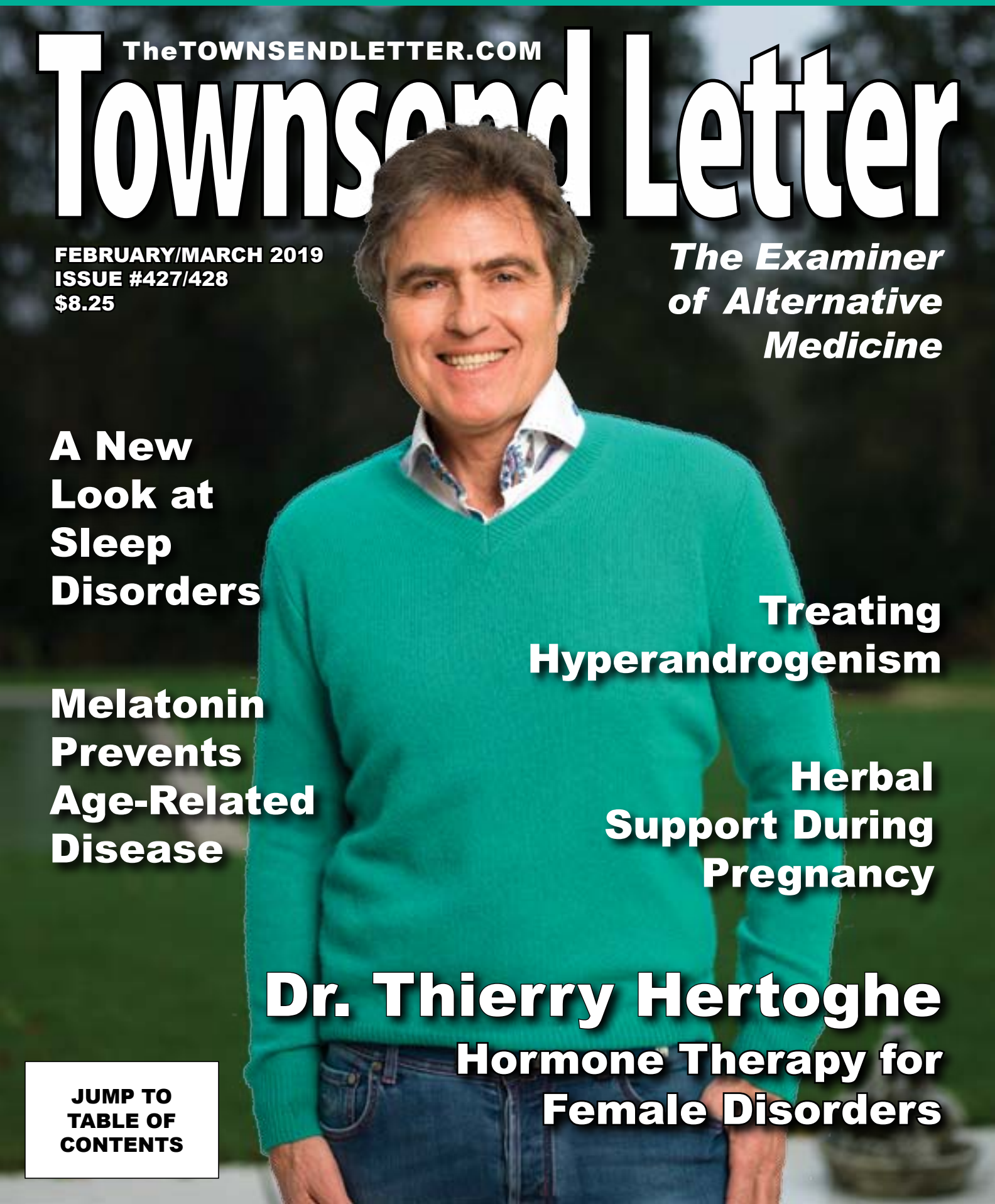
Women's Health



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Dr. Thierry Hertoghe
Hormone Therapy for Female Disorders

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

Clinical Study #2 (2007)

In another study involving 126 healthy pregnant women, *L. crispatus* and *L. gasseri* were the most dominant species found, followed by *L. jensenii* and *L. rhamnosus*.*

Kiss H, *et al. BJOG: An International Journal of Obstetrics & Gynaecology* 2007;114: 1402-1407.

