by scientists at the US National Institute of Environmental Health Sciences (NIEHS) that includes 50,884 women living in the United States and Puerto Rico. The women joined the study between 2003 and 2009. The women were between the ages of 35 and 74 when they joined the study and none of the women had been diagnosed with breast cancer, but all had at least one sister who had been diagnosed. The Sister Study is looking at the causes of breast cancer and other health issues in women, as well as factors that influence quality of life and outcomes after a breast cancer diagnosis.

Bottom Line: Go *au natural* on the hair color and hair structure. Mother Nature is a beautiful thing!!!

Eberle CE,et al. Hair dye and chemical straightener use and breast cancer risk in a large US population of black and white women. *Int J Cancer*; [Online 4 December 2019].

Could Curcumin Be an Option for Hot Flashes?

The most common symptom women experience in perimenopause and menopause is hot flashes – day and or night. They are also called vasomotor symptoms, which are a sudden feeling of heat, burning and/or sweating with a slight increase in body temperature due to increased metabolic rate and vasoconstriction in the periphery. These fluctuating levels of estrogen, and ultimately low levels of peripheral estrogen, affect the hypothalamus temperature control center and the central nervous system, which eventually alters the levels of neurotransmitter activity, including serotonin and norepinephrine – all of which lead to causing the hot flashes.

Anxiety is also a common issue in perimenopause/menopause although it is complex but can include the loss of self-confidence, the sleep disruption, less activity and mobility, financial stressors, and possible an increase in other chronic illnesses that come with aging.

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Women's Health Update

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A study out of Iran chose to investigate a combination of curcumin and vitamin E for hot flashes and anxiety in menopausal women. The polyphenols in turmeric and thus the essential turmeric compound curcumin have anti-inflammatory and antioxidant amongst its many mechanisms of action. Vitamin E contains tocopherols also with antioxidant activity. Oxidative stress can be induced by menopause and thus a resulting imbalance between free radicals and antioxidants. While perhaps not a strong choice to investigate for hot flashes and anxiety, this triple-blind randomized controlled trial enrolled women ages 40-60 years who were less than six years postmenopausal and had hot flashes at least twice per week. Participants were divided into three groups with one group receiving a curcumin capsule of 500 mg twice daily for eight weeks A second intervention group received oral vitamin E 200 IU twice a day for eight weeks. The third group received placebo twice daily for eight weeks.

Out of 320 menopausal women who were questioned, 160 women entered the study, and 93 women chose to participate. Each group had 31 women in it to start. Women completed the hot flash questionnaire one week before starting the intervention and again at four and eight weeks. They also filled out an Anxiety Scale form, and the Female Sexual Function Index (FSFI), and the Greene Climacteric Scale.

The average number of hot flashes in the curcumin group and vitamin E group was significantly lower than the placebo group after eight weeks. The first significant difference appeared in the curcumin group after four weeks. There was no effect of vitamin E on hot flashes compared with placebo, after four weeks, but was observed at the end of the eight weeks. This study seemed to report just number of hot flashes, not severity. There were no differences in anxiety, sexual dysfunction, or other menopause symptoms between curcumin, vitamin E, and placebo.

Commentary: Older research on vitamin E is mixed, and I've never included it as a robust option for vasomotor symptoms. Curcumin is an interesting choice as there is some PMS and depression research showing efficacy for mood and effects on serotonin. Since serotonin alterations do have a role in vasomotor symptoms, it seems like it is a possible therapy to pursue. Certainly, curcumin has a long list of other conditions that are relevant to aging women, including osteoarthritis, insulin resistance and aging vascular endothelial function relevant to cardiovascular disease. By and large, I will think of curcumin and vitamin E for other conditions other than vasomotor symptoms, although menopause is fraught with a laundry list of symptoms, including vasomotor symptoms, depression, arthralgias and weight gain. Curcumin in particular would be a logical choice when a woman has multiple symptoms and maybe not just vasomotor symptoms. But again, based on the results of this one study, curcumin could be considered an option for treating the pesky number of hot flashes and night sweats.

