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Deborah McKay, ND
Rebalancing Hormones

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1) Sinha R, Sinha I, Calcagnotto A, et al. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. Eur J Clin Nutr. 2018;72(1):105-111. doi:10.1038/ejcn.2017.132

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From the Publisher

The Winter of Our Discontent

Borrowing from the title of John Steinbeck's last book who in turn borrowed from the first two lines of William Shakespeare's *Richard III*, our country has certainly fallen into a state of exhaustion, not so much from moral decay as from decrepitude from social isolation and pandemic angst. The coronavirus has evolved into Omicron, a more contagious but apparently less virulent variant compared to Delta. With its detection in the US in November, a surge of cases, hospitalizations, and deaths has once again developed, although more cases and hospitalizations than deaths. While in the fall restaurants and theatres were opening up, the winter has shut down many public events. Airline cancellations have made travel a nightmare; who wants to face days of lumbering around an airport while awaiting a standby flight to or from a destination? Social media shows folks smiling as they manage to escape to a sunny beach, a brief respite from the insanity that continues in our daily lives. Many corporations ordered folks back to the office in the fall only to backtrack and okay working from home once again. Despite gargantuan shipping blockages in ports from Long Beach to Shanghai, the great Christmas Scrooge did not happen; and consumers were able to

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Dr. Iichiroh Ohhira: A Pioneering Genius in Probiotic Science

Malaysian Mystery – 'Drinking Fermented Elixir'

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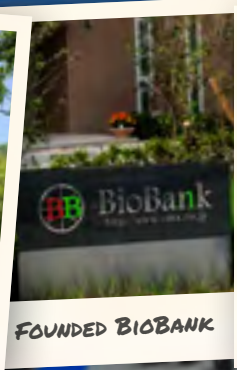

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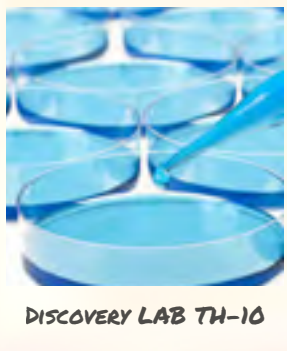

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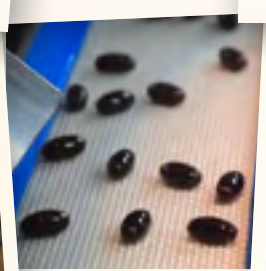

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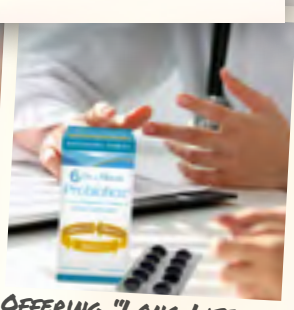

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Letter from the Publisher

➤ *continued from page 2*

buy ever more electronics, apparel, toys, and cars, a cosmetic panacea for our ills. The classroom is open once again, albeit with frequent COVID-19 case shutdowns; yet many kids are being left behind, not just intellectually a year or two, but also impaired from the ongoing social isolation and dependence on TikTok and Instagram for their emotional needs and gratification. Zoom is not how kids are meant to socialize, yet it is a staple of life now. How are we to "get our life back" as folks like to say?

The government has done everything possible to mandate vaccinations. And a growing portion of the population has vaccinated and gotten boosters. In some cities a vaccine passport is the gateway to entry. An "anti-vax" portion of the population refuses to vaccinate and, in some circumstances, wear a mask. The polemics for and against vaccination have become very loud, indeed. Those against vaccination seek tools to battle the virus such as nutraceutical supplements of vitamins D, C, A, glutathione, zinc, and herbals such as elderberry, turmeric, and ginger. Moreover, off-label drugs are requested, especially ivermectin, with pro-vaccinators belittling its use as horse medicine. The use of the psychiatric drug, fluvoxamine, as a treatment support for COVID-19 appears to be very promising, especially as it appears to not only be effective in reducing hospitalizations and death but have less side effects compared to the soon to be approved drug Paxlovid, which likely will experience shortages.

Yet, the biggest obstacle to life returning to normal is the ICU battle zone that continues to plague hospitals. As this is being written just prior to the New Year, hospitals are particularly hard hit in the north of the US, coincidentally the same places with the coldest temperatures and least amount of sunlight. This would ordinarily be the same prevalence of upper respiratory infection and flu that we experience each winter; it is again remarkable that with the Omicron surge, the flu and other respiratory infections have dramatically decreased. Does Omicron compete with other upper respiratory viruses preventing their infecting us? Likely.

Once upon a time we were a carefree albeit careless society and we took our colds and flus out to work, school, into society. We participated in life as we pleased and we took our chances whether we would come down with an illness or not. And the unlucky few did become sick, usually staying home nursing oneself back to health, with those too sick ending up in the hospital. COVID-19 has been a nasty pandemic and a great many folks did die especially in the first year; now the death rate from COVID appears to be tapering off and appears to be similar to what we typically face each year with upper respiratory infections. Sixty percent of the US population is vaccinated with an even higher percentage in those above 65 years old.

My crystal ball forecasts a gradual but definite decrease in this surge as we move through February and March. We have the tools to return society back to normal and we should no longer maintain draconian measures. We also need to regain our neighborliness and no longer socially isolate. Those of us who need additional immune support should avail themselves of all the tools, be it vaccine, nutraceutical, or drug agent. We do need to heal ourselves energetically, as well, by massage and acupuncture, by meditation and fasting, and by bringing in the light and love and prayer.

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Letter from the Publisher

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Cover Article: A Surprising Menopause Case Study by Deborah McKay, ND

The Women's Health Initiative published in 2002 caused a major upheaval in the treatment of menopausal women. The benefits attributed to the use of estrogen and progestins were largely limited to improvement in vasomotor symptoms; increased risks for developing cancer and cardiovascular disease impugned the use of hormone replacement. It was as if someone turned off the faucet. All at once doctors stop prescribing Prempro (equine estrogen and medroxyprogesterone acetate) and patients discontinued their prescriptions. A lot of women suffered with hot flashes and felt miserable throughout perimenopause without hormone support.

In the mid-2010s data from the Women's Health Initiative was reevaluated. Instead of the combined use of estrogen and progestin being held responsible for increased cancer and heart-related deaths, it was the progestogen, Provera, that was being prescribed ironically to prevent uterine cancer, that was thought to increase breast cancer risk and cardiovascular death. Estrogen hormone replacement was determined not only to be without such risks but beneficial for women during menopause. Now university medicine encourages estrogen hormone replacement during menopause and is attempting to reverse the disinformation that estrogen is harmful not only with patients but overly cautious practitioners.

The British physician Katharina Dalton clamored for the use of bio-identical progesterone in the treatment of younger women suffering from premenstrual syndrome. Raymond Peat, PhD, formerly a professor at the University of Oregon, also championed the use of bio-identical progesterone in PMS as well as menopause, condemning the use of progestogens such as Provera, citing evidence that only progesterone behaves appropriately as a hormone while progestins impair normal hormone activity. After the Women's Health Study threw a cold towel on treating menopausal woman with hormone replacement, Suzanne Somers advocated for the use of hormone replacement but only with the use of bio-identical hormones, writing about her own experiences in several best-selling books.

Jonathan Wright, MD, introduced colleagues in integrative and naturopathic medicine to TriEst, a bio-identical hormone combination of estrone, estradiol, and estriol. The latter, estriol, was an important cancer-sparing estrogen that Wright believed was missing from most hormone-replacement prescriptions. Wright was one of the earliest proponents of testing urinary hormone metabolites, a testing procedure that yielded far more useful information regarding hormone status than blood testing. Based on such testing, Wright proposed that it was necessary to individualize bio-identical hormone prescriptions based on normalizing metabolites that were reduced or increased. Over the past decade salivary testing of hormones and metabolites has developed – blood, urine, and saliva testing of hormones offer multiple means to monitor treatment.

Unfortunately, the FDA is now considering regulating and possibly outlawing compounding pharmacies from making bio-identical hormones. Without compounding, it is likely that women (and men) will be prescribed hormone prescriptions that are unsuitable and potentially harmful. **Please write to the FDA and your Congressperson to protest the FDA regulation of bio-identical hormones.**

Our cover story in this issue, "A Surprising Menopause," by Deborah McKay, ND, offers a very informative case review of a 50-year-old woman presenting not just with irregular periods but a "laundry list" of many other disturbing, chronic symptoms. For the practitioner, particular the clinic doc who has 15 minutes to see a patient, how does one manage such a laundry list? Usually by addressing the most pressing single concern verbalized by the patient. As McKay points out, such a limited focus ignoring the full picture portends a dismal treatment response and unlikely successful recovery. McKay discusses the challenging need to understand the multiple system dysfunction, each necessitating individual assessment and intervention. McKay, who is a bio-identical hormone specialist in Portland, Oregon, and is a founding member of EndoANP, emphasizes the need to educate the patient in order to achieve dietary and lifestyle changes and compliance with hormone, herbal, and nutraceutical prescriptions. McKay also emphasizes that one cannot ignore the emotional blocks that impact the healing process and offers some in-office tools for the practitioner to use.

The case is presented in two parts as originally published in *NDNR* in 2019. Part 2 of Dr. McKay's surprising case of menopause will be published in our April issue.

Reducing Osteoporosis Risk of Fractures by Tori Hudson, ND

A lot of my patients confuse osteoporosis with osteoarthritis. They are aware that untreated osteoporosis may lead to a hip fracture, but they will attribute arthritic pain to their osteoporosis. For some it is difficult to understand that thinning of the bones does not lead to pain unless a vertebral or wrist bone has fractured. Then there is the confusion when a hip is broken following a fall; was the fall first breaking the hip or vice-versa. In any case, until the fracture happens, like hypertension, osteoporosis is a silent condition. And like hypertension, unless you take a measurement, bone density, there is no evidence that bone loss is taking place.

The question that we need to ask is how do we reduce the chances of a fracture occurring? The logical assumption is that if we can stop bone loss or even better, regrow bone, the risk of a fracture is reduced. But growing back bone is not a simple task. Certainly, it is nothing like what a recent monthly doctor's newsletter claimed: "…the natural secrets you NEED to get bones of steel!" Bones of steel? Hah. The population we are focusing on are individuals over age 65 who are becoming more and more osteoporotic as each year slips by. If we can manage to get Mrs. Jones through her 80s without a bone fracture, that is the hallmark of good osteoporosis care. No one is seeking super strong bones.

Still patients are rightfully concerned about being placed on prescription medication to address osteoporosis. Many of these medications pose significant side effects, not a pleasant way to spend one's golden years. On the other hand, do we truly have effective nutraceutical tools to counter osteoporosis fracture risk? Tori Hudson, ND, tackles this question in this issue. No matter what our distaste may be for pharmaceuticals, if the bone density reveals worsening osteoporosis, drug therapy is probably required.

Jonathan Collin, MD

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Shorts

briefed by Jule Klotter
jule@townsendletter.com

Probiotics and GI Function in Pregnancy

Researchers at University of California-Davis recently showed that a commercial probiotic reduced nausea, vomiting, and constipation in 32 pregnant women. At enrollment, the women (age 31.6 ± 3.9 years), all in the first trimester of pregnancy, experienced a mean incidence of nausea of 7.0 ± 5.5 times per day and 10.3 ± 6.6 hours; the mean nausea score (1-5) was 3.6 ± 0.9. Twelve of the women vomited a mean of 2.0 ± 1.3 times per day; the mean vomiting score was 2.8 ± 1.0.

The 16-day study consisted of two cycles during which Probiotics 10 (Nature's Bounty, Ronkonkoma, NY) was taken daily for six days followed by two days without the supplement. The probiotic contained inulin (200 mg), nine *Lactobacillus* strains, and *Bifidobacterium lactis Bl-04.* The participants completed a daily survey that tracked GI symptoms (nausea, vomiting, constipation), energy level, and quality of life. Fecal samples were also taken, allowing the researchers to investigate gut metabolites, fecal microbiota, and bacterial genes.

Probiotic intake significantly reduced nausea incidence by 16%, nausea hours by 16%, and vomiting incidence by 33%. Stool hardness, a sign of constipation, also decreased. Quality of life measures, including ability to prepare meals, reactivity to smells, fatigue, and moodiness, improved.

The researchers reported some interesting associations between biomarkers found in stool samples and symptoms. Patients with high fecal α-tocopherol levels at baseline had low vomiting scores throughout the study. Also, vomiting incidence directly associated with the amount of *Akkermansia* bacteria in fecal samples. Probiotic intake decreased *Akkermansia* levels and increased α-tocopherol levels, although the changes were not statistically significant due to small sample size.

The researchers also looked for butyric acid-producing genes and bile acid-producing genes in fecal samples. While neither the butyric acid-producing genes (*bcoA* and *buk*) nor the bile acid-producing gene *baiJ* was affected by probiotic intake, the bile acid gene *bsh* (bile salt hydrolase), which generates free bile acids, was: "…the copy number of *bsh* increased significantly by 5.41-fold due to probiotic intake." Low *bsh* was associated with high vomiting scores. Bile acids, produced by gut microbial enzymes and by the liver, "regulate smooth muscle contraction, defecation, and sensation in addition to lipid metabolism and absorption." Both *Lactobacillus* and *Bifidobacterium* generate bile salt hydrolase.

The authors call for further investigation into the use of probiotics and their effect on bile acid during pregnancy. This study was neither randomized nor placebo controlled, and it did not look at long-term, possibly cumulative effects of probiotic supplementation.

Liu AT, et al. Probiotics Improve Gastrointestinal Function and Life quality in Pregnancy. *Nutrients.* 2021;13:3931

Heavy Metals, Trace Elements, and Childhood Blood Pressure

While many studies have correlated a single metal or element to a health outcome, trying to track nonlinear associations between metal-element combinations has been problematic. In June 2020, Johns Hopkins researchers published a study that used data from the Boston Birth Cohort (enrolled 2002-2013) and a newer statistical method, Bayesian kernel machine regression (BKMR), to examine the effect of metal co-exposures on children's blood pressure. Higher blood pressure during childhood is associated with cardiovascular disease and hypertension in adulthood.

The researchers included 1,194 mother-child dyads in their analysis. Blood samples taken from the mothers 24 to 72 hours after delivery provided red blood cell concentrations of three heavy metals (lead, mercury, cadmium) and two trace minerals (selenium, manganese). They looked for associations between these concentrations and the offspring's blood pressure taken at the most recent wellness visit. The researchers also collected data on the mother's health during pregnancy, socioeconomic factors, fish consumption, and cigarette smoking.

Although the researchers did not find an association between child blood pressure and either lead or mercury, cadmium (Cd) levels did directly correlate with child systolic blood pressure *when manganese* (Mn) *levels were low* and "inverse association between Mn and child SBP was stronger at higher levels of Cd." Smoking is a known source of Cd exposure. The researchers

found that Cd concentration in smoking mothers (median = 1.41 µg/L) was over twice the concentration in those who did not smoke or who quit before pregnancy (median = 0.65 µg/L). If the smoking mother also had a higher concentration of Mn in her blood, her child's systolic blood pressure (SBP) tended to be lower than children born of smokers with lower Mn levels – but not as low as SBP found in children with non-smoking mothers.

In a commentary on this study Breton and Farzan ask, "As more evidence emerges showing interactions between trace elements and metals in pregnancy, should we more seriously consider targeted use of essential elements in populations with known high exposures to potentially toxic metals? Might nutritional intervention mitigate risk?"

Breton CV, Furzan SF. Invited Perspective: Metal Mixtures and Child Health: The Complex Interplay of Essential and Toxic Elements. *Environmental Health Perspectives.* June 2021;129(6).
Zhang M, et al. *In Utero* Exposure in Heavy Metals and Trace Elements and Childhood Blood Pressure in a US Urban, Low-Income, Minority Birth Cohort. *Environmental Health Perspectives.* June 2021;129(6).

Microplastics and Pregnancy

Plastic is causing an ever-growing list of negative health effects. For years, studies have documented the endocrine-disrupting effects of plastic chemicals; such studies have shown an association between endocrine-disrupting compounds (EDCs) and infertility and gestational disorders, including miscarriage, preeclampsia, and fetal growth restriction. In addition to disrupting hormone-guided physiology, a 2021 Australian study, led by John E. Schjenken, reports that EDCs affect the maternal immune response to pregnancy that permits embryo implantation and placenta development. But the chemicals are only part of the health issue; microplastics are another problem.

A 2020 Italian study, led by Antonio Ragusa, found microplastic fragments in four placentas taken from healthy women who had a vaginal delivery. Microplastics (MPs), particles smaller than five millimeters, result from plastic degradation in the environment. These minute bits of plastic also have commercial uses. MPs have been found in marine life and in human intestines, but this is the first evidence of MP affecting the human fetus.

The Italian researchers collected three samples, each weighing 23.3 ± 5.7 grams, from each placenta (total placenta weight is about 600 g): one from the maternal side, one from the fetal side, and one from the chorioamniotic membranes. Using Raman microspectroscopy, they found 12 plastic fragments (ranging from 5 to 10 µm): four in the maternal side, five in the fetal side, and three in the membranes. The fragments were small enough to be transported in the bloodstream; the fragments could have entered the mother's body via ingestion or inhalation. The Italian researchers say, "… MPs may accumulate and exert localized toxicity by inducing and/or enhancing immune responses and, hence, potentially reducing the defence mechanisms against pathogens and altering the utilization of energy stores." They also suggest that MP presence may have transgenerational effects on metabolism and reproduction. Studies are needed to identify possible adverse effects on immune responses and pregnancy issues.

Babies are also exposed to significant amounts of microplastics from plastic (polypropylene) bottles. A team

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of Irish researchers looked at the amounts of MPs released from polypropylene infant-feeding bottles (PP-IFBs) when World Health Organization recommendations for cleaning and sterilizing the bottles and mixing up baby formula were used. They quantified MP-release from ten different polypropylene infant-feeding bottles, "accounting for 68.8% of the global market." Bottles with polypropylene bodies (n=8) released from 1,310,000 ± 130,000 to 16,200,000 ± 1,300,000 particles per liter – far above 1000 particles that WHO deems "low risk." Heat and agitation during cleaning/sterilization and the heating of formula or breast milk cause MPs to be released from the bottle. Microwave heating is particularly problematic because it produces "pockets of superheated water" that cause higher MP generation. Breast pumps with plastic parts can also degrade during cleaning and sterilization. Old fashion, glass bottles without plastic parts, of course, cannot produce MPs.

Endocrine and immune effects are not the only health issues with MPs. A 2021 study from the New Jersey Institute of Technology found that some bacteria found in wastewater plant sludge become antibiotic resistant when exposed to microplastic: "…certain strains of bacteria elevated antibiotic resistance by up to 30 times while living on microplastic biofilms…." The researchers collected sludge samples from three New Jersey wastewater treatment plants and inoculated the samples with polyethylene and polystyrene microplastics in order to identify which bacteria tend to grow on MPs. They also tracked genetic changes in the bacteria. Genes related to resistance to sulfonamides (a common type of antibiotic) increased up to 30 times with MP exposure, compared to sand-biofilm controls. When the antibiotic sulfamethoxazole was added to the sample, the antibiotic resistance genes further increased by up to 4.5-fold. Dung Ngoc Pham, first author of the study, told PHYS.org, "'Previously we thought the presence of antibiotics would be necessary to enhance antibiotic-resistance genes in these microplastic-associated bacteria, but it seems microplastics can naturally allow for uptake of these resistance on their own….The presence of antibiotics does have a significant multiplier effect however.'"

A quick look at Scholar.Google shows that microplastic pollution and bioremediation of the environment is a growing topic. Consumers need to be aware that these fragments are making their way into our bodies and lessen exposure whenever possible.

Jenkins J. New study shows microplastics turn into 'hubs' for pathogens, antibiotic-resistant bacteria. *Phys.org.* March 19, 2021.

Li D, et al. Microplastic release from the degradation of polypropylene feeding bottles during infant formula preparation. *Nature Food.* 2020;;1: 746-754.

Ragusa A, et al. Plasticenta: First evidence of microplastics in human placenta. *Environment International.* 2021; 146; 106274.

Schjenken JE, et al. Endocrine Disruptor Compounds – A Cause of Impaired Immune Tolerance Driving Inflammatory Disorders of Pregnancy? *Frontiers in Endocrinology.* April 2021;12:article 607539.

Jenkins J. New study shows microplastics turn into 'hubs' for pathogens, antibiotic-resistant bacteria. *Phys.org.* March 19, 2021.

Exposure to Nature and Children's Immune Function

Finnish researchers recently conducted a study that showed exposure to nature's biodiversity affects human commensal microbiota and immune function. The study involved 75 children (ages 3-5 years), living in one of two cities with populations over 100,000 people. None of the children were taking probiotics or antibiotics. The children attended a nature-oriented daycare (n=23); a standard, unmodified, urban daycare with gravel and little or no greenspace (n=16); or an "intervention" urban daycare (n=36) – standard urban daycares with forest floor (100 m^2), sod (200 m^2), peat blocks for climbing and digging, and planters added to their yards. The forest floor included vegetation (dwarf heather, blueberries, crowberry, mosses, and meadow grass).

Daycare workers encouraged children to have contact with the vegetation and natural materials during their time outdoors (0.5 to 2 hours twice a day; average 1.5 hours/day). Although the researchers could not control for home diet, they did have a central kitchen in each city prepare breakfast, lunch, and an afternoon snack for all the participants during the 28-day study (May to June 2016). The researchers looked at skin bacterial diversity, gut bacteria, and plasma cytokine changes in the three groups of children.

Before daycare yards were modified with vegetation, the children in the urban group and the intervention group had similar composition of the bacteria on their skin, including similar Proteobacterial communities. At the end of the 28 days, the intervention group had more diverse Proteobacterial and Gammaproteobacterial communities, similar to children attending nature-oriented daycares.

Greater skin Gammaproteobacterial diversity was associated with higher transforming growth factor β1 (TGF-β1) plasma concentration; TGF- β1 "is a multifunctional cytokine that down-regulates inflammatory processes, particularly in the gut-associated immune system." High Gammaoproteobacterial diversity in the skin microbiome is also associated with increased IL-10 plasma concentrations; IL-10 is an anti-inflammatory cytokine. By study's end, children in the intervention group had an increased IL-10:IL-17A ratio (more anti-inflammatory cytokines than pro-inflammatory cytokines). The researchers suggest, "…providing children with a chance for daily contact with diverse vegetation and dirt in safe urban green spaces…might improve child health by activating the regulatory pathways of the immune system. This could reduce overactive immune responses and, consequently, decrease the risk of developing immune-mediated diseases."

The intervention also changed gut bacteria composition. The relative abundance of Clostridiales decreased in the intervention group, compared to standard daycare participants; and alpha Rumioncoccacea communities became "slightly more divergent" after the 28 days. Ruminococcaceae contains butyrate-producing species. Interestingly, the forest floor and sod used in the intervention spaces did not contain the Ruminococcaceae strains found in children's stool samples. The researchers think the transplantation of the green materials may have rejuvenated microbial communities that were basically dormant: "We recommend following the effects of biodiversity intervention over a longer period to understand the microbial community dynamics on daycare yards and to see the longevity of changes in plasma cytokines."

Roslund MI, et al. Biodiversity intervention enhances immune regulation and health-associated commensal microbiota among daycare children. *Sci Adv.* October14, 2020; 6: eaba2578.

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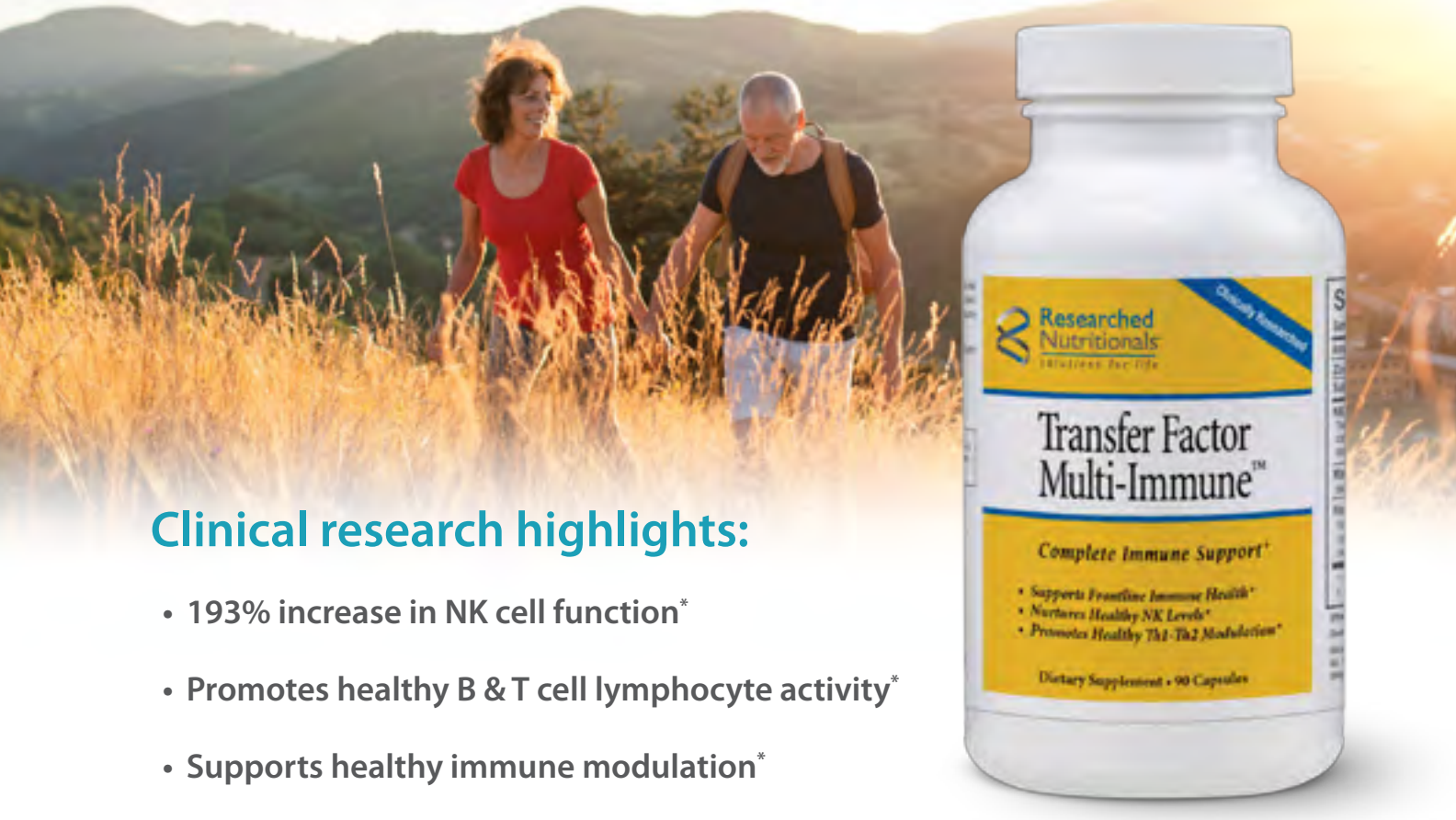
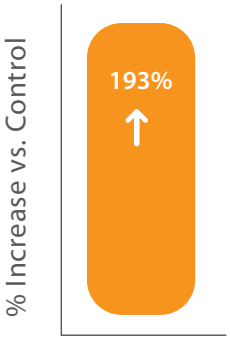


Clinical research highlights:

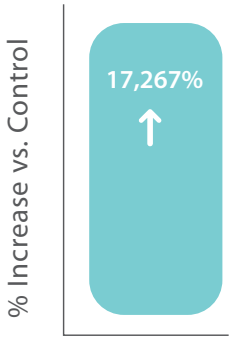
- 193% increase in NK cell function*
- Promotes healthy B & T cell lymphocyte activity*
- Supports healthy immune modulation*

NK CELL ACTIVATION*



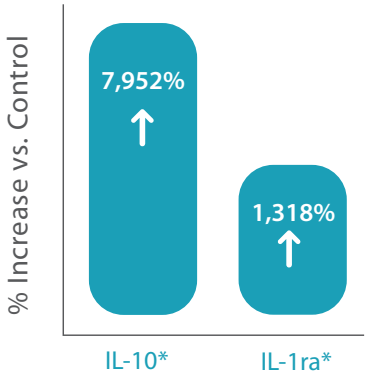
(*Mean fluorescent intensity for CD69 receptor on natural killer cells & CD69 / CD25 receptors for lymphocytes)

LYMPHOCYTE ACTIVATION*



(*Mean fluorescent intensity for CD69 receptor on natural killer cells & CD69 / CD25 receptors for B & T-cell lymphocytes)

IMMUNE MODULATION*



(* Mean fluorescent intensity on peripheral blood mononuclear cell cultures)

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Literature Review & Commentary

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

Does Eating a Plant-Based Diet Decrease the Severity of COVID-19 Infections?

Two thousand eight hundred eighty-four healthcare workers (95% physicians, 70% male) from six countries (France, Germany, Italy, Spain, United Kingdom, and United States) who had had substantial exposure to COVID-19 patients completed a survey from July 17, 2020 to September 25, 2020 regarding diet, demographic characteristics, and COVID-19 outcomes. Five hundred sixty-eight of these individuals had been infected with COVID-19 (defined as having symptoms consistent with COVID-19 and/or having a positive PCR or antibody test), and 2,316 had not been infected (controls) (defined as having a negative test and/or no history of symptoms consistent with COVID-19). Among the 568 COVID-19 cases, the illness was moderate-to-severe in 138 individuals and very-mild-to-mild in 430 individuals. After adjustment for potential confounding variables (including age, sex, race/ethnicity, smoking, physical activity, body mass index, and presence of a medical condition), those who followed a plant-based diet had a 72% lower risk of having moderate-to-severe COVID-19, compared with individuals who did not follow such a diet. Participants who followed either a plant-based diet or a pescatarian diet (plant-based diet that included fish and seafood) had a 59% lower risk of having moderate-to-severe COVID-19, compared with participants who did not follow one of these diets.

Comment: In this study, people who consumed a plant-based diet, with or without fish and seafood, had less severe COVID-19 infections than people who consumed omnivorous diets. While observational studies cannot prove causation, one of the strengths of this study is that it controlled for various factors that predict outcomes in COVID-19 cases, such as age, race, body mass index, and presence of comorbid conditions. If plant-based diets decrease the severity of COVID-19 infections, one possible explanation might be that such diets contain a higher amount of vitamin C and other protective micronutrients. In addition, plant foods tend to promote less inflammation than meats and other animal foods. It is conceivable that a person with chronic low-level inflammation would be less likely to tolerate the inflammatory response to a COVID-19 infection.

Kim H, et al. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries. *BMJ Nutr Prev Health*. 2021;4:257-266.

Ginger for Acute Gastroenteritis in Children

One hundred fifty children (aged 1-10 years; mean age, 5.5 years) with vomiting associated with acute gastroenteritis were randomly assigned to receive, in double-blind fashion, ginger or placebo. The dosage was 20 drops (containing 10 mg of ginger) every 8 hours until resolution of vomiting. Oral rehydration solution was started 30 minutes after the first dose of ginger or placebo. The primary outcome measure was the occurrence of one or more episodes of vomiting after treatment was started. The incidence of the primary outcome was 67% in the ginger group and 87% in the placebo group. This corresponded to an absolute risk reduction of 20%, indicating that for every five children treated with ginger, one child stopped vomiting who otherwise would have continued vomiting.

Comment: Most, but not all, studies have demonstrated that ginger can prevent motion sickness, nausea and vomiting of pregnancy, nausea and vomiting caused by cancer chemotherapy, and postoperative nausea and vomiting. It appears that vomiting associated with acute gastroenteritis in children can now be added to the list of conditions for which ginger is beneficial.

Nocerino R, et al. Efficacy of ginger as antiemetic in children with acute gastroenteritis: a randomised controlled trial. *Aliment Pharmacol Ther*. 2021;54:24-31.

Atkins Diet for Infantile Spasms

Ninety-one children (aged 9 months to 3 years) in India with infantile spasms that had failed to respond to adrenocorticotropic hormone (ACTH) or oral prednisolone and anticonvulsant medication were randomly assigned to consume a modified Atkins diet (diet group; n = 46) or their usual diet

(control group; n = 45) for four weeks. On the modified Atkins diet, carbohydrate intake was restricted to 10 g per day in children aged 18 months to three years, and 5 g per day in younger children. All children continued their antiepileptic drugs. At four weeks, the proportion of children who were free of spasms was higher in the diet group than in the control group (23.9% vs. 0%; $p \leq 0.001$). The median time before spasms stopped was 10 days (interquartile range, 9-20 days). Nine of the 11 children who became spasm-free had a resolution of hypsarrhythmia on electroencephalography. Thirty children (65.2%) in the diet group had a greater-than-50% reduction in spasms, whereas no child in the control group had that degree of improvement ($p < 0.001$). The most common side effect of the diet was constipation, which occurred in 34.8% of the children.

Comment: Infantile spasms (West syndrome) are a type of severe epilepsy characterized by recurrent seizures (spasms), an abnormal electroencephalographic pattern called hypsarrhythmia, and mental retardation. In some cases, the condition is secondary to brain damage caused by another disease, while in other cases the cause is unknown. Conventional treatments include ACTH, anticonvulsant medications, and vitamin B6.

The ketogenic diet has been used successfully in some children with infantile spasms. The Atkins diet is a low-carbohydrate, high-fat diet that has been used by millions of people for weight loss. Like the ketogenic diet, the Atkins diet can induce a state of ketosis, but it is less restrictive with respect to calorie and protein intake. In addition, unlike the ketogenic diet, the Atkins diet does not require fluid restriction and does not need to be started in the hospital. The improvements in the present study were similar to those seen with the ketogenic diet in children with infantile spasms. Because it is less restrictive, the modified Atkins diet may be considered as an alternative to the ketogenic diet in children with infantile spasms refractory to conventional therapy.

Sharma S, et al. Evaluation of the modified Atkins diet for the treatment of epileptic spasms refractory to hormonal therapy: a randomized controlled trial. *J Child Neurol*. 2021;36:686-691.

Low-Carbohydrate, Low-Glycemic-Index Diet for Children with Epilepsy

Forty children (aged 2-8 years; mean age, 3.9 years) in India with drug-resistant epilepsy were randomly assigned to consume a low-carbohydrate, low-glycemic-index diet for three months (n = 20) or to a control group that did not receive dietary advice (n = 20). On the intervention diet, carbohydrate intake was restricted to 10% of calories, or a maximum of 40-60 g per day. All children continued their antiepileptic drugs. The proportion of children who had more than a 50% reduction in seizure frequency (responders) was 30% in the diet group and 0% in the control group ($p = 0.02$). Of the six responders in the diet group, one was completely free of seizures during a follow-up period of 12 months and one had more than a 90% reduction in seizure frequency during a follow-up period of 10 months. Five patients successfully continued the diet after the study, for a total median treatment period of 8 months (range, 4-12 months). Three children on the diet had non-serious side effects (2 with lethargy, 1 with vomiting).

Comment: A classic ketogenic diet is effective in children with drug-resistant epilepsy, but it is not well tolerated. The results of the present study suggest that a low-carbohydrate, low-glycemic-index diet, which is less restrictive than a ketogenic diet, is also effective for some children and is reasonably well tolerated.

Lakshminarayanan K, et al. Efficacy of low glycemic index diet therapy (LGIT) in children aged 2-8 years with drug-resistant epilepsy: A randomized controlled trial. *Epilepsy Res*. 2021;171:106574.

Riboflavin for Pediatric Migraines

The authors of this study retrospectively reviewed data from 68 Japanese children (aged 6-15 years) with migraines, of whom 52 also experienced another type of headache. The children received 10 mg or 40 mg per day of riboflavin, based mostly on age. Migraine frequency per month was lower after three months of riboflavin supplementation than at baseline (median [interquartile range]: 4.0 [2-5] vs. 5.2 [3-7]; $p < 0.01$). Twenty-five children (36.7%) had a 50%-or-greater reduction in episode frequency (responders), while 18 (26.5%) had a 25-50% reduction. Children who had less than a 50% reduction

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Gaby's Literature Review

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in migraine frequency were classified as nonresponders. There was no significant difference between responders and nonresponders with respect to riboflavin dose, presence or absence of aura, age at headache onset, or age at consultation. However, nonresponders were more likely to have co-morbid non-migraine headaches (odds ratio = 4.11; p = 0.02), particularly tension headaches.

Comment: As the precursor of flavin adenine dinucleotide (FAD), a coenzyme involved in the electron-transport chain, riboflavin plays a role in mitochondrial energy production, which appears to be impaired in migraine patients. Riboflavin has repeatedly been shown to decrease migraine frequency in adults, but the results in children have been less clear. In an uncontrolled trial, of 41 children and adolescents with migraines who received 200 mg or 400 mg per day of riboflavin for up to six months, 68% had at least a 50% reduction in attack frequency.[1] However, in two double-blind studies in children and adolescents, supplementation with 50 mg or 200 mg per day of riboflavin for 12-16 weeks did not decrease the frequency or severity of migraines compared with placebo.[2-3] The results of the present study suggest that riboflavin is beneficial for children with migraines, especially if they do not also have tension headaches or other types of headaches. Perhaps the conflicting findings in children could be resolved by conducting a randomized trial in which children with co-morbid headaches are excluded.

Yamanaka G, et al. Effectiveness of low-dose riboflavin as a prophylactic agent in pediatric migraine. *Brain Dev*. 2020;42:523-528.

N-Acetylcysteine Shrinks Uterine Fibroids, or More Iranian Research Fraud?

Fifty women in Semnan, Iran, with uterine fibroids (leiomyomas) were randomly assigned to receive, in double-blind fashion, 600 mg per day of N-acetylcysteine (NAC) or placebo for 12 weeks. The mean decrease in fibroid volume was greater in the NAC group than in the placebo group (25.25% vs. 1.08%; p < 0.004).

Comments: As *Townsend Letter* readers know, I have been concerned that a large percentage of the nutrition research coming from Iran appears to be fraudulent. The present study has a number of problems.

1. Discrepancy regarding trial dates: The paper stated that the study was conducted in 2017-2019. The Iranian Registry of Clinical Trials (IRCT) document, which was registered on August 26, 2019, stated that the expected recruitment start date was February 7, 2018. The IRCT document also stated both "Registered while recruiting" and "Recruitment complete." Both of those cannot be true.

2. Discrepancy regarding funding: No funding source was listed in the paper. The IRCT document stated that the study was funded by Semnan University of Medical Sciences.

continued on page 18 ➤

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Gaby's Literature Review

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3. Ethical issue: The Ethics Committee approved the study on February 6, 2018. If the study began in 2017, as was stated in the paper, then it was begun before being approved by the Ethics Committee.

4. Discrepancy regarding inclusion criterion: The paper stated that the largest diameter of the fibroid had to be greater than 8 cm. The IRCT document stated that the leiomyoma had to be 3 to 8 cm in diameter.

5. Discrepancy regarding diagnostic methods: The paper stated that leiomyomas were diagnosed by transvaginal sonography. The IRCT document stated that the diagnosis was made by ultrasound, CT, or MRI.

6. Implausible baseline data: Although the women in the study had "recently presented with severe bleeding," all participants had a normal hemoglobin concentration. In contrast, a paper published in *J Family Reprod Health*. 2013;7(3):139-144 stated that the prevalence of anemia is 33% among women of reproductive age in urban and rural areas of Iran. Therefore, it is not plausible that all 50 women in this study with severe bleeding had a normal hemoglobin concentration.

7. Double-blind trials are expensive, and it is unusual to for researchers to conduct (or funding sources to fund) a double-blind trial when there is no prior evidence to suggest the treatment is effective (such as uncontrolled trials or case reports). In the paper cited above, the researchers stated, "To the best of our knowledge, there is no other article addressing the role of NAC in leiomyoma."

Aghaamoo S, et al. The effect of N-acetyl cysteine on the volume of uterine leiomyoma: A randomized clinical trial. *Int J Gynaecol Obstet*. 2021;154:521-525.

Vitamin D for Primary Dysmenorrhea, or More Iranian Research Fraud?

One hundred sixteen Iranian university students with primary dysmenorrhea and a serum 25-hydroxyvitamin D level below 30 ng/ml (mean, 19.75 ng/ml) were randomly assigned to receive, in double-blind fashion, 50,000 IU of vitamin D3 or placebo once a week for eight weeks. Compared with placebo, vitamin D decreased pain intensity at four and eight weeks, decreased the number of days with pain at four and eight weeks, and decreased number of pain medications used at four and eight weeks ($p < 0.001$ for each comparison).

Comment: Primary dysmenorrhea is a common condition characterized by pelvic or back pain during menstruation, often in association with headaches, nausea, or other symptoms. It is not uncommon for dysmenorrhea to be severe enough to cause absence from work or school. Vitamin D would be a welcomed advance in the treatment of primary dysmenorrhea, if it can be proven to be effective. One small double-blind trial conducted in Italy found that a single dose of 300,000 IU of vitamin D3, given five days before the expected onset of menstruation, significantly decreased menstrual pain, compared with placebo, during the next two cycles.[4] (My impressions regarding nutrition research from Italy are discussed below in relation to the study on alpha-lipoic acid.) Three other double-blind trials, all conducted in Iran, also found vitamin D to be beneficial. As I have stated repeatedly, I have doubts about the credibility of many studies coming from Iran. I have several concerns about the study reviewed above.

1. Discrepancies regarding inclusion criteria: The paper stated that the women had to be 18-32 years old to participate, whereas the Iranian Registry of Clinical trials (IRCT) document stated that they had to be 18-30 years old. The paper stated that the women had to have menstrual cycles of 22 to 35 days in order to participate, whereas the IRCT document stated that the cycles had to be 22 to 32 days.

2. Implausible baseline data: In Table 1, the mean menstrual cycle length was 23.2 ± 2.9 days in the vitamin D group and 23.9 ± 3.3 days in the placebo group. Assuming a normal (Gaussian) distribution, approximately 16% of the study participants would have had menstrual cycles lasting 20.45 days or less. However, women were ineligible to participate in the trial if their cycle length was less than 22 days.

3. Discrepancy regarding funding: The paper stated that there was no funding source, whereas the IRCT document stated that the study was funded by the School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences.

It is hoped that additional studies will be conducted by reputable researchers to determine whether vitamin D is an effective treatment for primary dysmenorrhea.

Rahnemaei FA, et al. Vitamin D supplementation for primary dysmenorrhea: a double-blind, randomized, placebo-controlled trial. *Obstet Gynecol Sci*. 2021;64:353-363.

Alpha-Lipoic Acid Improves Idiopathic Pain

Two hundred ten nondiabetic Italian adults with idiopathic pain (57 with neuropathic pain, 141 with arthralgia, and 12 with myalgia) who could not or did not want to take analgesic medication were randomly assigned to receive, in double-blind fashion, alpha-lipoic acid (ALA; 400 mg or 800 mg per day) or placebo for two months. Outcomes were assessed using the Numeric Rating Scale (0 to 10, with 0 indicating no pain and 10 indicating the worst pain imaginable) and the Visual Analog Scale (0 to 100, with 0 indicating no pain and 100 indicating the worst pain imaginable). In the group receiving 800 mg per day of ALA, the mean Numeric Rating Scale score improved from 6.2 (range, 3-10) at baseline to 1.7 (range, 0-4) after two months (mean improvement, 73%; $p < 0.001$). In that group, the mean Visual Analog Scale score improved from 57.7 (range, 10-100) at baseline to 6.6 (range, 0-30) after two months (mean improvement, 89%; $p < 0.001$). Similar (though somewhat less pronounced) improvements were seen in the group receiving 400 mg per day of ALA. No improvement was seen in the placebo group.