Clinical Study #3 (2014)

In a double-blind, randomized placebo-controlled trial, 1-week of oral supplementation with the four Astarte strains significantly enriched *Lactobacilli* in the vaginal tract and reduced Nugent score in the neo-vagina of post-operative transsexual women, an environment typically resistant to colonization by *Lactobacilli.*

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

Clinical Study #4 (2016)

In immunosuppressed pregnant women with herpes infection, oral supplementation with the four Astarte strains significantly reduced undesirable microbes in the intestines and vagina, and simultaneously increased vaginal *Lactobacilli* 3-fold compared to placebo.* This was accompanied by reduced incidence of placental insufficiency, pre-eclampsia and fetal distress in the probiotic supplemented women.

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

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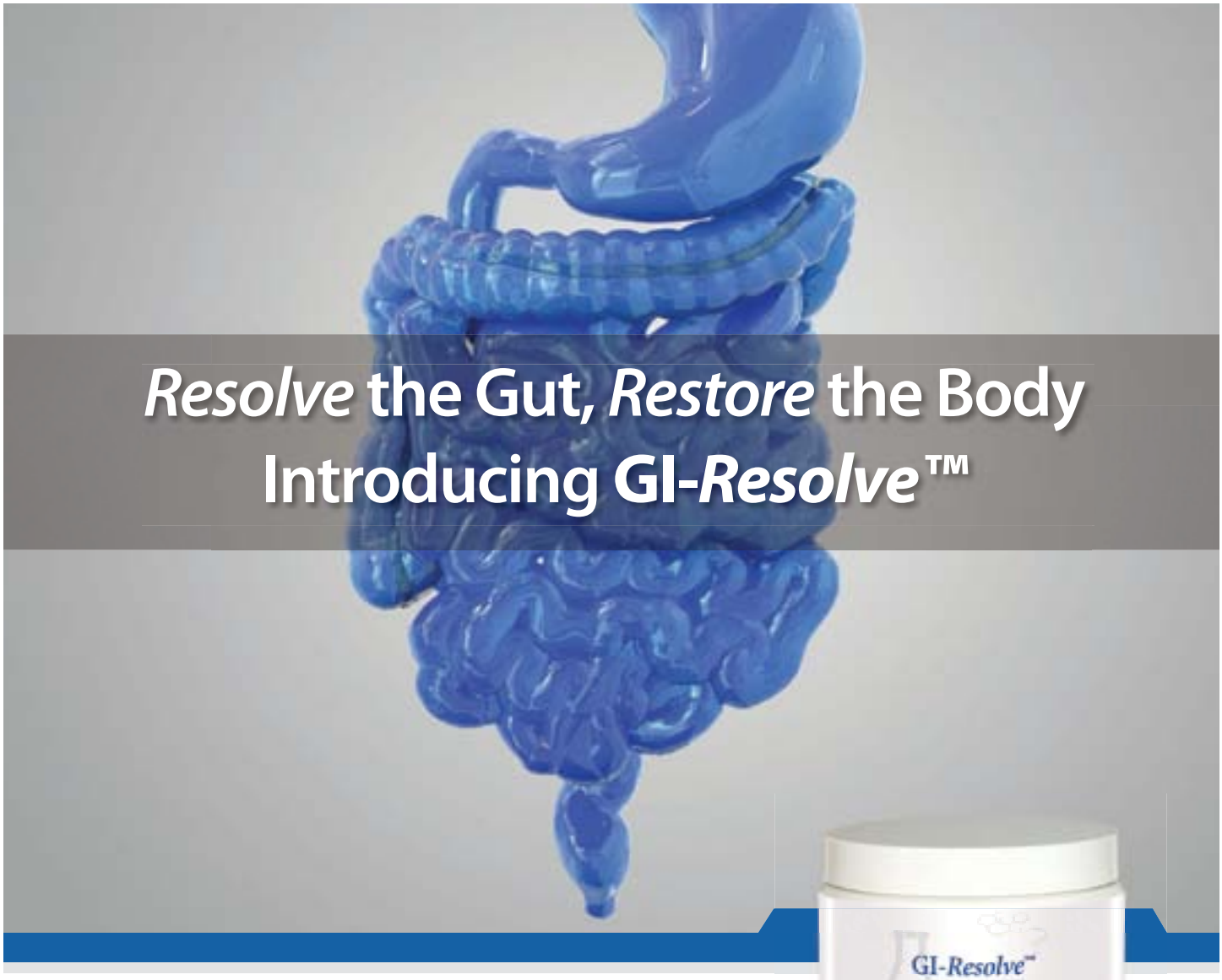