A note of concern about the legitimacy of this study: Studious and meticulous readers of research, colleagues of mine, have some concerns about at least some of the botanical and nutraceutical research coming out of Iran. In this study, a concern that has been pointed out involves the Iranian Registry of Clinical Trials (IRCT) document; the registration date was June 23, 2018. The expected recruitment start date was July 4, 2018, and the expected recruitment end date was October 5, 2018. For most studies, that would be an unrealistically short time period for assessing 320 women. Also, the IRCT document says, "Recruitment complete," which does not seem possible if the recruitment had not started when the study was registered (and there have been no updates to the registration document).

Ataei-Almanghadim K, et al. The effect of oral capsule of curcumin and vitamin E on the hot flashes and anxiety in postmenopausal women: A triple blind randomised controlled trial. *Complementary Therapies in Medicine*. 2020; 48:102267

The Effect of Global Climate Issues on Pregnancies

Two things to focus on here are air pollutants and heat from climate change. There are many other environmental exposure impacts on women's health, fertility, pregnancies and in utero exposure, but the systematic review of 68 studies from 2007 to 2019 evaluated the association between ambient heat, air pollution, and obstetric outcomes, including preterm birth (PTB), low birth weight (LBW), and stillbirth (SB). There were different types of air pollution components and degree of heat exposure, but air pollution was defined as fine particulate matter <2.5 microns.

In total in all 68 studies, >32 million US births were analyzed. A total of 57 studies showed a significant association with poor birth outcomes – assessing air pollutants in 48 or 58 studies and 9 out of 10 assessing heat exposure. The association of fine particulate air pollutants or ozone was associated with preterm births in 19 of 24 studies and low birth weight in 25 of 29 studies. The data related to stillbirths were limited. The pregnant women at highest risk were asthmatic and minority women, especially African American women throughout the US and Hispanic women living in California. The women with the lowest socioeconomic status and also those living close to power plants and highways had the worst outcomes.

Commentary: As if we did not need more discouraging information about the impact of the crisis of climate change...but this time, specific to pregnant women and their newborns. There are multiple factors involved in poor obstetrical outcomes, including poverty, nutrition, smoking, alcohol and drug use, select legal prescriptions, violence against the women during pregnancy, and more. But now we have more statistics on the inequities borne by minorities and exposure to air pollution and heat exposure during pregnancy, that appears to elevate risks for poor outcomes.

Women and their families and employers and health care providers should do everything possible to meet these additional challenges of pregnant women that affects their risk for preterm births, low birth weight babies, and possibly stillbirths. The bigger picture, of course, is for more of us to wake up to the climate crisis and the impact it has and will continue to have on our health. What can each of us do to meet this challenge? We could get involved in organizations with the mission to affect policy and change regarding air pollution, water and ground pollution; we could donate to such organizations; we could vote in local, state and federal initiatives and elections that affect policy and values and actions of the politicians. This blog may not sound like a women's health-related topic – but from pregnancy outcomes to fertility to breast cancer, trust me, it is.

Bekkar B, et al. Association of air pollution and heat exposure with preterm birth, low birth weight, and stillbirth in the US: A systematic review. *JAMA*. 2020; June 18.

Guidice L. A clarion warning about pregnancy outcomes and the climate crisis. *JAMA*. 2020 June 18.

Vaginal Lactobacillus for Bacterial Vaginosis

Bacterial vaginosis (BV) is the most common vaginal infection in women. It is characterized by vaginal fishy odor, vaginal discharge (usually thin, gray or white or even greenish) and irritation and/or burning and/or itching. Women and practitioners can easily conclude incorrectly that the symptoms are due to a yeast infection, but a test of vaginal pH and an amine test of the discharge confirm the diagnosis. It's not something you "catch" from someone else, meaning it is not considered a sexually transmitted infection, but rather a result of a displacement of the optimal lactic acid producing lactobacilli in the vagina by the already present, but now over-populated anaerobic organisms of BV. There are some potential complications of BV rather than just annoying, including risk of preterm birth if you have BV during pregnancy, an increased risk for sexually transmitted infections, pelvic inflammatory disease, and an increased risk of a pelvic infection post certain pelvic surgeries such as a hysteroscopy or dilation and curettage.