Comment: In this study, treatment with ALA produced marked improvement of pain in people with idiopathic arthralgia, myalgia, or neuropathic pain. If this study is believable, it represents a major advance in the treatment of chronic pain. However, I'm not so sure I believe it.

I have written a lot about the questionable and apparently fraudulent research coming from Iran, Egypt, and a few other countries. I have not written much about studies from Italy, but over the past 10 years there have been a number of Italian studies in which a nutritional treatment produced a surprisingly large beneficial effect. Some of the treatments that were found to be effective had not been investigated previously and have not since been confirmed by other investigators. For some

studies, there was no clear biochemical basis for expecting the treatment would be beneficial. Few of the Italian studies have had the types of blatant irregularities that are often seen in Iranian studies, but a significant amount of the Italian research has left me with an uneasy feeling. There are a few noteworthy issues regarding the study cited above.

1. Discrepancy regarding funding: The paper stated that the research received no external funding. However, the document registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Registry stated that the study was funded by the Italian Association of Health Products and Manufacturers.

2. Issues regarding the timing of the study: The ISRCTN document stated that the trial start date was September 9, 2020 and the end date was July 30, 2021. However, the ISRCTN document also stated that the recruitment start date was May 27, 2021 and the recruitment end date was June 10, 2021. Both of those statements cannot be true. If the recruitment period was indeed May 27 to June 10, 2021, that would mean that 210 patients were enrolled in 15 days. Such rapid enrollment of so many patients would be unusual for a clinical trial

3. Issue regarding the date the paper was submitted: The paper was received by the journal on August 29, 2021. The process of submitting the paper included collecting and analyzing the data, writing the paper, circulating the first draft to all nine authors, incorporating their changes into the final paper (it was stated that all 9 authors made revisions), returning the revised paper to the authors, and receiving final approval from each author. If the recruitment end date was indeed June 10, 2021, the study would have been completed on August 10, 2021 at the earliest, and there would have been only 19 days for the authors to complete the process described above. That would have been an unusually rapid turnaround time. If the trial start date was indeed September 9, 2020, then the trial was started before it was approved by the ethics committee on November 19, 2020.

4. Low dropout rate: Of the 210 participants, none dropped out and all completed the two-month study. It is quite unusual to have 100% of a relatively large number of participants complete a study.

5. Unusually large effect size: It is rare for a nutritional supplement to produce an improvement averaging as high as 73%.

Let's see if any other researchers can confirm the results of this study. And, *Townsend Letter* readers, if you have personal or clinical experience demonstrating that ALA is dramatically effective for pain, please let me know (drgaby@earthlink.net).

Esposito C, et al. Safety and efficacy of alpha-lipoic acid oral supplementation in the reduction of pain with unknown etiology: A monocentric, randomized, double-blind, placebo-controlled clinical trial. *Biomed Pharmacother*. 2021;144:112308.

References

1. Condo M, et al. Riboflavin prophylaxis in pediatric and adolescent migraine. *J Headache Pain*. 2009;10:361-365.
2. MacLennan SC, et al. High-dose riboflavin for migraine prophylaxis in children: a double-blind, randomized, placebo-controlled trial. *J Child Neurol*. 2008;23:1300-1304.
3. Bruijn J, et al. Medium-dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomised, double-blind, cross-over trial. *Cephalalgia*. 2010;30:1426-1434.
4. Lasco A, et al. Improvement of primary dysmenorrhea caused by a single oral dose of vitamin D: results of a randomized, double-blind, placebo-controlled study. *Arch Intern Med*. 2012;172:366-367.

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An exploration of why and how things happen.

GENERATIVITY

PETER D'ADAMO, ND

Data, Data, Everywhere. And Nor Any Drop to Drink.

Laborious: A Robust Laboratory/Symptom Dataset with AI Diagnostic Inference

It's quite surprising just how much readily available scientific data one can freely access nowadays. A myriad of taxpayer-funded initiatives is available through NCBI (National Center for Biotechnical Information) for direct interrogation. These include the ubiquitous PubMed, PMC and MeSH portals, in addition to more discreet gateways such as DbVar (formally DbSNP), Taxonomy, ClinVar, and Gene. As government-funded entities, these portals are open source and there is no charge for their usage. What makes these resources especially snazzy to the informatically inclined scientist is the availability to access this information programmatically through the NCBI Entrez E-Utilities toolbox. These are a collection of commands (usually called handlers) that allow a coder to integrate aspects of the NCBI universe into their own programs and act upon them in an analytical manner.

For example, in my program Opus23, a natural product listed as having some effect upon the expression of a specific gene will provide the doubting Thomas the option of clicking through and viewing the actual study (or studies) that have made that observation. This is accomplished by pinging the appropriate E-Utilities handler with the PubMed ID number. This also takes place behind the curtain that separates the Opus23 users and editors. For example, when an editor adds a new SNP to the Opus23 human-curated database, they plunk in a few basic details (such as the reference sequence number; the 'rs' that is every SNPs home address) and the editor pings a variety of services (DbVar, ClinVar, Pharmacogenomics, Gene, GWAS, etc.) and proceeds to build up the entry. This is known as 'scraping' the data.

In addition to NCBI and other academic and governmental data pipelines, a surprising amount of data is now accompanying original research, often as nothing more than the lowly comma separated value (CSV) file used by most spreadsheets. Most of the time these data are just the results of a specific operation or experiment and have only limited usefulness, but when provided as a result of thorough review articles or meta-analysis, these can be quite helpful. Finally, we should not underestimate the willingness of the average scientist to share data. Very often a respectful inquiry will result in an act of great generosity; in a few instances not only was I provided with the requested data, but the author took the time to perform regressions and other types of cleanups, simply out of professional courtesy. The

Figure 1. The Laborious Opening Screen

Figure 2. The Laborious Smart Table Showing Filter Function

interaction network data behind the 'Radiance' microbiome app I wrote about a few columns back was the result of just such beneficence.

Finally, we are left with the least exciting option and outcome: We have a plan for some sort of cool, awesome analysis but no form of relevant, centralized data exists. Then, sadly, it's time to roll your own.

I ran into this roadblock a few years ago when I became interested in using the Naïve Bayes Classifier AI algorithm to allow laboratory outcomes to probabilistically infer specific diagnostic odds. What made this an especially attractive idea was the subsequent link that could be drawn between the resulting diagnostic outcomes and the constellation of symptoms that accompany them. Thus, by inputting a selection of labs and their values, the user could calculate the odds of pathologies and then be provided with the relevant symptom cluster that should be anticipated from that outcome.

But back to the original problem. There is no centralized dataset of lab values that are classified according to their odds of implicating a specific pathology. It's not that the data is non-existent; it certainly is out there. It's just not coded in a way that allows for probability type analysis. Ironically, sometimes the data is too good, too specific, for this type of purpose. For example, if we were to meet in a hallway and I were to inquire about patient Joe Blow's diabetes, you might respond by saying 'His HgbA1c is 10.8.' Or, you might simply say 'His HgbA1c is awfully high.'

Since it is at heart a classifier, the Naïve Bayes algorithm prefers the latter depiction. Frankly, as a busy human, so do I.

So, before we can even begin to design our lab AI inference engine, we'll need to roll up our sleeves and get into the trenches. I'll spare you the gory details, but thanks to several of the University of Bridgeport Naturopathic Pathfinder Scholars, and most significantly to my friend and colleague Valentin Prisecaru, over the last three years we built a robust database of over 5000 individual data points linking lab outcome classes to specific pathologies. Then I coded a script that allowed for simple filtered queries via a smart table, or going deeper, queries with specific lab outcomes.

Here's how you can play with it.

The Laborious App

You can run this script (Laborious) from any laptop, pad, or desk computer (sorry, not great on smart phones) by pointing your browser (extensively tested on Chrome) here: https://www.datapunk.net/tlfd/.

To protect against tiresome robots, you may have to prove you are human by simply moving the slider's blue dot to the middle of the range. If you've been here recently, you'll already have the access cookie and will just be directed to the main splash page. From there click on the link that reads **Laborious (Lab AI Inference)** under the category **AI/ML.** That will take you to the front page of the app, which shows the data is a 'smart table' (Figure 1).

Figure 3. The Laborious Query Form

The smart table gives you the ability to look at the data behind Laborious. It is broken down into several columns (Pathology, Lab, Observed Value and Significance.) Each column is sortable by clicking on the column heading. There are a total of 4843 individual records, although only 15 are shown on a page. You can increase the amount shown, up to 100 entries at a time. You can filter results by using the Search field and typing in a full or partial search term. For example, if I type 'anemia' into the search bar, the table shows only entries with that text fragment in their field (Figure 2).

As you can see, filtering by 'anemia' the number of records shown now drops down to 83. Much more manageable! As a data analysis tool, the Laborious smart table provides enough function to be a standalone app on its own. However, we're just getting started.

Click on the link in the upper left of the screen that reads 'Run Query.' You'll be transported to the Laborious AI query form (Figure 3).

Choose up to ten lab biomarkers to include in your analysis. Entries will autocomplete as you begin to type. For each biomarker, select the appropriate result range, and if desired assign an additional

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Figure 4. The Laborious Run Query Results Upper Panel

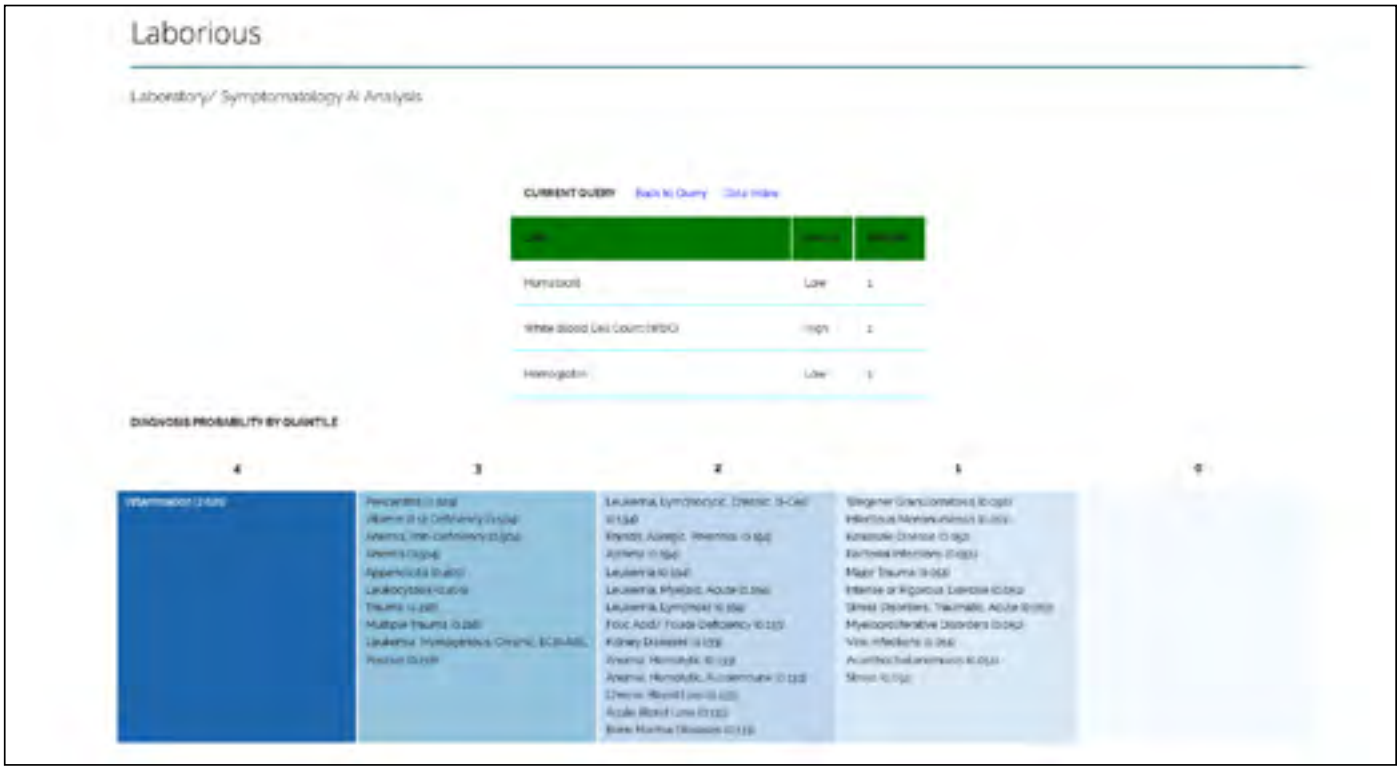
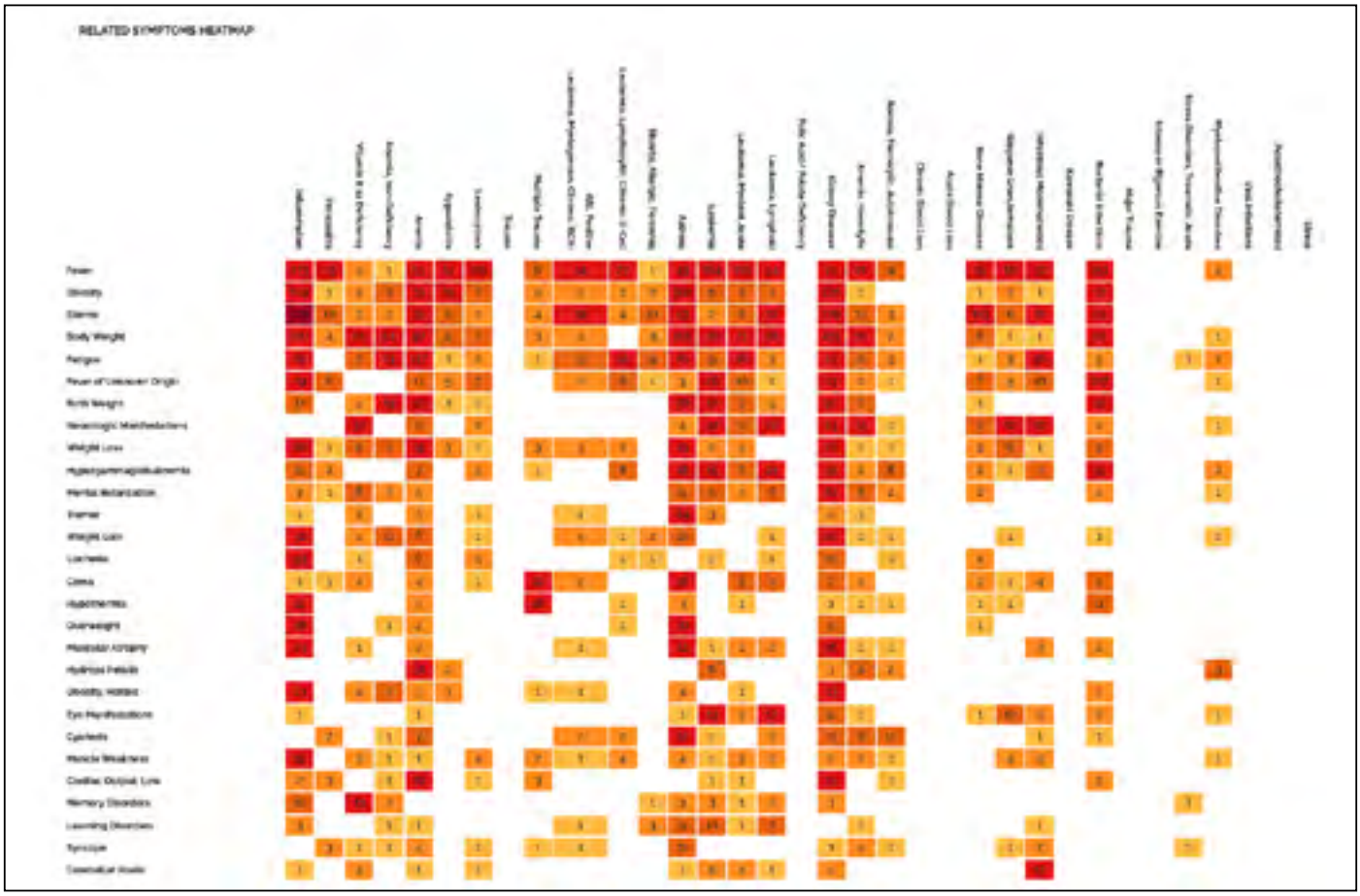


Figure 5. The Laborious Run Query Results Lower Panel



'weight' to the observation.' Although not mandatory, assigning a weight value tells the AI that you think this biomarker is especially noteworthy. In our case, we'll run a query that tells Laborious that we have a cluster of biomarkers that include a low hematocrit, a high white blood count (WBC), and a low hemoglobin. We'll leave the weight values at 1 for this test. After inputting our info, we then press the 'Run Laborious' and through the magic of television, Figure 4 appears.

The results screen is divided into two parts, an upper and a lower panel. The upper panel has a small table that just reiterates your search criteria and has a 'Back to Query Link' that returns you to the prior form, but with your original criteria maintained. The next table, 'Diagnosis Probability by Quantile' delivers the real punch line. As you can see it is a table of five columns containing a variety of diagnostic possibilities, and their relative probabilities displayed as a number between 0 and 4. The columns are quantiles (statistical cut point intervals) of the results, decreasing in probability from left (quantile 4) to right (quantile 0). Under these conditions, inflammation looks like the winner, although there are elements in the next quantile with significant possibilities as well.

I'm sure there are many readers who could have deduced many of these possibilities, but I like to think of an app like this helping me to define the 'negative state space' of all possibilities, i.e., the outcomes that I would not have thought of based upon my own sense-data. In that sense AI provides a glimpse into the invisible world of our limitations. And anything that decrease the chances of an error of omission is okay in my book.

Scrolling down, we see a heatmap based on the symptoms one might be expected to be presented with, given the resulting diagnostic possibilities (Figure 5). The values are colored on a glorious gradient from autumnal yellow to red. Now we can compare the client's presenting symptoms to see if they correlate more closely with a particular diagnosis.

I've shared Laborious with a few colleagues, and their feedback has been quite positive. One comment that I thought was particularly heartening came from a former protégé, now in a solo private practice in a far-off state. She said that this app made her feel like she had a colleague in the practice that she could bounce ideas and possibilities off, and perhaps just a bit less lonely and isolated.

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Peter D'Adamo is a physician and distinguished professor of clinical medicine at the University of Bridgeport School of Naturopathic Medicine. His *New York Times* bestselling books have sold over 8 million copies and have been translated into over 75 languages. He is the developer of the acclaimed *Opus23* genomic software suite and a variety of other generative apps that can be explored at www.datapunk.net. In his spare time, he brings old VW Beetles back to life at his garage on www.kdf20.com.

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Martin Bales
– Martin Bales L.Ac. DAOM

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(FEV1) Forced Expiratory Volume	1.07 L	2.02 L	**88.8%**
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Herbal Approaches to Supporting a Healthy Libido in Menopause

by Meagan Purdy, ND

Menopause is associated with many often-lamented symptoms that can drastically affect a woman's comfort, happiness, and daily life activities. Hot flashes, night sweats, and mood swings are commonly discussed, yet low sexual desire is a prevalent symptom in menopausal women that is commonly overlooked. One cross-sectional study of over 2,000 women found 52.4% reported low sexual desire compared to 26.7% of pre-menopausal women.[1] Not only because of the ubiquity but also because of the effect on quality of life, symptoms of sexual dysfunction in menopausal women deserve more attention and more treatment options, as the current choices leave much to be desired.

Testosterone and estrogen, critical hormones for sexual desire, decrease in menopause. Physical factors, such as vaginal dryness and dyspareunia, are largely common in menopause and can reduce interest in sex for many women.[2] Many women also report increased levels of depression, cognitive symptoms, and mood swings during menopausal transitions. While these may not have a direct effect on sexual desire, they can diminish the appeal of sexual activity.[1]

As the research on risks associated with hormone replacement therapy (HRT) continues to grow, many women are opting out of the mainstream treatments and seeking alternative medicine interventions for relief from menopausal symptoms. Fortunately, there are several medicinal herbs that can be of support to women struggling with lowered desire by improving hormone health, decreasing stress, or by aiding physical parameters of arousal.

Maca

Lepidium meyenii, or maca, has risen to superstardom in the past decade, as its online health claims and subsequent demand have grown. This increased interest has established maca as one of the premium exports of Peru. Traditionally consumed as a health food addition to soups or juices with a unique flavor and caramel notes, Peruvian maca is now mostly utilized in medicinal forms such as powders, pills, and extracts. Maca has been touted for its ability to increase energy, improve concentration, and balance hormones, and can be a valuable tool for women in the menopausal stage of life, particularly those struggling with a diminished libido.

The precise mechanisms of maca are still relatively unknown, though its results have been promising both clinically and in studies. Maca appears to significantly reduce parameters of sexual dysfunction as well as scores on the Greene Climacteric Scale (GCS), a measurement of menopausal symptoms. One group of researchers hypothesized that this may be due to a hormone modulating effect of maca, yet in their study they found no significant changes in estrogen levels of postmenopausal women. However, the women in their study did experience a decline in menopausal symptoms and reported significant improvements in libido and sexual function.[3]

It is feasible that maca's profound effect on sexual function is related to its effect on psychological symptoms. Maca has been shown to have beneficial effects on anxiety and depression, which may increase parameters of sexual desire. Flavonoids present in maca inhibit monoamine oxidase (MAO) activity, the same mechanism of action of a prominent class of anti-depressant medications.[4] Interestingly, many of the present studies on maca revolve around its use as a treatment for antidepressant-induced sexual dysfunction (AISD). In a double-blind, placebo-controlled study of menopausal Chinese women suffering from AISD, maca reduced symptoms of depression and improved GCS scores, even with no measurable changes to serum hormone levels.[5] Another 12-week double-blind, placebo-controlled study found similar results, with 3.0 g/day of maca supplementation showing marked improvements in AISD.[6] These results suggest that maca can be a powerful tool for women who have opted to treat their menopausal symptoms with SSRIs, only to succumb to the side effects of low libido.

Damiana

Turnera diffusa, or damiana as it is commonly known, is one of the most appreciated plant aphrodisiacs for both males and females. It was classically used in Native American cultures to regain strength after "alcoholic and sexual excesses" and has long been used in Latin cultures to stimulate sexual drive and performance. Damiana enhances nitric oxide synthesis, a mediator that plays a role in genital arousal in women as it does in men by relaxing smooth muscle tissue in the genitals and increasing blood flow to the region.[7] It has also been shown to exhibit adaptogenic properties, which may reduce stress and mental fatigue, lessening inhibitions to sexual activity.[7]

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One randomized, double-blind, placebo-controlled study evaluated the effects of damiana coupled with L-arginine, ginseng, ginkgo, and vitamins. After four weeks, women from both the perimenopausal and postmenopausal groups reported significant improvements in sexual desire compared to those in the placebo group.[8] Another study observed the effects of a supplement containing damiana along with *Tribulus terrestris, Gingko biloba*, and *Trigonella foenum*. Researchers noted significant improvement in Female Sexual Function Index scores for the treatment group.[9] The results of these trials suggest that damiana can be a valuable constituent of any herbal regimen aimed at improving libido and sexual function, particularly for menopausal women.

Shatavari

Shatavari, the common name for *Asparagus racemosus*, means "she who possesses a hundred husbands" referring to its historical use as a female reproductive tonic to increase fertility and vitality. In Ayurveda, it is known as the "Queen of Herbs" for similar reasons. Shatavari is an herb with a longstanding tradition of use for female sexual dysfunction and modern research is beginning to add validity to this history.

Shatavari exhibits phytoestrogenic activity and supports testosterone production both by enhancing primary secretion and increasing the availability of its precursors. This phytoestrogenic activity lends to additional benefits for menopausal women, providing relief from other symptoms of decreased estrogen such as hot flashes and vaginal atrophy.[10]

Outside of direct hormonal effects, shatavari appears to have adaptogenic and stress-relieving properties.[10] Stress can have major impacts on reproductive health by modulating ovarian physiology and reproductive hormones.[11] These physical and chemical effects are in addition to the mental-emotional effects of stress, which can also have a direct effect on sexual desire and function. Shatavari has been successfully used to modulate the hormonal imbalances associated with stress and restore reproductive function, which also supports the hormones responsible for sexual desire.[12]

Tribulus

Tribulus terrestris is primarily known for its actions with male hormonal dysfunction in historical circles. The same qualities that it's touted for in males lend to it being an incredible tool for menopausal women with low libido. Tribulus increases the release of nitric oxide, supporting more blood flow to the sexual organs for enhanced sexual function. Additionally, one of the known saponin constituents of tribulus, protodioscin, increases the conversion of testosterone into dihydrotestosterone, a potent androgen that directly increases sex drive.[13]

In one double-blind, placebo-controlled study, researchers observed the effect of tribulus extract on women with hypoactive sexual desire disorder. They found that 7.5 mg/day of tribulus significantly improved desire, arousal, lubrication, and sexual satisfaction compared to placebo.[14] Another prospective, randomized, double-blind, placebo-controlled trial observed improvements in sexual arousal, lubrication, orgasm, pain, and satisfaction for the tribulus group. The treatment group also exhibited increased levels of free and bioavailable testosterone.[15] These findings suggest that Tribulus is an effective agent at boosting multiple parameters of libido and sex drive.

Sexual dysfunction, particularly diminished libido, can be distressing for the patient. Unfortunately, this prevalent symptom can carry a negative stigma leading many women to avoid asking their care providers for assistance. When not addressed, symptoms of low sexual desire can present with decreased quality of life, relationship issues, and low self-esteem. With an increasing number of women seeking alternative therapies for menopausal symptoms, it is vital for us as practitioners to expand our toolbox of remedies. Herbal approaches to low libido can be a great fit for many women who would like to avoid HRT or SSRI interventions but would still like to improve their symptom profile and quality of life. Herbs can provide a valid solution for hormone balance, mood support, and provide a direct benefit to the uncomfortable symptoms associated with menopause.

Dr. Meagan Purdy is a naturopathic physician and founder of the multi-disciplinary Holistic Health Center of Dallas, where she and her team have helped thousands of patients recover from multiple ailments with a specific focus on anxiety, depression, and chronic fatigue. She is now the senior manager of scientific education at Allergy Research Group, has been a recurring guest on the popular morning show, *Good Morning Texas*, has appeared on multiple radio shows and podcasts, has attended as an expert speaker at numerous medical conferences, and is a regular contributor for many popular health blogs.

References

1. West, Suzanne L et al. Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of US women. *Archives of internal medicine*. 2008;168,13: 1441-9.
2. Scavello, Irene, et al. Sexual Health in Menopause. *Medicina (Kaunas, Lithuania)*. 2 Sep. 2019; 55,9: 559
3. Brooks NA, et al. Beneficial effects of Lepidium meyenii (maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content. *Menopause*. 2008 Nov-Dec;15(6):1157-62.
4. Thull U, Testa B. Screening of unsubstituted cyclic compounds as inhibitors of monoamine oxidases. *Biochem Pharmacol* 1994;47: 2307/2310.
5. Stojanovska, L et al. Maca reduces blood pressure and depression, in a pilot study in postmenopausal women. *Climacteric : the journal of the International Menopause Society* 2015; 18,1: 69-78.
6. Dording, Christina M et al. A double-blind placebo-controlled trial of maca root as treatment for antidepressant-induced sexual dysfunction in women. *Evidence-based complementary and alternative medicine:eCAM* . 2015; 949036.
7. Szewczyk K, Zidorn C. Ethnobotany, phytochemistry, and bioactivity of the genus Turnera (Passifloraceae) with a focus on damiana--Turnera diffusa. *Journal of ethnopharmacology* 2014; 152,3: 424-43.
8. Ito TY, et al. The enhancement of female sexual function with ArginMax, a nutritional supplement, among women differing in menopausal status. *Journal of sex & marital therapy.* 2006; 32,5: 369-78.
9. Palacios S, et al. Effect of a multi-ingredient based food supplement on sexual function in women with low sexual desire. *BMC women's health*. 30 Apr. 2019; vol. 19,1 58.
10. Sharma K, Bhatnagar M. Asparagus racemosus (Shatavari): a versatile female tonic. *Int J Pharma Biological Archives*. 2011;2(3):855-63.
11. Ebbesen SMS, et al. Stressful life events are associated with a poor in-vitro fertilization (IVF) outcome: a prospective study. *Hum. Reprod*. 2009; 24: 2173–2182.
12. Pandey AK, et al. Impact of stress on female reproductive health disorders: possible beneficial effects of shatavari (Asparagus racemosus). *Biomed Pharmacother*. 2018 Jul;103:46-9.
13. Chhatre Saurabh, et al. Phytopharmacological overview of Tribulus terrestris. *Pharmacognosy Reviews*. 2014;8,15:45-51.
14. Akhtari E, et al. Tribulus terrestris for treatment of sexual dysfunction in women: randomized double-blind placebo - controlled study. *Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences*. 28 Apr. 2014; vol. 22,1 40.
15. Vale FBC, et al. Efficacy of Tribulus Terrestris for the treatment of premenopausal women with hypoactive sexual desire disorder: a randomized double-blinded, placebo-controlled trial. *Gynecological Endocrinology*. 2018; 34,5: 442-445.

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On the cover

A Surprising Menopause: A Case Study, Part 1

by Deborah McKay, ND

Originally published in *Naturopathic Doctor News & Review*

I view the menopausal transition as "puberty in reverse," complete with shifts in hormones that dictate bodily changes. In some cases, this hormonal shift can hijack the brain. Personally, I remember looking in the mirror and saying, "Who are you? I don't even know you." This happened twice in my life – first during adolescence, and again at menopause.

I've heard it's possible to sail through the menopausal change of life with no muss and no fuss. Just skip a period here and there, then stop menstruating altogether – and on your 14th moon-cycle of no menses, it's time to throw a party celebrating your arrival into Revered Wise Elder status, queen of one's own life from now on. That's the concept, right? But do you actually know anyone so privileged? I've met a few, but most American women appear to be too toxic, too unsupported, and too often flooded with false expectations from faulty advice.

One of my new patients last year appeared at first to be a typical menopause case, with ovarian, thyroid, adrenal, glucose, and digestive deregulation (it's always a package deal at menopause). She ended up happily rebalanced, but by way of a surprising twist that I didn't see coming. In this article, I share my thinking as a holistic hormone doc seeking "optimal whole-person" health, as opposed to operating with the notion that "lab reference range is good enough." This will be a two-part story.

The Patient

First Visit. "Dorothy," a career-minded 50-year-old woman, came to my office in January 2019 and told me that it felt like her entire life was crumbling. Her wake-up call occurred the previous year with the sudden recognition of her burden of financial debt, followed by the "firing" of her dysfunctional significant other, and then the shocking recognition that her body was no longer her own – an extra 15 pounds had piled on for no apparent reason. Even her brainpower had suffered. She ate well, was devoted to yoga, and studied health; she seemed to be doing everything right, but somehow wasn't getting traction. She had recently peeled off five pounds with great difficulty.

Dorothy told me about a "foggy brain" and easy overwhelm; chronic tension, stress, and an anxious sense of impending doom; non-restorative sleep; decreased libido; constant chilliness; poor memory (especially recently); hair loss; recurrent sinus infections (for which she had been prescribed courses of antibiotics); loss of smell; difficulty breathing during stress; multiple sensitivities (foods, chemicals, inhalants), and malaise. Her mainstream primary care physician would typically address only one symptom at a time, and appeared to ignore altogether her sense of dread and impending doom. She suffered from chronic constipation (often 48+ hours between bowel movements) that was worsened by fiber, which she found confusing. Stools were typically Bristol #1-2 ("marbles" or "caterpillars"). She thought her GI symptoms might have started 20 years prior, when she experienced a food poisoning that seemed to shift her entire system. She was currently using OTC meds to achieve Bristol #4-5 (normal), but this required daily attention. Menstrual cycles had recently become irregular, with menses often skipping one or two months. Finally, she complained of some chronic irritation around her urethra and introitus.

Her goals in seeking my services were to feel better and thrive; determine appropriate nutritional supplementation; amend her diet if necessary; and lose another 10 pounds. Above all, she wanted to ease her menopausal transition. Meanwhile, she planned to depart the following week for a two-week women's yoga retreat in Mexico.

History included "many" childhood ear infections. This led to the removal of tonsils and adenoids at age 4 or 5, with a resulting partial loss of hearing in her right ear. She was abandoned at birth by her father, who suffered from depression. Her mother's menopause was surgical – she had a hysterectomy after four babies. Dorothy was born when her mother was just 20 years old. Her mom has borderline personality disorder. As the first-born, Dorothy worked long and hard to raise her three younger siblings – the source, she felt, of her habitual self-criticism. She reported past nervousness and depression. Another doctor had previously diagnosed Hashimoto's thyroid disease, based on positive anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies; however, she was never prescribed thyroid hormones. She had been a sporadic self-prescriber of various nutritional supplements over time. Currently, she was taking daily B-complex vitamins, vitamin D3 drops (dose unknown), and ashwagandha (intermittently).

Here are her laboratory test results from February 2017, ordered by another naturopathic physician:

TSH: High-normal (3.88 mIU/L); 1.0 mIU/L is my target "optimal"
Free T4: Low-normal (1.04 ng/dL)
Free T3: Normal (3.2 pmol/L)
Anti-TG antibody: High (520)
Anti-TPO antibody: High (56)
LDL-cholesterol: High (140 mg/dL)
Fasting glucose: High-normal (94 mg/dL);
85 mg/dL is my target maximum
Fasting insulin: High-normal (7 µIU/mL);
5 µIU/mL is my target "optimal"
HbA1c: High-normal (5.4%)
25-hydroxyvitamin D: Very low-~~normal~~ (28 ng/mL);
50 ng/mL is my target minimum
Ferritin: Low-normal (37 ng/mL);
50 ng/mL is my target "adequate"
Cortisol, serum (AM): Low-normal (16.7 µg/dL)
DHEA-S, serum: High (315 µg/dL)
Pregnenolone, serum: High-normal (143 ng/dL)
FSH: High, but normal for menopause (27.8 mIU/mL)
Progesterone, serum: Low-normal, but in range for ovulation or luteal phase (0.65 ng/mL)
Estradiol, serum: High-normal, but in range for ovulation or luteal phase (258 pg/mL); she couldn't recall her menstrual phase
Testosterone, serum: High-normal (36 ng/dL)

Examination. Objectively, Dorothy was bright and articulate but had obvious slow mental processing. I was aware of having to slow down my speech and allow extra time for her to make choices or process new information. BMI was 23.1 (optimal). Body fat content was 30.3% ("acceptable" but disproportionately high compared with her BMI). Muscle tone was average, and her posture was slouching; she appeared unfit despite all the yoga. Her hands were cold to the touch despite wearing two sweaters inside a warm clinic. Diffuse thinning of all scalp hair was apparent. Facial expression suggested worry. She would often hold her breath during our interviews. I would find myself unusually tired by the end of her appointments; I attribute this to breath-holding, since I tend to mirror my patient's body language.

Impressions.

My chief diagnosis was perimenopause. Additional diagnoses included hearing loss, right ear; anxiety; some adrenal over-activity (high DHEA-S); functional hypothyroidism (ie, euthyroid sick syndrome); Hashimoto's disease; hyperandrogenism; vitamin D deficiency; hypercholesterolemia; insulin resistance; and irritable bowel syndrome (IBS), constipation-predominant.

My reasons for suspecting chronic hypothyroidism were based on Dorothy's constant chilliness, thinning of hair, weight gain, constipation, and slow mental processing. Although Dorothy's TSH in 2017 was "within range," she felt and functioned poorly. Something was clearly wrong. I prefer using a TSH upper limit of 3.0 mIU/L. I have also come to adopt Dr Kent Holtorf's mistrust of TSH altogether,[1] primarily because many different factors can trigger the anterior pituitary gland to suppress TSH, but also because the deiodinase enzymes within the anterior pituitary occur in starkly different ratios from deiodinases in other bodily tissues. This causes the anterior pituitary to "feel satisfied" in the presence of a barely-adequate Free T4 level, even when Free T3 is running low and/or Reverse T3 is running high. Any TSH value, even a seemingly low one, must be handled in light of all of the patient's signs and symptoms. This approach takes time and patience, which most naturopathic physicians are willing and able to do. The patient's functional quality of life should always come first. We are treating a person, not a set of lab values.

I suspected that Dorothy's conspicuously slow mental processing was probably multifactorial, including perimenopausal hormone swings, thyroid imbalance, and her social/emotional/financial stressors. Hearing loss had also increased her baseline level of stress, causing her to be chronically hypervigilant. I hoped her two-week yoga retreat would help restore her body, mind, and spirit.

I suspected that her IBS was related to chronic SIBO/SIFO (small intestinal bacterial overgrowth/small intestinal fungal overgrowth), based on her chronic and severe

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constipation. Her sluggish bowel was likely caused initially by low thyroid, but by now was probably fostering bacterial and fungal overgrowth and excessive gut fermentation. In particular, her hallmark symptom of "constipation worsened by dietary fiber" suggested fermentation. (For the record, she was already consuming ample amounts of water each day.)

Based on her previous lab results, I suspected insulin resistance, despite her devotion to yoga and other physical exercise. My truncated HOMA-IR formula for estimating insulin resistance involves simply multiplying Fasting Glucose (mg/dL) by Fasting Insulin (μIU/mL). Optimal would be 405. Using this calculation, Dorothy's HOMA-IR was 658, indicating mild insulin resistance. Common effects of insulin resistance (even as mild as this case) include disproportionally high body-fat percentage, a tendency toward reactive hypoglycemia (with carbohydrate cravings, irritability, and disturbed sleep), and mood swings due to rapid blood-glucose fluctuations.

Initial Plan.

In order to get an up-to-date laboratory assessment, I recommended that she get a blood draw before departing for Mexico.

Meanwhile, I suggested that she "climb off the blood sugar roller coaster." I explained insulin resistance and how it can trigger hypoglycemia, swiftly and erratically. I advised her for now to keep a "foods & mood" journal for 10 days.

Because the gluten protein can induce anti-thyroid antibodies in susceptible individuals (via molecular mimicry),[2] I suggested a gluten-free diet.

For her chronic constipation, I gave her my handouts explaining SIBO/SIFO and its treatment. I asked her to skim them and bring her questions to her next visit. Launching treatment of SIBO is a project to be done only with adequate patient education and preparation. Only after that would I offer her the option of baseline breath-testing. If she declined, we would move ahead with treatment, but then do follow-up breath testing afterward.

I recommended additional vitamin D3 to help support her mood and immune system, and help regulate blood glucose. I explained to Dorothy that vitamin D is "the sunshine vitamin" whose production begins in the skin, and suggested immediate sun exposure during the next week as a way to start replenishing her vitamin D3 stores.

To address her recurring sinus infections, I recommended she utilize her pseudoephedrine prescription (a controlled substance in Oregon) on days of air travel to keep her sinuses "bone dry." At the same time, I educated her to keep her nasal mucosa "wet and flowing" on most days by using steam, N-acetylcysteine, and guaifenesin. Free-flowing mucus would help facilitate the shedding of microorganisms. I taught her hydrotherapy for the sinuses (ie, the "Granny Steam Bowl," using a big bowl of boiling water with a large towel draped overhead to make a tent), along with visualization of steam-cleaning the nose, sinuses, Eustachian tubes, bronchi, etc. I directed her to follow the steam treatments with the swabbing inside her nostrils of an essential oil blend (grapeseed oil with essential oils of thyme, eucalyptus, lavender, and peppermint). I have found this blend to be highly effective for preventing and treating even full-blown sinus infections, as well as protective against contracting viruses during air travel.

For her mildly inflamed urethra and introitus, I recommended *Lactobacillus acidophilus* capsules, to be used as vaginal suppositories (1 per day for 1 week). This was based on the likelihood that her vaginal flora had been compromised by antibiotics taken for recurring sinus infections.

To help her stay asleep at night, I recommended she take a proprietary oral combination of *Withania somnifera* (ashwagandha), L-theanine, phosphatidylserine, *Magnolia grandiflora*, and *Epimedium*. I also suggested she purchase a book by our esteemed elder, Dr James Wilson: *Adrenal Fatigue, 21st Century Stress Syndrome*, and to start with Chapter 5, which contains 18 cartoons depicting the look and feel of adrenal fatigue. Many of my patients describe both laughing and crying with recognition as they look at these cartoons. Dorothy didn't have "adrenal insufficiency" according to the conventional definition; however – functionally, holistically, naturopathically – she appeared to fit the "resistance phase" of Hans Selye's stress model, ie, functional lack of adrenal reserve. This pattern can include a constellation of imbalances such as high DHEA, low or normal cortisol, susceptibility to opportunistic infections, depression, and insulin resistance.[3]

Although new thyroid results would soon be available, she was heading out of town and I wanted, in the meantime, to reduce the amount of time she suffered by starting her on conservative doses of hormone – although only after her blood draw. I instructed her to take 25 mcg/d of levothyroxine (L-T4) and a starting dose of 5 mcg/d of liothyronine (L-T3). Assuming tolerance, I suggested gradually increasing the L-T3 dose every few days (T3's half-life is only 1.5 days[4]), with a target dose of three times daily (15 mcg/d), but also decreasing the dose if necessary. I coached her on tracking her bodily responses to thyroid status, including heart rate, mid-day oral temperature, blood pressure, and sleep quality.

Many doctors are uncomfortable prescribing L-T3, understandably so because it is perhaps the single

strongest hormone in the human body, acting to speed up metabolism of every tissue, organ, and gland. Mainstream state medical boards also frown on doctors who prescribe this bioidentical hormone – another reason for doctors' hesitancy. However, after two decades of working with endocrinology, I'm willing to prescribe L-T3 after assessing the patient's ability and willingness to follow my detailed instructions, which include substantial self-monitoring.

I decided against supplementing glandular products due to Dorothy's high anti-thyroid antibody count. In my clinical experience, I've seen glandulars trigger increases in antibody counts in about 50% of cases.

Finally, I urged baseline DEXA bone density testing before her 51st birthday.

At some point, I hoped to run some genetic testing on Dorothy. My suspicion of genetic abnormalities, particularly for MTHFR, was based on the combination of her multiple sensitivities, her pull towards negative emotions, and her intense family history (eg, bipolar disorder) suggestive of neurotransmitter imbalances.

Part 2 of this case study will appear in the April issue of *Townsend Letter*. Spoiler alert: Dorothy caught a GI infection in Mexico, we adjusted her hormones, and genuine healing took place rapidly when we addressed her underlying trauma.

Case Study: Menopause

References

1. Holtorf K. Peripheral Thyroid Hormone Conversion and Its Impact on TSH and Metabolic Activity. *J Resor Med*. 2014;3(1):30-52. Available at: https://restorativemedicine.org/journal/peripheral-thyroid-hormone-conversion-and-its-impact-on-tsh-and-metabolic-activity/. Accessed September 5, 2019.
2. Cusick MF, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. *Clin Rev Allergy Immunol*. 2012;42(1):102-111.
3. Friedman M. *Fundamentals of Naturopathic Endocrinology*. Toronto, Ontario: CCNM Press; 2005: 117-120.
4. Centers for Disease Control and Prevention. Laboratory Procedure Manual. Free Triiodothyronine, T3. 2007-2008. CDC Web site. https://tinyurl.com/y3tz29zm. Accessed September 5, 2019.

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Part 2 of Dr. McKay's article will appear in our April issue.