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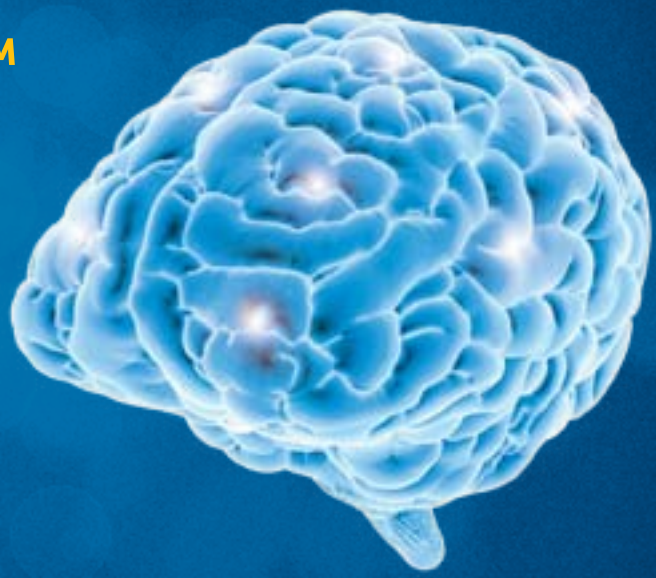

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From the Publisher

Aging Gracefully at the Sands Expo

The American Academy of Anti-Aging Medicine, A4M, holds their major conference the second week of December each year in Las Vegas. Rodeo riders also like that particular week prior to Christmas to hold their annual event. It is not unusual, walking the wide hallways of the Venetian and Bellagio Hotels, to have longevity doctors hobnobbing with cowboys. Of course, one wouldn't mistake the two: the former with their purposeful, determined professional expressions, cell phone in hand, and the latter striding casually attired in cowboy hat and boots – but don't think that wranglers don't appreciate lassoing a calf as seriously as the medicos do administering laser treatment.

Dr. Pamela Wible, MD, a family physician from Eugene, Oregon, was a keynote speaker at last year's A4M convention. Wible has a solution for physician burnout, a term that she

continued on page 6 ➤

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➤ *continued from page 4*

despises as it implies that the cause is the doctor's doing; instead, she blames the medical institution intentionally overworking the health professional as a cost-saving strategy. From a psychiatric viewpoint, she thinks doctors are victimized to such an extreme that they ultimately sustain post-traumatic stress disorder and not a few become suicidal, eventually committing suicide. Dr. Wible wants us to leave the institution or clinic and set up our own "ideal medical clinic." No more consulting with patients for seven minutes, no more seeing forty patients a day. Instead of having a 75 to 85% overhead, we could cut our expenses in half, leaving an overhead of 35%--greater physician income. But Wible doesn't want us to engage in "gimmicks." She claims we have all we need to help patients with our knowledge and experience; there is no need for extensive office instrumentation. We should abandon our draconian institutions and set up a new clinic by immediately seeking the support of the local community and arranging a meet-and-greet.