One of the most challenging aspects of BV is that it can easily recur, despite conventional standard of care treatment with antibiotics.

This study was funded by the National Institutes of Health to assess whether intravaginal replacement of *Lactobacillus crispatus*, considered a "good" vaginal bacteria, would reduce the risk of BV recurrence. This double-blind, placebo-controlled trial was conducted in 228 women who had recently been treated with a common antibiotic for BV, called metronidazole. The women inserted a preparation of *Lactobacillus crispatus* or placebo for four consecutive days during the first week, then twice weekly for 10 weeks.

At week 12, 30% of the women who received the *L. crispatus* had a recurrence and 45% of those receiving placebo had a recurrence of BV. At week 24, recurrence rates were 39% for the *L. crispatus* group and 54% for the placebo group. However, the recurrence rate for 19% of the women was unknown.

Commentary: There have been many good studies of lactobacillus species and strains for BV, and now we can add this one. However, I would want the results to be even better, and as you can see, at 24 weeks, the recurrence rates are higher, implying longer treatment is needed. Recurrence rates are famously high for even a first episode of acute BV making it a challenge for all practitioners and women who are dealing with BV, but even more so for women with recurring BV. About 30% of women experience a recurrence of symptomatic BV within 30 to 90 days, and 70% will have a recurrence within nine months. Clearly, a more effective approach is needed. While this one organism, *L. crispatus* is an important consideration, I find that better results could be achieved when incorporating the other research that has been done on other species as well, such as *L. rhamnosus* and *L. reuteri*, and in addition, vaginal vitamin C tablets, and boric acid.

Because the recurrence rate is high for a simple case of BV, I can make a compelling case for using an integrative approach with both antibiotics and natural agents. I also prefer to use vaginal antibiotics, rather than systemic, for this condition. The overriding concept is to restore normal vaginal ecology with lactic acid producing lactobacilli species to be dominant. A normal vaginal pH is more acidic in the range of 3.5-4.5, that is why you see the acidic items of vitamin C, boric acid, and lactic acid producing lactobacilli.

Sample Acute Bacterial Vaginosis Plan, Natural Medicine Only

- Insert vaginal vitamin C tablet (250 mg) daily for 6 days (consider proprietary product such as Vfresh from Vitanica), then
- Insert boric acid 600 mg suppository 1/day for 10 days, then once weekly for 6 weeks.
- Insert a women's probiotic that has *L. rhamnosus/L. reuteri* and with one or more others, including *L. acidophilus, L. plantarum, L. salivarius, L. crispatus*; insert once weekly for 6-12 weeks
- Oral women's probiotic same/similar to above: 10 billion per day for 1-3 months

Sample Acute Bacterial Vaginosis Integrative Plan

- Metronidazole gel 0.75% insert nightly for 5 days or clindamycin 2% intravaginally nightly for 7 days or clindamycin ovules insert once daily for 3 days.
- Follow with inserting the women's probiotic as stated above, daily for 4 days then twice weekly for 3-6 months
- Oral women's probiotic same/similar to above- 10 billion per day for 1-3 months