Women's Health: Overcoming Some of the Most Common Female Concerns

by Chris D. Meletis, ND, and Kimberly Wilkes

Women are more likely than men to seek out health care both for themselves and their children. However, women often have reproductive health concerns that present their own unique set of challenges. According to one group of researchers, "Menopause, premenstrual syndrome, dysmenorrhea [menstrual cramps], female fertility, and mastalgia [breast pain] are common problems not easily treated by conventional medicine. Women often seek alternative therapies to help address these conditions."[1] Getting to the root cause is essential, because for every action within the biochemistry there is an equal and sometimes greater ripple effect.

In this article, we will address common female health concerns and approaches that functional medicine providers can use to eradicate or improve women's health issues. While reading this article, it is important to recognize that it takes a while to change the ecology and microecology of the body to the point where efforts lead to significant improvement in women's health.

Female Health Starts with Cellular Support

Treating the entire human organism is so vitally important. This fact is sometimes put by the wayside in a world that is driven by ICD-10 coding and reductionism. Continuing to notice how all the insurance codable boxes can be connected allows the functional medicine provider to not be limited by merely one or two boxes, rather to exist outside of "in-the-box thinking." This is why we want to start our discussion of women's health with cellular health.

The human body – whether female or male – is constantly providing us clues as to the proverbial state of the union of the trillions of cells that comprise each and every one of us. This is true of both women and men, but we must start the healing journey in our female patients by paying attention to cellular health. Functional medicine clinicians are able to use the expected lifespan of cell types to determine nutritional status and whether a given patient falls within a healthy reference range. For example, the lifespan of a red blood cell (RBC) provides us a glimpse of the last 90-120 days of iron, folate, and B12 status based on total RBC count, hemoglobin, and mean corpuscular volume. In turn we often use RBC nutrient status of magnesium, zinc, etc. to help us ascertain intracellular nutrient status.

Cells take time to turnover, and cellular turnover can vary greatly depending upon where they are located. For example, the stomach lining is continually broken down by digestive acid and must be replaced every few days. Conversely, cells in the bones can take years to turn over. In some areas of the body, such as the brain, many cells can stick around from the time of a person's birth to late in life. We can expect that, depending on the lifespan of cells, it will take at least that long to start to see substantive results. On a woman's wellness journey, it takes a while to get lost, but it takes at least that long to get unlost. The table (on the left) indicates the lifespan of certain cells. If a woman is not given the tools necessary for these cells to be replaced, the result is damage to overall health.

Lifespan of Select Cells[2]

Neutrophils	3 – 4 days unless they ingest bacteria, in which case they die in about 12 hours
Eosinophils	3 weeks
Basophils	3 – 10 days
Red Blood Cells	120 Days
B lymphocytes	4 days to 5 weeks
T lymphocytes	A day or two or for months depending on the outcome of their fight with foreign substances.
Monocytes and platelets	Leave the circulation at random
Cells lining the stomach	About 5 days
Outer layer of the skin	Every 2 weeks

Cellular Health and the Skin

Female patients are particularly concerned about how their skin looks,

and female concerns are sometimes associated with skin problems, such as the connection between dysmenorrhea (painful periods) and acne (more on this later). The skin is the body's largest organ covering a surface area of 1.5 to 2 square meters. It weighs between 7.5 to 22 pounds, comprising approximately one-seventh of a body's weight. Yet, it's a mere few millimeters thick at its thickest point.

Because the skin is exposed to the world, skin cells must be regenerated frequently. If you cut or injure your skin, skin cells divide and multiply to replenish any lost skin. Skin cells also die and are replaced even if your skin isn't damaged. Each minute, a person sheds 30,000 to 40,000 skin cells, which amounts to about 50 million cells daily.

Whether a woman's skin has a radiant glow or looks drawn and ashen can tell a functional medicine provider a lot about the woman's health. The condition of the skin can reflect nutritional status, toxicology, and overall health. Therefore, for a woman to have healthy skin, it is best to address any nutrient deficiencies, detoxify the body, and go after any female-specific or overall health problems. Evening primrose oil is one supplement of interest to women concerned about their skin health. In one study, 500 mg EPO capsules twice per day for 12 weeks, significantly improved transepidermal water loss, skin firmness, elasticity, and roughness.[3]

Dysmenorrhea

Primary dysmenorrhea (i.e. menstrual cramps) is characterized by a lower abdominal pain that occurs during the menstrual cycle and is not correlated with any other disease or pathology. The word "dysmenorrhea" is derived from the Greek term for "painful monthly bleeding." It is one of the most common gynecological issues among all women independent of age or race. It's estimated that between 16% to 91% of women of reproductive age have dysmenorrhea, with 2% to 29% of those women suffering from severe pain.[4] One study found 79.7% of female adolescents have dysmenorrhea and of those about 38% suffer from a severe form of the condition.[5]

Risk factors for primary dysmenorrhea may include the following[6]:

- Age, although as noted above it can happen at any age during the reproductive years.
- Smoking
- Being on a diet
- Higher body mass index
- Depression or anxiety
- Having a first period at an earlier age
- Never having given birth to a child
- Longer and heavier menstrual flow
- Family history of dysmenorrhea
- Disruption of social networks

In addition to abdominal pain, symptoms of dysmenorrhea can include nausea, bloating, diarrhea or constipation (or both), along with vomiting and indigestion, as well as irritability, headache, and low back pain. Some women with dysmenorrhea also report tiredness and dizziness. Dysmenorrhea can prevent women from attending work, school, or social events.

Dysmenorrhea is linked to significant impacts on emotional and psychological health as well as the ability to function effectively. In addition, there is a relationship between having a history of dysmenorrhea and developing hypertensive disorders during pregnancy.[7] Because adult acne in women can often flare up during the premenstrual period due to cyclic alterations in hormones, it is often accompanied by menstrual abnormalities such as dysmenorrhea.[8]

Dysmenorrhea also is associated with increased levels of oxidative stress that results from the emotional stress a woman undergoes while experiencing painful periods.[9] To protect against excessive oxidative stress, a woman's body produces more of a substance known as adrenomedullin (AM) during menstruation, which in turn boosts production of nitric oxide (NO).[9]

Conventional treatments for dysmenorrhea include over-the-counter pain relievers or a prescription for oral contraceptives. Some dietary supplements have also been found to be effective. In three trials of women with dysmenorrhea, magnesium was more effective than placebo for pain relief. Furthermore, the women taking magnesium supplements needed less additional medication.[10] Magnesium is involved in the relaxation of the smooth muscle, including the smooth muscle tissue of the uterus (the myometrium).[11] Tending to the health of the smooth muscle is critical as hormonal alterations in women can alter not only the myometrium but also other areas where smooth muscle is present including the following[12]:

- GI tract
- Cardiovascular system
- Respiratory tract
- Ciliary muscle and iris of the eye
- Outer protective layer of the skin
- Bladder and urinary tract

Vitamin B1 (thiamin) is another nutrient that has garnered some support in helping women with dysmenorrhea. One large trial found that vitamin B1 was more effective than a placebo in reducing menstrual cramps.[10]

Additionally, a large study of 70,709 women and several smaller studies confirmed a possible link between a lower risk of endometriosis (a condition often associated with dysmenorrhea) and increased intake of omega-3 fatty acids,[13] which are important for the cell membrane.

There's also indication vitamin D can improve dysmenorrhea, as well as menstrual problems and premenstrual syndrome in adolescents.[14] Vitamin D plays an important role in female reproduction, possibly via its impact on calcium homeostasis, cyclic sex steroid hormone alterations, or neurotransmitter function.[14]

Supporting healthy nitric oxide levels through supplementation with a nitrate-rich supplement containing beetroot may defend against the oxidative stress that occurs in dysmenorrhea. Nitric oxide also has a relaxant effect on the smooth muscle of the myometrium and may inhibit uterine contractions, therefore suppressing dysmenorrhea.[15]

Mastalgia

Mastalgia is pain in the breast tissue. It is the most common breast symptom

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motivating women to seek help from their physicians. Up to 68% of women may have cyclic mastalgia at some point in their lifetime.[16]

Mastalgia is divided into two types: cyclic mastalgia and noncyclic. Cyclic mastalgia is related to the menstrual cycle. It usually begins one to two weeks prior to menstruation and ceases when bleeding begins. It is poorly localized, can affect both breasts, and is often described as a heaviness or soreness that often radiates to the armpit and arms. It usually occurs in women under 40 years old. Most often, it happens during the luteal phase of the menstrual cycle due to a rise in water content in breast tissue caused by increasing hormone levels.[17]

Enhancing nitric oxide levels through the use of beetroot juice may reduce oxidative stress and improve blood flow.

Risk factors of mastalgia may include emotional stress, drinking caffeine, smoking, breast feeding three times or more, and body mass index.[17]

Noncyclic mastalgia is unrelated to the menstrual cycle and can occur in only one breast. Women who have this type of pain often describe it as sharp and burning and it's localized to the breast. Noncyclic mastalgia occurs most often in women 40 to 50 years old.

Before implementing possible treatments for mastalgia, it is always a good idea to try to eliminate any external sources. A postmenopausal woman who once visited Dr. Meletis' clinical practice complained of pain in one breast and a strong family history of breast cancer. On her own, she sought annual mammograms. After she arrived at his clinic, he ordered bloodwork and an ultrasound. When those came back negative for any overt problem, Dr. Meletis postulated the problem was a change in physical activity. Ultimately, he determined that the amount of time she was spending as a grandmother taking care of and lifting two toddler twins, was likely the cause of her mastalgia. Upon changing her physical exertion, her symptoms completely abated.

When addressing cyclical mastalgia, a number of botanical substances have been found to offer support. These include *Vitex agnus-castus* (chaste tree), curcumin, *Zingiber officinale* (ginger), and *Ginkgo biloba*.[18] Furthermore, a double-blind, randomized, controlled study of 60 women with moderate mastalgia found that "chamomile presents a safe, well-tolerated and effective treatment for women with moderate mastalgia."[19] Evening primrose oil (EPO) also has a great deal of evidence backing its use in mastalgia.[20,21] One review of the medical literature that included 13 published randomized clinical trials and 1,752 patients observed that while there was no difference between EPO and a placebo, it was similarly effective for pain control as non-steroidal inflammatory drugs (NSAIDs), the endometriosis medication danazol, and vitamin E.[20]

We also know that some healthcare providers report that if they paint the cervix with iodine after performing a PAP test and exam, the patient has less breast pain during the following menstrual cycles. There is support for this concept in the medical literature. For example, a randomized, double-blind, placebo-controlled clinical trial was conducted with 111 otherwise healthy women with a history of breast pain.[22] The woman were given a placebo or 1.5 mg/day, 3 mg/day, or 6 mg/day of iodine. Patients reported statistically meaningful declines in pain by month three in the 3 mg and 6 mg/day treatment groups, but not the 1.5 mg/day or placebo group. More than half of the 6 mg/day treatment group reported a clinically significant reduction in overall pain. It's not surprising that these improvements may have taken up to three months to kick in; it takes time for iodine to reach and nourish the breast tissues and shift the microenvironment and tissue chemistry.

Balancing the estrogen and progesterone ratio is also critical to avoid estrogen dominance. After testing hormone levels, natural progesterone cream can be used to restore hormonal balance.

Perimenopause and Menopause as an Inflammatory State

While premenopausal women produce strong endogenous hormones, once a woman nears completion of perimenopause and enters into full menopause, factors affecting her health become even more unopposed by endogenous hormone production and the associated receptor activity. Perimenopause is actually a systemic inflammatory phase that can open the door to future neurodegenerative problems.[23] The perimenopause and menopausal transition is associated with pronounced hormonal alterations that exponentially increase a woman's risk of stroke and Alzheimer's disease.[23]

Accumulating evidence indicates that perimenopause is proinflammatory and interferes with neurological systems that are regulated by estrogen.[23] Estrogen receptor-beta is known to govern a critical component of innate immunity known as the inflammasome, and it also is involved in regulation of neuronal mitochondrial function.[23] By interfering with these actions, perimenopause leads to increased systemic and central nervous system inflammation and alterations in innate immunity.[23]

Supporting a healthy inflammatory response in this group of women is essential. This can be done using omega-3 fatty acids,[24] curcumin,[25] and avoiding sugar and processed carbs. Reducing estrogen dominance by balancing progesterone and estrogen levels is also key.

Obesity and Female Health

Obesity is linked to a number of female disorders, including reproductive problems such as menstrual irregularities, pregnancy complications, and infertility due to the inability to

ovulate (anovulation).[26] Obese women have lower levels of gonadotropin-releasing hormones (GnRH), which are made in the hypothalamus of the brain. GnRH triggers the pituitary gland to produce luteinizing hormone and follicle-stimulating hormone, which in turn cause the ovaries to make estrogen and progesterone. Obesity dysregulates the hypothalamic-pituitary-gonadal axis and impairs GnRH neuron function, the final brain signaling system for the regulation of reproduction.[26]

Toxins and Female Health

An extensive discussion of the effect of toxins on female health is outside the scope of this article. However, caution should be urged when implementing weight loss programs in female patients. This is because numerous studies indicate toxins are released from fat tissue into the body during weight loss.[27-29] Undertaking a detoxification program that includes drinking plenty of water and encouraging two to three bowel movements per day is essential in any woman before she begins weight loss. Additionally, enhancing blood flow and circulation can flush away toxins and metabolic waste products. This can be accomplished through use of nitrate-rich supplements that contain beetroot.[30] Eating an organic diet is also important to minimize toxin exposure.

Conclusion

This article was not intended to be an exhaustive discussion of all the possible therapeutics that can be used for female disorders such as mastalgia or dysmenorrhea or to reduce the inflammatory response associated with perimenopause and menopause. Rather, it is meant to touch briefly upon some of the female health strategies found to be most effective in science and/or clinical practice. We know that the peer-review literature lags and does not fully capture functional medicine therapeutics that we find helpful in clinical practice.

Women experience a number of health issues that are often frustrating, painful, and interfere with their quality of life. Using a combination of botanical support, nutrients like vitamin D and E, omega-3 fatty acids, and essential primrose oil, and hormonal support with natural progesterone can yield significant improvement. Furthermore, enhancing nitric oxide levels through the use of beetroot juice may reduce oxidative stress and improve blood flow to flush out toxins. Finally, to compensate for the increased inflammation that occurs during perimenopause and menopause, omega-3-fatty acids and curcumin are viable options.

References

1. Sidani M, Campbell J. Gynecology: select topics. *Prim Care.* 2002;29(2):297-321, vi.
2. Physiology of Self Renewal. Medical Science Navigator. https://www.medicalsciencenavigator.com/physiology-of-self-renewal/. Accessed December 6, 2021.
3. Muggli R. Systemic evening primrose oil improves the biophysical skin parameters of healthy adults. *Int J Cosmet Sci.* 2005;27(4):243-249.
4. Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. *Epidemiol Rev.* 2014;36:104-113.
5. Agarwal AK, Agarwal A. A study of dysmenorrhea during menstruation in adolescent girls. *Indian J Community Med.* 2010;35(1):159-164.
6. Nagy H KM. Dysmenorrhea. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK560834/. Published 2021. Accessed.
7. Nakayama M, Ono M, Iizuka T, et al. Hypertensive disorders of pregnancy are associated with dysmenorrhea in early adulthood: A cohort study. *J Obstet Gynaecol Res.* 2020;46(11):2292-2297.
8. Kim KI, Nam HJ, Kim M, Lee J, Kim K. Effects of herbal medicine for dysmenorrhea treatment on accompanied acne vulgaris: a study protocol for a randomized controlled trial. *BMC Complement Altern Med.* 2017;17(1):318.
9. Dikensoy E, Balat O, Pençe S, Balat A, Cekmen M, Yurekli M. Malondialdehyde, nitric oxide and adrenomedullin levels in patients with primary dysmenorrhea. *J Obstet Gynaecol Res.* 2008;34(6):1049-1053.
10. Proctor ML, Murphy PA. Herbal and dietary therapies for primary and secondary dysmenorrhoea. *Cochrane Database Syst Rev.* 2001(3):Cd002124.
11. Uberti F, Morsanuto V, Ruga S, et al. Study of Magnesium Formulations on Intestinal Cells to Influence Myometrium Cell Relaxation. *Nutrients.* 2020;12(2).
12. Hafen BB BB. Physiology, Smooth Muscle. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK526125/. Published 2021. Accessed.
13. Hansen SO, Knudsen UB. Endometriosis, dysmenorrhoea and diet. *Eur J Obstet Gynecol Reprod Biol.* 2013;169(2):162-171.
14. Bahrami A, Avan A, Sadeghnia HR, et al. High dose vitamin D supplementation can improve menstrual problems, dysmenorrhea, and premenstrual syndrome in adolescents. *Gynecol Endocrinol.* 2018;34(8):659-663.
15. Norman J. Nitric oxide and the myometrium. *Pharmacol Ther.* 1996;70(2):91-100.
16. Ader DN, South-Paul J, Adera T, Deuster PA. Cyclical mastalgia: prevalence and associated health and behavioral factors. *J Psychosom Obstet Gynaecol.* 2001;22(2):71-76.
17. Eren T, Aslan A, Ozemir IA, et al. Factors Effecting Mastalgia. *Breast Care (Basel).* 2016;11(3):188-193.
18. Niazi A, Rahimi VB, Hatami H, et al. Effective Medicinal Plants in the Treatment of the Cyclic Mastalgia (Breast Pain): A Review. *J Pharmacopuncture.* 2019;22(3):131-139.
19. Saghafi N, Rhkhshandeh H, Pourmoghadam N, et al. Effectiveness of Matricaria chamomilla (chamomile) extract on pain control of cyclic mastalgia: a double-blind randomised controlled trial. *J Obstet Gynaecol.* 2018;38(1):81-84.
20. Ahmad Adni LL, Norhayati MN, Mohd Rosli RR, Muhammad J. A Systematic Review and Meta-Analysis of the Efficacy of Evening Primrose Oil for Mastalgia Treatment. *Int J Environ Res Public Health.* 2021;18(12).
21. Balci FL, Uras C, Feldman S. Clinical Factors Affecting the Therapeutic Efficacy of Evening Primrose Oil on Mastalgia. *Ann Surg Oncol.* 2020;27(12):4844-4852.
22. Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J.* 2004;10(4):328-336.
23. McCarthy M, Raval AP. The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. *J Neuroinflammation.* 2020;17(1):317.
24. Ishihara T, Yoshida M, Arita M. Omega-3 fatty acid-derived mediators that control inflammation and tissue homeostasis. *Int Immunol.* 2019;31(9):559-567.
25. He Y, Yue Y, Zheng X, Zhang K, Chen S, Du Z. Curcumin, inflammation, and chronic diseases: how are they linked? *Molecules.* 2015;20(5):9183-9213.
26. Lainez NM, Coss D. Obesity, Neuroinflammation, and Reproductive Function. *Endocrinology.* 2019;160(11):2719-2736.
27. Lee YM, Kim KS, Jacobs DR, Jr., Lee DH. Persistent organic pollutants in adipose tissue should be considered in obesity research. *Obes Rev.* 2017;18(2):129-139.
28. Hong NS, Kim KS, Lee IK, et al. The association between obesity and mortality in the elderly differs by serum concentrations of persistent organic pollutants: a possible explanation for the obesity paradox. *Int J Obes (Lond).* 2012;36(9):1170-1175.
29. Brown RH, Ng DK, Steele K, Schweitzer M, Groopman JD. Mobilization of Environmental Toxicants Following Bariatric Surgery. *Obesity (Silver Spring).* 2019;27(11):1865-1873.
30. Jones T, Dunn EL, Macdonald JH, Kubis HP, McMahon N, Sandoo A. The Effects of Beetroot Juice on Blood Pressure, Microvascular Function and Large-Vessel Endothelial Function: A Randomized, Double-Blind, Placebo-Controlled Pilot Study in Healthy Older Adults. *Nutrients.* 2019;11(8).

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Osteoporosis in Women: A Look at Risk Factors, Risk Assessment, Bone Density Testing, and Overview of Treatments

by Tori Hudson, ND

Osteoporosis is one of the chronic health conditions for which many women seek my input and recommendations. This is a challenging area for practitioners who have a priority for natural medicines. While natural medicine and lifestyle issues are fundamental to prevention of osteoporosis and osteoporotic-related fractures, natural medicine-only treatment interventions can be naïve and insufficient for statistical and meaningful fracture prevention in what might be years from the present. On the other hand, the conventional medications come with risks along with the benefits... and some of the risks are not an acceptable risk for many patients. It is important to educate the patients on the risks of inadequate treatment, while also weighing the benefits and the risks of treatment options.

What I am going to focus on in this article is to point out some key aspects of osteoporosis, the prevalence, risk factors, and assessment and indications for bone density testing. The reason for this is that I find too many practitioners of all disciplines, just jump to exercise, vitamin D and other supplements and/or pharmacologic agents and do not do the due diligence of evaluation of the condition itself. I will not review with any depth the nonpharmacologic treatments and lifestyle modification and the pharmacologic agents for prevention of bone loss and treatment of osteoporosis.

Osteoporosis is the most common bone disorder in humans and is a general skeletal disorder characterized by a decrease in bone strength that then predisposes an individual to an increased risk of fracture with the most important sites being the spine and hip. Osteoporosis-related serious fractures occur most often in older postmenopausal women and can be life altering. The bone loss during the menopause transition and the early part of menopause is what results in osteoporosis. Fractures that are less serious than the spine or hip are those in the wrist in postmenopausal women often in their 50s and 60s that can be early warning signs of osteoporosis.

Fortunately, we can identify osteoporosis and identify those women who are at high risk of fracture. Evaluating skeletal health should be a skill set of all primary health care providers, especially those who offer primary care to postmenopausal women.

Osteoporosis is determined by bone densitometry and, according to the World Health Organization (WHO), is defined by a bone mineral density (BMD) T-score less than or equal to -2.5 at the total hip, femoral neck, or lumbar spine (with at least two vertebral levels in the posteroanterior position) in a postmenopausal woman or a man over age 50.[1,2] Most other organizations support this description. The presence of a fragility fracture also justifies a clinical diagnosis of osteoporosis.

There has been a shift in the thinking about the term "osteopenia." The diagnosis of osteopenia, or low BMD does not necessarily mean that she has experienced bone loss. The term is now thought to have limited clinical value because it includes young postmenopausal women without other risk factors who are actually at low risk of fracture while also including older women with other risk factors who are at very high risk of fracture.

In addition to BMD, a clinical diagnosis of osteoporosis can be made in postmenopausal women who have a fracture of their spine or hip or who have other factors that result in a high risk of fracture.

Osteoporosis is also categorized as either primary or secondary. Primary osteoporosis is related to bone loss that occurs after menopause as women age. Secondary osteoporosis is diagnosed when it is secondary to issues such as glucocorticoids, vitamin D deficiency, hyperthyroidism, hyperparathyroidism, renal calcium leak or other diseases that contribute to bone loss. It is important that clinicians learn to evaluate for secondary causes of bone loss to rule out these other causes.

Prevalence, Morbidity, and Mortality

In the National Health and Nutrition Examination Survey of 2013-2014, 16.5% of American women aged 50 years or older had osteoporosis at either the femoral neck or lumbar spine.[3] The prevalence of osteoporosis of the femoral neck increases with age from 6.8% in women aged 50-59 to a striking 34.9% in women aged 80 years and older.[4] Black American women have the highest BMD and Asian American women have the lowest.[5] Most osteoporosis fractures occur in

postmenopausal women, with two-thirds of them after age 75.[6] For a white American woman aged 50 years, her risk of having an osteoporotic fracture in her remaining years is about 40%; and if you break it down, it's 17.5% for the hip, 16.0% forearm, and 15.6% for a symptomatic vertebral fracture.[7]

Hip fractures after age 82 are the most life altering and up to a 25% increase in mortality within one year of the fracture.[8] And it's not just mortality – up to 25% of women require long-term care after a hip fracture and 50% will have some long-term loss of their mobility.[9]

Risk Factors and Risk Assessment

Risk factors for low BMD include advanced age, thinness (<127 lb), genetics, and smoking. Numerous diseases and medications have negative impact on bone, including eating disorders, rheumatoid arthritis, celiac disease, hyperparathyroidism, Cushing's syndrome, aromatase inhibitors, glucocorticoids and gastric bypass surgery. Proton pump inhibitors are associated with increased fracture risk without causing bone loss. Counterintuitive to many, It turns out lifetime intake of calcium or vitamin D, alcohol, caffeine, or current or past physical activity are not predictors of low BMD. In addition, disorders and drugs that affect muscle strength, balance, and eyesight increase the risks of falls and fracture.

The tools to evaluate risk include a comprehensive history and physical exam with an eye towards yellow and red flags. These include surgical menopause and not on extended menopause hormone therapy, premature ovarian insufficiency and not on menopausal hormone therapy until at least age 51, and early menopause (onset between 40-45) and not on menopausal hormone therapy until at least age 51. Other key historical findings are a parent with a history of hip fracture, being a current smoker, consuming more than three servings of alcohol daily, and the diseases and medications mentioned earlier. Other known risk factors for fracture include dementia, low physical activity, thoracic kyphosis, rates of bone loss, weight loss, and loss of height.[10]

The primary objective tool for assessing bone density is a DXA scan, but ultrasound and quantitative computed tomography (CT) can also be used – although they should not be substitutes for DXA and the T-scores of the hip or spine obtained with DXA scans.

Serum markers of bone turnover cannot diagnosis osteoporosis and have unpredictable ability in assessing fracture risk.

The most important risk factors for fracture in postmenopausal women are a history of a previous fracture or falls, older age, and low BMD. Combining these and other independent risk factors improves the clinician's ability to identify women at high fracture risk. The computer-based algorithm, FRAX is a tool that can easily be learned to determine risk and is available online at www.sheffield.ac.uk/FRAX/. The FRAX calculation is now often reported in DXA reports.

Indications for Bone Density Testing

Bone density testing should be done in postmenopausal women with risk factors for low bone density and where knowing that will influence the clinical management:

- Women with a history of postmenopausal fracture
- Women with known medical causes of bone loss or fracture
- Women 65 and older
- Women 50 and older and with one or more additional risk factors of
  - Weight less than 127 lb
  - Family history of hip fracture in a mother or father
  - Currently a smoker
  - Discontinuing her systemic menopausal hormone therapy with additional risk factors for fracture.

For postmenopausal women aged 50 to 64 years with baseline T-scores greater than -1.5, retesting can wait until age 65. Age 65 is the age at which routine BMD screening is recommended for all women. Retesting earlier can be considered in women within five years of menopause whose initial BMD T score was worse than -1.5 or in those with other risk factures such as a prior postmenopausal fracture or if they have medical problems or medications associated with bone loss.

A comprehensive physical exam for osteoporosis evaluation should include an assessment of kyphosis, muscle strength, balance, height, weight, oral health (gum disease, tooth loss, tooth fractures), bone tenderness of thoracic vertebrae and anterior tibia and joint laxity.

Laboratory testing should be done prior to any intervention for women with osteoporosis, to evaluate for secondary causes of bone loss. Routine tests include CBC, general serum chemistry (especially serum calcium, creatinine, alkaline phosphatase, albumin, serum phosphate), and serum vitamin D. A 24-hour urinary calcium excretion test is used to test for poor calcium absorption and hypercalciuria. Other special tests can be considered based on abnormal values of any of the above, other special cases of osteoporosis, or clinical indications of other diseases that affect bone loss. Serum markers of bone turnover, while popular amongst integrative, functional medicine, and alternative-minded practitioners, cannot diagnosis osteoporosis and have unpredictable ability in assessing fracture risk. Their primary value has been in clinical trials where large groups of women are studied and group responses to treatment are assessed. For individual patient evaluation of women with osteoporosis, it is not recommended.

Nonpharmacologic Treatments and Lifestyle Modifications

The whole point of management of bone health in postmenopausal women is to minimize bone loss and reduce the likelihood of fractures. All postmenopausal women, whether they have low bone density, osteoporosis or already have had a postmenopausal osteoporosis-related fracture, should ➤

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be educated and urged to make lifestyle modifications to support general health and bone health. Examples include a balanced, whole foods-oriented diet with adequate intakes of calcium, vitamin D, adequate physical activity and to avoid smoking and excess alcohol. However, it is important to appreciate that these efforts will not prevent bone loss in early menopause, will not significantly increase BMD in postmenopausal women, and are not adequate treatment interventions for women with osteoporosis.

Most of the research studies that have been done to evaluate non-pharmacologic treatments and lifestyle changes are small and short and as such, recommendations are usually based on systematic reviews, meta-analysis and opinions of expert committees. While it is true that intakes of calcium and vitamin D are required for normal skeletal growth in childhood, the data is less clear for healthy postmenopausal women. The Institute of Medicine (IOM) committee proposed daily intakes of calcium for postmenopausal women of 1,000-1,200 mg/day with an upper limit of 2,000 mg/day but note that these recommendations are based on uncertain and even inconsistent data. It is important to note that the average daily dietary intake of calcium for women in the US and Canada is 700 mg-800 mg daily. About one third of that comes from dairy products which would mean if a woman consumed an average dairy-free diet, her diet would contain only amount 500 mg/day of calcium. That leaves us with women consuming daily dairy of about 250 mg; and assuming the other 500 mg comes from non-dairy sources, she would need to add 250 mg to 450 mg/daily of supplemental calcium. For most dairy-free women, they would need to add 500 mg to 700 mg daily. When I review a woman's dietary calcium intake, I use a simple list of calcium content foods to estimate her dietary daily calcium. The National Institute of Health Osteoporosis and Related Bone Diseases National Resource Center has a simple list.

To highlight the importance of estimating dietary calcium, and then recommending women supplement the difference to get up to the total of 1,000-1,200 mg/day, in the Women's Health Initiative (WHI) calcium and vitamin D study, the average calcium intake was about 1,100 mg daily. In the group that added another 1,000 mg of daily calcium supplement, the risk of kidney stones was increased by 17%.[11] There have been reports of the possibility that a calcium supplement of 1,000 mg/day with a total diet plus supplement of 2,000 mg/day is associated with increased cardiovascular risk.[12,13] Any association of total calcium intake with cardiovascular risk was not seen in the WHI.[14] An analysis published in 2016 found that a calcium intake of 2,000 mg-2,500 mg/day was not associated with cardiovascular risk in health adults.[15] Due to any lack of benefit for a total of more than 1,200 mg/day of dietary plus supplemental calcium, the recommendation of about 1,200 mg/day total is still given for postmenopausal women with or without osteoporosis and for women of any age with osteoporosis.

The IOM recommends 600 IU/day of vitamin D for women between 50 and 70 years of age and 800 IU daily for women older than 70. However, the recommendations were based on the fact that these doses were sufficient to achieve a serum 25-OHD level of at least 20 ng/mL in most postmenopausal women. Not all are happy with this threshold and cite that it should be at least 30 ng/mL. While surprising, most studies report no benefit of calcium and/or vitamin D on fracture risk. This inability might be related to calcium and vitamin D being threshold nutrients, with severe deficiencies being harmful, but intakes more than the threshold to avoid deficiency does not really provide additional benefit. The effects of vitamin D with calcium on fracture risk have been mostly observed in women who are institutionalized or in older women with vitamin D deficiency.[16] Even the US Preventive Services Task Force (USPSTF) has chimed in concluding that there was insufficient evidence to assess the balance of the benefits and harms of a daily supplementation of vitamin D 400 IU or more and calcium of 1,000 mg or more for primary prevention of osteoporosis in non-institutionalized postmenopausal women.[17]

Even women with osteoporosis do not require more calcium or vitamin D than women with normal BMD unless they have what is defined as a deficiency.

A few other supplements of note. Strontium has received some attention, but it is important to realized that the drug, strontium ranelate, a strontium salt was never approved in the US or Canada and even now is not available in other countries due to concerns about increased cardiovascular risk. There is no evidence for other strontium salts sold as dietary supplements when it comes to support for bone health. Magnesium, manganese, copper, zinc, folic acid, boron, vitamin C and more have scant data but are often included in multi-ingredient bone health supplements to support the potential benefits on bone metabolism, bone strength, bone architecture, but doubtful for bone density.

Vitamin K is more interesting and does have individual study data of some compelling importance. I go into some detail here, as it is the one supplement I feel may have some hope for my patients who have osteoporosis and decline drug therapy. Vitamin K is required for the production of the bone protein osteocalcin. Osteocalcin draws calcium to bone tissue, enabling calcium crystal formation. Osteocalcin provides the protein matrix for mineralization and is thought to act as a regulator of bone mineralization.[18] Vitamin K plays a key role in the formation, remodeling, and repair of bone by attracting calcium to the site of this protein matrix.[19] A low dietary intake of vitamin K seems

to increase the risk of osteoporotic hip fractures in women, according to data from the Nurses' Health Study.[20]

There are various forms of vitamin K, but the human trials have been done on vitamin K1 (phylloquinone), MK4, (MK4, a form of vitamin K2) and menaquinone-7 (longer-chain MK7).

In a double-blind study, 452 men and women (ages 60-80 years) received a multiple vitamin/multimineral supplement providing 600 mg/day of calcium and 400 IU/day of vitamin D, plus either 500 mcg/day of vitamin K1 or no vitamin K1.[21] BMD (determined by DEXA) and bone turnover were measured at 6, 12, 24, and 36 months. There were no differences in BMD at the femoral neck, lumbar spine, or total body between the two treatment groups, indicating that vitamin K1 did not enhance the effects of calcium, vitamin D, or other nutrients in this patient population. In the double-blind ECKO trial,[22] a daily 5-mg supplement of vitamin K1 for two to four years did not protect against an age-related decline in BMD in postmenopausal women with osteopenia, but significantly fewer women in the vitamin K1 group than in the placebo group had fractures.

Epidemiologic evidence has shown associations between low dietary intake of vitamin K and increased bone loss in elderly men and women. A 2006 meta-analysis of 13 randomized controlled trials[23] that gave vitamin K1 or MK4 (a form of vitamin K2) supplements for longer than six months reported data on bone loss and fracture rates. All but one study showed a reduction in bone loss with supplemental vitamin K. All seven of the 13 studies that reported fracture data were in Japanese individuals and used MK4. Most of these trials used a high dose, 45 mg/day.

Although the recommended dietary intake of vitamin K is 90 to 120 mcg/day, the optimal dose and form of vitamin K supplementation to achieve a protective effect on bone loss and fracture reduction is not known. The majority of studies used MK4 at doses approximately 400-fold higher than dietary recommendations for vitamin K1. An additional issue is that these studies have been conducted almost exclusively in Japanese postmenopausal women. This population group may be influenced by unique dietary, environmental, and/or genetic factors, so it is not clear whether the findings from these studies can be generalized to other populations. In contrast to the seven positive Japanese studies, in a double-blind trial, 381 postmenopausal women received either phylloquinone (1 mg/day), MK4 (45 mg/day), or placebo for 12 months.[24] No effect of phylloquinone or MK4 on the bone density of the lumbar spine or proximal femur was observed. ➤

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Two long-term trials have previously been done evaluating the effect of vitamin K1 supplementation on bone loss. In one study using 1 mg/day of vitamin K1 plus calcium and vitamin D for 3 years in postmenopausal women aged 50 to 60 years,[25] bone loss was reduced at the femoral neck, but there was no beneficial effect on spinal bone density. In a second study,[26] 200 mcg/day of vitamin K1 plus calcium and vitamin D given for two years to nonosteoporotic women aged 60 years or above resulted in a modest increase in BMD of the radius but not the femoral neck.

Current drugs and doses approved in North America for preventing osteoporosis:

Conjugated equine estrogen (Premarin)	0.3, 0.45, 0.625, 0.9, 1.25, 2.5 PO daily
Estradiol (various)	0.5 mg, 1mg, 2mg; PO daily; transdermal 0.025 patches or greater (twice weekly or once weekly depending on which patch)
Estradiol + NETA (Activella, Amabelz)	Estradiol 1 mg + NETA 0.5mg; PO daily Estradiol 0.5 mg + NETA 0.1 mg; PO daily
Ethinyl estradiol + NETA (FemHRT,Jinteli)	Ethinyl estradiol 2.5 mcg+ NETA 0.5 mg; Ethinyl estradiol 5mcg + NETA mg; PO daily
Conjugated equine estrogen + MPA (PremPro)	CE + MPA doses: 0.625 mg + MPA 2.5 mg or 0.45 mg + 1.5 mg; 0.3 mg + 1.5 mg; 0.625 mg + 5 mg; PO daily
Conjugated equine estrogen + Bazedolixifene (Duavee)	Oral: CE 0.45 mg + BZA 20 mg PO daily
Tibolone (not in U.S.) (Livial; generics)	2.5 mg oral; PO daily
Raloxifene (Evista; generics)	60 mg PO daily
Alendronate (Fosamax; generics)	35 mg PO every week
Risedronate (Actonel; Atelvia; generics)	35 mg PO every week or 150 mg PO every month
Ibandronate (Boniva; generics)	150 mg PO every month
Zoledronate (Reclast; Aclasta; generics)	IV every 2 years

Current Drugs Approved in North America for Treatment of Postmenopausal Osteoporosis:

(Fracture Risk Reduction)	Vertebral	Nonvertebral	Hip
Raloxifene (Evista; generics) 60 mg/day PO	X		
Alendronate (Fosamax; generics) 70 mg q wk PO	X		X
Risedronate (Actonel; generics) 35 mg q wk PO or 150 mg q mo PO	X	X	X
Ibandronate (Boniva; generics) 150 mg PO q mo; or 3 mg IV q 3 mo	X		
Zoledronate (Reclast; generics) 5 mg IV q year	X	X	X
Denosumab (Prolia) 60 mg AQ q 6 mo	X	X	X
Teriparatide (Forteo) 20 mcg SQ daily	X	X	
Baloparatide (Tymlos=US only) 80 mcg SQ daily	X	X	
Romosozumab (Evinity) 210 mg SQ q mo	X	X	X
Calcitonin-salmon (Calcimar) (or generics) 200 USP units; nasal spray daily	X		

Menaquinone-7, or MK-7 (a longer-chain form of vitamin K_2), is found in natto (highest concentration in fermented soybeans) and cheese and in lower concentrations in meat and other dairy products; a very small amount is produced by gut bacteria from dietary vitamin K1.[27] MK-7 has been found in animal studies to be more potent and more bioavailable as well as to have a longer half-life than MK4. When taken as a daily supplement (0.22 µmol/day), MK-7 is more effective than K1 in carboxylating osteocalcin This is thought to be due to MK-7's much longer residence time and the higher serum concentrations of MK-7 achieved during its prolonged intake.[28] The longer-chain menaquinones such as MK-7 are much more hydrophobic, which contributes to their much longer half-lives (8 hours for K1 and MK-4 vs. 96 hours for MK-7).[29] In a study of Japanese postmenopausal women, a significant inverse association was found between natto consumption and the incidence of hip fractures.[30] In a study of osteoporosis after organ transplantation, one year of MK-7 supplementation (180 mcg/day) resulted in increased bone mineralization compared with placebo.[31] However, a study of early menopausal women given one year of supplementation of 360 mcg/day of MK-7 in the form of natto capsules did not show a significant improvement in bone density despite a reduction in uncarboxylated osteocalcin.[32] A likely reason for these inconsistent results is the confounding effect of vitamin D status. The study in post-transplant patients noted a high incidence of vitamin D deficiency, which was found to affect the results.

Lastly, a meta-analysis published in 2019 found no evidence that vitamin K affects bone density or vertebral fracture risk in postmenopausal women and the evidence confirming a reduction in clinical fractures was insufficient.[33]

Too much dietary protein or protein deficiency can be problematic for

bone. In older women who are prone to falling and losing weight, a higher protein intake has been associated with reduced frequency of falling.[34]

Phytoestrogens, namely isoflavones have moderately beneficial effects in slowing the bone loss associated with menopause in a systematic review.[35]

We know that bone mass is impacted by impact loading exercise during childhood and that immobilization is associated with low bone mass. But, a Cochrane review and several meta-analyses are sobering in that they found relatively small, statistically significant effects of exercise on BMD in postmenopausal women.[36-38]

Most fractures occur as a result of a fall and exercise programs that emphasize balance, gait, and muscle strength are very effective ways to prevent falls and perhaps fractures. In women aged 65 years and older, at least one-third of these women experience one or more falls each year. This risk only increases with age, as does the risk of fracture. Assuring adequate vision, a safe home, and attention to medications are important. Tapering the use of benzodiazepines, neuroleptic agents, and antidepressants can reduce the risk of falling by more than 60%.

Pharmacologic Therapy to Prevent Bone Loss and to Treat Osteoporosis in Postmenopausal Women

This section will be brief and only key points summarized. Much data is available for your perusal should you be interested. Benefits and risks are specific to each agent, dose and duration.

Prevention of Bone Loss. The mechanisms of action of all osteoporosis pharmacologic agents are to either inhibit or to activate bone metabolism. The anti-remodeling agents, also called antiresorptive drugs, include systemic estrogen, estrogen agonists/antagonists, bisphosphonates, and denosumab. They all inhibit bone resorption and to a lesser extent, bone formation. These medications maintain or improve BMD and reduce the risk of fracture but do not improve or repair trabecular bone structure.

Treatment. The primary objective of treating women with osteoporosis is to reduce the risk of fracture. All the approved drugs for treatment have been shown in randomized controlled trials to reduce the risk of fracture. Anti-remodeling drugs inhibit bone resorption by osteoclasts and, to a lesser degree, inhibit bone formation. Treatment with these agents fills in remodeling spaces in bone that are present before treatment starts and also results in opening of fewer new remodeling spaces. This results in an increase in BMD, bone strength, and decreased fracture risk.

Some of the newest bone drugs in use are actually bone-building drugs that stimulate bone formation and restore the trabecular bone structure while these bone-forming properties decline over time. For these reasons, these drugs are to be limited to treatment intervals of 12 to 24 months. When the osteoanabolic agents are discontinued, bone mineral density is rapidly lost, and these therapies are then followed by an anti-remodeling drug.

BMD testing is likely repeated one to two years after beginning osteoporosis drug treatment. For those women on bisphosphonates, the BMD test is done again at five years to consider the option of taking a bisphosphonate holiday.

The prescribing of these prevention and treatment drugs are likely best done by osteoporosis experts, most often an endocrinologist or rheumatologist.

The role of the integrative, natural medicine or functional medicine clinician is to know the benefits and risks of all treatment options, non-pharmacologic and pharmacologic, and then to integrative strategies in the safest way possible.

Conclusion

At the forefront of our minds, it should be known that osteoporosis is a chronic, progressive condition; and it affects a large percentage of postmenopausal women. Women's health care practitioners and especially menopause practitioners should be familiar and comfortable with assessment and management, or refer to those that are. A naïve and uninformed clinician can miss the opportunity to accurately diagnose, individually assess fracture risk, individualize treatment approaches and truly present women with options that include the whole spectrum of prevention and treatments. Under treatment is just as harmful or perhaps more so, than over treatment. In the end, educating women with accurate studious information and the tools to make informed decisions that they feel the most comfortable with and realistically confident in, is a critical aspect of offering good, respectful medical care. ◆

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

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Hypothermia to Treat Hypoxic Encephalopathy in Newborns

by Jacob Schor, ND

In recent years, hypothermia, the lowering of body temperature for therapeutic purposes, has been adopted in neonatal intensive care facilities across the country for the treatment of hypoxic encephalopathy in newborns. In simpler words, it's used to treat brain damage from asphyxia, or suffocation, often brought about by the umbilical cord wrapping around the neck. The babies are chilled down for three days, giving their brains a chance to heal. While use of hypothermia for this particular condition is likely outside the scope of practice of naturopathic physicians, hypothermia itself is among the most fundamental and traditional naturopathic therapies to treat illness. We might argue that hypothermia is indeed within our scope, but the required equipment is definitely outside our budgets. There is value to our being cognizant of this treatment's application in the neonatal realm. For those of us who, in the course of practice, may deal with hypoxic newborns, this article should be a timely reminder of the importance of having emergency referral systems in place and up to date. While hypothermia can be near miraculous in helping newborns recover from brain injury, it only helps if started within the six-hour window after birth. For the rest of us, knowing more about this specialized use of hypothermia may allow us to better understand the underlying mechanisms of action so we may translate this application into other situations where hypoxia and reperfusion injuries occur.