Certainly, preventing physician suicide is a serious issue and clearly extends longevity. Still burnout (I prefer to continue using the term despite Wible's objections) should be manageable at the institution and hospital without necessitating setting up a bare-bones medical office. Going without a receptionist? I suppose, but what doctors wants to answer phone calls, set up appointments, and collect payments? No devices or gimmicks? Puts a nice roadblock in ordering specialized lab testing, as well as administering IV therapies, laser aesthetics, and stem cells. No practice niche? May be a formula for financial failure.

While Wible TEDtalks that doctors shouldn't treat their burnout with meditation, exercise, and supplementation, that would be just my recommendation for their PTSD. A lighter work load would be great but think twice before opening a two-chair, no-secretary office.

Fasting Our Way to Life Extension

If there was one message to take away from the Las Vegas meeting it was if you want to extend your life span, you need to fast. Ugh! Yes, of all the treatment modalities to live longer, one has to not eat! Well, everyone has done a fast, some have done a series of fasts, and all recognize the difficulty, unpleasantness, and unrelenting hunger attendant to fasting. But the scientific literature is unequivocal about its benefits: better insulin sensitivity, decreased inflammation, reduced oxidation, elimination of edema, and improved cognition are only some of the improvements metabolically. So how does one go about fasting given the body's messaging to "EAT!" Other than nutritional fanatics and individuals engaged in hunger strikes, prolonged

continued on page 8 ➤

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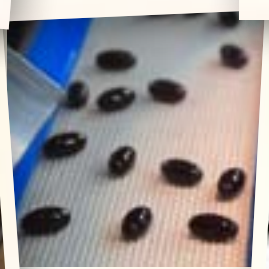
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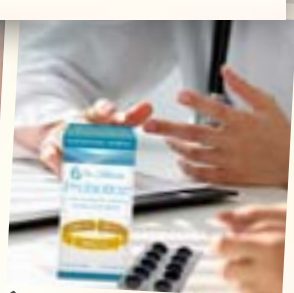
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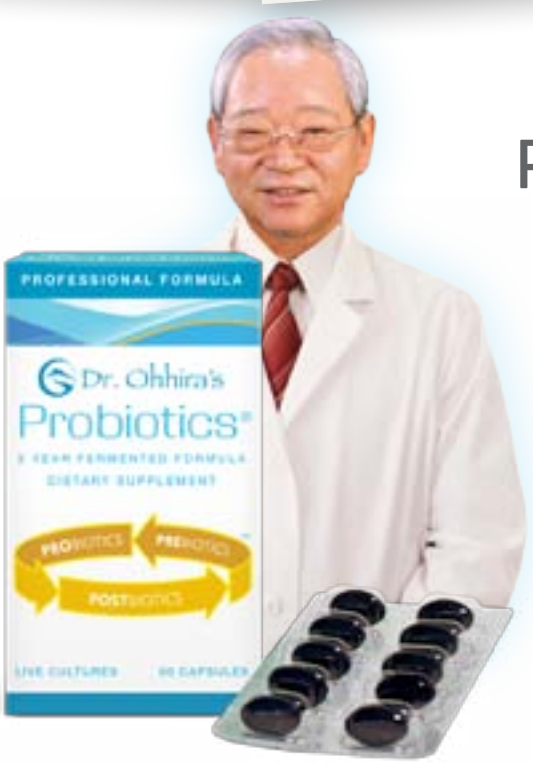

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➤ *continued from page 6*

fasting is not an appropriate strategy. A limited prolonged fast, for example, a three-day fast is manageable but would cause most individuals to experience severe hunger and fatigue interfering with work and day-to-day life. Complete or partial fasting on alternative days would seem reasonable for the patient to accomplish but, as some would say, "life gets in the way." A scheduled party or formal dinner interferes with fasting.