Sample Chronic Recurring Bacterial Vaginosis Integrative Plan

- Metronidazole gel 0.75% insert nightly for 5 days or clindamycin 2% intravaginally nightly for 7 days or clindamycin ovules insert once daily for 3 days
- Then insert Metronidazole 0.75% gel once weekly for 4 months.
- Also Insert a women's probiotic that has *L. rhamnosus/L. reuteri* and with one or more others including *L. acidophilus, L. plantarum, L. salivarius, L. crispatus*; insert once weekly for 4 months
- Oral women's probiotic same/similar to above: 10 billion per day for 4 months
- Insert boric acid capsules once weekly for 4 months (during the same 4 months as the vaginal antibiotic and the vaginal probiotic – just on different nights) .
- If heterosexual, use condoms to avoid the alkalinizing effect of semen. Oral sex with a woman or a man can also be a pH challenge to the vagina

Cohen C, et al. Randomized trial of Lactin-V to prevent recurrence of bacterial vaginosis. NEJM. 2020 May 14;382:1906

Disclosure: Dr Hudson is the director of education and formulator and co-owner of Vitanica.

The Potential Importance of Vitamin D and COVID-19

We've all read and heard many things the last three months about viruses, antibodies, testing, treatments and prevention for COVID-19. I've hesitated to write about any natural medicines that might have a protective or intervention role, but I have found this current update on vitamin D to be safe and valuable enough, to pass along.

Vitamin D has been well known for quite a long time for its role in bone health, cardiac health, mood, and even immune health. But now, there is emerging and a growing body of evidence that vitamin D status may be relevant to the risk of developing COVID-19 infection and to the severity of the disease.

Vitamin D is important to what is called innate immunity and boosts immune function against viral diseases. Innate immunity refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body. These mechanisms include physical barriers such as skin, ➤

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chemicals in the blood, and specific immune system cells that attack these foreign antigens. We also know that vitamin D has an immune-modulating effect and can lower inflammation. This may be one of the relevant mechanisms involved in the respiratory response during the COVID-19 cytokine storm.

In some laboratory studies of respiratory cells, some of these effects of vitamin D have been documented. In addition, it has been detected that if one has lower levels of 25-hydroxy-vitamin D in the blood (which can easily be tested in a blood test), then they may be more susceptible to respiratory infections. There is now some evidence that this is also true in COVID-19 patients. In one observational study from three different South Asian hospitals, vitamin D deficiency was much more prevalent in those individuals with more severe COVID illness compared to those who were mildly ill. Specifically, there was about an eightfold higher risk of having severe illness if they had vitamin D deficiency compared to those who did not.

Two years ago, there was a meta-analysis of randomized clinical trials looking at vitamin D and acute respiratory infections. The results showed that vitamin D supplementation was associated with a 12% reduction in these acute respiratory infections. While this is statistically significant, it is small. However, if the deficiency was more profound, in the range of less than a blood level of 10 ng/ml of 23-hydroxy-vitamin D, there was a robust 70% lower risk of respiratory infection when vitamin D was supplemented.

The best source of vitamin D is sun exposure. This leads to increased synthesis of vitamin D in the skin. While we are spending more time indoors – both wintertime as well as "lock-down" guidelines – attention to vitamin D is even more important. Food sources are small, so supplementation becomes the most consistent method of assuring adequate levels. If you cannot or don't get tested, then most people will get enough from 2,000 I.U. per day of vitamin D in a pill. Some individuals will need more, at least for three months, if they are indeed vitamin D deficient or insufficient, which is determined from a blood test.

You can also look at food labels that list the vitamin D content. Food sources that are higher in vitamin D (although still not necessarily very much) include fortified dairy products, fortified cereals, fatty fish, and sun-dried mushrooms.

Researchers are in the process of planning a randomized clinical trial of vitamin D supplementation in moderate to high doses to see whether it has a role in the risk of developing COVID-19 infections and also in reducing the severity of disease and improving clinical outcomes. I look forward to these results.