We were exposed to the basic ideas of hypothermia when we studied hydrotherapy as naturopathic students. Water transfers heat to and from the body well so is often employed to raise or lower body temperature. However, in hydrotherapy we typically use cold water to trigger reactive responses in the body in order to direct blood flow to a cooled area to warm it. Hydrotherapy is of course far more complex and that was an oversimplification. In an excellent 2014 article published in *NDNR*, Sussanna Czerenko reviewed the distinctions between the goals of four forms of hydrotherapy – fluxion, reaction, retrostasis, and revulsion: "… *fluxion* speeds up the flow of blood, *reaction* initiates the body's healing responses, *retrostasis* moves blood from the surface of the skin to the organs, and *revulsion* moves blood from one part to another distally."[1]

In this article, hypothermia, even if achieved through cold water, describes the actual reduction of body temperature and maintaining it lower than normal, overriding compensatory attempts the body makes to rewarm.

Hypothermia treatments are directed to cool either one specific area of the body or systemically to cool the entire body. Those of us who work with cancer patients are aware of the cooling caps now in fashion used during chemotherapy to prevent or reduce hair loss. In their case, the effect is directed only toward the scalp to prevent damage to the hair follicles. Hypothermia treatment of neonates can be either whole body or directed to the head, and while recent reviews suggest possible greater benefis to limiting cooling just to the head,[2] my impression is that whole body cooling is currently the more common method used. Using what is essentially a crib-sized waterbed with tightly regulated water temperatures, the infant is cooled to a core temperature (measured as an esophageal temperature) of 33.5°C for 72 hours (92.3 degrees F).

While we might consider hydrotherapy a naturopathic discipline dating back to Priessnitz,[3] this modern usage to cool the brain and treat hypoxic encephalopathy dates back only to the early 1980s when case reports were published of children who survived cold water drowning with negligible neurologic damage.[4,5] Such reports led to animal experiments that then led to human trials.[6] The first clinical trials on babies were published in the late 1990s[7] and early 2000s.[8-11] We should note that, "….hypothermia is one of the few therapeutic modalities in neonatology that was studied extensively in animal models before clinical application in humans."[12] (A Russian article suggests that hypothermia was being used for this purpose as early as 1977.[13])

In the years since, hypothermia has been studied repeatedly to the degree that we now look to meta-analyses and Cochrane Reviews to confirm benefit. An early Cochrane review published in 2007 included eight randomized controlled trials and concluded that "…therapeutic hypothermia treatment for term infants with moderate to severe HIE [hypoxia induced encephalopathy] significantly reduced death as well as long-term neurodevelopmental disabilities to 18 months of age. Most importantly, therapeutic hypothermia improved mortality and neurodevelopmental outcomes among survivors."[14] A 2013 Cochrane review updated these findings. Analyzing 11 randomized controlled trials (n=1505 term and late preterm infants

with moderate/severe encephalopathy), "Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (typical RR 0.75 (95% CI 0.68 to 0.83); typical RD -0.15, 95% CI -0.20 to -0.10);…. Cooling also resulted in statistically significant reductions in mortality (typical RR 0.75 (95% CI 0.64 to 0.88), …."[15]

In China, where hypothermia is not fully accepted, over half of the hospitals surveyed recently provided this treatment.[16] A statistic summarizing the percentage of US hospitals possessing the necessary equipment to offer hypothermia remains elusive, but it seems that the number might be lower: "Because the majority of infants who have neonatal encephalopathy are born at community hospitals, centers that perform cooling should work with their referring hospitals to implement education programs focused on increasing the awareness and identification of infants at risk for encephalopathy, and the initial clinical management of affected infants."[17] In the US infants are transported to tertiary hospitals with neonatal intensive care units for treatment. The American Academy of Pediatrics maintains an online search tool to locate the nearest neonatal intensive care unit (NICU) to a specified location.[18]

The most recent studies have expanded the list of possible uses. A February 2021 metanalysis evaluated data on kidney function, as acute kidney injury is a frequent complication of perinatal asphyxia. The authors report a 19% reduction in acute kidney injury in infants treated with hypothermia (RR: 0.81; 95% CI 0.67-0.98; p = 0.03). Additionally, four out of five identified studies, reported significant reductions in cardiac biomarkers and less myocardial dysfunction on ECG and cardiac ultrasound.[19]

Use has expanded beyond newborns and children: "Hypothermia is widely accepted as the gold-standard method by which the body can protect the brain. Therapeutic cooling – or targeted temperature management (TTM) – is increasingly being used to prevent secondary brain injury in patients admitted to the emergency department and intensive care unit. Rapid cooling to 33°C for 24 h is considered the standard of care for minimizing neurological injury after cardiac arrest…."[20]

In recent years neonatal specialists have begun prescribing hypothermia treatment more liberally and treating children outside of the initial criteria that signal severe brain injury. Now studies are assessing more subtle indications of injury and applying hypothermia to milder cases. At this point questions remain whether this is justified.

Our patients are not average people. Often, they come to see us in part because they have unusual health responses. Their health conditions may make their lives more challenging or hold world views on the fringes of normal. We need to be prepared for the unexpected. If your practice includes neonates, you need to know which hospitals in your area offer hypothermia and have their phone number handy. Many NICUs dispatch specially equipped ambulances so that cooling can be started while the infant is being transported to the hospital.

This discussion is about neonates and not preterm babies. Infants who emerge from the womb too early often suffer from hypothermia, that is being too cold. This is a life-threatening situation and preterm infants need to be kept warm.[21] Being able to distinguish between infants who need to be warmed and those that should be cooled is a skill set that we won't attempt to teach here. What you need to learn is the phone number of a neonatal intensive care unit to reach out to when help is needed.

Three Phases of Brain Injury

Understanding the mechanisms by which hypothermia helps these injured neonates may be useful for us as it may add a dimension of understanding to how some naturopathic therapies work. Let's focus first on brain injuries in hypoxic infants. A cascade of brain injuries is triggered by lack of oxygen. For ease of explanation this cascade is often divided into three phases.[22] In the acute phase of injury, "… the culmination of energy failure, acidosis, glutamate release, lipid peroxidation, and the toxic effect of nitric oxide leads to cell death via necrosis and activates apoptotic cascades."[23]

The acute phase is followed by partial recovery and a latent phase that lasts up to six hours, but then secondary deterioration occurs. This secondary phase begins 6 to 15 hours after the initial injury and may last hours to days. Hypoxia activates a switchover from oxidative to anaerobic metabolism that progresses to energy failure, mitochondrial dysfunction, intracellular calcium overload, free radical production leading to an inflammatory response and apoptosis of injured cells; all of which contribute further to brain injury.[24]

Hypothermia is useful for injuries that result from switching over to anaerobic metabolism and produce mitochondrial failure.

The third phase involves processes that can occur months after initial injury and include late cell death, remodeling of the brain, and "… astrogliosis due to persistent inflammation and epigenetic changes."[25] "It is the time period following resuscitation, before the secondary phase of injury, that provides a potential window for neuroprotection or diminution of injury."[26] In other words, hypothermia comes into play during this second stage where damage continues to accumulate even though oxygen has been restored. **Astrogliosis** is a defense mechanism to minimize and repair the initial damage after CNS injuries and is characterized by remarkable molecular, cellular, and functional alterations in glial cells, especially in reactive astrocytes.[27]

Hypothermia is currently so well accepted as the primary treatment for hypoxic encephalopathy that much of the current research is focused instead on adjunctive therapies that might make hypothermia more effective[28] such as xenon or hydrogen inhalation,[29,30] melatonin,[31] CBD,[32] erythropoietin,[33] and carnosine.[34] A number of natural products are being considered as prophylactic agents to administer during pregnancy that might offer the fetus and neonate protection. These include polyphenols, omega-3 fatty acids, vitamins, plant-derived compounds (tanshinones, sulforaphane, and capsaicin), and endogenous compounds (melatonin, carnitine, creatine, and lactate).[35]

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Hypothermia

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These agents all seem to share, anti-inflammatory, anti-oxidative, anti-apoptotic, and neurofunctional regulatory properties.[36]

Additionally, animal data theoretically suggest additional plant extracts that might be protective in human newborns including pomegranate,[37] grape seed extract,[38] quercetin,[39] saffron,[40] and *Salvia miltiorrhizae.*[41]

It is conceivable that an expectant mother might be encouraged to drink pomegranate juice days or weeks prior to delivery. Yet it is difficult to imagine women even those at high risk for birth complications, making the effort to take nutritional supplements just in case.

Some combination of these herbal extracts could be helpful for the percentage who are proactive, yet mothers should be understandably hesitant until strong human evidence supports use.

Hypothermia, Heart Disease, and Cancer

Knowing how hypothermia reduces hypoxic brain injury may help us translate its use to other conditions. The idea that hypothermia is useful for injuries that result from switching over to anaerobic metabolism and prevention of resultant mitochondrial failure may inspire us to list other conditions where anaerobic metabolism leads to injury. We already use cold in the form of ice for post-exercise muscle pain and injury.

What about with cancer? Many of us talk about how cancer cells switch to anaerobic respiration so could cold be employed against cancer? We think first of hyperthermia as a cancer treatment, but could hypothermia also have use? There are recent indications that this indeed may be the case. A March 2021 report described how hypothermia restores function to mutated p53 enzymes, a major promoter of cancer cell death. Then in May 2021 another study reported on in vitro experiments with glioblastoma cells and tells us that cooling these tumors enhanced standard treatments significantly.[42]

We may eventually fall back on our old therapy. alternating heat and cold. For the moment, hypothermia is an avenue of therapy that we should be keep our eyes on.

References

1. Czeranko S. Hydrotherapy Terms Defined: Fluxions, Reactions, Retrostasis, and Revulsions. NDNR. September 29, 2014 https://ndnr.com/nature-cure/hydrotherapy-terms-defined-fluxions-reactions-retrostasis-and-revulsions/
2. Assis FR, et al. From systemic to selective brain cooling - Methods in review. *Brain Circ*. 2019 Dec 27;5(4):179-186.
3. Czeranko S. Vincent Priessnitz (1799-1851). *Integr Med* (Encinitas). 2019;18(4):25.
4. Young RS, Zalneraitis EL, Dooling EC. Neurological outcome in cold water drowning. *JAMA*. 1980 Sep 12;244(11):1233-5.
5. Sekar TS, et al. Survival after prolonged submersion in cold water without neurologic sequelae. Report of two cases. *Arch Intern Med*. 1980 Jun;140(6):775-9.
6. Young RS, et al. The effect of graded hypothermia on hypoxic-ischemic brain damage: a neuropathologic study in the neonatal rat. *Stroke.* 1983 Nov-Dec;14(6):929-34.
7. Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. *Pediatrics.* 1998 Oct;102(4 Pt 1):885-92.
8. Battin MR, et al. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. *Pediatrics*. 2001 Mar;107(3):480-4.
9. Zupan V. Systemic hypothermia in infants with hypoxic-ischaemic encephalopathy: a French pilot study. *Dev Med Child Neurol Suppl*. 2001 Mar;86:32.
10. Debillon T, et al. Whole-body cooling after perinatal asphyxia: a pilot study in term neonates. *Dev Med Child Neurol*. 2003 Jan;45(1):17-23.
11. Battin MR, et al. Treatment of term infants with head cooling and mild systemic hypothermia (35.0 degrees C and 34.5 degrees C) after perinatal asphyxia. *Pediatrics*. 2003 Feb;111(2):244-51.
12. Hypothermia and Neonatal Encephalopathy. Committee on Fetus and Newborn. *Pediatrics*. June 2014, 133 (6) 1146-1150; DOI: https://pediatrics.aappublications.org/content/133/6/1146.long
13. Young RS, Olenginski TP, Yagel SK, Towfighi J. The effect of graded hypothermia on hypoxic-ischemic brain damage: a neuropathologic study in the neonatal rat. Stroke. 1983 Nov-Dec;14(6):929-34.
14. Jacobs S, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003311.
15. Jacobs SE, et al. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013 Jan 31;2013(1):CD003311.
16. Wang Z, et al. Neonatal hypoxic-ischemic encephalopathy diagnosis and treatment: a National Survey in China. *BMC Pediatr*. 2021 Jun 5;21(1):261.
17. Hypothermia and Neonatal Encephalopathy. Committee on Fetus and Newborn. *Pediatrics*. June 2014, 133 (6) 1146-1150; https://pediatrics.aappublications.org/content/133/6/1146.long
18. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/nicuverification/Pages/NICUSearch.aspx
19. van Wincoop M, et al. Effect of therapeutic hypothermia on renal and myocardial function in asphyxiated (near) term neonates: A systematic review and meta-analysis. *PLoS One*. 2021 Feb 25;16(2):e0247403.
20. Choi HA, Badjatia N, Mayer SA. Hypothermia for acute brain injury – mechanisms and practical aspects. *Nat Rev Neurol*. 2012 Feb 28;8(4):214-22.
21. Mank A, et al. Hypothermia in Preterm Infants in the First Hours after Birth: Occurrence, Course and Risk Factors. *PLoS One*. 2016;11(11):e0164817. Published 2016 Nov 3.
22. Hassell KJ, Ezzati M, Alonso-Alconada D, Hausenloy DJ, Robertson NJ. New horizons for newborn brain protection: enhancing endogenous neuroprotection. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2015;100(6):F541-52.
23. Ferriero DM. Neonatal brain injury. *New England Journal of Medicine* 2004;351(19):1985-95.
24. Douglas-Escobar M, Weiss MD. Hypoxic-ischaemic encephalopathy: a review for the clinician. *JAMA Pediatrics* 2015;169(4):397-403.
25. Fleiss B, Gressens P. Tertiary mechanisms of brain damage: a new hope for treatment of cerebral palsy?. *Lancet Neurology* 2012;11(6):556-66.
26. Fleiss B, Gressens P. Tertiary mechanisms of brain damage: a new hope for treatment of cerebral palsy?. *Lancet Neurology* 2012;11(6):556-66.
27. https://www.sciencedirect.com/science/article/pii/B9780128017326000112
28. Mohsenpour H, et al. A Review of Plant Extracts and Plant-Derived Natural Compounds in the Prevention/Treatment of Neonatal Hypoxic-Ischemic Brain Injury. *Int J Mol Sci*. 2021;22(2):833. Published 2021 Jan 15.
29. Rüegger CM, Davis PG, Cheong JL. Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy. Cochrane Database Syst Rev. 2018 Aug 20;8(8):CD012753.
30. Domoki F. Hydrogen-induced Neuroprotection in Neonatal Hypoxic-ischemic Encephalopathy. *Curr Pharm Des*. 2021;27(5):687-694.
31. Pang R, et al. Melatonin for Neonatal Encephalopathy: From Bench to Bedside. *Int J Mol Sci*. 2021 May 22;22(11):5481.
32. Martínez-Orgado J, Villa M, Del Pozo A. Cannabidiol for the Treatment of Neonatal Hypoxic-Ischemic Brain Injury. *Front Pharmacol*. 2021 Jan 11;11:584533.
33. Yang G, Xue Z, Zhao Y. Efficacy of erythropoietin alone in treatment of neonates with hypoxic-ischemic encephalopathy: A protocol for systematic review and meta-analysis. *Medicine* (Baltimore). 2021 Jun 18;100(24):e26365.
34. Byun JC, Lee SR, Kim CS. Effects of carnosine and hypothermia combination therapy on hypoxic-ischemic brain injury in neonatal rats. *Clin Exp Pediatr*. 2021 Feb 24.
35. Reyes-Corral M, et al. Nutraceuticals in the Prevention of Neonatal Hypoxia-Ischemia: A Comprehensive Review of their Neuroprotective Properties, Mechanisms of Action and Future Directions. *Int J Mol Sci.* 2021 Mar 3;22(5):2524.
36. Mohsenpour H, et al. A Review of Plant Extracts and Plant-Derived Natural Compounds in the Prevention/Treatment of Neonatal Hypoxic-Ischemic Brain Injury. *Int J Mol Sci*. 2021 Jan 15;22(2):833.
37. Ahmed MAE, El Morsy EM, Ahmed AA. Pomegranate extract protects against cerebral ischemia/reperfusion injury and preserves brain DNA integrity in rats. *Life Sci.* 2014
38. Feng Y, et al. Grape Seed Extract Suppresses Lipid Peroxidation and Reduces Hypoxic Ischemic Brain Injury in Neonatal Rats. *Brain Res. Bull.* 2005;66:120–127.
39. Wu M., Liu F., Guo Q. Quercetin Attenuates Hypoxia-Ischemia Induced Brain Injury in Neonatal Rats by Inhibiting TLR4/NF-κB Signaling Pathway. *Int. Immunopharmacol.* 2019;74:105704.
40. Huang A., Jia L. Crocin Enhances Hypothermia Therapy in Hypoxic Ischemia-Induced Brain Injury in Mice. *Acta Neurol. Belg.* 2019.
41. Li MY, et al. [Protective effect of pretreatment of Salvia miltiorrhiza Bunge. f. alba plasma against oxygen-glucose deprivation-induced injury of cultured rat hippocampal neurons by inhibiting apoptosis]. *Sheng Li Xue Bao*. 2012 Feb 25;64(1):41-7.
42. Fulbert C, Chabardès S, Ratel D. Adjuvant therapeutic potential of moderate hypothermia for glioblastoma. *J Neurooncol*. 2021 May;152(3):467-482.

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Psychological Causes and Treatments for Insomnia

by Catherine Darley, ND

Insomnia, that inability to sleep that may have your mind racing or your body tossing and turning, can cause a profound disruption to people's lives. About 10-30% of the population experience insomnia.[1] Sleep problems have gotten a lot more attention by the public in the last year due to the pandemic. Insomnia is increased in survivors of COVID-19 infection.[2] People suffering insomnia often seek care in their primary provider's office, making it a condition most of us will be called upon to treat.

What is insomnia? According to The International Classification of Sleep Disorders, the patient must have difficulty sleeping or resistance going to bed, and daytime consequences due to the nighttime sleep difficulty, which cannot be explained by insufficient time in bed or sleep disruption.[3] For a diagnosis of chronic insomnia the sleep problem must be experienced at least three times a week for three months. For short-term insomnia all criteria are the same, except that there is no criteria for number of times per week, and the duration is less than three months. (For the full criteria see Table 1)

Insomnia can be found in people of all ages, with 36% of preschoolers, 20% percent of children, and 24% of teens experiencing insomnia.[4] Women tend to report more insomnia, at 19% versus 13% of men,[5] and 75% of seniors.[6]

Mechanisms/Causes

There are many possible causes of insomnia. As holistic providers, treating the cause is our aim; and for that, we must first identify it. Insomnia can originate from the physiological or psychological. In this paper we will focus on the psychological, though of course there is an interplay between the physical and psychological.

For people with insomnia due to hyperarousal, these cognitive behavioral strategies can re-build positive sleep.

Hyperarousal is a key component of insomnia. Part of that is the idea of sleep reactivity, which is the extent to which sleep is disrupted by stress. People with normal sleep who have high sleep reactivity are at increased risk of future insomnia. Family history, genetics, and stress along with gender all increase sleep reactivity. Nighttime rumination and worry, both types of cognitive-emotional reactivity, contribute to insomnia as well.[7]

Other psycho-emotional states that contribute to insomnia include depression. Depression and insomnia have a bi-directional relationship, each contributing to the other, without a clear first cause. Newer research has indicated that insomnia may be a prodromal symptom of depression.[8] With this thinking, it's important to treat both simultaneously.

A little-known factor that contributes to insomnia, and may be particularly important in these times, is loneliness. It's thought that we need to feel socially secure in order to sleep well, thereby setting aside vigilance. The relationship between sleep and loneliness appears bi-directional, suggesting that treating sleep problems may decrease loneliness.[9]

Treatments

The recommended first line treatment is cognitive behavioral therapy for Insomnia (CBT-I). First developed by Charles Morin and presented in his book *Insomnia*,[10] there are four main components, which are implemented in a series of appointments over the course of weeks. At each appointment the clinician advances treatment in each of the four components that are relevant for that patient.

The first component of CBT-I is sleep restriction (this is a misnomer, it really is "time in bed restriction" which somehow doesn't roll off the tongue as easily). In sleep restriction, you first identify how much sleep the person is getting on average. You then start the treatment process by giving a scheduled time in bed that allows only that amount of sleep. Then, at each appointment, you evaluate the patients' sleep efficiency, which is total sleep time divided by time in bed. So long as their sleep efficiency is 85% or more, you increase their opportunity to sleep by 15-20 minutes each week. This strategy increases

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their sleep drive, making it easier to fall asleep and stay asleep through the night. Once they are getting the amount of sleep they need, an increase in time in bed will result in more wake time. At that point you can stop increasing their time in bed, or even take one step back to the total time in bed where they had high sleep efficiency. In my experience, it is best to take a slow steady approach increasing their total sleep time. The slow approach allows them to have success and reverse the negative sleep associations they have built up over the course of their insomnia experience. Including this component of CBT-I is essential. Sleep restriction is contraindicated in untreated sleep apnea, parasomnias, bipolar disorder, and seizure disorder.[11] In my clinic, I'm cautious about recommending less than six hours in bed and always advise people that more time out of bed should not mean more time on tasks.

This strategy may help insomniacs in terms of the "Sleep to remember, sleep to forget" theory. In REM sleep memories are consolidated and also pruned so that our synapses aren't overwhelmed with information. In healthy sleepers this function is intact. In animal models of medical conditions known to have sleep disorders such as PTSD and autism, this forgetting function is impaired. By consolidating sleep and potentially restricting some REM sleep, the insomniac may be spared some time when unhelpful information is being re-enforced rather than pruned [12]

The next principle is called 'stimulus control,' which aims to re-associate the bed with sleep. The patient is instructed to avoid all wakeful activities in the bed and even in the bedroom. In the evening, or in the morning after waking, they need to do their restful activities elsewhere. Sometimes people lament the loss of that cozy experience – in bed, in their comfy clothes, supine with low lighting, pillows and blankets. In that case, I encourage folks to have that pleasant experience, simply move to another place in their home such as the sofa or a bean bag chair. This is especially important for those insomnia patients who find they are able to sleep well elsewhere, just not in their own bed. This principle also comes into play in the middle of the night, with patients being instructed to get out of bed if they have been awake for approximately 15 minutes. They should do something boring in low light. I've found that the 'boring' part is important, as you want to avoid re-enforcing those mid-night awakenings with a pleasant experience. C.S. Lewis said, "Many things – such as loving, going to sleep, or behaving unaffectedly – are done worst when we try hardest to do them." Getting up when not sleeping gets your patient away from trying hard.

The third piece is cognitive reframing. This component is meant to raise to awareness of any dysfunctional beliefs and attitudes that are making sleep difficult. A good tool to start the process is the Dysfunctional Beliefs and Attitudes Scale (DBAS). There are both short and long versions with sleep statements the patient is asked to rate from strongly agree to disagree on a ten-point scale. One example is: "I am worried that I may lose control over my ability to sleep." Often patients tell me that they start to have these thoughts after dinner, continuing until they get into bed hours later. Once those sleep-disrupting thoughts are identified, the work is to intentionally shift to sleep-promoting thoughts. With the patient, examine one of their dysfunctional thoughts, then discuss ways in which it may not be true. You're simply trying to gently introduce other possibilities. It's important to work with their specific thoughts, and the time of day these come up. For instance, people may have sleep-disrupting thoughts during the day, possibly attributing every difficulty to their sleep. Sometimes it's useful to

Table 1. The clinical criteria for chronic insomnia as excepted from The International Classification of Sleep Disorders; all must be present.

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep.
   3. Waking up earlier than desired.
   4. Resistance to going to bed on appropriate schedule.
   5. Difficulty sleeping without parent or caregiver intervention.

B. The patient reports, or the patient's parent or caregiver observes, one of more of the following related to the nighttime sleep difficulty:
   1. Fatigue/malaise.
   2. Attention, concentration or memory impairment.
   3. Impaired social, family, occupational or academic performance.
   4. Mood disturbance/irritability.
   5. Daytime sleepiness.
   6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression).
   7. Reduced motivation/energy/initiative.
   8. Proneness for errors/accidents.
   9. Concerns about or dissatisfaction with sleep.

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep.

D. The sleep disturbance and associated daytime symptoms occur at least three times per week.

E. The sleep disturbance and associated daytime symptoms have been present for at least three months.

F. The sleep/wake difficulty is not better explained by another sleep disorder.

write down sleep-positive alternatives for people to read when their thoughts turn negative. The clinical key is that these sleep positive statements must have the power of truth for that individual patient; generic affirmations will not be as effective, if at all.

The last piece is sleep education or sleep hygiene, depending on the author. Here is where the patient receives sleep hygiene recommendations such as no caffeine after noon, no alcohol or meals three hours before bed, to observe whether exercise in the evening interferes with sleep, etc. Education on how sleep works can also be useful. For instance, patients may report a sensation of lighter sleep or more dreams close to wake time. Teaching them about REM sleep being close to wake time and the brainwaves being more similar to waking brainwaves can help them understand their experience is normal.

Cognitive behavioral therapy for insomnia has been proven helpful in some special populations, including depression, for breast cancer survivors, fibromyalgia patients, and children, among others.[13-16]

Case Study

First office call: M.P., a 34-year-old single male with chronic insomnia of three years.

Until the insomnia began, M.P. would sleep 10:30 pm to 5:30-6:00 pm. He feels best with 7-7.5 hours of sleep but is now getting only 4-6 hours per night total. Daytime impairment includes difficulty concentrating at work, especially in meetings. He will walk into rooms and not remember why and is more clumsy around the house. His girlfriend has also noticed he's been more low energy, especially at the end of the day.

Treatment Plan #1:

1. Sleep times – 11 pm to 5 am, which is the 6 hours he is currently reporting. This is the first step of sleep restriction.
2. At 5 am get up and use your dawn simulator light box so that it's at full light at 5:30a, and leave on full brightness until 5:40a. Light therapy in the morning strengthens the circadian rhythm.
3. Journaling exercise 1 hour before bed. Then once you are in bed, use thought-stopping and sleep promoting exercises. See handout (Table 2).
4. For the hour before bed be in low light. If you'd like to measure use lux meter, goal is 3-10 lux
5. L-Theanine 200 mg 2-3 times a day. Morning, afternoon, and evening to decrease stress and anxiety. This is in effort to decrease hyperarousal.
6. 3 mg of melatonin 30 minutes before bed for sleep and tinnitus.

Return office call, two weeks later: MP was on vacation, so it was harder to keep the recommended sleep hours. Before vacation he had at least two nights that he slept the entire six hours. He shifted his sleep hours to 11:30-5:30am. Feels good about that progress. Using the light box as instructed, feels good "like waking up to the sun." On vacation he got an up-close view of his dad's health problems that worry him. We discussed the three steps of calming his mind at night. In the night he will tell himself

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Table 2. Calm Your Mind Handout

Put Your Thoughts to Rest, So You Can Sleep

Many of us have intrusive thoughts during sleep time. This can come from being so busy during the day that there's literally no time to think things through as we need to, or could be a long-term habit, or be from a particularly eventful period in life. Whatever the reason, these thoughts can prevent the sleep we need to be at our best and cope with life's challenges.

A good way to think about sleep time is that it serves an entirely different purpose, and even is "time out of time." In other words, that during the day we take care of our roles and responsibilities, but during the night we set them aside in order to rest and restore. We do not (should not!) take those wake time responsibilities to bed with us. (The exception being for those people who must care for others during the night).

Put Your Thoughts to Rest

Write down those thoughts that tend to come up in the night, with the intention of "putting them to bed." The writing can take any format, from a full sentence narrative or problem-solution chart, to simple thought bubbles or even a drawing. Then have an enjoyable wind-down for the remaining time before bed. If thoughts arise in the night, do some gentle thought stopping along the lines of "I already thought about that, and will have time tomorrow, now's time to rest." It may take a little practice to learn what thoughts need to be discharged with the journaling, and to learn this internal limit setting. Journal every night for a month so you have the chance to figure out what works for you. The goal is to ensure time to process worry during the day, so it's been taken care of, and does not need to emerge during sleep hours.

Do a Sleep Promoting Practice

Now that you've "kicked your thoughts out of bed," do a sleep-promoting activity instead. Do this any time you realize that you are awake in bed, either at the beginning of the night, or in the middle. This is also a skill, and different strategies will work better for different people. Choose the one that appeals to you the most and use it regularly for a week. Then if need be try another strategy until you have an effective one.

- Tell yourself a gentle story, maybe a favorite book or movie from childhood. Review the same story in your mind night after night as your "bedtime story."
- Do progressive muscle relaxation starting with the toes and working slowly towards the head. Tense an isolated muscle group for a count of 7, then relax it. Go slowly with the goal of being asleep before getting to your head.
- Visualize yourself falling asleep. Bring in as many senses as possible. You may use a time you recall falling asleep, or create a visualization maybe of falling asleep in the sun, or in a hammock, or during a nap.
- Do a gratitude practice or prayer. Focus on the good things in your life, the things that make you happy and content. (Avoid any problem solving or planning).
- If you wake from a dream, purposefully go back into the dream and let it carry you back into sleep.

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"I'm organized, and I know from past experience I'm on top of it. I want to spend this time sleeping. I will take care of stuff tomorrow when I can think." He is doing something relaxing for the hour before bed – house work or journaling in low light – and thinks it helps him sleep. He will insert another 30 mins between journaling and bedtime. His anxiety has been much lower in the last couple weeks, even before the vacation. He thinks L-theanine is helping.

Treatment Plan #2:

1. For another week, sleep 11:30p-5:30a. After that, evaluate your "sleep efficiency" by dividing your total sleep by the time in bed. So long as you are sleeping 85-90% of the time in bed then increase your sleep hours by 20 minutes. After each week you can do this, until you are getting how much sleep you need.
2. Move journaling another 30 minutes before bedtime, so you have a full hour of wind-down.
3. Keep the wind-down time as calm as possible. Discuss with your girlfriend the importance of being in the parasympathetic state before getting into bed and that problem solving will be much better in the light of day.
4. In the night if your mind starts reviewing tasks, tell yourself "I'm organized, and I know from past experience I'm on top of it. I want to spend this time sleeping. I will take care of stuff tomorrow when I can think." Modify this statement as needed so it has the power of truth. Then instead do one of the sleep-promoting activities on the "Put Your Thoughts to Rest" handout.

Return office call, three weeks later: Did well on East coast sleeping 1 am to 7:30 am, with intention of staying on PST. Sleep was good before travel, sleeping most of the night straight through, over 85% of time in bed. Daytime impact – feeling more tired at bedtime at 11:30 pm (previous bedtime was 10 pm), feels that he has more energy in the middle of the day. Getting 5.5 hours sleep nightly. Still waking 15-30 minutes before his alarm. Moving journaling earlier helped, and what especially helped was the affirmations that things are handled and he doesn't need to think in the night. He talked with his girlfriend about no negative conversations in bed.

Treatment Plan #3:

1. Sleep 11:10-5:30 am for 7-10 days. Then assess, if you are sleeping more than 85% or more of your time in bed, then go to bed 15-20 minutes earlier the next week.
2. When doing your journaling and thought-stopping before wind-down time, add in that you're not going to think about concerns until 6:30 am. If you wake up thinking, tell yourself "That is handled, and I'll have time to think about it later, now is time to sleep." Goal is to go back to sleep, by training yourself not to think about things before waketime.

In further appointments M.P. was instructed to continue adding to his total time in bed, as long as additional time translated into additional sleep. The sleep education component continued as questions arose, and cognitive reframing was addressed as sleep-disrupting thoughts were identified. Once his sleep is as he wishes, supplements will be evaluated and withdrawn if possible.

Conclusion

For people with insomnia due to hyperarousal, these cognitive behavioral strategies can re-build positive sleep while unraveling negative associations with the bed, and shifting dysfunctional sleep thoughts to sleep-promoting thoughts. With established efficacy and minimal negative side effects, this is a great tool to use. In the integrative clinic, we can also combine this strategy with nutrient and botanical medicine to help our patients sleep well, and get all the benefits of a good night's rest.

References

1. Roth, T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med*. 2019;3(5):S7-S10.
2. Taquet M., Geddes J.R., Husain M., Luciano S., Harrison, P.J. 6-month neurological and psychiatric outcomes in236,379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry.* 2021; 8: 416–27.
3. *The International Classification of Sleep Disorders*, 3rd Edition. 2014. American Association of Sleep Medicine.
4. Donskoy, I., Loghmanee, D. Insomnia in adolescence. *Med Sci (Basel)*. 2018;6(3)72.
5. Chen Y, et al. Characteristics and correlates of sleep duration, daytime napping, snoring and insomnia symptoms among 0.5 million Chinese men and women. *Sleep Med*. 2018;44:67-75.
6. Nguyen V. George T, Brewster GS. Insomnia in older adults. *Curr Geriatr Rep*. 2019;8(4):271-290.
7. Kalmbach DA, et al. Hyperarousal and sleep reactivity in insomnia: current insights. *Nat Sci Sleep*. 2018;10:193-201.
8. Fang H, et al. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. *J Cell Mol Med*. 2019 Apr;23(4):2324-2332
9. Griffin SC, et al. Reciprocal effects between loneliness and sleep disturbance in older Americans. *J Aging Health*. 2020;32(9):1156-1164.
10. *Insomnia: Psychological Assessment and Management.* Charles Morin. 1996.
11. *Behavioral Treatments for Sleep Disorders.* Editors Michael Perlis, Mark Aloia Brett Kuhn. 2011.
12. Poe GR. Sleep is for forgetting. *J Neurosci*. 2017;37(3):464-473.
13. Carney CE, et al. Cognitive behavioral insomnia therapy for those with insomnia and depression: a randomized controlled clinical trial. *Sleep*. 2017;40(4):zxs019.
14. Zachariae R, et al. Internet-delivered cognitive-behavioral therapy for insomnia in breast cancer survivors: a randomized controlled trial. *J Natl Cancer Inst*. 2018;110(8):880-887.
15. McCrae CS, et al. Cognitive behavioral treatments for insomnia and pain in adults with comorbid chronic insomnia and fibromyalgia: clinical outcomes for the SPIN randomized controlled trial. *Sleep*. 2019;42(3):zsy234.
16. Ma ZR, Shi LJ, Deng MH. Efficacy of cognitive behavioral therapy in children and adolescents with insomnia: a systemic review and meta-analysis. *Braz J Med Biol Res*. 2018;51(6)e7070.

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DHEA Physiology, Deficiency, and Treatment

by Alan B. McDaniel, MD

Introduction: "You never forget your first."

Case 1*:* In the early 1990s, a slender, older man asked Doc to help him regain some energy. He had been fatigued for nine years, ever since operative treatment for base of tongue cancer followed by external beam radiotherapy. On examination, his palms were not anemic, but his facial capillaries were so under-perfused that he was the same color as Doc's manilla-folder chart.

Doc ordered a lab workup, recommended nutritional supplements (including desiccated neonatal adrenal cortex) and having heard it might support adrenal function, made him the first patient he ever treated with DHEA. Six weeks later, on returning to review his laboratory results, the patient virtually radiated energy and enthusiasm. His cheeks were ruddy, and he said he had not felt so well in fifteen years. He thanked Doc and then never returned! What is DHEA and why did it help this man so much?

The Scientific Basis of DHEA Therapy

What is DHEA? Made from cholesterol, dehydroepiandrosterone (3β-hydroxy-5-androsten-17-one, DHEA; Figure 1) and its sulfated metabolite DHEA-S (Figure 2) are the major steroid secretory products of the human adrenal glands. DHEA is also produced in the gonads, brain, and gastrointestinal tract.

DHEA and DHEA-S are the most abundant circulating steroids, present in quantities second only to cholesterol.

Dehydroepiandrosterone is a precursor for both androgenic and estrogenic steroids and of neurosteroids.[1]

How DHEA is produced and processed? All *ster*oid hormones are derived from chole*sterol*. The first step occurs in mitochondria, when cholesterol is converted to pregnenolone. This is regulated in the adrenals by adrenal corticotropic hormone (ACTH); luteinizing hormone (LH) in the gonads and in other mitochondria by an independent side-chain cleavage enzyme.

The steroidogenic enzymes and pathway for DHEA synthesis in the adrenal gland are reviewed by Miller and Auchus, 2011.

In the adrenal cortex's zona reticularis, pregnenolone is converted in two steps to DHEA by the enzymes 17α-hydroxylase and then 17,20-lyase (the latter is regulated by LH).[2]

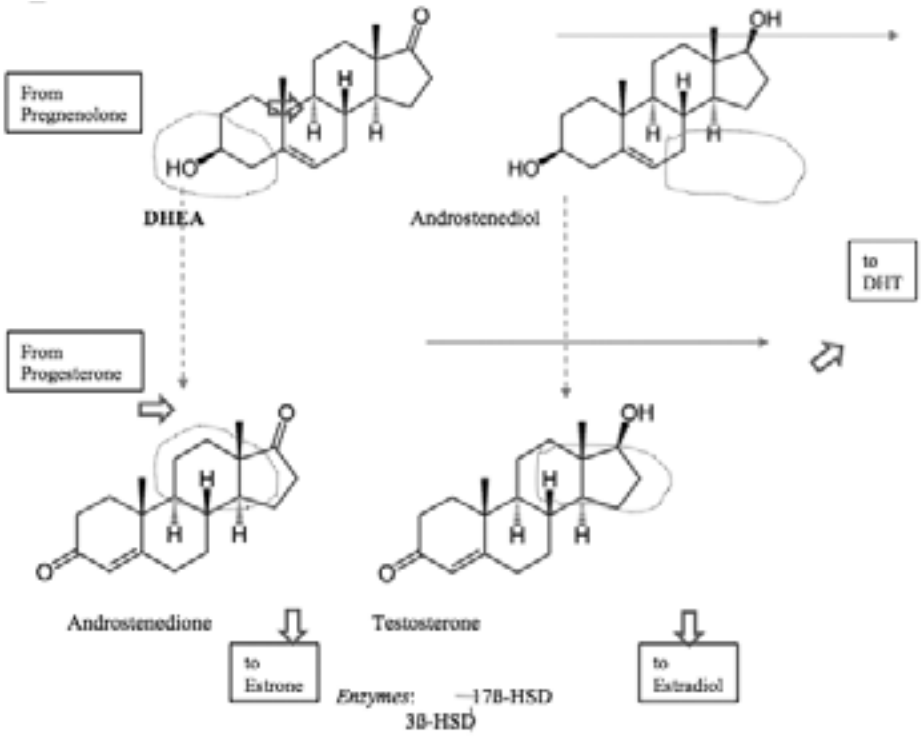
At this point, DHEA diverges onto two paths, which later rejoin: The enzyme 3ß-HSD takes DHEA "south" to produce androstenedione (of Mark McGwire fame). The enzyme 17ß-HSD (of which there are *five* isoforms) moves DHEA "east" to become androstenediol.

Then, in a "onesie-twosie," each enzyme will then move the *other* product of DHEA respectively "east" and "south" and both pathways end at testosterone (Figure 1).

DHEA production is regulated by LH, which controls 17-20 lyase activity. Testosterone production is governed by the rate-limiting action of 17β-HSD. Its many isoforms are controlled by various agents relevant for specific tissue type and function – in the testes, it is largely by FSH. Activity of the enzyme 3β-HSD is less strictly governed but can be enhanced when needed and is down-regulated as downstream products accumulate.[1]

Testosterone is a "reasonably potent androgen" but it also should be considered ➤

Figure 1: Metabolism of DHEA to testosterone



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a precursor.[2] Testosterone is the parent of both the strongest feminizing hormone, estradiol, via the enzyme aromatase *and* of the *most* potent androgen, dihydrotestosterone (DHT), through 5alpha-reductase.[3,4]

DHEA is *both* a precursor and a (weak) hormone. In the classical sense, DHEA is a hormone precursor. It is converted to testosterone, then to either estradiol or DHT, both in gonads and in various other tissues.[3] DHEA (but not DHEA-S) binds with weaker affinity to various nuclear receptors (NRs), including androgen-receptor, estrogen-receptors (both alpha and beta), PPAR and others.[5] In addition to directly binding to NRs, DHEA has been shown to modulate the *levels* of NRs.[2] "DHEA actions are classically associated with age-related changes in cardiovascular tissues, female fertility, metabolism, and neuronal/CNS functions"[2,6] and this list is incomplete.

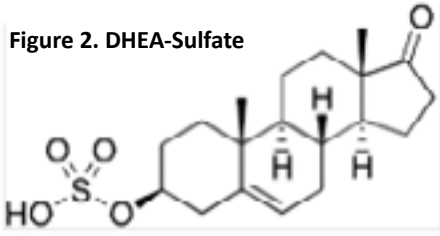
Additionally, DHEA intrinsically has potent biological effects via binding to non-genomic receptors on cell-surfaces.[7] It also acts on various neuroreceptors, including GABA, NMDA and sigma-1 receptors.[8] The consequences include activating various membrane receptors and inhibiting voltage-gated T-type Ca2+ channels.[2]

The neurosteroid effect of DHEA is of particular interest. It and DHEA-S easily enter the brain across the blood-brain barrier. The brain itself also locally synthesizes them, so their concentrations in the CNS are particularly high.[9] The CNS actions of DHEA and DHEA-S include neuroprotection, neurite growth, and antagonistic effects on oxidants and glucocorticoid activity.[10] Most effects of these neurosteroids (or "non-classical steroids") are non-genomic, influencing immune reactions, mood and emotions, and behavior.[11] Therefore, it is observed: "DHEA has considerable effects on mood, well-being and sexuality in patients with adrenal insufficiency, and also in those with mood disorders."[12]

The immune-modulatory effect of DHEA is reported in the elderly, in whom it increases the number of monocytes, T cells expressing T-cell receptor gamma/delta (TCRγδ) and natural killer (NK) cells. It also can improve their physical and psychological well-being, muscle strength and bone density. DHEA reduces body fat and age-related skin atrophy by stimulating procollagen and sebum production.[13]

The relationship of DHEA and DHEA-S. In the adrenal cortex, DHEA is conjugated with a sulfate ester to form DHEA-S (Figure 2). Such conjugation hinders it – as it does many other steroids – from binding to nuclear receptors and acting on the genome.[13] However, DHEA-S retains *non*-genomic neurosteroid-activity.[14] In years past, DHEA and DHEA-S were thought to be rapidly inter-converted; this has been revised: While DHEA-S can be processed into DHEA and sex hormones in the peripheral tissues (by "intracrinology"),[15] DHEA-S is largely a "*one-way* conjugation product," *not* a significant hormone precursor.[4] Significantly, oral DHEA doses are extensively sulfated in the hepatic first pass.[16] Clinically, it is prudent to consider DHEA and DHEA-S as similar but separate actors.