The type of fasting that has "passed muster" both in animal as well as human experimentation is the fasting mimicking diet (FMD). What is a fasting mimicking diet? Basically, it is five consecutive days in a month of eating 800-1100 calories; the first day would be 1100, the next four would be 800 calories. The diet, for those who are non-vegan and non-vegetarian, would be a very limited portion of animal protein, fruit, and vegetables. In setting up human trials using the FMD, the low-calorie diet is provided in packaged nutritional formulas. It has been observed that it is more convenient using the proprietary formulas then preparing meals of limited calories. Studies carried out at USC Medical Center by Dr. Kurt Hong have shown that the FMD can be done five days per month for three months resulting in long-term metabolic improvement without need to repeat fasting. One would assume that further cycles of FMD may be necessary for obese patients.

It is ironic that such a low-tech process like fasting could have such profound life extension benefits. Fasting has long been recognized as a health restorative. In a society that equates a fine meal and wine with elegance and prosperity, a prescription for fasting is generally rejected out of hand. The fasting mimicking diet is a technique that is do-able and should be acceptable for most patients.

Thierry Hertoghe, MD: Hormone Therapy for Premenopausal and Postmenopausal Women

Our cover story for this issue is authored by international hormone authority, Thierry Hertoghe, MD, author of the best-selling book, *The Hormone Handbook for Physicians*, a complete practical guidebook on the 18 most frequently used hormone therapies. He is also the author of the *Atlas of Endocrinology for Hormone Therapy, The Textbook Of Health Aging Medicine,* and the *Textbook of Nutrient Therapy.* His most recent text, *Reversing Physical Aging*, illustrates and details protocols of hormone therapies to reverse aging disorders of the head and senses. (All of Thierry's books are available through University Compounding Pharmacy in San Diego.) Hertoghe is the president of the International Hormone Society as well as World Society of Anti-Aging Medicine. Hertoghe supervises the Hormone Therapy Specialty Program as well board certification

continued on page 10 ➤

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From the Publisher

➤ *continued from page 8*

and international post-graduate education in several societies. He has been a regular contributor to the *Townsend Letter*; be sure to read his two-part series on cortisol deficiency in the January and February/March 2018 issues.

At the A4M meeting in Las Vegas, Hertoghe lectured on using hormone therapies to reverse memory loss and support dementia and Alzheimer's disease. Hertoghe argues that most laboratory tests for hormone therapies do not provide adequate insight to assess whether a patient has optimal hormone levels. While most endocrinologists are satisfied that a low normal hormone level in an older patient is "okay," Hertoghe disagrees. He feels that hormone levels should be optimal, not too low, not too high, whether one is 30 or 80 years of age. An older individual with severe memory loss and low normal hormone levels deserves to be treated with hormones, not for "replacement" but for optimization. Moreover, hormone therapy in the dementia patient can yield major symptomatic response.

Why use a psychiatric drug like Thorazine for treating hostility, anger, screaming and yelling? Turning the dementia patient into a zombie didn't work well for Jack Nicholson in *One Flew Over the Cuckoo's Nest*, and it does not work well for the elderly. Instead one should consider controlling anti-social behavior with the hormone oxytocin. Hertoghe notes that treated individuals become happy and warm hearted, eager to cuddle. A sublingual dose or intranasal dose of 5-10 i.u. works well. Dementia patients tend to experience insomnia and "sundowning." Generally, these patients have reduced melatonin levels. Low-dose treatment, 0.2mg to 1 mg is frequently sufficient to modify the sleep disorder.

It is expected that a female with dementia would have low estrogen and progesterone levels. However, Hertoghe has found low-dose estradiol and progesterone, used separately, is very important for the patient with memory impairment. Similarly, testosterone therapy is needed to support male memory. Low-dose combination T3 and T4 thyroid therapy is needed for both sexes with low normal thyroid functioning. Perhaps the most intriguing memory therapy is the use of IGF1, growth hormone, to support memory function. Hertoghe prefers to inject the IGF1, approximately 0.3 mg subcutaneous peri-orbitally; he feels that this reaches the brain more effectively. Unfortunately, growth hormone treatment is considered controversial by most medical boards so that it may not be available to implement in the US as compared to in Belgium where Hertoghe practices. Other important hormones to consider are vasopressin and pregnenolone.