Resources

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➤ *continued from page 84*

diet or a diet in which all foods high in nickel content were prohibited. Starting on day 15 of the diet, all patients were treated with 15 mg of lansoprazole, 500 mg of clarithromycin, and 1,000 mg of amoxicillin, each twice a day for seven days. *H. pylori* eradication was assessed by the urea breath test 4 weeks after the end of treatment. The eradication rate was significantly higher with the low-nickel diet than with the standard diet (84.6% vs. 46.2%; $p < 0.01$).[6]

Discussion

A definitive demonstration that ingested nickel is the cause of symptoms requires a double-blind oral challenge with a nickel salt while patients are consuming a low-nickel diet. One of the dermatological studies described above conducted such a challenge, but the studies on IBS and *H. pylori* eradication did not. IBS is caused or exacerbated in many cases by allergic reactions to foods or by highly fermentable, poorly absorbed carbohydrates (collectively referred to as FODMAPs) present in certain foods. A low-nickel diet excludes corn (which is a common allergen); cauliflower, peas, mushrooms, and onions (which are high in FODMAPs); and wheat (which is both a common allergen and high in fructans [one of the FODMAPs]). With regard to *H. pylori* eradication, there is a plausible physiological rationale for using a low-nickel diet, and there is no evidence that avoiding allergenic foods or high-FODMAPs foods influences the eradication rate.

While further research is needed, the available evidence suggests that consumption of a low-nickel diet is beneficial for some patients with dermatological conditions or irritable bowel syndrome, and for those undergoing *H. pylori* eradication therapy.

Information on the nickel content of foods is available from a number of different sources.[7-10] It should be noted that nickel may leach from nickel-plated or stainless steel food utensils and from stainless steel cookware, particularly during exposure to acidic foods at high temperatures. Among the naturally occurring organic acids that dissolve stainless steel, oxalic acid is the most active. Citric acid and malic acid may also dissolve nickel.[11] In addition, nickel may leach into tap water from plumbing; this source of exposure can be minimized by discarding the first liter of tap water in the morning.

Alan R. Gaby, MD

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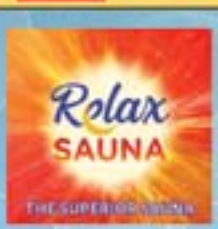

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Conditions That May Benefit from a Low-Nickel Diet

Nickel is a metallic element that is present in small but varying amounts in most foods. Although nickel is an essential nutrient for chicks, rats, and swine,[1] it has not been demonstrated to have a biochemical function in humans and is not considered an essential nutrient for humans. Nickel is best known to healthcare practitioners as a substance that can cause contact sensitivity, resulting in eczema, urticaria, and other skin conditions. It is not as well appreciated that these conditions can also be triggered in sensitive people by ingestion of nickel that occurs naturally in food or that leaches into food from sources such as stainless steel cookware. The adverse dermatological effects of ingested nickel are generally dose-related and are influenced by individual differences both in the capacity to absorb nickel and in sensitivity to the metal. In many patients with nickel-induced dermatoses, consumption of a low-nickel diet results in clinical improvement. Recent research indicates that consuming a low-nickel diet may also improve symptoms of irritable bowel syndrome, and can increase the effectiveness of eradication therapy in patients with *Helicobacter pylori* infection. Studies examining the effects of a low-nickel diet are summarized below.

Skin Conditions

Two hundred four patients with chronic dermatitis (mostly eczema) that was thought to be due to nickel sensitivity were studied. Nickel sensitivity was suspected in 61 patients because the dermatitis flared after oral challenge with 2.5 mg of nickel, despite having a negative patch test to nickel. The rest of the patients had a positive patch test and were not challenged orally with nickel. All patients adhered to a low-nickel diet for at least one month. After one to two months on the diet, the dermatitis was markedly improved in 59% of the patients, including 16% who experienced complete resolution of the lesions. The diet was equally effective among patch test-positive and patch test-negative patients. The majority of patients identified one or more foods that caused their dermatitis to flare on at least two separate occasions, the most common of which were wine, beer, and chocolate.[2]