Figure 2. DHEA-Sulfate



https://en.wikipedia.org/wiki/Dehydroepiandrosterone_sulfate

Circulating DHEA and DHEA-S are not maintained in equal balance, as once was believed. Sex hormone binding globulin (SHBG) has high affinity for DHEA-S but only weakly binds DHEA. Thus, DHEA is largely free and highly metabolically active, while DHEA-S (being carried by protein) is much the most abundant circulating steroid, after cholesterol.[17]

DHEA in maturation and aging. After briefly robust levels decline shortly after birth, circulating adrenal antigens remain quite modest in childhood. The production of DHEA, DHEA-S and androstenedione again increases around age 8 or 9, as the zona reticularis matures in an event called adrenarche.[18-21] These effects remain subtle for a few years: Most DHEA is inactivated by conjugation to DHEA-S until near-puberty.

Following puberty, serum DHEA levels rise and peak between age 20 and 30 years. The majority of it is made in the adrenals, with about 15% arising from the gonads.[22] Serum DHEA and DHEAS levels thereafter drop by 2% every year, due to attrition of adrenal cortical and (in men) of Leydig cells. In women at menopause, only 60% of the former peak values are present.[23] At age 70, amounts are just 20-23% of what they had once been and by age 80, can fall to as little as 10% of the former supply.[24]

Serum androgens were tested yearly in women ages 45 to 54 and no independent effect of menopause was noted.[25] After menopause, the ovaries contribute a significant amount of DHEA (up to 50%) even ten years later.[26] Postmenopausal oophorectomy causes a significant drop in androgens, including testosterone.[31] Labrie states that intracrine metabolism of DHEA to sex hormones supplies menopausal women's tissues with essential sex steroids – and that low DHEA leads to a deficiency of these hormones.[27]

Conditions Associated with Low DHEA

Stress: The acute stress response is associated with a transient (one-hour) increase of circulating DHEA,[28] which arises from the adrenal cortex.[29] Women, young adults, and obese individuals produced the greatest levels.[30] DHEA will be increased following acute mental stress, whatever the type or duration. Overall, DHEA is increased in the successful response to stress.[31]

When the stressful event is prolonged, hypothalamic release of ACTH is enhanced and cortisol rises. Simultaneously, LH and FSH are inhibited, and androgens fall.[32] Following a significant injury, sixty patients lost testosterone, DHEA, and DHEA-S.[33] Importantly, plasma androgen levels correlated with the Sequential Organ Failure Assessment (SOFA) scores and sepsis. Muscle wasting peaked at six weeks. Normal amounts of testosterone were restored after two months, DHEA in four months and DHEA-S after more than six months. This may indicate a "hierarchy of need" for a depleted but recovering resource, DHEA.

In most cases, the chronic stress response features continued up-regulation of the hypothalamic-pituitary-adrenal (HP-A) axis and the ongoing inhibition of sex hormones.[34] While the concept of "adrenal fatigue" (academicians *always* use the quotation marks!) is controversial, adrenal reserve capacity can be depleted and thus, DHEA production would be also.[34,35]

It is observed that "HPA axis dysregulation has been found in a high proportion of chronic fatigue syndrome

(CFS) patients."[36] Investigations show these CFS and chronic inflammation patients have low DHEA values.[37,38] However, a later meta-analysis of 17 studies of post-traumatic stress disorder patients found *no* significant differences from control groups in either DHEA or DHEA-S.[39]

Toxins: Endocrine disrupting chemicals alter androgens.[40] Prenatal xenobiotics cause fetal HP-A axis dysfunction, which may affect the brain's neurosteroids, neurotransmitter function, cognitive ability, and neural immune-regulation in the child.[41]

Aging: A substantial decline of serum DHEA values in men after age 20 - 30 was mentioned above.[42] In what way is this physiological decline related to the process of aging? It has been persuasively demonstrated that men with lower *testosterone* levels have a *worse* state of health[43,44] and that lower levels of testosterone may be a risk factor for frailty in aging men.[45,46]

A similar association is reported for lower circulating DHEA levels and frailty.[47,48] A greater decline in circulating levels of androgen over five years is associated with increased all-cause and cause-specific mortality in older men.[49] Indeed, falling DHEA and DHEA-S levels are associated with many age-related disorders, including metabolic and cardiovascular diseases, poor physical performance, mood and memory defects, poor sense of wellbeing, and sexual dysfunction.[50,51]

Women also suffer from age-related declining DHEA. As above, Labrie believes low DHEA is important, as intracrine activation of DHEA to sex steroids protects menopausal women. In a study of post-menopausal women aged 50 to 90 years, age-adjusted loss of DHEA was significantly associated with sarcopenia.[52]

Depression is associated with lower DHEA values.[53-55] A neurosteroid effect seems likely, as NHANES data shows serum testosterone values are inversely associated with cognitive performance in older men in the US (but not in women).[56]

Anorexia nervosa: Decreased secretion of DHEA in this condition is accompanied by other endocrine abnormalities due to malnutrition and chronic stress. Along with high cortisol, the low levels of IGF-1, estrogen, testosterone, and DHEA are associated with "profound bone mineralization disorders."[57]

Elevated DHEA in women: The overproduction of adrenal androgens occurs in nonclassical 21-hydroxylase-deficient congenital adrenal hyperplasia.[57] Androgens are also elevated in polycystic ovarian syndrome, although perhaps less of adrenal origin than due to the dose-related effects of insulin on the ovary.[58,59] Acanthosis nigricans is associated with elevated DHEA-S due to insulin resistance.[60]

In the author's practice, most menopausal women benefit from adding estradiol and progesterone (or pregnenolone) to DHEA.

Controversy: Is DHEA Supplementation Beneficial?

The rationale is simple: DHEA production declines significantly with age, stress, and illness. The levels of steroid hormones derived from DHEA also fall. These reductions (or deficiencies) impair normal function and are significantly associated with many degenerative conditions, as well as earlier mortality. Replacement may help: "Epidemiological evidence from humans and animal studies suggest that DHEA/DHEA-S may have cardioprotective, anti-obesity, antidiabetic, and immuno-enhancing properties."[61]

Supplementing DHEA should replenish its loss, making the precursor available for glandular and intracrine conversion[56] and for its neurosteroid effects. Furthermore, this supplement bypasses 17-20 lyase, the enzyme that is "inactivated" when LH is inhibited by chronic stress. As proof of this concept, DHEA supplements yield twice as much testosterone as will equally dosed precursors "upstream" of 17-20 desmolase: Pregnenolone, progesterone &17α-OH progesterone.[62] Adding DHEA "distal" to 17-20 lyase also raises progesterone levels (and probably the other listed precursors),[63] presumably because less are converted to DHEA. Patients' responses indicate this increases the synthesis of cortisol and aldosterone (as needed).

DHEA is sold over-the-counter in the US; and in sensible hands, the use of a precursor instead of an active hormone is quite safe.[56] Because "downstream" enzymes are regulated (by feedback from their products, by FSH and probably more), the provision of excessive precursor will not force the production of unwarranted hormones.[64] Reliable proof of this safety is found in studies of men with *normal* testosterone given labeled DHEA supplements; they did *not* make any excess of testosterone, though some exogenous DHEA had been transformed into testosterone.[65-68] The undesirable effects of injudicious dosing (largely intracrine) are reviewed in "Side Effects."

Case 2 is a 32-year-old police officer whose chief complaint in 2020 was "I just feel like I'm tired." His mother is hypothyroid and his family history is positive for diabetes and other conditions related to insulin resistance. He feels stressed, is irritable and easily loses his temper. He has been treated for allergies since childhood.

His baseline laboratory evaluation showed: total testosterone$_{LCMS}$= 211.6 L (264-916 ng/dL); free testosterone$_{ED}$= 5.5 (5.0-21.0 ng/dL) and total estradiol$_{LCMS}$= 17 (8-35 pg/mL) with calculated tTest/ E2 ratio=12.4 (units not corrected). After treatment with desiccated adrenal cortex and liothyronine (T3) to correct dysfunctional deiodination[69] (ratio of tT3/ RT3= 5.7 was raised to 13.0), he began taking DHEA 25 mg daily at bedtime.

On these treatments and a somewhat healthier diet, his next lab values showed: total testosterone$_{LCMS}$= 466.2; free testosterone$_{ED}$= 14.56 and total estradiol$_{LCMS}$= 21. His calculated tTest/ E2 ratio= 22.2 (units not reconciled), which is much more to his doctor's liking.

Evidence That Treatment with DHEA Is Beneficial

Although this caution seems hardly necessary in an article for practitioners, let it be recognized: "It is important to remember that numerous medical conditions and medications can result in low androgen levels in women."[70] That's true for men, too. Now, assuming patients have been appropriately evaluated, let us consider treatment with DHEA and androgens.

Testosterone: DHEA can restore testosterone and androgenic effects to ➤

patients with Addison's disease. Many studies have proven this, particularly in women, for whom the adrenal glands had been the major source of DHEA.[73-78] Beyond Addison's, a recent meta-analysis of 42 RCTs demonstrated that testosterone level was significantly increased after DHEA administration.[79] Other particular situations in which testosterone levels rise with DHEA supplementation include hypogonadal men[80-82] and soldiers stressed during survival training.[83]

Male sexual function: Despite the encouraging testosterone gains from DHEA, publications studying male sexual function find inconsistent results. Some studies report positive effects on male sexual function.[84-86] Others discover no effects at all for men.[87,88] Beyond the essential role of nitric oxide in erections, it may be that the endocrinology of libido is not completely understood. It is also noteworthy that no man got *worse* on DHEA.

Women's sexual function: The "global consensus position statement" on *testosterone* for women's sexual function, based on the available evidence from placebo/comparator randomized controlled trials (RCTs), is positive.[89] It states: "Testosterone therapy, *in doses that approximate physiological testosterone concentrations for **pre**menopausal women* (original emphasis), exerts a beneficial effect on sexual function." This includes many domains, including sexual desire, arousal, orgasmic function, pleasure, responsiveness and more (Level I, Grade A). The statement **reverses** older, *negative* position-papers.[90-91]

This is not proof that DHEA will be successful. However, we have seen that DHEA supplementation can significantly increase women's testosterone.[79] It is also unlikely that DHEA could produce supra-physiological levels of testosterone, against which italicized emphasis in the recent global position statement warned us. Still, authors from the Mayo Clinic and Cleveland Clinic caution us: "DHEA currently is not approved to treat sexual dysfunction."[76] It seems fortunate that DHEA is OTC-available in the US and that the only required approval is the patient's informed consent. When recommending it to women, follow their therapeutic levels and bear in mind: A good clinical response is often realized but it is not a certainty.

Women's fertility: Meta-analysis of nine studies involving 540 women pre-treated with DHEA for diminished ovarian reserve (DOR) found clinical pregnancy rates were significantly increased (OR=1.47).[92] Women with DOR who received 75 mg of DHEA daily had increased baseline follicular phase progesterone and no adverse effects on the cycle outcome.[89] Beyond its classical role as sex hormone precursor, DHEA (and DHEA-S) may be "oocyte factors," through their nongenomic effects on calcium channels.[93]

Among 22 in-vitro fertilization patients, pre-treatment with DHEA improved many measures significantly over the control group, including anti-Mullerian hormone, antral follicle count, serum estradiol, the number of recovered oocytes, fertilized oocytes, the fertilization rate and most importantly, the live birth rate ($P < 0.05$).[94] The usual dose of DHEA employed is a robust 75 mg daily, which reportedly has "no serious side effects."[95] Unfortunately, the more severe "premature ovarian insufficiency" has not responded to DHEA supplementation.

Menopause: Having earlier noted that androgens fall but little after menopause, it should be no surprise that aromatase and 17β-HSD alterations, not DHEA deficiency, explain the great postmenopausal decline in estradiol. Even in large doses, DHEA cannot restore follicular blood levels of estradiol in menopausal women.[96]

While a meta-analysis of randomized controlled trials (RCTs) involving 1,233 women found DHEA 50mg/day supplementation increased estradiol significantly, the gain was small (weighted mean 7.02 pg/mL and aged ≥60 years, WMD: 8.56 pg/mL).[97] Unfortunately, this study does not report the resulting testosterone gain or its ratio to estradiol, that one could compare the relative changes in these counter-balancing hormones. The author's experience suggests testosterone would be increased relative to estradiol.

While these estradiol gains are very small, Labrie, the Mahatma of Intracrinology, suggests they are sufficient. He states locally made, sex steroids exert their action and are then inactivated intracellularly without significant release into the systemic circulation. Thus, although DHEA supplements hardly increase estradiol blood levels, sufficient tissue effect would be received due to intracellular aromatization.[98]

In the author's practice, most menopausal women benefit from adding estradiol and progesterone (or pregnenolone) to DHEA. It seems desirable to keep all steroid sex hormones in a physiological balance normal for young women. This statement is validated by patient care and research: "…A reasonable dose of DHEA given to perimenopausal women demonstrated that normal testosterone levels may be achieved consistently in most if not all of many published reports."[96,99] Noting that **testosterone** replacement therapy in women is generally discouraged (except for sexual function),[90,100] the success of OTC DHEA is reassuring.

Osteopenia: Until lately, review articles had claimed "no evidence" to support testosterone therapy for women's bone health.[101,102] Two recent meta-analyses of RCTs[103,104] reverse this and show DHEA supplementation increases women's bone density, as it does their serum testosterone. An intracrine effect contributes to bone density, as androgens are converted to estradiol in the bone.[105]

Vaginal atrophy: A position statement of The North American Menopause Society on the management of the genitourinary syndrome of menopause (GSM) concluded: Vaginal DHEA is effective treatment for moderate to severe GSM.[106] The human vaginal smooth muscle cells synthesize "downstream" androgens from DHEA.[107] Vaginal DHEA (prasterone) has been approved to treat moderate to severe dyspareunia.[76] Compared to placebo and moisturizers, intravaginal DHEA (prasterone) 6.5 mg for 12 weeks improves vaginal pH, cell maturation, dyspareunia and significantly improved sexual health and related domains ($P < .0001$).[108-109]

Intravaginal DHEA has no adverse effects on the endometrium after 12 months of therapy.[111] Most studies suggest no significant increase in serum levels of steroid sex hormones with the use of vaginal DHEA.[112] Breast cancer survivors were studied. While intravaginal DHEA increased circulating DHEA-S, testosterone, and estradiol values, they remained within the normal postmenopausal ranges.[112] Authors of a recent review cautiously stated: "Women who have no history of estrogen-dependent cancers should be routinely

offered treatment for GSM with vaginal estrogen or DHEA."[76]

Breast Cancer: There is neither consistent data nor a substantial association of either DHEA or DHEA-S to women's risk of breast cancer.[113-115] It is hypothesized that the effects of androgens depend on concurrent estrogen levels. In-vitro, DHEA-S (but perhaps not DHEA) can compete with estradiol for ERα and ERβ-binding.[16,117] Thus, before menopause, DHEA/S will exhibit anti-estrogenic effects but after menopause it becomes *weakly* estrogenic. DHEA was also found to inhibit the proliferation and migration of tumor cells derived from the breast.[118]

Supplementation should not be to an excess, though: *Elevated* levels of androgens (free testosterone, DHEA-S and androstenedione) have been correlated with an increased post-menopausal breast cancer risk.[119] It is believed the activated androgen receptor can stimulate cellular proliferation of estrogen receptor-*negative* breast cancer.

Fibrocystic breast disease: Androgens may protect women from fibrocystic breast disease.[120]

Primary hypoadrenalism (Addison's): As above, many reports validate the benefit of DHEA supplementation in Addison's disease, from replenishment of androgens. In addition to restoring circulating DHEA, DHEA-S and androstenedione levels to these people, DHEA supplementation reduces total cholesterol, improves well-being, sexual satisfaction, and insulin sensitivity; and it prevents the loss of bone mineral density.[19]

Adrenal "fatigue": The chronic fatigue syndrome (CFS) shares at least 36 features with Addison's disease.[121] Whilst Cleare *et al*. have shown low-dose hydrocortisone successfully improves the symptoms of CFS,[122,123] he does not recommend it as a chronic therapy, for it suppresses the already dysfunctional HPA-axis and further depresses steroid sex hormones.[124] DHEA has been evaluated as an alternative to hydrocortisone.

Some studies report low DHEA in chronic fatigue syndrome patients.[59] As above, adding DHEA "distal" to 17-20 lyase increases the quantities of progesterone and other precursors of aldosterone and cortisol.[69] Thus, DHEA might help relieve adrenal symptoms without the drawbacks of using hydrocortisone. This outcome was reported in a small study.[125]

Depression: Neurosteroids significantly affect mood and DHEA-S enhances glutamatergic signaling. A meta-analysis of RCTs found a significant effect in favor of DHEA treatment for depression compared to placebo.[126] The authors concluded that DHEA may be an additional, effective alternative to antidepressants.

Insulin resistance – Cortisol: The metabolic syndrome is associated with functional hypercortisolemia.[127] A meta-analysis confirmed that DHEA has a cortisol-blocking effect: It found supplementation with DHEA significantly decreased cortisol levels and there were no differences in adiponectin, leptin, or liver transaminases. The authors concluded DHEA may be used to treat hypercortisolemia and it is safe for the liver.[128]

Insulin resistance – Obesity: A meta-analysis of 25 placebo-controlled trials of DHEA supplementation in elderly men (n= 1,353) with 36 weeks mean-follow-up confirmed a reduction of body fat-mass.[129] A more recent meta-analysis of 23 RCTs also found DHEA supplementation decreases fat mass and increases lean body mass.[130] Some of this benefit may be due to the ability of DHEA and its metabolite androstenediol to activate nuclear peroxisome proliferator-activated receptors (PPARs) – transcription factors, which are involved in regulating the body's lipid homeostasis.[131]

Insulin resistance – Lipids: DHEA activates PPARs. Gemfibrozil activates PPARα; pioglitazone selectively stimulates the gamma (PPARγ) and to a lesser extent, PPARα. Therefore, one would expect DHEA to have a beneficial effect on lipid metabolism and blood lipids, of which there is "much experimental evidence."[132] However, a recent meta-analysis of RCTs failed to substantiate this.[133] They reported no significant difference in total cholesterol, LDL-cholesterol, and triglycerides but rather a statistically significant (but clinically insignificant) decrease in women's HDL-cholesterol (not men's).

Insulin resistance – Diabetes: Blood levels of DHEA are inversely correlated with the risk of type-2 diabetes,[134] which might be coincidental. Importantly, studies reported that DHEA replacement improved insulin sensitivity,[135,136] and glucose tolerance (GT) but only in participants with *initially* abnormal GT. It also reduced plasma triglycerides, and the inflammatory cytokines IL6 and TNFα.[137] While a meta-analysis revealed that once diabetes is established, DHEA supplementation improves the fasting glucose by a statistically significant number, it was by only a tiny 2.2 mg/dL.[138]

Cancer: DHEA protects against several types of cancer,[139] particularly cervical cancer. DHEA inhibits proliferation and induces the death of cervical cancer cells (regardless of HPV status) by mechanism(s) independent of androgen and estrogen-receptors.[140] This anti-proliferation effect on cervical cancer cells was associated with decreased cellular adhesion and migration. These findings, along with reduced angiogenesis and capillary tube formation were earlier described in-vitro, at high concentrations of DHEA.[141]

Inflammation and immunity: Here again, authors' cautions may temper our enthusiasm over the following information: "Much of the research is conducted on rodent models using very high concentrations of hormone supplements, which may not meaningfully translate to human physiology. The convoluted nature of DHEA-immune interactions makes direct effects difficult to interpret."[142]

DHEA has differential actions on human immune function and its effects are shaped by the concurrent concentrations of other hormones. DHEA is generally considered immune-supportive but has also been shown to inhibit certain facets of innate and cell-mediated immunity, suggesting complex roles.[143] DHEA has an anti-glucocorticoid effect.[142] In asthmatic airways, DHEA/DHEA-S attenuate T helper-2 allergic inflammation and reduce eosinophilia and hyperreactivity.[19] DHEA specifically inhibits interleukin-6, which could be useful for COVID-19 infections.[144]

A 2014 review catalogued beneficial effects of DHEA for inflammatory processes, both demonstrated and hypothesized.[19] DHEA exerts an anti-inflammatory, vasorelaxant, and anti-remodeling effect to modulate cardiovascular signaling pathways. It is consistent that its low levels correlate with increased cardiovascular disease and all-cause mortality. DHEA/DHEA-S appear protective in asthma and allergy. In an unblinded study, it induced remission in

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most patients with inflammatory bowel disease. In systemic lupus erythematosus, DHEA is steroid-sparing. Its use for rheumatoid arthritis has been proposed.

Growth hormone: Meta-analysis of 24 trials found that serum IGF-1 increased significantly with DHEA treatment compared to controls.[145] Subgroups showed significantly increased IGF-1 in women (but not men) aged >60 years without underlying co-morbidity, who took 50 mg DHEA daily for at least 12 weeks.

Cognition: A systematic review of RCTs studying the effects of DHEA supplementation on cognitive functioning in non-demented men of middle-age and older reports the existing evidence is scanty and "severely inconsistent."[146] Despite the known neurosteroid and protective effects, the authors found no evidence of any benefit.

Aging: Chrousos *et al.* state regarding anti-aging use: "DHEA supplements do not comply with evidence-based medicine."[56] The AMA House of Delegates resolved in 2009 that "The use of hGH and DHEA as anti-aging agents is not recommended."[147]

The clinical response of selected patients to DHEA supplementation would contradict these statements (Case 1). No published trial has joined the nutrients provided in desiccated adrenal glandular with DHEA treatment, as described below in Case 3. An automobile will not function well, regardless of the amount of gasoline in the tank *if* there is no oil in the engine.

The position statement of the Polish Menopause and Andropause Society is current and sensible.[148] They write: "DHEA supplementation *is effective* in women with adrenal insufficiency and chronically treated with exogenous glucocorticoids, postmenopausal women with low bone mineral density and/or osteoporosis, premenopausal women with sexual disorders and low libido, and in women with vulvovaginal atrophy due to menopause or genitourinary syndrome of menopause."

They continue: "Currently available clinical trials also suggest that DHEA supplementation is *probably effective* in postmenopausal women with hypoactive sexual disorders, infertile women with diminished ovarian reserve, women suffering from depression and anxiety, and women with obesity and insulin resistance. No serious adverse effects have been reported." It is pleasant that they do not forbid using DHEA in any particular circumstance due solely to "lack of evidence."

Successful DHEA Therapy

Goals and rationale: The goal of DHEA supplementation is to improve deficient patients' health by restoring their hormone balance at optimal levels. We hope to normalize adrenal function, to restore the steroid sex hormones to physiological levels of younger adults, and to facilitate optimal neurosteroids so they may reap the many benefits catalogued above.

Biochemical bottlenecks exist at multiple levels, which can prevent DHEA synthesis. In both acute and chronic stress, depressed gonadotropin secretion (LH and FSH) reduces the actions of 17-20 desmolase and 17β-HSD.[38] If ACTH secretion is impaired, the adrenal produces less pregnenolone, the universal steroid precursor from which steroid hormones are made. Supplying the body with DHEA and pregnenolone gives the adrenal glands access to supplementary precursors.[149] These precursors provide the body with partly assembled pre-hormones that either can be processed to hormones or expelled as waste products.

Supplementing DHEA bypasses the step impaired by the loss of LH and replenishes the pathways to testosterone and its products, estradiol and DHT.[144] As evidence, we see that giving DHEA yields *twice* as much testosterone as can equally dosed precursors "upstream" of 17-20 desmolase: Pregnenolone, progesterone, and 17α-OH progesterone.[68]

Safety: Enzymes that produce "downstream" steroids are regulated. Therefore, precursors *cannot force* the excessive production of hormones.[70] People given even large doses of DHEA will not make too much cortisol.[96] It has repeatedly been demonstrated that no amount of DHEA supplementation will cause a man with normal testosterone to make more than a normal amount of it.[71-74]

Excessive amounts of DHEA are generally conjugated to DHEA-S and

cleared.[71,151] On 24 hour-urine adrenal steroid profile, elevated androstenedione "waste" products (androsterone and etiocholanolone) also indicate an overly large DHEA dose. Do not take this to mean that correct dosing is irrelevant! Signs and symptoms of androgen excess (e.g., acne of the face and back, hair loss and hirsutism) can follow a large dose due to its intracrine activation in the skin, which is a capable steroidogenic organ.[152] This is particularly true for women with polycystic ovary syndrome, for whom a "normal" dose of DHEA is often too much.

Diagnose low-DHEA. Patients with adrenal dysfunction should be tested for DHEA at some time in their therapeutic course. The 2016 Endocrine Society clinical guidelines for diagnosing adrenal dysfunction are freely accessible online.[153] As noted above, exogenous suppression of adrenal function can also depress DHEA (which can occur unexpectedly, even with steroid inhaler use). Do not cling to obsolete guidelines stating even that laboratory tests of women's testosterone levels are not necessary and should be used only to monitor replacement therapy for deficiency – which diagnosis must be *intuited*, one assumes.[154]

How then should we diagnose low DHEA? Symptoms are generally nonspecific. Aging is not – but its consequences at a given age are individually variable. Chronic stress and altered HPA-axis can be related to fibromyalgia and persisting pain, chronic fatigue syndrome, burnout and post-traumatic stress disorder.[155,156] Guidelines for diagnosing women's hypoactive sexual desire disorder/dysfunction and female sexual arousal disorder[89] and for the genitourinary syndrome of menopause are established.[106]

When planning tests for DHEA, bear in mind a few physiological facts: DHEA levels have strong diurnal variation, as little is bound to SHBG, while DHEA-S levels (tightly bound to the transport protein) fluctuate only a little. The ratio of these two will vary through the day. Also, large amounts of oral DHEA doses are converted to DHEA-S (a largely one-way step) in the hepatic "first pass"; consider this in monitoring therapy.

Tests are easily available for both DHEA and DHEA-S in blood, urine, and saliva. AJ Cleare found saliva the less reliable medium, commenting there is excessive variance between steroid levels in saliva and those in blood and urine.[157] In blood testing at national labs, only total DHEA and DHEA-S are available; free (unbound) levels are not offered.

Knowing that excessive DHEA is conjugated to DHEA-S, it would seem plausible that the earliest marker of DHEA-deficiency may be low plasma DHEA-S. A better method may be "Metabolomics," the study of precursors and by-products.[158] This principle has been very useful in clinical practice, when applied to results of a 24-hour urine adrenal steroid profile (GC/ mass spec.). This collection removes confusion caused by the diurnal rise and fall of steroid levels.[159] A similar alternative is the dried urine test for cortical hormones.

DHEA decline, due to aging, is associated with many degenerative changes.

There is convenience and clinical utility in testing blood for "classical" steroid sex hormones instead of DHEA, particularly to follow the results of treatment. Remember that non-bioidentical steroid hormones (e.g., oral contraceptives, budesonide) are chemically altered and thus "invisible" to the laboratory. When test results are inexplicably low, ask about such hormone use before considering any replacement! Other pharmaceuticals can interfere; for example, ketoconazole inhibits 17-20 desmolase and reduces DHEA and its products.

Case 3 is a 42-year-old man, allergic on immunotherapy, taking "natural" thyroid for a goiter and S/P successful operation (UPPP) for sleep apnea. His residual symptoms led to an adrenal workup, which in February 1997 yielded the following: Blood tests showed elevated AM ACTH=338 H (9-52 pg/mL) and normal cortisol=16.1 (4-22 mcg/dL). Anti-adrenal autoantibody test was negative. His 24 hour-urine ACTH-stimulating test was abnormal: Baseline cortisol=28 (10-80 mg/24 Hr.), cortisone=98 (18-101 mg/24 Hr.) and androgens were low (DHEA, androsterone). After ACTH injection, his adrenal function fell: Cortisol=11 L, cortisone=34 L – what Jonathan Wright has called "the stumbling runner phenomenon." The DHEA remained low.

He began taking DHEA 25 mg daily at bedtime and then, twice daily (morning and bedtime). His ACTH value improved to 59 H, still elevated. He started taking desiccated neonatal bovine adrenal cortex. His ACTH returned to normal, 29 and subsequently remained no higher than 37 (last follow-up 4/2021). Some years later, he briefly stopped his desiccated adrenal cortex and felt much worse. On resuming it, he promptly returned to normal.

Before Starting DHEA

Long ago, Doc found that his patients responded better to DHEA and pregnenolone when they had first started taking desiccated neonatal bovine adrenal cortex (AKA "glandular"). This hormone-free supplement is believed to provide nutrients and co-factors for the synthetic enzymes of the steroid-synthesis pathways. These enzymes are in the adrenals and ovaries; in the brain (to make neurosteroids); in the skin; and importantly, in mitochondria (to make energy). In fact, some people on starting it have bewildering energy, even a re-feeding syndrome.

For about four months in the 1990s, Doc tried giving DHEA without the adrenal glandular, hoping to save patients some money… he failed parlously. DHEA alone helped very few and not very much when it did. His patients quit taking it and refused all suggestions to start the glandular and then resume DHEA. Metaphorically, they had put gasoline in their tank without first putting oil in the engine. If the synthetic enzymes lacked necessary co-factors, the DHEA could go nowhere but out.

Informed consent is essential before treatment. Women should be cautioned that their fertility can be increased. Some who thought they were in menopause have started cycling again for a few years more. The risk of side effects should be reviewed (see the discussion following). All people with insulin resistance should know their risk of potential problems is increased, so their initial dosing will be more conservative.

Sources of DHEA

Currently available DHEA products are manufactured from yams. Years ago, the

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purity and potency of the commercially available products were highly irregular, with content ranging from 150% to 0% of the labeled amount.[160,161] Follow-up using 24-hour urine adrenal steroid profiles show the "bad" products have elevated values of DHEA and androsterone and etiocholanolone, the products of androstenedione (which is not measured). However, testosterone was slightly lower; presumably, the "bad" precursor was blocking the pathways.

Thus, Doc used compounded DHEA when he first recommended it. When the patient had good results, a trusty health-food store owner suggested less expensive OTC supplements for comparison and thus, reliable brands were found. Currently, the quality is much improved – though questions linger around some manufacturers.

Start DHEA Supplements

Men: Once the adrenal "glandular" is at the full dose (two in the AM, perhaps one at noon and two at bedtime), patients can start DHEA. Men take 25 mg at bedtime, so it will be available in the wee hours of the morning when the HPA- and HPT-axes crank up hormone production. After a week or more, a few men need 50 mg daily. No patient has been observed to require a larger dose for a desirable outcome – or to take more than 75 mg daily without some androgenic side-effects. Some men like to divide the DHEA: Half at bedtime and half on waking; it is a matter of individual preference.

Women: Over about ten years of clinical efforts, it became apparent that most women benefit *more* from equally dosed pregnenolone than from DHEA. Thus, after the "glandular" is up to speed, women are offered pregnenolone 10 mg at bedtime, then 20 mg daily and sometimes more. If this does not correct low testosterone, DHEA 5 mg is recommended. On pregnenolone up to 30 or even 40 mg daily, very few women need more than 10 mg DHEA to restore total testosterone to the midst of the physiological range.

To repeat, long experience indicates the "maximum" dose of DHEA – or of DHEA combined with pregnenolone – that combines effectiveness with freedom from side-effects is about 50 mg daily. Current literature reports the common use of larger amounts: A recent meta-analysis of 42 RCTs demonstrated that testosterone level was significantly increased after DHEA administration. The gain was greater when more than 50mg/day was administered.[79] Studies cited above using DHEA to restore fertility to women with diminished ovarian reserve usually give 75 mg daily (in three divided doses). The highest dose, the most *egregiously* excessive dose found in the medical literature was reported in 1990, when women were given 400 mg DHEA orally four times daily – 1,600 mg a day[162] – *wowzah!*

Why does this literature show larger doses of DHEA are needed than some 27 years of clinical experience would indicate? Amidst various plausible explanations, the experience of Case 3 offers an attractive hypothesis: DHEA supplements are more beneficial at lower doses when accompanied by the nutritional cofactors necessary for the synthetic enzymes of the steroid synthetic pathways to process the DHEA.

What is the optimal dose? The optimal dose is the least that will accomplish the maximal desired response. There is a tipping point, at which undesirable side effects increase more rapidly than therapeutic benefit. We've seen a report in which women were given large doses of DHEA and this androgen caused "no serious side effects."[95] In fact, no report claiming such a problem was discovered. Despite the freedom from severe complications, there are reasons to dose cautiously: Excessive DHEA can cause cosmetic, behavioral, and possibly anatomical side effects.

Risks, Complications and Side-Effects

Since desiccated neonatal adrenal cortex has been recommended, it is proper to mention that patients who are significantly deficient in the nutrients it provides can have "re-feeding syndrome" on starting it. This has been discussed in detail elsewhere.[163] Similarly, as Paracelsus wrote: "The dose makes the poison"[164] and complications of DHEA are related to the dose given and the rate of its increase.

In a two-year-long randomized, prospective, placebo-controlled double-blinded study of DHEA supplementation, older men took 75 mg daily and women took 50 mg daily. Prostate volume, PSA, liver function, electrolyte levels and hemoglobin were not significantly worse in the treated group compared to controls.[74] Meta-analysis of the evidence supporting the use of systemic DHEA in postmenopausal women with normal adrenal function reported no serious adverse effects and no worsened serum lipids, serum glucose, weight, or body mass index.[165] Intensivists caring for severe trauma victims report: "The current data suggest that DHEA, certainly in short-term supplementation, should be regarded as safe without significant side effects."[166]

In practice, the most common clinical side effects of DHEA treatment are caused by the fact that it is effective. Doc calls them "the three A's of androgens": First is *attitude*, due to the restoration of testosterone and neurosteroids. A positive, outgoing and assertive outlook are desirable, but some men become aggressive and irritable – downright disagreeable. When this occurs, they are getting too much testosterone too quickly. Reduce the dose and build it

back more slowly. Perhaps the androgen receptor population is "over-expressed" when testosterone is deficient, as is the thyroid receptor in hypothyroidism.[167-169] An unusually large number of "hungry" nuclear receptors can excessively respond to the rapid replenishment of a *normal amount* of hormone.

The second "A" is *alopecia*. This also can be physiological, the predictable result when normal testosterone is converted normally to DHT in men with the gene for male-pattern hair loss. Unfortunately, women with PCOS and insulin resistance over-express 5alpha-reductase and can excessively produce DHT, sometimes with the same effect.[10] Doc found that women with PCOS get androgenic side effects on as little as 15 mg DHEA daily, even when taking the "glandular."

The third "A" is *acne*, another consequence of DHT in the skin. A meta-analysis of 16 RCTs in which women were given DHEA for perimenopausal or menopausal symptoms reported increased androgenic side effects (odds ratio 3.77), principally acne. This occurred whether DHEA was taken orally or applied topically.[170] Experience indicates that women with PCOS and insulin resistance, who already tend to hyperandrogenemia, seem most vulnerable.

Hirsutism is also an undesirable androgenic complication. Watch for darkening hair on the upper lip and sides of the chin; also circumareolar hair and down the hypogastric midline. These hairs do not always regress after DHEA is withdrawn. If this seems trivial to the practitioner, few affected patients share that perspective.

As previously noted, the restoration of adrenal nutrition and sex hormone precursors can increase fertility and restore normal menstrual cycling. This is not considered a side-effect unless an unwanted pregnancy occurs. Some patients have not been happy about the resumption of their menses.

Though DHEA has relatively low affinity for the androgen receptor, it and its androgenic byproducts *can* compete with DHT and testosterone for receptor binding sites. Conceptually, the more DHEA in circulation, the less the androgen receptor may be able to act, due to binding the low-potency precursors.

Laboratory follow-up also shows that older men particularly will convert excess DHEA via androstenedione to estrone. This estrogen can cause prostate enlargement by stimulating medullary estrogen receptors,[171] particularly if it is configured as 16α hydroxy-estrone.[172] This also could affect the incidence of malignancy.[173]

Metabolic syndrome patients are endocrine-disrupted, which can lead to apparent treatment failure. Women's elevated 5a-reductase excessively produces DHT, as above.[10] Men have increased aromatase[174] that doubles the risk of low-testosterone in metabolic syndrome,[175] while almost 50% of men with type-2 diabetes have low testosterone.[176] Supplemental DHEA will increase their androgen production … but these promptly will be converted to estrogens. Limit the amount of DHEA you pour in: There is "a hole in the bottom of their bucket."

Monitor Treatment Results

The route of administration is relevant. A study of intravaginal DHEA suggested that women using vaginal DHEA "should not have blood hormone levels checked, as the serum concentration of sex steroids is minimally affected by this route of administration."[76]

When monitoring is indicated, it is proper to be consistent and use the same body fluid for following therapeutic outcomes that was used to diagnose the problem. Blood tests are useful, convenient, and covered by insurance in Doc's practice. If saliva was your initial medium, then use it for follow-up.

If you began with a 24-hour urine adrenal steroid profile, follow-up with another. Using metabolomics, excess supplementation is *first* revealed in the 24-hour urine by high amounts of its products: DHEA-S and importantly, androsterone and etiocholanolone (from androstenedione). On larger doses, we can see high DHEA.

When you have chosen your pre-treatment tests wisely, they need only to be repeated to validate outcomes. Because oral DHEA is so greatly converted to DHEA-S in the liver first-pass, it is sensible to follow therapeutic levels with unconjugated DHEA. Since DHEA augments testosterone, measure it too! Because testosterone is the precursor of estradiol and DHT, they may be tested – at least once.

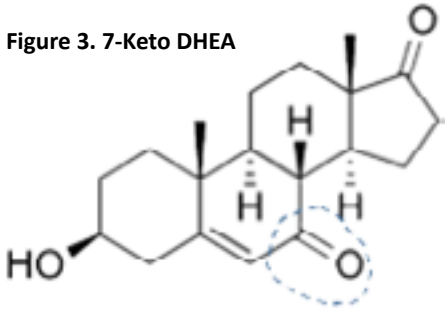
Knowing that age increases SHBG (sex hormone-binding globulin) and metabolic syndrome reduces it, Doc orders blood tests for both total testosterone (by LC/MS) and free testosterone (by ED) – at least for the first follow-up. Age, obesity and metabolic syndrome increase men's aromatase, so it is wise also to test total estradiol (by LC/MS). Sometimes it is indicated to test women's DHT also, for comparison to total testosterone.[10]

Guidelines for monitoring testosterone therapy in women might be relevant for DHEA. The Endocrine Society suggested testing after three to six weeks on treatment to avoid toxicity and excessive dosing.[90] It is reassuring that the "Global consensus" stated: "When serum testosterone levels remain in normal physiologic ranges, studies show that neither oral nor nonoral testosterone (*implied "androgen"*) therapy significantly affects the lipid profile, glycemic markers, blood pressure, body mass index, or hematocrit."[76]

Alternatives to DHEA

7-keto DHEA is chemically-modified DHEA (Figure 3). This alteration prevents it from becoming converted to testosterone and estradiol. Most users entering Doc's practice have been women, who say they use it to gain the benefits of DHEA without making testosterone. They hope, as enumerated by RxList, to speed up the metabolism and heat production to promote weight loss; to improve lean body mass and build muscle; to increase the activity of the thyroid gland, boost the immune system, enhance memory, and slow aging.[177] Athletes have used it, believing it was an undetectable androgenic "doping" agent but current testing technology can now identify the substance[178] and it has been banned by some organized sports.

Figure 3. 7-Keto DHEA



https://en.wikipedia.org/wiki/7-Keto-DHEA#/media/File:7-Keto-DHEA.svg

➤

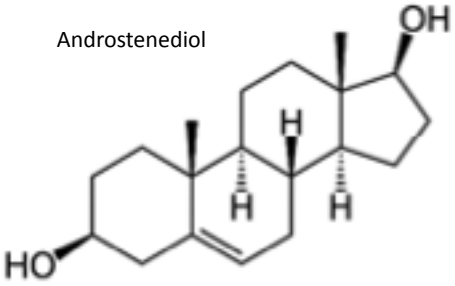
The 24-hour-urine adrenal steroid profile of people taking 7-keto DHEA resembles that of "bad" DHEA (as above). As an advocate of using biologically identical hormones and precursors, Doc is uncomfortable with this peculiar strategy. He has yet to see anyone who clearly benefitted from taking it – and acknowledges that he would not see people for whom it relieved all their problems.

Pregnenolone has been mentioned above as the universal precursor of adrenal-gonadal steroids.[179] In research and clinical use, its supplementation can increase progesterone production,[7,180-182] along with its benefits of replenishing steroid pathways,[183] reduction of pain and the stress response[184] and a mild GABAergic effect.[185] Feedback inhibition from downstream products (DHEA, androstenedione, estrone and testosterone) inhibits the enzyme (3β-HSD) that converts pregnenolone to progesterone.[7,70,96] Thus, it is remarkably free of any effects besides those caused by replenishment of cortisol, aldosterone, progesterone and the other sex hormones (which *can* be increased uncomfortably quickly).

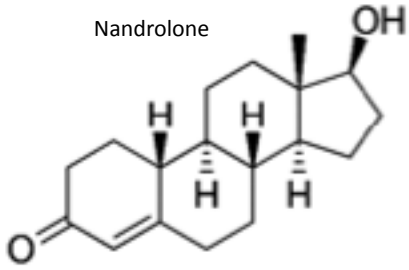
As above, women respond to pregnenolone supplementation well, unless excessive 5alpha-reductase converts it excessively to the neurosteroid, allopregnanolone, which in menopausal women, can cause headaches.[10] Doc had a small series of middle-aged men who tried 10 mg pregnenolone at bedtime. Everyone liked it (perhaps from the GABA effect) but most men's blood levels of progesterone became too high, up to 3 ng/dL (0.3-1.2). This caused mild gynecomastia and perhaps increased abdominal adiposity. It is likely that 5 mg daily would be successful.

Figure 4.

Androstenediol



Nandrolone



4-Androstenediol (Figures 1 and 4), has been used to supplement testosterone production. In fact, its use for this purpose was patented by Patrick Arnold in 1998, then allowed to expire in 2018. Doc has no experience of using this precursor. Its naturally occurring near-twin nandrolone is normally present in the human body fluids in trace amounts. Nandrolone also can be found some physicians' offices with other parenteral medications, but it has no role in the author's practice.

Testosterone and estradiol are the ultimate products of DHEA. It was an early disappointment to Doc that, while he could achieve follicular-phase levels of progesterone with OTC pregnenolone and normal women's testosterone values with DHEA, neither one could restore follicular blood levels of estradiol. Some patients, particularly those with primary gonadal failure need to receive these hormones.

Summary

Dehydroepiandrosterone (DHEA) is neither a miracle hormone nor a wonder drug. It is a moving part in a vehicle that is wonderfully constructed. It serves as a precursor and an agonist of both genomic and non-genomic messages. Its deficiency is noteworthy.

In ordinary circumstances, insufficient DHEA is troublesome. With age, its decline is associated with many degenerative changes. When the maladaptive stress responses of illness, pain, or injury have inhibited DHEA production, significantly ill consequences can follow.

With some understanding – and having prepared the patient with desiccated neonatal adrenal cortex to receive DHEA as a farmer fertilizes his fields – correctly dosed DHEA supplementation can be very beneficial. ◆

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

Alan McDaniel, MD, is a 1977 Tulane medical graduate. He trained in general surgery and emergency medicine before becoming Board-certified in otolaryngology with sub-specialties in neurotology and allergy. He has practiced privately since a two-year faculty appointment at the University of Louisville.