In this issue Hertoghe offers his tips on optimizing hormones of the pre- and postmenopausal woman.

Jonathan Collin, MD

Pathways to Healing

by Elaine Zablocki

Natural Biochemistry Defeats Cancer

Dana F. Flavin, MD, brings an unusual body of knowledge and skills to her pursuit of safer, more effective treatments for a wide range of diseases. She started out studying psychology and chemistry, then moved on to nutrition, biochemistry, and neuropharmacology. She worked for the Food and Drug Administration as a pharmacologist and wrote a book on the molecular pathology of cancer.

Then, when she married and moved to Germany, the country didn't recognize her previous training. She decided to attend a German medical school. "It was total madness," she recalls. "In the end I had more than 56 semesters of education, but I had no choice."

Because she combines so many different ways of looking at the human healing process, she seems to have a knack for uncovering simple but effective means of treating disease. She recalls one case when a five-year-old boy with Epstein-Barr virus had an extremely swollen liver and spleen. He was treated with salmon oil, alpha-tocopherol, beta carotene, and nicotinamide. Within 24 hours his fever went down, and the swelling was completely gone.

In another case a woman with breast cancer had multiple metastases to the brain. Flavin treated her with detox and diet, including *Boswellia serrata.* After 10 weeks, a CT scan showed that the metastases to the brain had disappeared.

"A patient with stage four breast cancer, who supposedly had only three months to live, was put into total remission after these natural treatments, and lived more than six years. This is something I never expected as a physician," Flavin says. "I thought that natural substances would just help you feel better. When I saw these changes, when I saw the tumors disappearing, I was so flabbergasted I felt that it is my duty to share this information with people."

Nutrients Inhibiting Molecular Targets in Cancer Cells

Cod liver oil	Butyric acid
Vitamin D3	Iodine (Nascent)
Boswellia serrata	Fish oil
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Ascorbic acid	Nicotinamide
Sodium selenite	Lactoferrin

Nutrients Effective in Mitochondrial Targets of Cancer Cells

Beta carotene	Alpha tocopherol succinate
Retinoic acid	Quercetin
Betulinic acid	

Dana F. Flavin, MD

Flavin has developed therapies for many diseases, including autoimmune diseases, rheumatoid arthritis, and viral diseases. Currently much of her research focuses on cancer. "The tumor itself releases substances which support its own increased growth," she says. "Many over-the-counter and off-label drugs can affect these environmental growth parameters and often need to be combined for a stronger anti-cancer growth effect."

She emphasizes nutritional support for cancer patients.

Flavin also notes that there are many factors in cancer patients that down-regulate the immune system. Some of the interleukins down regulate the immune system, but this effect can be reduced by off-label drugs. Gastrointestinal bacteria are dramatically affected by lactic acid, pointing out the importance of reducing lactic acid with off-label drugs and diet. Some low-dose chemotherapy given once can down-regulate T suppressor cells and up-regulate the immune system.

"Combination therapies including pharmacology and nutrients/nutrition used together are so important to complement each other," Flavin says. "One must do both, inhibit the immune suppressors and raise the immune system. Nature provides excellent possibilities for raising the immune system including beta glucans from mushrooms, mistletoe therapy, and much more."

➤

Pathways to Healing

➤

"Reversing cancer with biochemistry utilizes the pathological targets in cancer to down-regulate these targets, weaken tumor cells' defense, up-regulate the immune system, and increase the ability of the body to reverse the disease," she adds. "Biochemistry wins over surgery!"

A Duty to Share Information

In 2001 Flavin founded The Foundation for Collaborative Medicine and Research (CollMed), a research institute devoted to helping people find new ways to improve their health. The global collective of physicians utilizes treatments based on integrative, complementary, and conventional medicine.