One hundred twelve patients with contact sensitivity to nickel salts (determined by a positive patch test) who suffered from chronic urticaria, pruritus, atopic dermatitis, pruriginous eczema, or other skin disorders were placed on a low-nickel diet for four weeks. Those whose symptoms improved greatly were challenged, in double-blind fashion, with oral doses of 2.23 and 4.47 mg of nickel (from 10 and 20 mg of nickel sulfate hexahydrate, respectively). The low-nickel diet resulted in significant improvement or complete resolution of symptoms in 39% of the patients, including 37% of those with urticaria. The challenge test was positive in all but one of the patients, and the reaction was severe in a substantial minority of patients, including 4 of 15 with urticaria. In the patients with anaphylactoid reactions to the oral challenge, skin-prick tests were negative and no serum-specific IgE antibodies against nickel were found.[3]

Irritable Bowel Syndrome

Twenty adults (mean age, 42 years) with irritable bowel syndrome (IBS) and a positive patch test to nickel were prescribed a low-nickel diet for three months. It was not stated what proportion of the IBS patients that were screened had a positive patch test. Significant improvements were seen in bloating, abdominal pain, epigastric pain, abdominal cramps, flatulence, constipation, and diarrhea. For most of these symptoms, the mean improvement was 50% or more.[4]

Twenty women with celiac disease in remission on a gluten-free diet, who were experiencing IBS-like symptoms or extraintestinal symptoms and who did not have evidence of lactose intolerance, underwent a nickel patch test on the oral mucosa. In this test, a 5% nickel sulfate solution is applied to the mucosa of the upper lip and held in place by an adhesive film. The test is considered positive if the patient develops local reactions (such as edema, hyperemia, or aphthous lesions) or general symptoms (such as swelling, abdominal pain, diarrhea, headache, foggy mind, or itching). All 20 women had a positive patch test, and all went on a low-nickel diet, for three months. On this diet, 20 of 24 symptoms (12 of 15 gastrointestinal symptoms and 8 of 9 extraintestinal symptoms) improved.[5]

***Helicobacter pylori* infection**

Helicobacter pylori contains a nickel-dependent enzyme, NiFe-hydrogenase, which helps the organism survive the acid environment of the stomach. Urease is another nickel-dependent enzyme produced by *H. pylori*. This enzyme catalyzes the hydrolysis of urea in gastric juice to form ammonia, which protects *H. pylori* by increasing gastric pH. In a randomized controlled trial, consumption of a low-nickel diet significantly increased the *H. pylori* eradication rate in patients receiving eradication therapy.

Fifty-two patients with newly diagnosed *H. pylori* infection were randomly assigned to consume a standard

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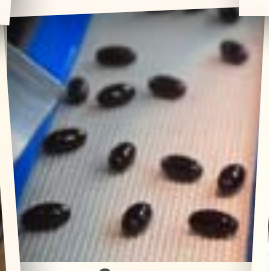

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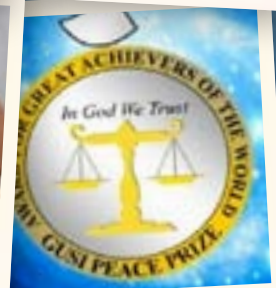

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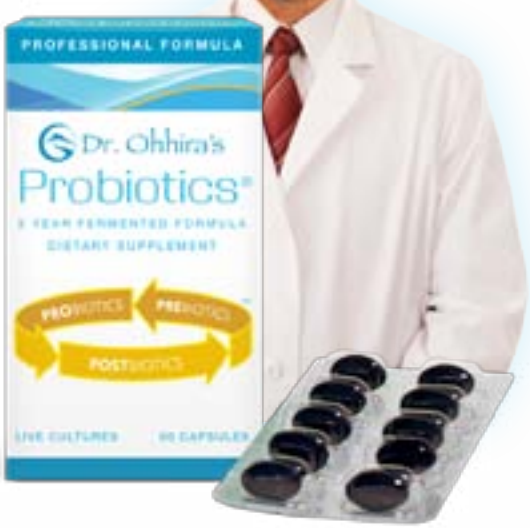

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