He has presented at various national meetings in the US (AAO-HNS, AAOA, ANS, AAEM, IFM, PAAS) and Mexico. Topics of his lectures and publications have included general surgery and otolaryngology; otology and neurotology; allergy; chronic fatigue and endocrinology. He has been a faculty member for the American Academy of Otolaryngic Allergy Basic and Advanced Courses and for the American Academy of Environmental Medicine. His two-day course "New Endocrinology" has been presented at the AAEM and elsewhere since 2005, to physicians from five continents. Work with dizziness and allergy in the 1980s led him to seek solutions for chronic fatigue syndrome. In turn, these investigations extended to the endocrine aspects of this and related conditions.

Since basic surgical training emphasizes the need to know several alternative approaches to an operation, he saw the logic of studying integrative and controversial medical methods. He has endeavored to understand these in the light of new facts from research, mindful that medical history shows innovation begins as a minority opinion.

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The Effect of HSOP (Hokkaido Scallop Oil Plasmalogen) on POMS2 Test Score

by Naoki Igari[1], Kentaro Ninomiya[1], Hideki Katano[2,3]

Introduction

According to the World Health Organization (WHO), the number of patients with dementia as of 2019 was 55.2 million in the world, and this number is estimated to increase to 78 million in 2030 and 139 million in 2050.[1] In addition, as of 2015, an estimated 322 million people had depression. The population of patients with depression exceeded 4% of the total world population, indicating that one in 25 people had depression.[2] These statistics clearly show that it is urgent to take measures concerning dementia and psychiatric disorders. Although dementia is categorized into several types, including Alzheimer's disease and others, brain inflammation due to oxidative stress is commonly involved in its onset. Although psychiatric disorders are considered to be triggered by genetic or environmental factors, their pathogenesis has not yet been elucidated. However, autopsies of the brains of patients with psychiatric disorders and analyses of animal models suggest that their onset is caused by brain inflammation due to oxidative stress.

Plasmalogen is a type of phospholipid and a major component of cell membranes. This substance possesses potent antioxidant properties compared to other types of lipids, which are attributed to its specific molecular structure, known as vinyl ether bonds. Plasmalogen is quickly oxidized when active oxygen is generated, thereby protecting the cells. Plasmalogen is ubiquitous in the human body and is especially abundant in the brain and heart.[3] The weight of the human brain accounts for approximately 2% (1.2 to 1.6 kg) of total body weight in adults; however, the brain consumes 20% of the body's total oxygen supply and 25% of the body's blood glucose supply. These ratios are significantly high when the weight ratio is considered. The brain is constantly exposed to oxidative stress due to its high oxygen consumption. One of the reasons why plasmalogen is more abundant in the brain than in other organs may be that the brain needs to be maintained in healthy conditions by suppressing oxidative stress.

Plasmalogen is a type of phospholipid and a major component of cell membranes.

Plasmalogen is known to decrease with age. The blood plasmalogen levels in older individuals (average age, 65.5 years) are reported to be approximately 40% lower compared to the levels in young people (average age, 23.5 years).[4] Furthermore, it has been reported that patients with Alzheimer's-type dementia have lower blood plasmalogen levels than healthy subjects, especially in the type of plasmalogen that is bound to docosahexaenoic acid (DHA).[5,6] In addition, plasmalogen levels are correlated with the severity of dementia symptoms. Patients with severe symptoms of dementia were shown to have lower plasmalogen levels in the brain than those with mild symptoms.[7]

A previous study showed that administration of scallop-derived plasmalogens at 0.5 or 1 mg per day to patients with mild cognitive impairment or Alzheimer's disease improved their cognitive functions and increased blood plasmalogen levels.[8, 9] Previous animal studies have demonstrated that oral administration of plasmalogen suppresses inflammation in the brain and improves memory impairment.[10] Plasmalogens have been reported to inhibit cell death in the hippocampus by activating phosphoinositide 3-kinase-dependent serine/threonine-specific protein kinase and extracellular signal-regulating kinase.[11] Based on these results, we propose that the effect of plasmalogen in reducing inflammation and inhibiting neuronal death may be effective in improving cognitive function.

As mentioned above, brain inflammation caused by oxidative stress is believed to be involved in the onset of mental disorders; therefore, plasmalogens are expected to be effective for mental disorders because they can inhibit brain inflammation. In this study, we administered scallop-derived plasmalogen to healthy participants and investigated changes in their mental status to evaluate the effect of plasmalogen.

Materials and Methods

Test supplement. HSOP (Hokkaido Scallop Oil Plasmalogen) (Daiwa Pharmaceutical Co., Ltd.) is scallop-

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derived plasmalogen. Softgel capsules containing 0.5 mg HSOP per capsule were prepared. Scallop-derived plasmalogen contains higher concentrations of omega-3 fatty acids (DHA and EPA [eicosapentaenoic acid]) than does chicken-derived plasmalogen.

Participants. Forty-six healthy participants (average age, 43.9 years; 20 males and 26 females) were provided adequate information in advance, and informed consent was obtained from them.

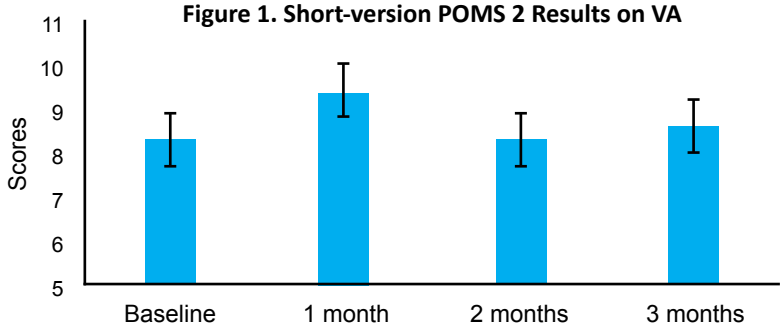
Administration of test food. All participants received the HSOP capsules, 1 capsule daily for three months. The test period was from June 8 to September 8, 2020.

Evaluation of psychological status. The short version of POMS2 (Profile of Mood States 2), which is internationally applicable as a tool to objectively evaluate psychological states, including mood, feelings, and emotions, was used in this study. A set of 15 questions was added to this test. This evaluation was carried out four times in total: at baseline and at one, two, and three months post-baseline.

In the short version of the POMS2, participant's self-ratings for each question were quantified as follows: 0, not at all; 1, a little; 2, some; 3, well; and 4, very well. Each self-rating for all 35 questions was composed of seven scales of measure: anger-hostility (AH), confusion-bewilderment (CB), depression-dejection (DD), fatigue-inertia (FI), tension-anxiety (TA), vigor-activity (VA), and friendliness (F). The Total Mood Disturbance (TMD) was determined by calculating the above factors.

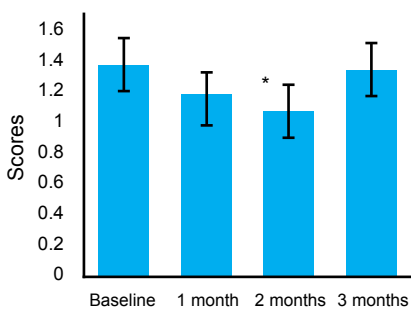
The additional questions were as follows: "Stuffy head or dull feeling," "memory relapse (e.g., difficulties in remembering other person's name)," "difficulties in maintaining concentration and persistence," "difficulties in hearing conversations or TV sounds," "excessively sensitive to smells," "blurred vision and eye fatigue," "improvement of

Figure 1. Short-version POMS 2 Results on VA

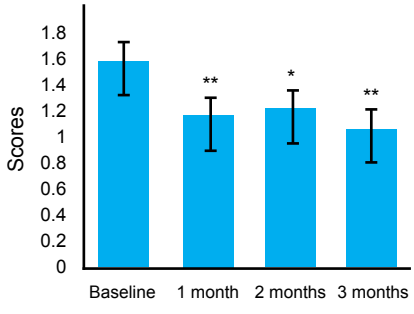


Vertical bar = ±SE (n=46), *p<0.05

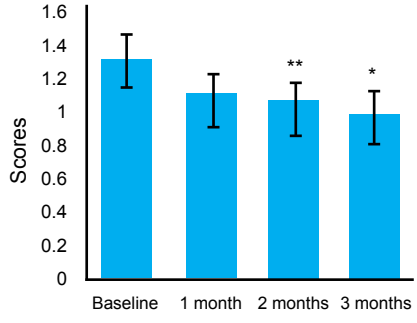
Figure 2. Results of Additional Questions



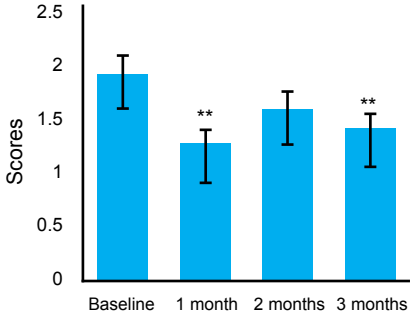
a. "Stuffy head or feel dull"



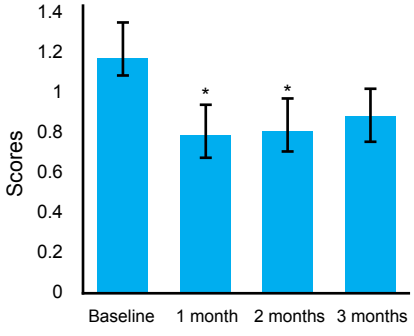
b. "Memory relapse"



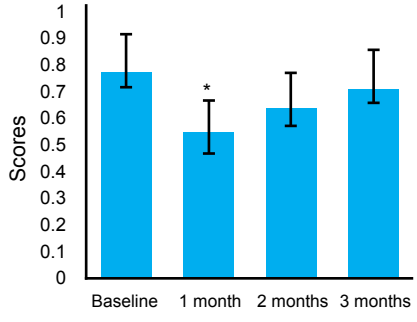
c. "Difficulties in maintaining concentration and persistence"



d. "Blurred vision and eye fatigue"



e. "Non-continuous sleep"



f. "Frequent constipation"

Vertical bar = ±SE (n=46), *p<0.05, **:p<0.01

quick witted or reaction speed," "having difficulty falling asleep or sleeping badly," "non- continuous sleep," "waking up several times for bathroom during the night," "having trouble in getting up," "constipation," and "frequent diarrhea." Self-rating scores for additional questions were quantified using the same procedure.

Results and Discussion

The results of the short version POMS2 showed that vigor-activity (VA) significantly increased one month after baseline (p=0.040) (Figure. 1).

The results of the self-rating scores for additional questions showed that "stuffy head or dull feeling" significantly decreased two months after baseline (p=0.036) (Fig. 2a). A significant decline in "memory relapse (e.g., difficulties in remembering other person's name)" was observed one, two, and three months after baseline (p=0.008, p=0.014, and p=0.002, respectively) (Fig. 2b), and "difficulties in maintaining concentration and persistence" significantly improved after two and three months (p=0.044 and p=0.031, respectively) (Fig. 2c). "Blurred vision and eye fatigue" were significantly reduced after one and three months (p=0.000 and p=0.007, respectively) (Fig. 2d). A significant decrease was observed in "having difficulty in falling asleep or sleeping badly" after one and two months (p=0.028 and p=0.048, respectively) (Fig. 2e). A significant decrease was seen in "constipation" after one month (p=0.017) (Fig. 2f). There was no significant difference in the self-rating scores for the other questions.

Plasmalogens have potent antioxidant activities and are expected to suppress brain inflammation caused by oxidative stress. Considering that brain inflammation may be involved in mental disorders, including depression, fatigue, the results of this study can be attributed to the effect of scallop-derived plasmalogen in suppressing brain inflammation.

This study suggests that the administration of scallop-derived plasmalogen (0.5 mg/day) may be effective for the prevention of mental disorders; enhancement of vitality, memory, and concentration; and improvement of eye fatigue, sleep, and constipation. This study was limited by its small sample size. Therefore, further studies are needed in the future to evaluate the effect of scallop-derived plasmalogen on mental states.

References

1. World Health Organization, Global status report on the public health response to dementia: executive summary, 2021
2. World Health Organization, Depression and Other Common Mental Disorders, Global Health Estimates, 2017
3. Braverman NE, Moser AB. Biochimica et Biophysica Acta. 1822 (2012) 1442–1452
4. Maeba R, et al., Journal of Atherosclerosis and Thrombosis. Vol.14, No.1, 12 - 18, 2006
5. Oma S, et al., Dement Geriatr Cogn Disord Extra. 2012;2:298–303
6. Yamashita S, et al., Journal of Alzheimer's Disease. 50 (2016) 527–537
7. Goodenowe DB, et al., Journal of Lipid Research. Vol 48, 2007
8. Fujino T, et al., EBioMedicine. 17 (2017) 199–205
9. Fujino T, et al., J Alzheimers Dis Parkinsonism. 2019, Vol 9:4
10. Hossain MS, et al., Biochemical and Biophysical Research Communications. 496 (2018) 1033e1039
11. Hossain MS, et al., PLOS ONE. December 2013, Vol 8, Issue 12, e83508

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The Sexual "Headaches" That Women Don't Want to Talk About

by Sue Visser

When it comes to sex, a "headache" is an easy excuse for avoiding intimacy, but aspirins do not work! Modern drugs can eradicate infections, but vaginal issues still cause the untold misery that women are usually too shy to mention. It is worth knowing that soap is public enemy No. 1, followed by antibiotics, harsh deodorants, bleached toilet paper, and certain drugs. Allergies, too, can cause these "headaches"!

We will discuss the causes and cures of vaginal disorders that emerged during the years I was troubleshooting as well as developing products for a leading gynecologist in Cape Town. He was a very polite, discreet elderly Dutch gentleman who had a passion for natural medicine, especially homeopathy. He did not understand women and how they think, feel and understand, so I provided a viewpoint from the fairer sex. The vagina resembles a tube that connects the cervix or door of the womb, to the vulva (inner and outer labia: the folds of tissue that enclose the entrance to the vagina). These regions can be affected by a number of disorders that often seem more alarming than they actually are. Most ladies refer to this whole group of organs as the vagina, but this is not correct, according to the good Doctor. The cervix and vagina are always covered with a mucous lining that keeps them moist, but the outer labia do not have this lining. This ongoing natural lubrication prevents the epithelium from chafing, but often we experience a degree of discomfort. Vaginal dryness usually refers to insufficient lubrication of the vulva from secretory glands.

Vaginal pH is acidic, so avoid normal soap. I was asked to make herbal tinctures from urtica, calendula, witch hazel and ledum and formulate a vaginal douche. The beloved physician explained that these herbs help to ease the "pain and discomfort of the vagina." But, he whispered, "How you can get rid of that other stuff?" Something to do with a yeast infection, I presumed, a common curse – one that is exacerbated by washing with normal (alkaline) soap. It was twenty years ago, when I formulated an intimate cleanser with an acidic pH of 3.5 and that alone, helped to solve many a "headache." The use of broad-spectrum anti-bacterial agents that contain triclosan will kill off natural friendly bacteria and also cause more resistant strains of infection to mutate and breed. Weakened, inflamed skin encourages bacterial and fungal infections to multiply very quickly.

Harsh cleansing with soap and shower gel also removes the lubricating secretions from the outer labia, leaving them dry, sensitive, and itchy. The problem is made worse by the use of vaginal sprays and other deodorants that may inflame sensitive skin and upset the acidic pH balance. We also advised women to add a little salt and vinegar to a rinse, douche, or even a sitz-bath for immediate relief from the burning. The vaginal biome is acidic, that is why it reacts to soap (pH10). Menstrual blood has a pH of 7.4 so it is alkaline. The vagina cannot maintain the acidic balance during the menstrual cycle, hence the potential for odor. It takes over eight hours for the vagina to return to the normal acidic level after sex because semen is very alkaline at a pH of 8 to 10. A healthy vagina does not have an unpleasant smell and does not require soapy washes, scrubbing, or perfumed chemical deodorants that may be aggravating the condition.

The vaginal biome needs beneficial bacteria (probiotics). Today we are more familiar with taking probiotics when we use antibiotics to compensate for the loss of beneficial bacteria. They can also be introduced topically, when added to a pH-balanced cleansing solution. "Yes," the doctor agreed, "but how you get it up the vagina?" Well, women know how to wash, bath and shower; we do it every day without the need for any special apparatus I explained. The general complaint we hear from women is that they have candida. We all have colonies of candida yeast; but if our beneficial strains of bacteria dwindle; the yeast proliferates excessively. This causes a host of unpleasant effects such as itchiness, discharges, and inflammation collectively known as candidiasis.

Probiotics are live bacteria that inhabit the gut, nasal and chest cavities, and vagina. They make up over 80% of the immune system and survive by consuming yeast and other microbes. Probiotics neutralize toxins, remove heavy metals, and create vitamins; but they need candida (yeast) for food! Yoghurt is a source of *Lactobacillus acidophilus*, but it is not about the amount of each microbe you need but more the variety of strains. Microbes grow by themselves, so the latest trend is to provide a larger selection to establish a healthy population of beneficial bacteria. Probiotic supplements will grow on food, molasses, yoghurt or even a glass of water at room temperature. Try emptying out a capsule and letting it soak in water. The TMA (total microbial

action) doubled within a few days when I left a teaspoon of my probiotic concentrate in a glass of water at room temperature. It just keeps on growing!

Fermented food provides a host of gut flora that help to control candida and a whole lot more. Today our traditional food-enhancing skills have flown out of the window. Natural and slow give way to quick and easy, and we take pills to compensate for a lack of probiotics, a major cause of candidiasis that causes serious discomfort in the nether regions. We toss out food that goes moldy, milk that is sour and vegetables that look rotten. Yoghurt and amasi (rotten milk) provide bacteria like *Lactobacillus acidophilus*; and for vegans, fermented cabbage (sauerkraut) and other anaerobically fermented vegetables provide a tasty alternative. Trillions of microbes are provide by other fermented delicacies such as yoghurt, buttermilk, kefir, amasi, cheese, beer, wine, Kombucha, soybeans, olives, and even cocoa, tea and coffee.

Antibiotics and also an excess of echinacea, goldenseal, oregano oil, and propolis kill off our valuable probiotic colonies. Even copious amounts of garlic or cloves destroy pathogenic as well as beneficial bacteria. Supplement with sauerkraut: One or two tablespoons of sauerkraut a day keeps the yeast families, especially the *Candida albicans* strains, at bay and balances the acid/alkali levels within the small and large intestines. It creates the perfect growth medium for probiotics to flourish. As a digestive aid, sauerkraut converts lactose from milk into lactic acid. Lactic acid is essential to stop the growth of harmful bacteria, yeasts and molds connected to cancer, chronic fatigue syndrome, and candidiasis. A bit of the juice (lactic acid) can also be added to a douche to correct the vaginal pH and encourage the growth of lactobacillus plantarum.

Do allergies and a vitamin B deficiency cause vaginal rashes? One day the gynaecologist was really baffled by a persistent vaginal rash that was bothering a young lady. No amount of pathology could determine its cause and no anti-fungal, anti-septic, antibiotic or, corticosteroids could resolve it. I knew it had to be an allergy, but to what? She was a chef, so it could be anything. I narrowed it down to trigger foods for her blood type. Wheat was a good starting point for her blood type O. After eliminating it from her diet for a few weeks, the rash abated. Sometimes a persistent, red, burning itchy vulva can cause untold misery. Infections or even discharges may not be present.

Harsh cleansing with soap and shower gel removes the lubricating secretions from the outer labia, leaving them dry, sensitive and itchy.

Food that does not agree with you can make the body react in strange ways. Some foods or additives cause asthma, skin rashes or emotional disturbances. Rashes can also break out in the vagina. Liquid amino acid supplements may also cause a nasty rash in the vaginal area. The irritation subsides as soon as the offending substance is no longer used or consumed. Even toilet paper can cause a severe rash. Ironically, the super white, ultra-bleached brands are the worst offenders. So too, the bio-friendly rolls of paper derived from sugar-cane pulp can make one very itchy and scratchy. This was often the case with lady patients who feared they had contracted a nasty pathological 'headache'. Apply a soothing cream or gel for immediate relief. Use cotton wool with a gentle lubricant if the region is inflamed.

Dryness, contraceptives, and hormonal imbalances. Oral contraceptives can cause vaginal inflammation in some people and often deplete your riboflavin (B2) and vitamin B6. Hormonal imbalances can be responsible for occasional bleeding and spotting that may be coming from the womb (the endometrial lining of the uterus) and not the vagina. A gynecologist should attend to this problem. The body often tries to fight inter-uterine devices (IUD). An alerted immune system causes tissue inflammation, especially in the vaginal area as well as sporadic discharges of blood or heavy bleeding and cramps in the uterus. Ask your practitioner if the device can be removed or a new one can be fitted of a smaller size or different type. Raspberry leaf tea or tablets help to soothe away piercing uterine cramps. The tissue salt MAG PHOS is a good anti-spasmodic and FERRUM PHOS has an anti-inflammatory action.[1] However, like me, you may be intolerant to all types of IUD'S.

Constant dryness of the vulva is due to hormonal deficiencies during and after the menopause when the secretion of natural lubricants diminishes. I was once phoned late at night by my doctor friend as he was panicking about a patient who was allergic to KY jelly. Fortunately, I had found out how to make a natural cellulose gel and it worked wonders. With a pH of 3,5 it was very soothing; and I added a little salt. This in turn, enhanced its conductivity when used with ultrasound equipment. It also became a favorite of his for womb scanning. I introduced a variant called Wild Rose – pink with a gentle floral fragrance – but he did not get the point. "For fun, sex is to enjoy, doctor!" He nodded nervously.

Wear long flowing skirts and loose-fitting cotton underwear if you travel long distances. Tight pants were never designed to be kind to the genitals and the seams of jeans and stringy underwear can creep into the folds of the vulva. Sweat, vigorous exercise and dancing makes it worse. Adam and Eve would not have had these problems! One is more prone to infections just prior to menstruation when estrogen and progesterone levels are at their lowest or at menopause when the protective vaginal mucous is not so

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active or it becomes too alkaline. If the problem persists ask your doctor to help correct these imbalances or find alternatives such as the sweet potato method[2] that do not have adverse side effects. A dry vagina or vulva is not automatically an excuse for hormone replacement therapy. Using the sweet potato naturally raises your progesterone levels. Other herbal tinctures such as red clover and black cohosh are also helpful, according to Dr Marilyn Glenville, author of *Natural Alternatives to HRT.*[3]

Diseases

Side effects from diseases such as diabetes can give rise to severe vaginal inflammation because high levels of sugar in the urine produce more acidity than usual. Urinary acidity can be reduced with sodium citrate, calcium and magnesium supplements and the tissue salt NAT PHOS. Diabetes needs to be controlled to reduce the urinary sugar levels. Autoimmune diseases can also cause vaginal inflammation when the immune system is out of control.

Lichen sclerosus, especially, is distressing and the general treatment with steroid drugs and creams does not solve the problem.[4] Stress can trigger a major outbreak in the skin of the labia, plus the lesions can become extremely inflamed and sensitive. Taking immune boosters such as echinacea may over stimulate a sensitive immune system especially if a stressed lifestyle and nutritional deficiencies are contributing factors. Hormone levels need to be checked as levels of sex and thyroid hormones may have dropped. Food allergies and nutritional deficiencies also contribute to the severity of lichen sclerosus. Cutting out trigger foods by means of blood type parameters[5] can be helpful, and it often saves a lot of time. Antiinflammatory protocols with omega-3 supplements, multivitamins, and adaptogens are also of benefit. The Budwig combination of cottage cheese and flaxseed oil will help to strengthen the skin and has an immunomodulatory effect.[6]

Bacterial vaginosis is the most common vaginal complaint in sexually active women between the ages of 15-44. It is not identified as a sexually transmitted disease but somehow an overgrowth of bacteria causes burning, itching, odors, and a white discharge of a distressing nature. Antibiotics are generally given but do not always clear up the problem and often destroy the beneficial bacteria we call probiotics. By now we know that we need to eat more fermented foods and take probiotic supplements to improve the outcome.

Having sex with an infected partner increases the risk of contracting sexually transmitted organisms that result in vaginal disorders and can disrupt sexual enjoyment for many months or even years. Protect yourself from possible infection by insisting on the use of condoms if you are sexually active and change partners frequently.

Sexually transmitted diseases (STD) are a separate problem. They need to be identified and immediate treatment is required as some of the organisms responsible for causing them are very dangerous. They can be transmitted even before you are showing symptoms – such as vaginal burning, rashes, pustules, discharge or abdominal pain. Watch out for unexplained fevers, trembling, fatigue, depression or nausea. If you are not sure, seek professional help. Even if you cannot afford a doctor, go to your local clinic for free treatment and advice if it is available. Your sexual partner may also need attention. Professional advice is available online.[7,8]

Then, if you still have a headache, take an aspirin!

References

1. Tissue Salts: Homeopathic Uses, Benefits, and Side Effects (healthline.com)
2. The Sweet Potato Story. - Free Online Library (thefreelibrary.com)
3. https://www.goodreads.com/book/show/7901546-natural-alternatives-to-hrt
4. Lichen Sclerosus: A Roadmap to Treatment Beyond Steroids - Townsend Letter
5. https://naturefresh.co.za/?s=blood+type+diet
6. https://naturefresh.co.za/?s=budwig
7. https://www.cdc.gov/std/bv/stdfact-bacterial-vaginosis.htm
8. https://www.cdc.gov/std/treatment-guidelines/default.htm

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Losing Trust

Vaccines save lives. For Peter Aaby, MSc, DMSc, and Christine Stabell Benn, MD, PhD, DMSc, these words are a proven fact that go beyond public health dogma. Aaby, an anthropologist by training, developed a large health surveillance system that has tracked child mortality in the west African nation Guinea Bissau since 1978. Benn, a professor of global health at the University of Southern Denmark, conducts epidemiological and immunological studies of vaccines and vitamin A in Africa and Denmark that focus on overall health. These researchers have been instrumental in raising the discussion about the complexity of the immunological response to vaccinations and their non-specific effects.

For decades the assumption has been that a vaccine simply protects against a target infection. Yet, when the live standard measles vaccine program was initiated in low-income countries where death rates from measles were about 10%, all-cause mortality decreased by over 50% – not just 10%.[1] Likewise, the live oral polio vaccine increased survival rates beyond what was expected with polio prevention; and the Danish strain (but not the Russian strain) of the live Bacillus Calmette–Guérin (BCG) vaccine to prevent tuberculosis has been associated with a 38% reduction in deaths among newborns.[1]

Not all vaccines, however, show such beneficial non-specific effects. The non-live diphtheria, tetanus, and pertussis (DTP) vaccines, prevent the targeted illnesses; yet, mean all-cause, overall mortality among DPT-vaccinated children is twice as high [2.07 (95% CI 1.60-2.67)] as that among unvaccinated children. And the higher mortality rate is sex-linked; "girls have 1.47 (1.18-1.84) higher mortality than boys."[1] Other non-live vaccines – including the inactivated polio vaccine, a hepatitis B vaccine, a pentavalent (DTP, hepatitis B, *Haemophilus influenzae b)* vaccine, and the H1N1 influenza vaccine – have also been associated with higher mortality in girls than in boys.[1] The order in which vaccines are given also affects overall mortality. When the non-live DTP vaccine is given after the live measles vaccine, all-cause mortality is higher than if the live vaccine is given last.[1]

In high-income countries, where sanitation, clean drinking water, better nutrition, and access to medical care is widely available, morbidity, rather than mortality rates, indicate a difference between live and non-live vaccines. European and US studies "suggest that admission to hospital for unrelated infections may be reduced by live measles vaccine and BCG vaccine but increased by non-live DTP vaccine,"[2] according to Katie L. Flanagan, Director of Infectious Diseases for north/northwest Tasmania, and Frank Shann, who is researching non-specific vaccine effects at the University of Melbourne (Australia). These researchers and others[2] are finding that increasing survival with the help of vaccines is far more complex than simply adding another biologic product to a public health schedule.

Unfortunately, we have reached a point where *any* product labeled "vaccine" – even the new mRNA injections that, unlike traditional vaccines, instruct cells to make the spike protein antigen – are being promulgated by government agencies without discretion. These agencies are closely tied to pharmaceutical companies that manufacture vaccines. The US Food and Drug Administration (FDA) collects fees from pharmaceutical companies to review their products for government approval; "In 2017, pharmaceutical companies paid 75% ($905 million) of the agency's scientific review budgets for branded and generic drugs, compared to 27% in 1993."[3] In addition, many physicians on FDA advisory panels that evaluate drugs (and on CDC's vaccine committee) receive personal payments and/or research funding from drug companies or profit by owning stock. "'Instead of a regulator and a regulated industry, we now have a partnership,'" Dr. Michael Carome, a former US Department of Health and Human Services official and current director of Public Citizen, told ProPublica reporter Caroline Chen.[4]

Government agencies are in the vaccine business themselves. Few people realize that the National Institutes of Health (NIH), CDC, and their researchers take part in vaccine research and own patents – yet another potential for conflict of interest. CDC lists "Available Technologies for Licensing and Collaboration." The Moderna mRNA coronavirus vaccine was developed with the help of NIH researchers, which led to a patent dispute.[5] Federal employees receive royalties from drug companies for their work.

When a biologic (vaccine) gains FDA approval – or, in the case of the COVID-19 injections, emergency use authorization – the Centers for Disease Control (CDC) adds it to its list of recommended vaccines. When CDC's Advisory Committee on Immunization Practices (ACIP) recommends a vaccine, federal funds become available to buy and administer the product; and the manufacturer cannot be sued for adverse effects except in the case of fraud, as attorney Aaron Siri explained in a November 2021 interview.[6] Schools usually follow CDC recommendations and require students to receive the product – although most states permit medical and religious/philosophical exemptions. (California, New York, and West Virginia do not accept religious exemptions and restrict medical exemptions.) Clearly, CDC recommendation is the pot of gold for vaccine makers. Billions in profit and no liability.

Government agencies are not the only ones to depend on pharmaceutical money. The media receives billions of dollars from advertising pharmaceutical products.[3] Drug companies also donate millions to politicians and lobbyists. Even non-profit groups like the American Academy of Pediatrics and the Immunization Action Coalition, both of which push vaccination, receive funding from vaccine manufacturers as well as the vaccine-advocating CDC.[7] Given the amount of money being spread around, is it any wonder that questions about a vaccine's safety are ignored or even suppressed?

Even when data shows reason to be cautious or concerned, the signals are disregarded. A June 17, 2021, *NEJM* report by CDC-affiliated doctors concluded "Preliminary findings did not show obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines," and "…827 had a completed pregnancy, of which 115 (13.9%) resulted in a pregnancy loss and 712 (86.1%) resulted in a live birth (mostly among participants with vaccination in the third trimester)."[8] Yet, in a letter to the editor, Hong Sun, PhD, points out that 700 of the 827 women in the study did not receive a Covid vaccination until their third trimester (which starts week 28); 104 of the pregnancy losses occurred before week 20. As Sun explains, "The risk of spontaneous abortion should be determined on the basis of the group of participants who received the vaccination before week 20 and were followed through week 20 or had an earlier pregnancy loss."[9] Calculating pregnancy loss rate with a denominator of 127 or less (instead of 827) puts the spontaneous abortion rate at ≥81.9%, well above the published incidence of 10-26%. Yet, CDC and public health agencies have used this study to recommend mRNA vaccination for all pregnant women, regardless of trimester.

In a letter to *BMJ*, Christine S. Benn and Peter Aaby point out a discrepancy between the conclusion of a Pfizer-sponsored, randomized, phase 3 trial of its BNT162b2 COVID-19 vaccine involving 2260 adolescents and the study's data.[10] The conclusion says the vaccine "had a favorable safety profile." Data in supplementary table 2, however, showed an increase in severe adverse events in both the 12-15 years age group and the 16-25 years group: "The combined results indicate a 3.28 (95% confidence interval 1.21 to 8.94)-fold increased risk in severe adverse events in the vaccinated adolescents/young adults. In absolute numbers, 1 of 100 vaccinated experienced a severe event, vs. 3 of 1000 unvaccinated."[10] These long-time vaccine advocates explain that natural immunity may be a better choice than vaccination for children.

Among the Pfizer Covid vaccine documents released by the FDA, in response to a lawsuit, 25,957 adverse events involving the nervous system were reported through February 21, 2021 – two and a half months after the vaccine's emergency use authorization. Yet, Pfizer wrote to FDA, "'The findings of these signal detection analyses are consistent with the known safety profile of the vaccine.'"[11] What, exactly, does that mean?

Clinicians, like ICU physician and surgeon Patricia Lee, have reported serious COVID-19 vaccine-related injuries, including transverse myelitis, cerebral venous sinus thrombosis, and organ failure, to FDA, NIH, and CDC and had their concerns ignored.[12,13] At a press conference[14] and a public expert hearing,[15] patients enduring ongoing adverse neurological and cardiac disorders after COVID-19 vaccination – some of whom are doctors – relate how difficult it is to get help, largely because agencies have not told practitioners that injury is possible. Healthcare workers who are too public about injuries are smeared as being "anti-vax" and risk losing their jobs.

And there are even bigger questions about using mRNA technology to create more vaccines, questions raised by Robert Malone, MD, who pioneered mRNA technology, by virologist and vaccine expert Geert Vanden Bossche, DMV, PhD, who worries about mass vaccination during a viral pandemic,[16] and by Stephanie Seneff and Greg Nigh, whose review article appeared in the December 2021 issue of *Townsend Letter.* But like vaccine injury, these questions and concerns are ignored or censored. And if the authors gain too much attention, *The Atlantic, New York Times,* or other corporate media outlet publishes an *ad hominin* "hit" piece with "anti-vax" in the headline to discredit them and deflect attention from the questions.

The perjorative term "anti-vax" has become a primary weapon to disparage and nullify any person who raises questions about any biologic product labeled "vaccine." Only a very small percentage of the population is truly against the use of vaccines for any reason. Many become skeptical because they have seen a vaccine's ineffectiveness or injury in a family member or experienced it themselves. Others become skeptical when they do a deep investigation into the rampant conflicts of interest, corruption, and skewed studies that lead to their use. As attorney Aaron Siri wrote:

> According to mainstream media, if you raise questions about the safety of COVID-19 vaccines – anti-vaxxer! If you raise questions about the efficacy of this vaccine – anti-vaxxer! If you question FDA, CDC, or White House guidance on this vaccine – anti-vaxxer! If you want pharma companies to be liable for vaccine injuries – anti-vaxxer! If you want long term placebo-controlled trials prior to licensure – anti-vaxxer! If you raise concerns about breakthrough cases – anti-vaxxer! If you think natural immunity has anything to offer without a vaccine – anti-vaxxer!!![17]

Moreover, anyone who believes in health freedom to choose and opposes vaccine mandates – even if they personally get every vaccine available – is an "anti-vaxxer," according to the Merriam-Webster dictionary.

Benn and Aaby rightly believe that vaccines can be used to save lives. But the highly compromised regulatory agencies, the heavy censorship that prevents debate and transparency, and the smear campaigns against anyone willing to ask questions are enough to make a person cautious. Hiding problems and widespread propaganda campaigns will never increase confidence in a vaccine. Indeed, obfuscation will undermine trust in public health.

Jule Klotter

References

1. Benn CS, et al. Vaccinology: time to change the paradigm? *The Lancet.* October2020; 20:e274-e283.
2. Aaby P, et al. The non-specific and sex-differential effects of vaccines. *Nature.* August 2020; 20:464-470.
3. Children's Health Defense. The FDA, CDC, Media and Politicians Receive Money from Vaccine Makers. January 26, 2021. https://childrenshealthdefense.org/vaccine-secrets/video-chapters/the-fda-cdc-media-and-politicians-receive-money-from-vaccine-makers/
4. Chen C. FDA Repays Industry by Rushing Risky Drugs to Market. ProPublica. June 26, 2018.
5. Tin A. Moderna offers NIH co-ownership of COVID vaccine patent amid dispute with government. CBS News. November 15, 2021.
6. Meet ICAN Attorney Aaron Siri. *The Highwire.* November 1, 2021.
7. Doshi P. The unofficial vaccine educators: are CDC funded non-profits sufficiently independent? *BMJ.* 2017;359:j5104.
8. Shimabukuro TT, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *New England Journal of Medicine.* June 17, 2021;384(24):2273-2282.
9. Sun H. On Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. NEJM.org. September 8, 2021.
10. Benn CS, Aaby P. Should COVID-19 be a vaccine disease or a childhood disease? *BMJ.* July 9, 2021.
11. Siri A. FDA Produces the First 91+ pages of Documents from Pfizer's COVID-19 Vaccine File. November 19, 2021.
12. Siri A. Whistleblower: FDA and CDC ignore reports of serious COVID-19 vaccine injuries from highly credentialed pro-vaccine ICU physician. October 12, 2021.
13. Siri A. One Brave ICU Physician Reporting Covid-19 Vaccine Injuries Leads to a Dozen More. November 1, 2021.
14. Fox6 News Milwaukee. Sen. Ron Johnson with families on adverse reactions to COVID vaccine. YouTube. June 28, 2021.
15. Full Hearings – Ron Johnson's Expert Panel on COVID Vaccine Injuries. https://brandnewtube.com. November 2, 2021.
16. Vanden Bossche, G. To all authorities, scientists and experts around the world, to whom this concerns: the entire world population. March 6, 2021. Available at www.reddit.com.
17. Siri A. A Majority of Americans Are "Anti-Vaxxers"? November 21, 2021. ◆

Ask Dr. J

by Jim Cross, ND, LAc
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Diabolically Metabolical

Let's face the undeniable facts: humans are the only species clever enough to make their food, mindless enough to poison that very same food, and then myopic enough to actually eat it. Robert Lustig, MD, retired professor of pediatric endocrinology at UCSF, intricately expounds on the above point in his 2021 book, *Metabolical: The Lure and the Lies of Processed Food, Nutrition, and Modern Medicine* (HarperCollins, 2021). His book basically demonstrates what food can do for health versus what the food industry undeniably does for disease through its manipulation and adulteration of various foods that are initially grown on farms.

Dr. Lustig also makes an incredibly powerful statement in the book: "Food is the only lever we have to affect biochemical change in order to improve our health and to affect political change in order to improve our economy and environment." He understands that it takes more than just a willingness to alter the food we imbibe. We also need to use the purchasing power of food to alter how it is grown, processed, moved, and sold. I firmly believe that true change in our eating choices must also include a political alteration, which will be overall much harder to successfully achieve.

Dr. Lustig makes any number of impressive points in his book. Space allows for only the ones I found overly exceptional. First, he states that "he learned nutrition in college and then unlearned nutrition in medical school." He calculates that in four years of medical school, students receive on average 19.6 hours of class time in nutrition, which averages out to a stunningly low 0.27% of their class time. This lack of educational nutrition would seem to explain why most doctors have no interest or expertise in utilizing nutrition in their practices.

He also feels doctors and medical students are exposed to a biased point of view. Dr. Lustig makes a point similar to Dr. Marcia Angell in her deeply researched book, *The Truth About the Drug Companies*: pharmaceutical companies have their tentacles entangled in every aspect of medicine. He cites, as an example, a metanalysis on the relationship between sugar and obesity where 26 studies sponsored by food companies found no connection between sugar and obesity whereas 33 independently funded studies did. The 26 industry studies are also the ones that made it into major medical journals and helped allay any unsuspecting doctor's fears about obesity stemming from excess sugar (Readers of the *Townsend Letter* and my articles will also understand that sugar is only one tiny part of the complex obesity puzzle.).

The next Lustig point is that while what most Americans eat looks like food, tastes like food, and maybe even tastes better than food, in reality, it is a plate of gastronomical poison. Unlike Salmonella which quickly causes severe abdominal pain and diarrhea, junk food presents itself as a slow poison, like cigarettes. Even if you copy Morgan Spurlock and eat at a fast food restaurant every day for a month, you won't have developed an obvious case of heart disease or cancer. You are laying the groundwork in your internal milieu for that chronic disease, but manifestation will be far into the future.

Basically, industrial agriculture has slowly morphed from what was once real food into a slow-acting poison that will leisurely erode the weak constitutional organs in your body until a chronic disease manifests itself. It's more than what's in the food that is the core issue. It's what's been done to the food. "You are what you eat" has morphed into "you are what they did with what you eat."

Our next super Lustig point revolves around his contention that obesity is only a red herring. Is obesity the problem or the symptom? He claims that up to 80% of obese individuals were metabolically ill before they became obese. To quote Dr. Lustig: "metabolic syndrome is the inappropriate storage of energy in the wrong form in cells that shouldn't store them." He is proposing, then, that metabolic syndrome occurs first, leading to insulin resistance, which then segues into obesity. This makes perfect sense as only muscle cells become insulin resistant, not fat cells. This culminates in excess fat and sugar

being stored in fat cells. He empirically proved this point at UCSF where the majority of his obese pediatric patients only began to lose weight after their insulin levels started to drop.

Lustig Super Point #4 tries to establish the fact that the cause of various chronic diseases in Americans are diseases that aren't listed as diseases in a medical pathology book. Cells are true magicians, but they will begin to become dysfunctional over time if exposed to the following eight processes: glycation, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, membrane integrity, epigenetics, and autophagy.

Readers of *Townsend Letter* will recognize all eight of the above factors and their contributions to any chronic disease. Essentially, if the above eight factors are optimally working, this will lead a person on a path to longevity and good health. If they function suboptimally, a person will endure a life fraught with vague, debilitating symptoms that will slowly worsen and contribute to a life not well lived.

Finally, Dr. Lustig asks the question: what does "healthy" really mean? He feels that the key to fending off all chronic diseases lies in optimizing the eight subcellular processes above. For him, there are two mantras that must be addressed for this to occur: Protect the Liver; Feed the Gut.

Protecting the liver requires preventing hepatic fat accumulation, protecting against oxidative damage, and nipping insulin resistance in the bud. Feeding the gut follows Dr. Walter Crinnion's dictum: feed them and they will come. I'm not going to go into detail on possible treatments for either of his assessments as this has been beaten into submission by many *Townsend* articles. What I will say is that it feels like these two courses of action have been substantiated by a large reservoir of research and are a good beginning cornerstone for patients to begin their long healing journey of whatever chronic disease happens to occupy their bodies.

As a final Lustig point, we have laws for two killers in American society, alcohol and tobacco. Unfortunately, there are no laws limiting, eliminating, or regulating processed or junk food. Our politicians have made sure of that. One of the only paths leading to change is for health care providers to bring up this information to their patients and emphasize how important altering their lifestyle and food choices are to their personal and family health plus environmental health, which of course dovetails back onto more optimal personal health.

Dr. Lustig also makes a comment along the line of no matter what he says, he always pisses someone off. For me, that is most definitely a reason to enter into a dialogue with patients or people I encounter in life. If I have shaken their safe, comfortable, uneducated box that they live in, awesome! Next, I must engage them in a deep conversation concerning the above. If I accomplish this, I have probably a 90% success rate in convincing them that my recommended changes will make them feel 100% better and save them a ton of money in the long run. So, don't be bashful, engage your patients in meaningful conversations. It is one of the only ways that consequential and worthwhile change will happen in our small universe. ◆

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

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.

New Column

The Lobay Viewpoint

by Dr. Douglas Lobay, BSc, ND
douglobay@gmail.com

The Basil Meikle Social Club

What if I told you that I discovered a drug that would add 9.7 years to your life? What if I told you the drug was free, and I would forego my royalties of billions of dollars and give away the medicine? What if I told you that the drug was actually a simple and active lifestyle that could improve longevity dramatically? Welcome to the Basil Meikle Social Club.

The Basil Meikle tennis courts are a group of six public tennis courts located in the center of the city of Kelowna where I live and practice naturopathic medicine. The courts are named after Basil Meikle, who was the son of a prominent pioneering family who operated a land and orchard business in Kelowna from the 1930s onward. Basil was a championship badminton player who passed away tragically in 1975 in a boating accident on Okanagan Lake. The courts are named in honor of him. The courts are also colloquially known as the Parkinson's courts as they are just behind the Parkinson's Recreation Centre. And this is where I play tennis most Saturday and Sunday mornings during the late spring, summer and early autumn months with a group of friends.

The group is a loose cadre of twenty or thirty middle-aged and older individuals who want to play mostly doubles tennis with like-minded players of similar caliber. The group is fairly informal with the occasional email about start times. The skill level of the group is similar and is probably between 3.0 and 4.0 tennis rating standards. If you want to play, you show up and play. There is no membership fee, drop-in charges, and no sign up to play. Doubles tennis is the majority of the play with many players passed their prime, but who still have a passion for the game. There is an unwritten code of conduct and behavior. You play fair and you behave yourself. If there are more than four players per court you rotate after every game with the server going off and a new player coming in. The tennis is fun and can be competitive. Over the years I have played a lot of tennis with this group. I will be the first to admit that my competitive days of tennis are probably over. My knees can get sore and my single days are behind me now. However, I still enjoy the game, have fun, like being outside, and like to adapt to the challenge of playing different players.

I also enjoy the social interactions associated with doubles tennis play. After playing the same players over time you get to know them a little. You observe, examine and scrutinize their style of play. You discover their habits: how they serve, how they hit their forehand or backhand, how they move, and the general patterns of their play. You learn to read them and adjust your play accordingly. I enjoy the social camaraderie and the talking between play. Of course, there is the usual tennis banter and jousting that occurs between players. There can be light-hearted comments about the play or match. You can tease another player, but never out-rightly put them down or embarrass them. You also talk about other things in life. You talk about work, family and activities outside tennis. Over the years, you get to know players beyond their tennis play. Sometimes they open up and tell you things, about what is occurring in their lives. They share private intimate details and through innuendo you can read between the lines about what is going on. At the Basil Meikle tennis courts, I have met a lot of interesting people, with different jobs and from vastly different walks of life who are committed to playing group tennis.

Minh, who tries hard and loves the game, is the originator and organizer of the group. Tony is an immigrant from Ecuador who has the hand of a skilled soccer player and who is generous with his positive comments. Another Tony is a younger and quiet player with pretty good skill who rushes his play sometimes. Martin, a husky accountant with pretty good dexterity who shares with me a passion of playing acoustic guitar. Young Patrick is a tall and slender alternative thinker who plays the game with a controlled fluidity. Old Patrick is close to 80 years but plays and moves like a man thirty years his junior. Harold is a retired firefighter who can play with bursts of brilliance or bouts of mediocrity. Sepp is a former Austrian ski champ whose body is getting older than his mind. Steve is a quiet, steadfast Croatian player who equally matches my ability and play on any given day. Leo is a short, but very fast Turkish player who makes up his lack of strength with his speed. Andis is a university professor who plays the game with a cerebral and analytical temperament. Duane is a self-defeating IT expert who moved here from Calgary and is fast and loves playing the game. Dave is a plumber who plays with a wicked slice and periods of inattention. Bruce is a Hawaiian transplant who rides his fat tire mountain bike everywhere, plays ukulele and always seems to be happy on the courts. Ron is a smart and recently

retired general practitioner who is a smart player with a good serve and has pretty good hands. Larry is a relocated anesthesiologist from Toronto, who makes up for his lack of skill with unbridled exuberance for the game. Thomas is a retired businessman and mushroom farmer from Vancouver who is deceitfully skilled with his spin shots. Al is a retired pilot who has a big, strong forehand, but is a bit slower in his response to the short shots. Frank is a retired Italian soccer player whose failing eyesight lets him down on the courts. Cathy is one of the few female associates of the group who usually plays strong and is usually happy and positive. There is also a robust collection of part-time players that include Charlie, Chris, Kim, Geoff, Peter, Nigel Alex, Reiko, Colin and others that belong to the Basil Meikle tennis group.

Lifetime participation in sports, such as tennis, provide health benefits such as a lower risk of cardiovascular disease, obesity and depression. Compared to non-participants greater than 45 years of age, active participants reported being in good or better health, had lower levels of obesity, and lower levels of cardiovascular disease compared to sedentary non-participants.[1]

In a prospective study to assess the effect of mortality with different types of physical activity, a group of 13,375 males and 17,265 females were randomly selected and were followed for an average of 14.5 years. Level and type of physical activity were assessed by self reporting and periodic examination. The main outcome was the effect of physical activity on all-cause mortality. Leisure time physical activity was inversely associated with all-cause mortality in both male and females in all age groups. Benefit was found with moderate leisure time physical activity as well as decreased all-cause mortality for all sport activities and cycling as a mode of transportation to work.[2]

The Copenhagen City Heart Study was a large prospective study of the incidence of cardiovascular disease in 19,329 people; 9145 were male and 10184 were female, between 20 to 93 years of age. The study investigated the association between physical exercise and all-cause mortality. The study found that it was not the duration of physical activity, whether it was cycling or walking, but the intensity of exercise that was important for reducing mortality. A "U" shaped effect was noted with mortality increasing for both a sedentary lifestyle with no exercise and also too much, intense exercise. Slow jogging at a duration of less than 2.5 hours duration and a frequency of three times per week showed the best effects on lowering all-cause mortality. Also those who jogged greater than four hour duration more than three times per week appeared to lose their health benefits.[3]

A further investigation in the Copenhagen heart study looked at the association between persistence and non-persistence in leisure time activity on coronary heart disease and all-cause mortality in 12,314 participants for 33 years. Compared to a sedentary lifestyle, light activity showed a hazards ratio or HR of 0.76, moderate activity showed a HR of 0.52 and high level activity showed a HR of 0.51. This translated to an increase in longevity of 2.8, 4.5 and 5.5 years for each group respectively. Overall, an increase in the level of physical activity that was persistent was associated with a decrease in cardiovascular disease. Also, a decrease in physical activity or non-persistence was associated with a corresponding decrease in longevity.[4]

A subset of the Copenhagen heart study evaluated the differential improvements in life expectancy associated with participation in various sports. A group of 8,577 participants were followed for twenty-five years to March 2017. Multi-variate adjusted life expectancy was calculated using statistical analysis and was compared to the no exercise or sedentary group. The results were as follows: Tennis showed the best improvement in longevity with an average increase in 9.7 years. Badminton showed a 6.2 year increase, followed by soccer at 4.7 years, cycling 3.7 years, swimming 3.4 years, calisthenics 3.1 years and health club activities at 1.5 years. The investigators were quick to point out that this study showed an association and no firm causal relationship was proven. The investigators further surmised that the difference in life expectancies with different sports may have to do with an increase of social activity of the specific sport. That is, those sports with the highest level of socialization showed the greatest increase in life expectancy. In this study, tennis was the clear winner and extended life expectancy by a staggering 9.7 years compared to a sedentary, no exercise lifestyle.[5]

A prospective study of 80,306 Scottish and English cohorts examined six different exercise and sports in relation to all-cause mortality and cardiovascular disease. Fifty-four percent of the group were female and the mean age was 52 years plus or minus 14 years. The hazard ratio or HR of all cause mortality for racquet sports was 0.53 with a 95% confidence interval between 0.40 and 0.69. The HR for cycling was 0.85, swimming was 0.72, aerobics was 0.73. No difference in HR was calculated for European football and running. The hazard ratio for mortality due to cardiovascular disease was 0.44 for racquet sports with a 95% confidence interval between 0.24 and 0.83. The hazards ratio for swimming was 0.59 and 0.64 for aerobics. No significant difference in hazard ratio was observed in cycling, running, and soccer.[6]

A study among four-year college students examined the cross-sectional association between vigorous physical activity and mental health, perceived stress, and socialization. A cohort of 14,804 undergraduate college students were recruited for this study. Self reporting of vigorous physical activity, perceived stress, mental health and socialization was undertaken. The effect of vigorous activity on poor mental health was associated with an odds ratio (OR) of 0.79. The effect of vigorous exercise and perceived stress showed an OR of 0.75. The researchers concluded that physical activity helps improve mental health and levels of perceived stress and can help improve social interactions.[7]

The role of physical activity was studied against stress-related mental issues in a small group of college students. Forty-two undergraduate college students, of which 22 were female and 20 were male, were involved in this study. Vigorous physical activity was associated with a lower incidence of stress-related problems and better overall levels of mental health. Vigorous physical activity improved physiological and psychological stress resilience among these college students. Better levels of adaptation and coping skills to perceived stress was noted with vigorous physical activity. Participants also reported improved sleep patterns. Increased total sleep time, more stage 4 and REM sleep, and better overall sleep quality.[8,9]

The results are clear. Physical activity can decrease the incidence of all-cause mortality and cardiovascular disease and increase longevity and physical and mental well being. Those activities or sports with a higher degree of social interaction show the most benefit in reducing mortality and improving longevity. Sports like tennis show the greatest decrease in all-cause mortality and highest increase in longevity. So get active.

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Basil Meikle Social Club

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It is late November in Kelowna and it snowed yesterday, Minh sent a text that play begins an hour later than usual. Some diehard players take snow shovels and other ice and snow removal apparatus to the tennis court. They continue to play right through winter. I take a little bit of time off through the winter months. If the courts are clear I will play. If they are covered with snow or ice, I don't play and do another activity like swimming, cross country skiing or skating. I realize I am lucky to belong to the Basil Meikle social group and grateful for the friendships that I have developed there over the years. Tennis and other forms of physical activity can be strong drug and powerful elixir for health and longevity. Play on.

References

1. Spring KE et al. Long-term Tennis Participation and Health Outcomes: An Investigation of "Lifetime" Activities. *Int J Exerc Sci*. 2020 Sep 1;13(7):1251-1261.
2. Andersen LB et al. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. *Arch Intern Med*. 2000 Jun 12;160(11):1621-8.
3. Aguib Y and Al Suwaidi. The Copenhagen City Heart Study (Osterbroundersogelsen). *Glob Cardiol Sci Pract*. 2015;2015(3):33.
4. Schnohr P et al. Impact of persistence and non-persistence in leisure time physical activity on coronary heart disease and all-cause mortality: The Copenhagen City Heart Study. *Eur J Prev Cardiol*. 2017 Oct;24(15):1615-1623.
5. Schnohr P et al. Various Leisure-Time Physical Activities Associated With Widely Divergent Life Expectancies: The Copenhagen City Heart Study. *Mayo Clin Proc*. 2018 Dec;93(12):1775-1785.
6. Oja P et al. Associations of specific types of sports and exercise with all-cause and cardiovascular-disease mortality: a cohort study of 80 306 British adults. *Br J Sports Med*. 2017 May;51(10):812-817.
7. Vankim NA and Nelson TF. Vigorous physical activity, mental health, perceived stress, and socializing among college students. *Am J Health Promot*. Sep-Oct 2013;28(1):7-15.
8. Gerber M et al. Increased objectively assessed vigorous-intensity exercise is associated with reduced stress, increased mental health and good objective sleep in young adults. *Physiol Behav*. 2014 Aug;135:17-24.
9. Weyerer S and Kupfer B. Physical exercise and psychological health. *Sports Med*. 1994 Feb;17(2):108-16.

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CALENDAR

JANUARY 27: 2nd INTERNATIONAL CONFERENCE ON CONTROVERSIES IN NEUROPATHIC PAIN online. CONTACT: https://neuropathic-pain2022.com/registration/

FEBRUARY 4-5: GPL MASTER PRACTITIONER WORKSHOPS live online. Also, **JUNE 10-12.** CONTACT: https://www.gplworkshops.com/

FEBRUARY 25-27: A4M/MMI BIO-IDENTICAL HORMONE REPLACEMENT THERAPY SYMPOSIUM in Nashville, Tennessee. CONTACT: https://www.a4m.com/bio-identical-hormone-replacement-symposium-a4m-2022.html

FEBRUARY 25-27: A4M/MMI MODULE – GASTROENTEROLOGY: THE CROSSROADS OF HEALTH in Nashville, Tennessee. CONTACT: https://www.a4m.com/module-iv-a4m-2022.html

FEBRUARY 25-27: A4M/MMI MODULE 1 – Peptide Therapy Certification in Nashvile, Tennessee. CONTACT: https://www.a4m.com/peptides-certification-module-i-2022.html

FEBRUARY 25-27: A4M/MMI MODULE VI – Clinical Strategies to Optimize Metabolic Resilience, Immunocompetence, and Biotransformation (Part A) in Nashville, Tennessee. CONTACT: https://www.a4m.com/module-vi-a4m-2022.html

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

FEBRUARY 26: 2022 VANCOUVER NATUROPATHIC CONFERENCE – Naturopathic Approaches to Pediatric Mental Health online. CONTACT: http://www.collaborativeeducation.ca/pediatricmentalhealth/

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

MARCH 4: KETOGENIC DIETS IN PSYCHIATRY – FAD AND FACTS online. CONTACT: https://www.psychiatryredefined.org/ketogenic-diets-in-psychiatry-conference/

MARCH 4-6: EXPANDING THE CLINICAL TOOLBOX FOR PATIENTS WITH COMPLEX, CHRONIC ILLNESS online. CONTACT: https://forumforintegrativemedicine.org/

MARCH 4-6: 10th ANNUAL INTEGRATIVE MEDICINE CONFERENCE – Planetary Health to Human Health: Strategies and New Insights online. CONTACT: http://cim.med.miami.edu/clinical-nutrition/annual-conference/

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

MARCH 25-27: SOUTHWEST CONFERENCE ON BOTANICAL MEDICINE online. Botanicals for acute panic disorder, insomnia, frailty in elders, nurturing GI microbiota, herpes/shingles, multiple drug resistance, opiate use disorder and more. CEUs. CONTACT: www.botanicalmedicine.org

MARCH 25-27: GPL ENVIRONMENTAL TOXIN SUMMIT live online. CONTACT: https://www.gplworkshops.com/

APRIL 3-10: ANTHROPOSOPHIC THERAPEUTIC FOUNDATIONS TRAINING CONFERENCE – Physical, Functional, Emotional, Spiritual in Watsonville, California. CONTACT: https://www.anthroposophicmedicine.org/annual-training-week

APRIL 8-10: CARDIOMETABOLIC HEALTH CONGRESS – Great Debates in Cardiometabolic Medicine in Scottsdale, Arizona. CONTACT: https://www.cardiometabolichealth.org/cmhc-spring-2022/

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

APRIL 21-24: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING for Doctors, Dentists, & Health Professionals with Simon Yu, MD, in St. Louis, Missouri. Detecting parasites, Dental and Fungal. CONTACT: 314-432-7802; https://preventionandhealing.com/training/

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

APRIL 23-24: 2022 TORONTO NATUROPATHIC CONFERENCE – Frontiers in Naturopathic Medicine online. CONTACT: http://www.collaborativeeducation.ca/toronto-naturopathic-conference/

APRIL 28-30: A4M SPRING CONGRESS – Eat, Fuel, Health: Nurturing the Second Brain in Hollywood, Florida. CONTACT: https://www.a4m.com/

APRIL 28-30: A4M/MMI MODULE – Advanced Endocrinology: The Hormonal Symphony in Hollywood, Florida. CONTACT: https://www.a4m.com/module-i-a4m-2022.html

APRIL 28-30: A4M/MMI MODULE – Triads: A Systems Biology Approach in Hollywood, Florida. CONTACT: https://www.a4m.com/module-v-a4m-2022.html

APRIL 29-30: CONNECTING THE DOTS IN CARDIOMETABOLIC MEDICINE Integrative Approaches to Improve Patient Care in Hollywood, Florida. CONTACT: https://www.cardiometabolichealth.org/

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

MAY 6-8: INTERNATIONAL CONSORTIUM ON MANUAL THERAPIES CONFERENCE 2022 in Phoenix, Arizona and online. https://www.icmtconference.org/

MAY 12-14: ASSOCIATION FOR THE ADVANCEMENT OF RESTORATIVE MEDICINE SPRING HERB SEMINAR online. CONTACT: https://restorativemedicine.org/conferences/2022-spring-herb-seminar/

MAY 23-26: INTERNATIONAL CONGRESS ON INTEGRATIVE MEDICINE AND HEALTH in Phoenix, Arizona. CONTACT: https://www.consortiumcongress.org/

JUNE 2-4: IFM ANNUAL INTERNATIONAL CONFERENCE in Dallas, Texas. CONTACT: https://www.ifm.org/learning-center/

JUNE 3-6: MEDICINES FROM THE EARTH HERB SYMPOSIUM in Black Mountain, North Carolina. Botanicals for resetting circadian rhythm, targeting VEGF in cancer treatment, geriatric mental health, long-term drug use, and more. CEUs. CONTACT: www.botanicalmedicine.org

JUNE 25: KEY COLLABORATIONS IN HOMEOPATHY RESEARCH online. CONTACT: https://www.hri2022.org/

AUGUST 25-28: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING for Doctors, Dentists, & Health Professionals with Simon Yu, MD, in St. Louis, Missouri. Detecting Parasites, Dental & Fungal. CONTACT: 314-432-7802; https://preventionandhealing.com/training

OCTOBER 28-29: INTERNATIONAL CONFERENCE ON PREVENTIVE MEDICINE AND INTEGRATIVE MEDICINE in Los Angeles, California. CONTACT: https://waset.org/preventive-medicine-and-integrative-medicine-conference-in-october-2022-in-los-angeles

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Pediatric Pearls

by Michelle Perro, MD

Present Challenges in Immune Health in Teens

Upon the introduction of genetically modified food-like products (GMOs) into our diets, the wary *Townsend Letter-reading* practitioner was on an all-systems-alert as to the potential hazards of these novel, unidentified proteins into the naive tummies of our children. Along with the rising levels of associated pesticides applied to these herbicide-tolerant crops, the concerns were validated as children developed a subsequent massive rise in gut disorders such as gastroesophageal reflux, abdominal pain/constipation, intestinal permeability, and dysbiosis. These changes have created a new baseline of immunologic mayhem for kids, with an unregulated state of chronic inflammation as a baseline. GMOs 2.0 (CRISPR/gene editing) ushered in an even more chilling scenario with an ominous casual lack of rigor and study regarding the potential effects of these new industrialized foods on health. The majority of eaters are unaware of the potential immunologic dysregulation awaiting them with each forkful eaten at the dinner table.

With the knowledge that GMO foods produce harm, the illogical next step followed, which is the injection of genetically engineered products into our children to create an immunologic response (from a non-threatening pathogen). The appropriate response should be 'abort mission'. Instead, the government has decided that an experimental gene therapy with documented harm should now be administered to children and teens with the pending introduction into babies. The CEO of one of the manufacturers of these products, Albert Bourla of Pfizer, himself noted that indeed they are "gene edited products" in his conversation with the Atlantic Council. Instead of 'abort mission', we have pursued the path of injecting experimental mRNA therapies surrounded by nanoencapsulated PEG-containing mRNA biospheres into our children. This may have been the straw on the camel's immunologic back.

The larger question is how these impacts might manifest in the clinical setting. Two of my recent patient visits underscore how unprecedented changes in immune function may present in the post-CoV-2 injection era. On the same afternoon, two different young women had clinic visits via Zoom with an almost identical presentation. Both women were 18 years old and recently began college, living in a dorm setting. They both reported persistent infections that they were unable to clear despite all the usual modalities. This was unusual as per both patients. Sarah had developed chronic sinusitis that would not clear despite a course of amoxicillin-clavulanate antibiotic and some supplement support with vitamins C and D after two months. The second patient, Anya, had a rattling cough that persisted several months, also treated with an antibiotic and a homeopathic cough formulation. Both gals were otherwise healthy, reported no other underlying medical conditions and claimed to eat well (although this may be dubious in a college setting). The only other similarity was that they had both received their second Pfizer vaccination one month prior to entering college as a mandatory requirement for in-person attendance at their respective colleges. Both women reported significant side effects after the second shot mostly consisting of headache and malaise. Of interest, both women also reported that although they felt "better," neither felt as good as they felt prior to the injection.

Pre- and post-CoV-2 era has changed my practice of medicine. My suspicion is that the vaccine is responsible for impairing part of the immune system, but how that may happen is not clear. Is the spike protein causing secondary damage? How quickly should it have been broken down? What is the effect of the spike protein on bone marrow since it has an affinity for fatty tissue, and subsequent production of immune cells? Scanning the literature did not provide any solid studies showing the effects of the mRNA injection on subsequent immune function. However, many experts have spoken out regarding injection toxicity such as Dr. Ryan Cole and his demonstration of the vaccine effects in autopsies.[1] Dr. Robert Malone, inventor of mRNA technology, raised serious concerns regarding mRNA vaccinology,[2] and the former Pfizer VP, Michael Yeadon reported on the dangers of the mRNA injections as well.[3] These are just a few of the many experts sounding alarms regarding the long-term side effects of this genetically engineered technology. It is important to note that a search on the internet would not have revealed any of these sources and only a savvy or questioning reader could figure out the sites where this information could be gleaned.

Back to the clinical drawing board…

While both patients had different infections and organ involvement, there was an apparent similarity regarding their baseline health, development of a persistent infection, and a

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history of the recently administered Pfizer shot. Other factors were also considered such as their new environments/diets and stress being additional determinants. These issues were also taken into consideration. Despite my suspicions, I could not 100% confirm how much of the injection played into their issues if at all. However, due to a significant number of teens reporting unusual health symptoms post jab in the office, my radar was up. The treatment formulation created was based on the idea that a multi-pronged integrative approach would be their best option. Therapeutic goals included the following:

- Reduce possible bacterial/concomitant viral load
- Support immune function
- Bolster the microbiome
- Enhance nutrition
- Decrease stress

Because of their location, lack of the support they would have had at home, and somewhat limited finances, I created a cost-effective approach that would also be partially covered by their insurance plans.

Reduce possible bacterial/concomitant viral load. I prescribed azithromycin, the usual prescribed dosing for both gals, since it has been reported that it might have a chloroquine-like effect on respiratory epithelial cells via modulation of the pH of endosomes.[4] The thinking was that if there was a spike-protein involvement in their illness, azithromycin could have a dual-benefit. Because of pharmacy restrictions, obtaining other potential spike-protein binding drugs was nearly impossible.

Support immune function. I added *Andrographis paniculata*, a common Chinese medicine and Ayurvedic herb known to have antiviral, anti-inflammatory, and antioxidant properties, 400 mg two times a day. A meta-analysis of 33 studies published in 2017 showed that Andrographis was beneficial for relieving upper respiratory infections.[5] Additionally, I added NAC, 900 mg daily and selenium, a component of antioxidant glutathione reductase at 200 mcg daily. I have found that in addition to its antioxidant capabilities, selenium also can boost both innate and adaptive immunity. Selenium would not have been one of my regular 'go-to' supplements in the past. However, it has been found that it can be a key nutrient in fending off the development of viruses.[6] In the case of my two patients, I suspected there may have been multiple organisms involved.

Bolster the microbiome. Not wanting to wipe out their microbial flora (which they already had and I was about to induce further harm), I began *Saccharomyces boulardii* to prevent *Clostridium difficile* overgrowth, and a probiotic containing strains of *Lactobacilli rhamnosus, L. plantarum* and various *Bifidobacteria* species daily ongoing. *L. plantarum* PS128 has become one of my favorite probiotics to include due to its effect on stress and mental health.[7]

Enhance nutrition. This may have been one of the hardest aspects to cover consider that they were both eating college food, which was not organic and carbohydrate heavy. I decided that the best thing I could do was to add an organic supplement that they could easily mix up, containing protein and a green superfood powder.

Decrease stress. To start off a new college, first semester, sick for the first two months and not have the usual support systems in place created additional stressors for both of these patients. A discussion ensued on how best we could optimize their care while they recovered. A call to both of the RAs in their dorms provided the additional support they needed. Also, letters to their academic advisors creating modified academic work schedules while they recovered also provided a sigh of release for both Sarah and Anya.

I would still like to believe in happy endings, unicorns, and fairies, but as we all know not everyone responds to our best efforts. Sarah, the patient with sinusitis, had to take a leave of absence and come home for the rest of the semester while recovering. However, Anya, the patient with a persistent cough, got better within two days of treatment and is back to her base line even several months later.

A persistent question in my mind is whether children will be able to navigate the usual course of pathogens they encounter having been subjugated to experimental gene/immune altering therapies. It is clear that there should be an immediate cessation of gene-edited injectables until quality, unbiased research is performed. However, there are many teens who have already been subjected to this live experiment and may need on-going support. Practitioners should consider in addition to recommending their usual protocols, the addition of some of the following supplements to increase NK cells, which can fend off CoV-2 as well as other viral infections:

- Turmeric
- Ginseng
- Resveratrol
- Andrographis
- Vitamin C
- Glutathione
- NAC, Vitamin E, alpha lipoic acid
- Garlic
- Echinacea
- Ashwagandha
- Medicinal mushrooms (i.e., Reishi and cordyceps)
- Probiotics (*S. Boulardii*)

In sum, genetically engineered products have been released not only in our food supply, but also as mandatory injectable medicinals in children without adequate health assessments. This has occurred with the understanding that recapture is impossible. The looming question is how will these gene therapies ultimately affect our children? In April of 2021, a chilling direct quote from the financial statement from BioNTech (Pfizer's partner) regarding the "CoV-2 vaccine" made a confirming declaration: "*mRNA therapies are classified as gene therapy medicinal products"*; so by the company's own admission, children are being administered yet another gene therapy, not a vaccination, without any investigation of the health sequelae.[8]

The most effective way to care for kids and their immunologic well-being is to ***speak up*** on behalf of children while helping families navigate and decipher health fact from fiction.

References

1. https://www.bitchute.com/video/jm2euik7MlCV/
2. https://www.bitchute.com/video/yn3u9ETcxCbV/
3. https://www.bitchute.com/video/qs9X8Blr4Ucv/
4. Poschet, et al. Azithromycin and ciprofloxacin have a chloroquine-like effect on respiratory epithelial cells. *Immunology Network* (preprint)
5. Hu XY, et al. Correction: Andrographis paniculata (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis. *PLos ONE*, 2018;13(11):e207713.
6. Hoffman and Berry. The influence of selenium on immune responses. *Mol Nutr Food Res;* 2008. Nov;52(11): 1273-1280.doi:10.1002/mnfr.200700330
7. Liu, Y-W, et al. Psychotropic effects of *Lactobacillus plantarum* PS128 in early life-stressed and naive adult mice; *Brain Research*; Volume 1631, 15 January 2016, Pages 1-12
8. https://rumble.com/vpqhux-felony-crimes-end-pharma-immunity-us-criminal-conspiracy-strikes-root-of-co.html

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Environmental Medicine Update

by Marianne Marchese, ND
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Breast Density – Environmental and Lifestyle Factors

What Is Breast Density?

Breast density is a finding on mammography and correlates with the amount of fibroglandular tissue versus fatty tissue. Density is categorized by the radiologist as almost entirely fatty, scattered fibroglandular densities, heterogeneously dense, and extremely dense. The last two categories (heterogeneously dense and extremely dense) are commonly lumped together, and a woman with these finding is considered to have "dense breasts." About 43% of women aged 40–74 in the US have heterogeneously or extremely dense breasts on mammography.[1] In general, breast density decreases as a woman gets older, increases with hormone replacement therapy, and decreases with increasing body mass index (BMI). Yes, being thin, younger, and on hormone replacement therapy are risk factors for breast density. Around menopause, breast density tends to decrease unless other risk factors are present such as being thin or taking hormone replacement therapy.

The reason density is even noted on mammography is that women with breast dense have an increased risk of breast cancer. It is estimated that women with extremely dense breasts have four- to six-fold higher risk of developing breast cancer compared to those with fatty, non-dense, breasts.[2] Density accounts for 39% of premenopausal and 26% of postmenopausal breast cancer.[2] Density noted on mammography means there is an increased risk for the radiologist not being able to detect breast cancer, often called a masking effect. Aside from density masking the detection of breast cancer, it is important to note that some risk factors for developing breast density are similar to the risk factors for developing breast cancer. This is especially true of lifestyle and environmental factors.

Lifestyle and Environmental Factors Linked to Breast Density

Alcohol. Recent research has shown that alcohol consumption among women increased during the pandemic. In 2020 heavy drinking increased 41% in women compared to 2019. One in 10 women reported an increase in alcohol-related problems in 2020.[3] Whether this was due to stress, boredom, or isolation during the pandemic is unclear, but the consequences of excess alcohol intake on breast health is clear. Women who drink greater than seven drinks a week have five times higher odds of having mammographic breast density compared to women who drink less than one drink per week.[4,5] Alcohol intake is also linked to breast cancer. Alcohol may increase aromatase activity, decrease liver catabolism of androgens, and increase adrenal steroid production. Alcohol intake of more than one drink a day is associated with an 82% greater risk for breast cancer.[4,5]

Sugar. A 2014 study looked at the association of sweet foods and sugary drinks with mammographic density among 776 premenopausal and 779 postmenopausal women. Overall, postmenopausal women consumed more sweet foods (11.8 servings versus 7.7 servings per week), than premenopausal women, with a higher total caloric intake per day. The intake of high sugar content beverages was similar in both groups (1.9 versus 2.1 servings per week for postmenopausal and premenopausal women respectively). Fourteen items were classified as sweet foods (ice cream, chocolate, candy with chocolate, candy, homemade cookie, commercial cookie, brownie, donut, homemade cake, commercial cake, homemade pie, commercial pie, other homemade pastries, and other commercial pastries). Four items were classified as sugar-sweetened beverages (cola with sugar, cola with sugar but caffeine free, other carbonated beverage with sugar, and sweet fruit juice). The study found that sugar-sweetened beverage intake was positively associated with mammographic density among all women, both premenopausal and post-menopausal. The intake of sweet foods – mostly desserts – was associated with breast density in postmenopausal

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women and sugar-sweetened beverages intake of more than three servings per week presented a 3% difference in percent density compared with those who did not drink sugary drinks.[6] Sugar is also linked to breast cancer. In a 2020 study of over 100,000 women, even after accounting for weight and other risk factors, it found that breast cancer was associated with the intake of added sugars, free sugars, sucrose, sugars from milk-based desserts, dairy products, and sugary drinks, but not sugar from fruits.[7]

Air pollution. Air quality across the world is getting worse each year. Climate change, wildfires, dust storms, pesticide use in agriculture, increased auto exhaust, and population density all contribute to air pollution. The recent wildfires in the West and Southwest are contributing to poor air quality across the US. According to the US Department of Agriculture, wildfire smoke emits toxic chemicals such as carbon monoxide, particulate matter, silica, aldehydes, formaldehyde, solvents, polyaromatic hydrocarbons, sulfur dioxide, benzene, and acrolein, volatile organic compounds, nitrous oxide, heavy metals and more. Studies looking at the link between air pollution and breast health show that women with dense breast were 20% more likely to have been exposed to higher levels of air pollution PM 2.5.[8] There is also a link between emissions of nitrogen oxides, carbon monoxide, sulfur dioxide and volatile organic compounds (VOCs) and an increase in the incidence of breast cancer.[9] These are common chemicals in cities with known air quality and air pollution problems. The American Lung Association each year lists the cities in the US with the worst pollution based on particulate matter and ozone. Most are in the Southwest and West. You can find the updated list at https://www.lung.org/research/sota/city-rankings/most-polluted-cities.

Phthalates and BPA. Both phthalates and bisphenol-A are known endocrine-disrupting compounds. They are linked to breast cancer, thyroid disease, uterine fibroids, endometriosis, polycystic ovarian syndrome, and many other hormonally driven conditions.[10] A 2019 study looked specifically at the link to phthalates and breast density in adolescent girls and found that exposure during the critical window of development during adolescent could affect breast health later in life. It concluded that adolescent exposure to dietary phthalates is linked to higher percent volume of breast density and fibroglandular tissue and an increased risk of adult breast cancer.[11] Phthalates have been found in dairy products, meats, fish, oils and fats, baked goods, infant formula, processed foods, and fast foods. Phthalates easily escape from food processing equipment, food packaging, and food preparation materials, and contaminate food at points all along the supply chain. Phthalates are in vinyl products, carpeting, personal care products, fragrances, cleaning products, and paints and primers used in the home.[10,11] Several studies link blood bisphenol-A levels to breast density on mammography in post-menopausal women.[12,13] Bisphenol A (BPA) can be released from consumer products such as canned food, hard plastic beverage bottles, paper receipts, dental materials, and personal care products. Some recent reviews have summarized the known mechanisms of endocrine disruptions by BPA in human diseases, including obesity and reproductive disorders.[13] There is an association between increased incidence of breast cancer and BPA exposure at doses below the safe reference doses.

Case Example

A healthy 53-year-old, post-menopausal woman presented with recent abnormal mammogram. She has been in menopause for three years and never took hormone replacement therapy. Her MD had ordered routine screening mammogram, which showed a right breast 1.8 cm fibroadenoma and VERY dense breast tissue. It was labelled at 75% fibroglandular density and given a BI-RADS rating of 0 and additional imaging was recommended. A diagnostic mammogram with ultrasound was ordered by her MD and showed very dense breast tissue and the same 1.8 cm mass present but now labeled a benign cyst and not fibroadenoma. The ultrasound was better able to visualize the mass through her dense breast tissue. This imaging was rated a BI-RADS three- and a six-month right side targeted ultrasound was recommended. She didn't want to wait six months; she wanted to be proactive and came for a consult. She had a BMI of 20, normal vitals, and the physical exam was unremarkable. A thorough history and labs were done.

Medical history

- No Medications
- Supplements: B12 (1,000 mcg); Fish oil (1,500 mg); Calcium (600 mg); Magnesium (300 mg); Vitamin D (4000 IU a day)
- Never took HRT, no family history of BRCA, and no personal history of benign breast disease
- Diet is high in sugar – loves deserts and sweets. Eats candy, desserts, and sweets daily. No sodas or juices
- Drink 8-10 alcoholic drinks a week

Environmental exposure history (all past)

- Grew up in Iowa on a farm with well water
- Lived in Arizona for 26 years. Since 2014 Phoenix has an increasing air pollution problem due to population grow, traffic (auto exhaust), dust storms, and wildfires.
- Uses revere osmosis water for cooking and drinking!!!!
- No occupational or hobby exposures, no smoking, some dietary fish
- Uses standard cleaning and personal care products and lots of plastics

Labs ordered

- CBC, CMP, LIPID, iron, ferritin, ESR were all normal
- TSH was 1.5, iodine was 61, Vitamin D was 49, B12 was 986
- Blood mercury was 3 (ordered because she ate some fish)
- Blood lead was <2
- 24-hour urine arsenic was 15

At this point she has very dense breast tissue and a benign cyst. Her thin body size, higher than average alcohol

and sugar intake, use of standard personal care products, cleaning products, plastics, and non-organic foods, and Phoenix air quality issues are her only risk factors for breast density and breast health concerns. In the past she grew up on a farm with well water, which indicates possible pesticide exposure but doing a pesticide panel now would not capture exposure from so long ago. Treatment began with education on avoidance of BPA, phthalates, and other toxicants at home and in her cleaning and personal care products. She got rid of plastics and changed her products and bought mostly organic dairy, meats, and other foods. She purchased a HEPA room air filter to run at night in the bedroom and during the day on high pollution advisory days, which are now common in the Phoenix metropolitan area. A detailed list of avoidance can be found in my book *8 Weeks to Woman's Wellness*. She agreed to stop eating all refined sugars – candy, sweets, treats and deserts and cut back alcohol to three drinks a week.

She embarked on a diet plan that included the following:

- Organic and Non-GMO foods
- 1 Tbsp ground flax meal a day
- 1 teaspoon of psyllium husk powder a day
- 3-4 cups of green tea either regular or de-cafe is fine
- No refined sugar, no artificial sweeteners, no candy, no sweets, no treats
- No cow milk products
- Fish low in mercury is okay
- 3-4 servings of cruciferous veggies a day
- Complex carbohydrates like quinoa and brown rice are okay
- Increase legumes, fruits, veggies
- Limit alcohol to two-to-three times a week

She was given three supplements to take for four months.

- Liver herbs – Milk thistle, burdock root, dandelion root, beet root, artichoke leaf.
- Estrogen metabolism – Methyl donors, DIM, calcium-d-glucarate, ALA, NAC
- Cofactors – High-dose multivitamin and mineral with methylated forms, green tea, and turmeric

She completed the treatment plan and felt great. She stuck with the diet and stayed off sugar and limited alcohol and dairy and mostly ate organic. The room air filter helped her husband's nasal congestion. She did not do the six-month right breast target ultrasound and, instead a year later, did both a diagnostic mammogram with U/S. The mass was no longer seen on mammogram and the breast density reduced from 76% to 50%. The ultrasound showed that the cyst shrunk from 1.8 mm to 9 mm and imaging was rated a BI-RADS 2. She stopped the supplements after four months but stuck with the diet changes and avoidance measures. The following year, two years after initial visit, she did both a diagnostic mammogram and ultrasound and the cyst was gone, and breast density rated at 40% (initially was 75%). The imaging was given a BI-RADS rating of 2, and she was placed on an annual breast screening plan with both diagnostic mammogram and ultrasound due to the density.

Breast Density

Summary

Dense breast tissue is becoming a common finding on mammography. When imaging shows that there is more glandular and connective tissue than fatty tissue, the breast is considered dense. Breast density makes it difficult to see potential cancer on mammograms. Some states have passed legislation that require health care providers to inform women of the increased risk of breast cancer and reduced sensitivity of mammography, and several states require additional testing such as ultrasound for women with dense breasts. About 43% of women aged 40–74 in the US have heterogeneously or extremely dense breasts by mammography. Some women are more likely to have dense breasts, such as those who are premenopausal, use menopausal hormone replacement therapy (HRT), and have a lower body mass index (BMI). Often overlooked risk factors linked to breast density include a diet high in sugary foods and drinks, having more than seven alcoholic drinks a week, living in areas of high air pollution and poor air quality, and exposure to endocrine disrupting chemicals from food, personal care products, and plastics. When practitioners are discussing mammographic findings of breast density, it is important to address these modifiable environmental factors.

References

1. Lee CI, Chen LE, Elmore JG. Risk-based Breast Cancer Screening: Implications of Breast Density. *Med Clin North Am*. 2017;101(4):725-741.
2. Vourtsis A, Berg WA. Breast density implications and supplemental screening. *Eur Radiol*. 2019;29(4):1762-1777.
3. Pollard MS, Tucker JS, Green HD. Changes in Adult Alcohol Use and Consequences During the COVID-19 Pandemic in the US. *JAMA Netw Open.* 2020;3(9). E2022942.
4. Frydenberg H, et al Alcohol consumption, endogenous estrogen and mammographic density among premenopausal women. *Breast Cancer Res*. 2015;17(1):103.
5. Duffy SW, Morrish OWE, Allgood PC, et al. Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer. *Eur J Cancer*. 2018; 88:48-56.
6. Duchaine CS, Dumas I, Diorio C. Consumption of sweet foods and mammographic breast density: a cross-sectional study. *BMC Public Health*. 2014;14:554.
7. Charlotte Debras, et al. Total and added sugar intakes, sugar types, and cancer risk: results from the prospective NutriNet-Santé cohort. *The Am J of Clinical Nutrition*, 2020:112(5); 1267–1279.
8. Yaghjyan, L., Arao, R., Brokamp, C. *et al.* Association between air pollution and mammographic breast density in the Breast Cancer Surveilance Consortium. *Breast Cancer Res* 2017:19;36.
9. Gabet S, et al. Breast Cancer Risk in Association with Atmospheric Pollution Exposure: A Meta-Analysis of Effect Estimates Followed by a Health Impact Assessment. *Environ Health Perspect*. 2021;129(5):57012.
10. Marchese, M. 8 Weeks to Women's Wellness. Petaluma, CA. Smart Publications 2011.
11. Binder AM, Corvalan C, Pereira A, et al. Prepubertal and Pubertal Endocrine-Disrupting Chemical Exposure and Breast Density among Chilean Adolescents. *Cancer Epidemiol Biomarkers Prev*. 2018;27(12):1491-1499.
12. Sprague BL, et al. Circulating serum xenoestrogens and mammographic breast density. *Breast Cancer Res.* 2013;15(3):R45.
13. Wang Z, Liu H, Liu S. Low-Dose Bisphenol A Exposure: A Seemingly Instigating Carcinogenic Effect on Breast Cancer. *Adv Sci (Weinh)*. 2016;4(2):1600248.

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Women's Health Update

by Tori Hudson, ND
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A Year in Review in Women's Health Research and Writings from 2021

As I look back on the year 2021, it would be easy to talk about all things COVID-19 or COVID-19 and vaccines. I'm going to do neither and, rather, recognize that issues in gynecology and primary care for women roll on and the need for natural therapies in women's health continues to be dominated by those we are accustomed to – menopause symptoms, pelvic tumors, breast cancer, dysmenorrhea, bladder and vaginal infections, insomnia, primary dysmenorrhea, endometriosis, PMDD, pregnancy, fertility, depression, anxiety, cystitis, and on and on.

For this women's health issue of the *Townsend Letter*, I usually look back at studies I've read and written about in the year previous and then select those that I have found to be influential in my clinical practice, or compelling or intriguing in the use of a natural medicine or lifestyle habit in women's health. Here are a few.

The Effect of N-Acetylcysteine on Uterine Fibroids

Uterine fibroids (aka leiomyomas) are a common benign uterine tumor that originates from the smooth muscle of the uterus. They are not cancerous growths. The incidence, in general, in US women is about 9.6% of the female population, but it is more common in black women with an incidence of 18.5% (and possibly other nonwhite women). Approximately 25% to 50% of women with fibroids are symptomatic, experiencing heavy menses, reproductive issues, pain, increased urinary frequency, and anemia, and are more symptomatic in black women.

Uterine fibroids are the most common cause of gynecologic surgery worldwide; yet still, the underlying cause remains unclear. More than 100 gene abnormalities are identified in leiomyomas, involving the genes for hormone receptors, growth factors, extracellular matrix and collagen. The current factors that may be involved include genetic factors, estrogen/progesterone receptors in the uterine muscle cells, growth factors such as insulin-like growth factor, and extracellular matrix, which is the material that makes cells stick together.

When we do not understand the cause of a medical condition, it makes it very hard to identify prevention and treatments. The current state of affairs offers three basic conventional options: 1) surgery (hysterectomy or myomectomy or hysteroscopic removal of intrauterine fibroids; the surgical options depend on fibroid location, size/mass of the fibroids, symptoms and other medical issues that might influence the best surgical option) 2) hormonal drugs that can temporarily shrink the fibroids prior to surgery; or, hormonal drugs that can improve some of the symptoms such as heavy bleeding 3) uterine artery embolization. In general, conventional medicine is left with insufficient non-invasive treatments where no pharmaceutical agent is known to shrink the fibroids in a long-term way.

The premise for N-acetyl cysteine (NAC) is as an antioxidant that inhibits free oxidative radicals and hopefully results in neutralizing the proliferation of uterine fibroid tumor cells. The hope is that the known antioxidant mechanism of NAC that reduces oxidative stress by inhibiting free radicals and glutathione synthesis, thus preventing the peroxidation of membrane lipids and preventing their release, may also lead to a reduction in uterine fibroid volume.

The current study is a randomized, double-blind controlled pilot study in Iran, 2017-2019. Women included in the study were diagnosed with uterine leiomyoma based on transvaginal ultrasounds and had a fibroid at least 8 cm or more, less than four uterine fibroids, and just one type of fibroid (either submucosal, intramural or subserosal), with no pedunculated fibroids, were premenopausal, not pregnant, had not taken hormonal medications in the previous six months and no hormonal medication for their fibroids in the past three months and did not have certain diseases that were listed as exclusionary criteria. Women also had to have regular menstrual periods, onset of menses between ages 12 and 14, and had previously presented with heavy bleeding and painful periods.

A total of 50 women were accepted into the study with half being given NAC 600 mg/day for three months and the other half the placebo. Pelvic ultrasounds were performed before and after taking medication. No statistically significant difference was found between the two groups in terms of number and type of fibroids, and menopause status. The mean rates of volume reduction in group A (NAC group) were 25.25% and group B (placebo) was 1.08%. At the beginning of the study, heavy bleeding and painful menses were reported by women in both groups. The bleeding pattern changed during and after NAC treatment with a significant reduction in volume of bleeding and menstrual pain. There was also a significant reduction in fibroid and soft tissue tumor size in the treatment group. The average severity of pain in the NAC group

was between 8 and 9 out of 10 before treatment and between 4 and 5 after treatment. Before NAC, women had heavy bleeding and after, a pattern of moderate bleeding was reported.

Commentary: I am not sure of the fundamental logic for considering NAC for uterine fibroids. However, given that we have a significant lack of non-invasive treatment options, I'm certainly open to ideas and pilot studies. I also consider 600 mg/day of NAC to be a low dose when compared to the studies on polycystic ovary syndrome and endometriosis; although for endometriosis it was 600 mg three times daily for three days/week and for PCOS we usually see the studies at 500 mg three times daily. The study results lacked specificity for me…especially in its reported reduction in heavy bleeding; we do not know how many women improved and what defined heavy vs moderate. I can believe a reduction in symptoms after three months of any herbal or natural agent, but to reduce volume size within three-months' time is harder to believe. Believable or not, I will certainly try this non-invasive safe, natural therapy for my patients with non-pedunculated uterine fibroids with less than four fibroids. I will likely also not just limit my patients to those with a fibroid of at least 8 cm. There is only a small amount of other published research on natural agents, including green tea and black cohosh. While I will continue to make efforts with natural therapies to reduce bleeding and pain, to actually reduce size and number of fibroids has left me with very little optimism after 36 years of clinical practice. It is important for the woman with fibroids and her medical provider to recognize when it's time for surgery or uterine artery embolization (UAE) and the benefits and risks of each kind of pelvic surgery or if UAE is a viable option.

Aghaamoo S, et al. The effect of N-acteyl cysteine on the volume of uterine leiomyoma: A ranrdomized clinical trial. *Int J Gynecol Obstet.* 2021. 2021:00:1-5.

Uterine Fibroids May Be Reduced with Green Tea Plus Vitamin D

Uterine fibroids are the most common benign tumor in the uterus. Most do not cause any symptoms and don't require any investigation or treatment. But, for some women, maybe about a third, uterine fibroids, also called uterine myomas, may need a therapy – either to control abnormal uterine bleeding, reduce the size due to pressure and effects on bladder and/or digestive function, interference with fertility, or just plain aesthetics and discomfort due to size and abdominal distention. Conventional treatment options included medications to control bleeding or shrink the fibroids temporarily or surgical options. All of this depends on the scope and severity of the symptoms, the size, number and desire for pregnancy. Minimally invasive surgical procedures are possible for some but not all fibroids. Others might require a hysterectomy – either abdominally or vaginally.

Women often seek alternative or integrative medicine options to see if non-surgical or non-pharmaceutical treatments may help. The research is sparse, and the success is hit and miss. The most likely help we can offer is to help control abnormal bleeding. The least likely help we can offer is actually reducing the size of fibroids, especially larger ones. However, a small amount of research has emerged, including in the area of green tea. In the current study, vitamin D and epigallocatechin gallate (EGCG) offers some hope with women who had symptomatic fibroids.

Women were included in the study if they were 18 or older, premenopausal and had at least one myoma >2 cm (either intramural or subserosal and/or submucosal fibroids), as detected on a vaginal and abdominal ultrasound, with moderately severe myoma-related symptoms…and required no other treatment.

This pilot study enrolled 30 women with myomas, who were divided into two groups. One group (n=15) received one tablet of 1,000 IU (25 mcg) vitamin D plus 150 mg EGCG plus 5 mg B6, twice daily for four months. The second group (n=15) received no treatment for four months. The primary outcome was the change in volume of myomas as detected by transvaginal and/or transabdominal ultrasound. The secondary outcomes were variation of the number of myomas, heavier menstrual bleeding, pelvic pressure, fatigue, quality of life, and the severity of any of these symptoms.

None of the women dropped out of the study in either group, and there were no discernable side effects of the treatment. The total number of myomas in the treated and control group was 23 and 21, respectively. In the treated group, the incidence of intramural myomas was 43.7%, subserosal 12.5%, and submucosal 43.75%. In the control group it was 47.4% intramural, 10.5% subserosal, and 42.1% submucosal.

A significant reduction in the volume of myomas in the treated group was 10.84 cm at baseline to 8.04 cm after four months. The reduction of the volume of myomas was unrelated to the type of myomas. In the control group, the volume was 10.17 at baseline to 10.94 after four months of treatment. This translates to a 34.7% reduction in the volume of myomas in the treatment group and an increase of 6.9% in the control or untreated group. The number of myomas did not change in either group.

While the specifics were vaguely reported, there was an improvement in quality of life and reduction in severity of symptoms in the treatment group.

Commentary: Uterine myomas, aka uterine leiomyomas, aka uterine fibroids are monoclonal tumors of the smooth muscle cells of the myometrium. Myomas consist of an accumulation of collagen, fibronectin, and/or proteoglycan that can form in or on the uterus. Where they form determines the classification of intramural, subserosal, or submucosal. A woman can have any combination of these or just one kind. They are most common between the ages of 35 and 50 and may vary by ethnic groups with African American women having three-to-four times higher risk of developing myomas as compared with Caucasian American women. Uterine fibroids are the leading cause of hysterectomies in the US accounting for about 39% of all hysterectomies. Clearly, we are not doing enough to understand the cause and offer successful treatments.

The exact cause of myomas is still unknown but their development and growth is at least in part affected by estrogen and progesterone. But also, we must consider the roles and influence of the hormone receptors and that the dysfunction is at the receptor rather than any particular rise or fall of the hormones. It is a mistake to think that fibroids are only under the influence of estrogen. For some women, it's progesterone that can actually adversely affect growth of myomas. It's a much longer discussion, and discussion and theories are the name of the game rather than true knowns. But, we might consider growth factors, cortisol dysregulation, dysfunctions in hormone metabolizing enzymes, environmental endocrine disruptors, body fat and obesogens…and more. And speaking of more, a robust research effort would be welcomed to explore these theories, questions, and attempts at solutions.

Back to vitamin D and EGCG. There is at least one study showing an association between hypovitaminosis D and a higher prevalence of uterine fibroids, along with more severity related to the fibroids. (*Int J Womens Health.* 2013; 5: 93-100.) Mild symptomatic fibroids may be able to improve once an outright vitamin D deficiency ➤

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(<30 ng/mL) is corrected. (*Medicine* (Baltimore) 2016; 95: e5698.) In one previous green tea study, EGCG for four months reduced the myoma size in premenopausal women. (*Int J Womens Health* 2013; 5: 477-486.)

The current study, along with support of the small amount of previous data on vitamin D and EGCG, supports the possibility that a simple and safe approach could at least offer something more than wait and watch – and possibly for some, may spare them a surgery and improve their myoma symptoms and quality of life. In addition, we could consider an integrative plan, offering the herbal/nutraceutical treatment along with other pharmacological therapies that are being used to control heavy bleeding. A uterus is worth saving, if possible, and avoiding any surgery, if possible, is wise and worth an effort. If surgery is necessary, a good surgeon with a broad understanding of pelvic floor support and implications for menopause is an important part of an integrative treatment team.

Porcaro G, et al. Vitamin D plus epigallocatechin gallate: a novel promising approach for uterine myomas. *European Review for Medical and Pharmacological Sciences*. 2020; 24: 3344-3351.

Valerian Root for Sleep Disorders – A Further Understanding

Insomnia comes in all sizes and shapes; but in essence, it is a common sleep disorder that can make it hard to fall asleep, hard to stay asleep, or cause you to wake up too early and not be able to get back to sleep. Insomnia is considered chronic if it occurs at least three nights per week and has been going on for at least three months. Insufficient sleep and/or disrupted sleep can lead to fatigue, poor ability to handle stressed, mood disorders, cognitive impairment, poor performance during the day, and even increase the risk for chronic conditions such as hypertension, hyperlipidemia, type 2 diabetes, heart disease, and dementia. While conventional medicine has a plethora of treatment options, including over the counter and prescription medications, most if not all of these have been associated with cognitive decline when used regularly for years. Some of the prescription medications can be addictive as well.

Valerian root is one herb that has a long tradition of use for sleep disorders. The results of studies have been mixed. The current paper is a systematic review and meta-analysis with the hope of bringing some clarity as to efficacy and to offer possible explanations for the inconsistent research.

Three searches were conducted for both controlled and observational studies. Search A included clinical trials found on PubMed between January 1980 and November 2019. Search B was conducted on ScienceDirect between January 2000 and November 2019. Search C identified all clinical trials in the Cochrane Library through December 2019.

A total of 696 articles were identified. Of those, 629 did not meet inclusion criteria which leaves 67, although 7 of those were excluded for unknown reasons. Of the 60, 40 studies evaluated valerian as a single herb and 36 of those were randomized controlled trials, two were observational studies, and two studies evaluated potential induction of CYP. Others used valerian/herbal combinations.

Of those 40, 23 tested the efficacy of valerian for sleep problems and 13 studies found valerian to be effective as a sleep aid, although only four of the studies included patients with diagnosed insomnia. Of the remaining 10 studies, three showed no significant effect of valerian as a sleep aid when compared to a placebo.

The information for analysis also classified herbal preparations into four groups: hydroalcoholic extracts, aqueous extracts, unspecified solvents, and whole root/rhizome. Here is where it gets interesting. A single dose of valerian hydroalcoholic extract did not improve sleep quality; however, it did improve REM sleep in patients diagnosed with insomnia. Repeated doses demonstrated inconsistent outcomes with four studies reporting efficacy, three reporting no improvement, and one reporting improvement in sleep latency after repeated doses for two weeks but no improvement after a single dose.

Out of three studies evaluating the use of an aqueous extract, two studies found improved subjective sleep quality and latency in healthy participants after a single dose. One study found improved deep sleep for elderly participants after one week of a repeated dose. Of the three studies using unspecified solvents, two RCT reported negative outcomes and one observational study reported a positive outcome.

All five studies evaluating the use of dried root/rhizome showed improved sleep in at least one subgroup (four RCT and one observational study).

The anxiety-reducing potential of valerian was also analyzed. It did exhibit antianxiety benefits with high variability in results using the extracts and more positive outcomes using the whole dried root. Other effects of valerian included reduced symptoms of obsessive-compulsive disorder (OCD), improved cognition in patients receiving hemodialysis, and preventative benefits against a decline in cognition after coronary bypass surgery.

A different species of valerian was also evaluated, taproot valerian (*V. edulis*). It showed some effectiveness for sleep latencies and sleep quality in kids with intellectual challenges along with primary sleep problems. Another taproot valerian study showed a reduction in the number of awakenings in patients diagnosed with insomnia and showed an increase in REM sleep.

Better sleep quality and reduced wake time after sleep onset was seen in patients diagnosed with insomnia after they received a combination of valepotriates from Indian valerian (*V. jatamansi* syn. *V. wallichii*) over 15 days.

Nineteen studies used herbal combinations. The most common combination was valerian and European hops. Valerian and lemon balm had positive outcomes on sleep disorders, anxiety and reduction in hyperactivity and improvement in concentration in children who struggle with these symptoms. Two observational studies used valerian and St. John's wort in patients diagnosed with depression and children with affective disorders. A reduction in anxiety and depression, and improved sleep was seen.

Commentary: There is a robust list of underlying causes of sleep disorders and this paper did not consider that. However, the results do suggest that valerian is most useful in treating those with insomnia associated with anxiety. In reading this, I came away thinking the best results in the most ways are seen with the dried root (sleep quality, sleep latency, decreased wakefulness) although the water extract can shorten the time it takes to fall asleep, ease return to sleep if early wakening, and improve REM sleep and overall sleep quality. Combining valerian root with lemon balm appears optimal for sleep disorders with anxiety, as well as improving concentration and hyperactivity in children with sleep issues.

Shinjyo N, Waddell G, Green J. Valerian root in treating sleep problems and associated disorders - A systematic review and meta-analysis. *J Evid Based Integr Med*. January-December 2020;25:25

Vitamin D Supplementation May Help Primary Dysmenorrhea (your average case of menstrual cramps, not caused by endometriosis)

Primary dysmenorrhea is defined as menstrual pain without any pelvic pathology. This is the most common menstrual symptom in adolescent girls and young women. The onset of menstrual pain usually occurs just before or at the first onset of the menstrual flow and typically lasts a half day to three days. Some women have additional symptoms such as headache, fatigue, and even nausea/vomiting and diarrhea.

In the current double-blind, randomized, placebo-controlled clinical trial in Iran in women aged 18 to 32 years, with regular menstrual cycles and with a pain score of 4 or more out of an 11-point rating scale. These women also had a laboratory value of 25-hydroxyvitamin D <30 ±ng/mL which means some were insufficient (20-30 ng/mL) and some were deficient (<20 ng/mL). There were 58 participants in the vitamin D supplement group and 58 in the placebo group. Women received vitamin D3 capsules 50,000 once weekly for eight consecutive weeks or placebo.

Results: The serum level of 25 (OH)D significantly increased from 20 to 37 ng/mL in the vitamin D group and no significant changes in the placebo group. Even with this robust dosing of vitamin D for eight weeks, 24% of the women receiving vitamin D supplements still showed low levels of 25(OH)D <30 ng/mL at week 8. A significant change in pain intensity was found in the vitamin D group and no significant change in the placebo group. The significant reduction in pain intensity was measurable at week 4 (the first menstrual period), as well as week 8. The average pain intensity at baseline was 7.0 ± 1/7; 6/3 ± 1.7 at week 4; and 5.6 ± 1.7 at week 8. There was also a significant change in the number of days with pain in the vitamin D group and none and no significant change in the placebo group. By week 8, the reduction in number of days went from 2 at baseline and 1 at week 8. Even the number of pain relief medications used per day was reduced in the vitamin D group by half vs no significant change in the placebo group. Lastly, there were even improvements in the systemic symptoms associated with their dysmenorrhea in the vitamin D group, including headache severity and diarrhea, with no significant change in the placebo group.

Commentary: One of the things I was curious about was whether or not there was an association between the increase in serum vitamin D level and the improvement in pain intensity. The researchers found no such correlation and surprisingly, there wasn't even a difference in pain intensity in the vitamin D group with those who did achieve normal serum levels (> 30 ng/mL) and those who did not achieve that.

A suggested mechanism causing primary dysmenorrhea is the increased production of prostaglandins in the endometrium (line of the uterus). This rise in prostaglandins in women with primary dysmenorrhea increases uterine tone and high-amplitude contractions. Both upregulation of cyclooxygenase activity and prostaglandin synthesis are generally observed in women with primary dysmenorrhea. Consequently, whether herbal or pharmaceutical, non-steroidal anti-inflammatories that inhibit the expression of cyclooxygenase enzyme that is involved in the synthesis of prostaglandin should be considered first-line options for treating acute primary dysmenorrhea. The herb ginger root has some nice, published research for this purpose.

Given the frequency of vitamin D insufficiency or vitamin D deficiency, the possible role of these insufficient levels should be considered as a possible role of causing or exacerbating primary dysmenorrhea.

Rahnemaei F, et al. Vitamin D supplementation for primary dysmenorrhea: a double-blind, randomized, placebo-controlled trial. *Obstetrics Gyn Sci*. 2021, May 18 (epub ahead of print).

Milk Thistle for Hot Flashes of Menopause: Yet Another Option

Hot flashes and/or night sweats, collectively called vasomotor symptoms (VMS), are the most common symptom of perimenopause/menopause. The average duration of VMS is about seven years, so more options to address this frequently significant symptom, is always welcomed. While VMS can come in all sizes and shapes, varying from mild to severe and infrequent to frequent, they are bothersome for a large number of women, interrupting sleep, altering mood, and affecting quality of life.

This trial of milk thistle was conducted in Iran between September 2018 and December 2019. Women were postmenopausal between the ages of 40 and 60 years, and who had experienced VMS ≥14 times weekly for the past two months, and who had a total Greene Climacteric Scale (GCS) score between 15 and 42 and a Hot Flash Related Daily Interference Score (HFRDIS) ≥ 40.

Women were excluded if they used tobacco, had an underlying chronic disease, history of allergy to herbal medicines, use of other treatments to treat hot flashes, history of asthma and allergies, history of abnormal pap smears and pelvic ultrasounds, and history of a breast, ovarian, or uterine cancer.

A dry extract of milk thistle in the form of a powder was encapsulated with 400 mg per capsule of milk thistle standardized to 80% silymarin. Eighty women were randomized into two even groups, and each group took a 400 mg capsule twice a day for eight weeks: one group milk thistle and one group placebo. Women recorded the frequency and severity of hot flashes for twelve weeks including the four weeks after stopping the capsules. Data was collected every four weeks with a visual analog scale to evaluate the severity of hot flashes; women reported the average of their frequency and severity for each day.

The GCS was used to measure menopausal symptom severity and HFRDIS assessed the vasomotor interference level during their daily activities. The mean age of women in the study was 52.5 years. Seven dropped out of the study: two from the milk thistle group and five from the placebo group due to gastric pain, bloating, and increased symptoms.

The women in the milk thistle group reported a decrease in the frequency and severity of hot flashes, while the placebo group saw no significant changes. The GCS questionnaire mean score and HFRDIS mean scores decreased in the milk thistle group while the placebo group had no significant changes. The conclusion was that the milk thistle reduced postmenopausal VMS within the first month and lasted a month after discontinuation as well.

Commentary: We still do not know the exact mechanism for VMS but the most recent thinking is that there are abnormalities in the hypothalamic thermoregulatory center due to fluctuating estrogen levels and ultimately lower estrogen levels.

The primary conventional treatment for VMS includes estrogen therapy, but other therapies are SSRIs, gabapentin, and a selective estrogen receptor modulator (SERM) in combination with an estrogen and clonidine. There are a host of botanical and nutrient therapies that have published research. The conventional pharmaceuticals all have benefits and risks, with hormone ➤

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therapies having the most benefits, with very small risks in most women. The botanical/nutraceuticals have benefits and small to no risks, although the benefits for VMS do not statistically meet the same level of results as with systemic estrogen. That said, what we care most about is what are the individual benefits and risks for each woman and the individual results she achieves with her treatment, whatever the treatment is.

I am most familiar with the use of milk thistle (*Silybum marianum*, Asteraceae) for liver and gallbladder conditions, but there are other historical uses for fever, kidney, and spleen diseases.

The primary active constituent in mild thistle, silibinin, could have an agonistic effect on estrogen receptor b, or one might also theorize it is affecting serotonin receptors via the gut/grain axis

Saberi Z, et al. Evaluation of the effect of Silybum marianum extract on menopausal symptoms: A randomized, double-blind placebo-controlled trial. *Phytother Res*. December 2020;34(12):3359-3366.

Good News for Breast Cancer Patients – Drink Coffee and Tea, Especially Coffee

In July 2018, I reported on a meta-analysis of coffee intake and breast cancer risk. The design of that meta-analysis was to assess associations between amounts of decaffeinated and caffeinated coffee (from 0 to 7 cups of coffee per day) and breast cancer risks, including categories of body mass index, hormone receptor status, and menopause status.

The analysis included 13 prospective studies totaling over 1 million participants and concluded in showing *no* significant association between coffee consumption and breast cancer risk. However, when the analysis was specific to postmenopausal women, there was an inverse relationship to the tune of consumption of four cups of coffee per day was associated with a 10% reduction in postmenopausal cancer risk, no matter body mass index or hormone receptor status, or caffeinated or decaffeinated coffee. Conclusion: coffee consumption is associated with a decreased risk of postmenopausal breast cancer. (Lafranconi A, et al. Coffee intake decreases risk of postmenopausal breast cancer: a dose-response meta-analysis on prospective cohort studies. *Nutrients*. 2018;10(2). pii:E112.)

The more recent study I want to report on is the role of post-diagnostic coffee and black tea consumption among women with breast cancer in prospective cohort studies. The women who were included in this analysis were 8,900 women diagnosed with stage I through stage III invasive breast cancer from 1980 through 2010 who were part of the Nurses' Health Study (NHS) and then also from 1991 through 2011 who were part of the NHS II.

A food frequency questionnaire (FFQ) of coffee and black tea consumption every four years after the diagnosis of their breast cancer was assessed. Total coffee consumption included regular and decaffeinated coffee, and total tea consumption included regular and decaffeinated tea.

Approximately 70% of the women in the study had data, including estrogen and progesterone receptor status, human epidermal growth factor receptor 2, cytokeratin 5/6, Ki-67 and epidermal growth factor receptor. These are common markers analyzed from breast tumor biopsies. Researchers gathered data every two years post diagnosis.

The investigators reported on 1,054 deaths due to breast cancer and 2,500 total deaths over 30 years of follow-up. A higher post-diagnostic coffee consumption was associated with a lower mortality specific to breast cancer. Women who drank >3 cups of coffee per day had a 25% lower risk when compared with non-coffee drinkers. There was also a lower mortality rate due to any cause observed in the coffee drinkers. Compared with women who did not drink coffee, >2 to 3 cups per day was associated with a 24% lower risk and >3 cups/day was associated with a 26% lower risk. Post-diagnostic tea consumption was also associated with lower all-cause mortality. Greater than 3 cups/day was associated with a 26% lower risk compared to nondrinkers but not a reduction in breast cancer specific mortality.

In addition, the more you drank the better the effect. For each one cup/day greater intake, the breast cancer mortality hazard ratio dropped 7% for regular coffee and 2% for decaffeinated coffee. There was also a benefit for reduction of all-cause mortality for greater intake for both regular and decaffeinated coffee. For each one cup of caffeinated coffee per day, the hazard ratio dropped 7% and 5% for decaffeinated.

When the intakes of coffee and tea were added together, an inverse association with breast cancer specific mortality was seen for consumption of >3 cups/day vs nondrinkers, but not for tea of >3 cups/day vs nondrinkers. For all-cause mortality, significant inverse associations were seen for both coffee and tea at >3 cups/day vs nondrinkers.

In breast cancer survivors, higher amounts of coffee consumption after breast cancer diagnosis were associated with better survival rates from breast cancer and from any cause.

Commentary: I can't tell you how many patients tell me they are going off of coffee, or they already went off coffee. I then ask… why? More often than not, I recommend they continue their coffee (and black tea) habit. If they don't have heart palpitations or a rapid heart rate or chronic insomnia, or perhaps breast tenderness, I do not see a reason to discontinue, and in fact proceed to tell them the benefits.

You might be surprised to learn that coffee is a robust source of antioxidants and in 2005, it was listed as the #1 source of antioxidants in the American diet, providing almost 1,300 mg of antioxidants daily in the form of polyphenols. Black tea provides 294 mg and bananas 76 mg. I list these two because they are the second and third dietary sources of polyphenols in the American diet. That's actually not particularly fabulous in my view… as I would prefer a diet richer in other polyphenol-rich foods (berries, citrus, red fruits, apples) and then preferably lower glycemic fruits than bananas (berries again). And, we haven't even gotten to the other robust nutrients and fibers in the long list of polyphenol-rich foods.

Past studies examining the relationship between coffee consumption and breast cancer mortality are inconsistent, but the current study is the most comprehensive. It's curious why coffee drinking spurs negative health concern; now, it could be the sugar added, or the croissant or scone with the coffee. Worse, smoking a cigarette with your coffee. I would agree with those negatives. But when it comes to having breast cancer, coffee should be encouraged, not discouraged. And while not all like the taste of coffee, she can at least be encouraged to drink her black tea as it will reduce her risk of all-cause mortality, even if not breast cancer mortality.

Cheers!

Farvid M, et al. Post-diagnostic coffee and tea consumption and breast cancer survival. *Br J Cancer*. 2021; 124(11):1873-1881.

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Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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The First Vaccine Mandate – February 5, 1777

Coming up on February 5, 2022, will be an anniversary that few people are aware of. It was on February 5, 1777, that George Washington made a strategic decision that many historians credit with allowing the American military forces to win the War of Independence against Britain. This coming year will mark the 245th anniversary of George Washington's order that those who bore arms for our fledgling democracy either had to show proof of immunity or undergo vaccination.

At the time, far more American troops were dying of smallpox than enemy gunfire…. British troops arrived on the continent possessing a herd immunity to smallpox that Americans did not have. American troops were vulnerable to this disease in a way the British were not. Smallpox was endemic in England and most of the British troops had the disease when children. Less than a quarter of the American troops were immune.

Washington had considered ordering vaccination in 1775, during the battle of Boston but had not gone through with the plan.

Obviously, the terms "vaccine" or "vaccinate" were still years off in the future. Technically, these terms should be used to describe the inoculation technique Edward Jenner developed in 1796 using cowpox pus. Earlier doctors had noticed that milkmaids who became infected with cowpox did not get smallpox. During his apprenticeship at age 13, Jenner heard a milkmaid say, "I shall never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face." In May of 1796, he inoculated an eight-year-old boy, James Phipps, with the fluid from a fresh cowpox lesion taken from milkmaid Sarah Nelmes. Phipps suffered mild symptoms that healed in a few weeks. When exposed to infectious smallpox, Phipps was protected from the disease. "Vacca" is Latin for cow, so the term vaccine applies to immunization using pus from an individual infected with cow pox. The anti-vaxers of Jenner's era argued that the vaccine would turn them and their offspring into cows. The term vaccination was unheard until 1800 when Jenner's friend Richard Dunning started to use it.[1]

For those of us who tend toward diligence in our choice of words, we might want to reserve the terms "vaccine" and "vaccinate" specifically for the use of cowpox to produce immunity to smallpox. It is not just the source of the pox in cows that the term distinguishes. Cowpox was a 'lesser disease,' an idea reminiscent of weaker versus stronger diseases that Samuel Hahnemann touches on in his writings. Technically, a stickler might say that the term "vaccine" should only apply to immunizations using smallpox derivatives and that in the case of other diseases for which immunizations are prophylaxis, the term "vaccine" is inappropriate. Popular convention appears to have overruled such distinctions.

The World Health Organization makes a different distinction between the two terms. According to the WHO a vaccine is the stuff while immunity is the goal, "you can be exposed to it without becoming infected."

> **Vaccine:** A preparation that is used to stimulate the body's immune response against diseases. Vaccines are usually administered through needle injections, but some can be administered by mouth or sprayed into the nose.
>
> **Immunity:** Protection from an infectious disease. If you are immune to a disease, you can be exposed to it without becoming infected.[2]

The command George Washington actually delivered to his troops was that new recruits had to show proof of immunity, (the disease leaves obvious recognizable scars on those who survive it) or undergo a process called variolation.

Variolation was far more serious than vaccination would eventually prove to be. "Variolation used a lancet or needle to introduce pulverized dried smallpox scabs or pustule fluid into the skin of an individual." The term "variolation" is from Latin, "variola," for smallpox. Some medical historians trace the origin of the practice of variolation to tenth century China,[3] or perhaps 16th century China.[4] Still others date the origin much earlier, back to 1000 BC in India.[5] The practice arrived relatively late to Europe and by extension the American Colonies.

Credit for introducing variolation to England is unarguably given to Lady Mary Wortley Montague in 1721. In 1717, Lady Mary Wortley Montagu, the wife of the then British ambassador to the Turkish Empire, learned about variolation in the bath houses of Constantinople. She herself had suffered from the disease as a young woman so the value of prevention was obvious. On her

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return to England, she encouraged experiments that subjected several prisoners and orphans to variolation. When later deliberately exposed to the disease, these subjects were immune.

When acute smallpox infection is acquired through a small localized wound, a healthy person was more likely to survive the infection than if they had acquired the disease naturally through aerosolized viral particles.

When none of these people contracted the disease, variolation was deemed safe and members of the royal family were inoculated. The procedure became fashionable among the well-to-do of Europe. It was only safe in comparison to the full-fledged disease. Patients became quite ill, and mortality rates are estimated to have been from 2-3%. Still, the disease itself was much more lethal. In the 1721 American epidemic that started in Boston April 22, the fatality rate was high. Of the city's population of 10,600 people, 844 died in less than a year, nearly 8% of the total population.[6]

Variolation reached the American colonies about the same time as it did England. In Massachusetts, Cotton Mather promoted variolation as a way to prevent smallpox during the 1721 epidemic in Boston. You may recognize Mather's name for his role in the Salem Witch Trials. Mather first learned about inoculation from a West African slave named Onesimus, writing, "he told me that he had undergone the operation which had given something of the smallpox and would forever preserve him from it, adding that was often used in West Africa.'' After confirming this account with other West African slaves and reading of similar methods being performed in Turkey, Mather became an avid proponent of inoculation.[7]

Mather collaborated with Boston physician Zabdiel Boylston, inoculating patients while keeping records of outcomes. They reported that only 2% of the inoculated died as a result while 14.8% of those with naturally occurring disease succumbed.[8] Not everyone supported variolation. The greatest opposition was based on religious arguments, that preventing the contagion blocked God's will. Other's opposed variolation based on what we might consider sensible grounds, that the procedure was not adequately tested, mechanism was unknown, and that it posed risk to healthy people. Keep in mind that this argument occurred in 1721. Acceptance of the germ theory of disease was still a century and a half in the future.

There have been at least two major variants in smallpox, Variola Major and Variola Minor. The Major variant was dominant in the 1700s and persisted until about 1927 after which the minor strain was responsible for most infections. The minor version was relatively mild with a case-fatality rate of less than 1%.

Back to George Washington. Among the Continental regulars that were under Washington's command, 90% of deaths were caused by disease, and smallpox was the leading cause. Washington wrote to Congress on the 5th of January 1777 informing them of his decision to inoculate the troops. On the 6th he wrote to Dr. William Shippen Jr, explaining that: "Necessity not only authorizes but seems to require the measure, for should the disorder infect the Army…we should have more to dread from it, than from the Sword of the Enemy."

Most British troops were already immune to smallpox, a clear military advantage against the colonists. Americans remained fearful of the immunization process. The Continental Congress had actually issued a proclamation in 1776 prohibiting Surgeons of the Army to inoculate.

Washington knew that a mass inoculation put the entire army in a dangerous position should the British discover what was going on. Variolation still had a fatality rate of 5-10% and even when things went well it took a month to recover one's health. This could not have been an easy choice for Washington.

Less than a quarter of the Continental Army had had the virus. Inoculating the remaining three quarters and every new recruit would have been a daunting task. Washington well knew that variolation would sicken his troops, leaving them invalids for a month. Keeping the plan secret must have only added to the complexity.

There was no precedent to Washington's plan. He secretly gave orders to his commanding officers to oversee the inoculation of their troops. At least eleven hospitals were built where invalided soldiers could recuperate.

"…Washington conducted the first mass inoculation of an army at the height of a war that immeasurably transformed the international system. Defeating the British was impressive, but simultaneously taking on Variola was a risky stroke of genius."[9]

Looking back on these events, one must wonder about the mindset of both Washington and the troops he led. Knowingly committing themselves to variolation, a process that had known risks of being fatal, speaks of a commitment to both their cause and their fellow troops that is now difficult to fathom. Even at the time the concept of herd immunity was understood and the soldiers accepted the risks knowing that they were protecting others from harm.

Vaccination did not end smallpox quickly. The disease continued to be endemic in the world for two centuries. It is estimated that smallpox killed over 300 million people during the 20th century.[10]

The World Health Organization (WHO) initiated a plan to eradicate smallpox originally in 1959. This campaign failed to reach its goal. The WHO launched a second attempt in 1967 conducting immunization and disease surveillance around the world. This time they were successful. The last person to have naturally acquired variola major was a three-year-old in Bangladesh in 1975. The last naturally acquired case from variola minor occurred in October 1977 in Somalia.

The WHO declared smallpox eradicated in 1980, making it the first and only infectious disease that has been eradicated, well almost. The virus now officially exists in two places in the world, the Centers for Disease Control and Prevention in Atlanta, Georgia, and the VECTOR Institute in Koltsovo, Russia. One hopes they are forever secure there.

References

1. Baxby D. Edward Jenner's inquiry after 200 years. *BMJ*. 1999;318(7180):390. doi:10.1136/bmj.318.7180.390.
2. https://www.cdc.gov/vaccines/vac-gen/imz-basics.htm
3. S.R. Eagle, S.C. Gad, in *Encyclopedia of Toxicology* (Third Edition), 2014
4. Jennifer Louten, 15.4.1 Origin of Smallpox Vaccination in *Essential Human Virology*, 2016
5. Stephen N.J. Korsman and Wolfgang Preiser. *Virology*, 2012
6. Hasselgren PO. The Smallpox Epidemics in America in the 1700s and the Role of the Surgeons: Lessons to be Learned During the Global Outbreak of COVID-19. *World J Surg*. 2020;44(9):2837-2841. doi:10.1007/s00268-020-05670-4
7. Buhr, S. To Inoculate or Not to Inoculate?: The Debate and the Smallpox Epidemic of 1721. *Constructing the Past* 2000. 1:61-67.
8. Best, M. Neuhauser, D. and Slavin, L. "Cotton Mather, you dog, dam you! I'll inoculate you with this; with a pox to you": smallpox inoculation, Boston, 1721. *Quality and Safety in Health Care* 2004.13:82-83.
9. https://www.loc.gov/rr/scitech/GW&smallpoxinoculation.html
10. https://www.historyofvaccines.org/timeline/smallpox

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and Drug Administration approved a DHEA vaginal insert (brand name, Intrarosa) to treat dyspareunia (painful sexual intercourse) that is caused by vulvovaginal atrophy secondary to menopause. Intrarosa is very expensive, but DHEA for intravaginal administration can also be obtained at a much lower price from many compounding pharmacies.

DHEA and Osteoporosis

At least six clinical trials have found that treatment with DHEA (usually 50 mg per day) prevented bone loss or increased bone mineral density in postmenopausal women.[11-16] In contrast, two other studies found that administration of DHEA (50 or 100 mg per day for 6 months) had no effect on bone mineral density in women aged 50-65 years or in frail elderly women (mean age, 77 years).[17,18] While there is no obvious explanation for the conflicting results, they might be due in part to differences in baseline status of DHEA or its main metabolites (estrogen and testosterone).

The dosages of DHEA used on most studies (50-100 mg per day) are supraphysiological. One group of investigators reported, based on measurements of various hormone levels, that 10 mg per day seems to be the proper DHEA dose to correct androgen deficiency in postmenopausal women.[19] Physiological doses of DHEA have not been systematically studied with respect to osteoporosis prevention and treatment. However, I saw a woman in her late 30s who had osteoporosis and a subnormal DHEA-sulfate concentration as a result of adrenal insufficiency. After one year of treatment with 10 mg per day of DHEA (with no other changes in her treatment program), the bone mineral density of her lumbar spine increased by 10%.

DHEA and Aging

There is evidence,[18] though conflicting, that the age-related decline in DHEA levels contributes to some of the manifestations of aging. I have seen many elderly patients who were "aging poorly" and whose serum concentration of DHEA-sulfate was below the normal range for young adults of the same sex. Supplementation with DHEA (5-15 mg per day for women, 10-20 mg per day for men) often reversed various manifestations of aging, such as poor appetite, loss of muscle mass, weakness, and depression. Improvement was seen in some cases after as little as two weeks, and the benefits became more pronounced with continued treatment.

Dosage and Administration

When treating osteoporosis or age-related decline in physical or mental function, I have generally recommended oral DHEA. It has been my practice to consider DHEA treatment for patients who have low or low-normal serum DHEA-sulfate levels, when compared with the levels in young adults of the same sex.

As noted above, research suggests that the physiological dosage of DHEA is around 10 mg per day for women; much lower than the amount used in most clinical trials. My clinical experience supports the idea that relatively low doses of DHEA can be effective. In addition to the woman mentioned above with osteoporosis and adrenal insufficiency, I saw two other middle-aged women with severe adrenal insufficiency who had dramatic improvements in various physical and psychological symptoms after 5-15 mg per day of DHEA was added to their treatment regimen. Based on these clinical observations, I have limited the DHEA dosage in nearly all cases to 5-15 mg per day for women and 10-20 mg per day for men (although higher doses may be used to treat autoimmune diseases).

These relatively low doses appear to be sufficient to produce clinical improvements. In addition, the use of low doses minimizes the theoretical concern that DHEA, because it is converted in part to estrogen, could increase the risk of developing estrogen-dependent cancers such as uterine, ovarian, and breast cancer. Such an adverse effect has not been demonstrated to occur; but when using steroid hormones, it is prudent to err on the side of caution.

Alan R. Gaby, MD

References

1. Tsuji K, et al. Specific binding and effects of dehydroepiandrosterone sulfate (DHEA-S) on skeletal muscle cells: possible implication for DHEA-S replacement therapy in patients with myotonic dystrophy. *Life Sci*. 1999;65:17-26.
2. Weksler ME. Hormone replacement for men. Not enough evidence to recommend routine treatment with dehydroepiandrosterone. *BMJ*. 1996;312:859-860.
3. Cumming DC, et al. Evidence for an influence of the ovary on circulating dehydroepiandrosterone sulfate levels. *J Clin Endocrinol Metab*. 1982;54:1069-1071.
4. Monroe SE, Menon KM. Changes in reproductive hormone secretion during the climacteric and postmenopausal periods. *Clin Obstet Gynecol*. 1977;20:113-122.
5. Elias AN, et al. Serum levels of androstenedione, testosterone and dehydroepiandrosterone sulfate in patients with premature ovarian failure to age-matched menstruating controls. *Gynecol Obstet Invest*. 1997;43:47-48. (Although the 25% decline in DHEA-sulfate levels was not statistically significant, it was consistent with findings from other studies.)
6. Labrie F, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. *Menopause*. 2009;16:907-922.
7. Matarazzo MG, et al. Intravaginal 6.5 mg prasterone administration in postmenopausal women with overactive bladder syndrome: A pilot study. *Eur J Obstet Gynecol Reprod Biol*. 2021;263::67-71.
8. Genazzani AD, et al. Long-term low-dose dehydroepiandrosterone oral supplementation in early and late postmenopausal women modulates endocrine parameters and synthesis of neuroactive steroids. *Fertil Steril*. 2003;80:1495-1501.
9. Stomati M, et al. Endocrine, neuroendocrine and behavioral effects of oral dehydroepiandrosterone sulfate supplementation in postmenopausal women. *Gynecol Endocrinol*. 1999;13:15-25.
10. Barnhart KT, et al. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. *J Clin Endocrinol Metab*. 1999;84:3896-3902.
11. Weiss EP, et al. Dehydroepiandrosterone replacement therapy in older adults: 1- and 2-y effects on bone. *Am J Clin Nutr*. 2009;89:1459-1467.
12. Villareal DT, et al. Effects of DHEA replacement on bone mineral density and body composition in elderly women and men. *Clin Endocrinol*. 2000;53:561-568.
13. Labrie F, et al. Effect of 12-month dehydroepiandrosterone replacement therapy on bone, vagina, and endometrium in postmenopausal women. *J Clin Endocrinol Metab*. 1997;82:3498-3505.
14. Jankowski CM, et al. Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: a randomized, controlled trial. *J Clin Endocrinol Metab*. 2006;91:2986-2993.
15. Baulieu EE, et al. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. *Proc Natl Acad Sci*. 2000;97:4279-4284.
16. von Muhlen D, et al. Effect of dehydroepiandrosterone supplementation on bone mineral density, bone markers, and body composition in older adults: the DAWN trial. *Osteoporos Int*. 2008;19:699-707.
17. Morales AJ, et al. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol*. 1998;49:421-432.
18. Kenny AM, et al. Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. *J Am Geriatr*. Soc 2010;58:1707-1714.
19. Pluchino N, et al. One-year therapy with 10 mg/day DHEA alone or in combination with HRT in postmenopausal women: effects on hormonal milieu. *Maturitas*. 2008;59:293-303.

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Dehydroepiandrosterone (DHEA) for Age-Related Health Issues in Women

Dehydroepiandrosterone (DHEA) is a weakly androgenic steroid hormone secreted by the adrenal glands and testes and to a lesser extent by the ovaries. DHEA is metabolized in part to estrogen and testosterone. In addition, DHEA may have physiological actions that are unrelated to its function as a precursor hormone, as suggested by the fact that DHEA receptors are present on human muscle cells.[1]

Circulating DHEA levels (usually measured as DHEA-sulfate) peak around age 25 and decline progressively thereafter. The levels in 70-year-old individuals are only about 20% as high as those of young adults.[2] Although most of the DHEA produced by women is synthesized in the adrenals, the contribution of the ovaries appears to be physiologically significant, as suggested by the observation that premature ovarian failure and ovariectomy each results in a decline in circulating DHEA or DHEA-sulfate levels.[3-5] There is evidence that the menopause-related decline in DHEA levels contributes to the development of menopausal symptoms, and that DHEA-replacement therapy can improve these symptoms in some cases. Moreover, DHEA has shown promise for preventing or treating postmenopausal osteoporosis in some cases, and it may also be useful for treating some of the manifestations of aging in elderly people.

DHEA and Menopausal Symptoms

In a double-blind study, intravaginal administration of DHEA in doses of 3.25, 6.5, or 13 mg per day for 12 weeks resulted in marked improvement in signs and symptoms of vaginal atrophy in postmenopausal women. Each of these doses was similarly effective. Intravaginal administration of DHEA did not cause endometrial proliferation and produced little or no change in serum concentrations of estrogen and testosterone.[6]

In a recent uncontrolled trial, the effect of DHEA was examined in 32 postmenopausal women (mean age, 52.8 years) with overactive bladder in association with the typical genitourinary symptoms of menopause. Overactive bladder is characterized by urinary urgency, frequency, and nocturia, with or without urge incontinence, in the absence of urinary tract infection or other pathologies. In the study, intravaginal administration of 6.5 mg of DHEA daily for 12 weeks resulted in significant improvements in urinary frequency, urgency, nocturia, and urge incontinence. The severity of symptoms of overactive bladder (as assessed by the mean score on the International Consultation on Incontinence Questionnaire Overactive Bladder) improved by 65.4% ($p < 0.001$). DHEA also improved vulvovaginal atrophy and improved quality of life, as assessed by the 12-item Short Form Health Survey.[7]

Orally administered DHEA has also been reported to improve menopausal symptoms, although the results of studies have been conflicting. In an uncontrolled trial, 22 postmenopausal women (aged 50-65 years) received 25 mg per day of DHEA for 12 months. The mean Kupperman score (an 11-item questionnaire that measures the severity of menopausal symptoms) showed progressive improvement. After 12 months the degree of improvement was 76% in women who were two-to-three years postmenopausal and 67% in women who were five or more years postmenopausal.[8] In another study, oral administration of 50 mg per day of DHEA for three months improved the Kupperman score (including improvements in vasomotor and psychological symptoms), and the benefits were similar to those seen with transdermal estradiol (50 µg per day).[9] However, a double-blind trial found that, while treatment with 50 mg per day of DHEA for three months produced significant improvement in perimenopausal symptoms, the improvements were not significantly greater than those in the placebo group.[10]

When treating genitourinary symptoms related to menopause, intravaginal administration of DHEA appears to more effective than oral administration. In 2016, the US Food

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