At this point Flavin and CollMed have developed a substantial body of valuable knowledge and are seeking the most effective ways to share this information more broadly. Starting in 2019, Flavin expects to publish a series of e-books, starting with "Autoimmune Disease Therapy with Natural Substances." Future books will cover treatments for breast cancer and prostate cancer.

Flavin lives in Germany, but she consults with patients throughout the world via Skype.

She focuses on methods to

- Reverse factors that prevent patients' immune systems from protecting them,
- Enhance the efficacy of conventional medicine, and
- Provide complementary immunotherapy in advanced cancers without adjuvant therapies.

"Regardless of the kind or stage of the cancer, my primary goal is to change my patient's life from hopelessness to a cure," she says. After each consultation she provides a detailed nutritional and supplement protocol and discusses any needed lifestyle changes.

How would Flavin sum up what she has learned for *Townsend Letter* readers? "There are many ways of destroying a cancer, but healing it, so it stays away, is even better," she says. She lists an array of preventive measures we all can implement, such as eating pure foods, exercising, and avoiding heavy metals, plastics, and pesticides. "We have to be our own adults, our own parents, in making our lives healthy," she says. "Many of us know what we should do; we have to find the emotional discipline to do it."

When treating cancer patients, she emphasizes detoxification and emotional support, as well as treatment. "Patients need to know first and foremost that they are not alone. One of my jobs is to help them want to get well. The last hurdle is emotional – to reduce stress factors, to bring forward their reasons for seeking health."

Resources

The Foundation for Collaborative Medicine & Research (CollMed) – http://collmed.org/; 203-987-5322

For personal consultations with Flavin: http://collmed.org/consultations/

Also see research papers and videos: http://collmed.org/health-matters-videos/
http://collmed.org/dr-dana-flavin-white-papers/

The website includes a blog: http://collmed.org/blog/

Recent topics include: Can an Off-Label Drug Stop Multiple Sclerosis, Help Viral Diseases...and Cancer?
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From Bipolar to Schizophrenia: Parasites and Psychiatric Disorder
What Causes Diabetes 2? (Sugar isn't the problem.)
Smart Food, Smart Kids (or Why junk food is making us stupid)

Elaine Zablocki is the former editor of CHRF News Files. ◆

Let's Face It… Successful Aging is More than Just Hormones

While it's the case that many menopausal women find themselves contemplating hormone replacement therapy, there are new and equally important supplement considerations. Offsetting chronic disease – which impacts physical health and mental well-being – is a top priority, especially if you want to live a long life with vitality and mental clarity and without pain or disability. Exciting new research is fueling our growing understanding of the gut microbiome and how these microorganisms can regulate gene transcription, translation, and human metabolic processes. Aging is associated with reduced microbial diversity, and healthy aging correlates with increased microbial diversity. Simply put, take good care of your gut bugs, and they'll take care of you.

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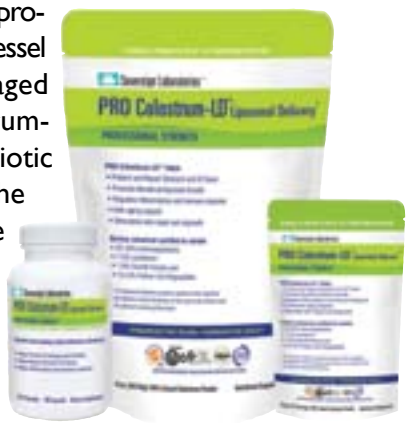

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Preventing Falls
A serious matter:
One in four falls in the elderly proves fatal.
by Ralph K. Campbell, MD

Being a physician doesn't qualify me as an expert on falling. But because I am 91 years old, I have mighty good motivation to keep learning. In my experience, many geriatrists (specialists in the problems of older people) seem to lack the curiosity needed to listen to, and learn from, their patient's questions. Curiosity is motivated by a desire to really know the "whats" and "whys" of the changes that come with age and also by the desire to hear the patient's story. They can't get into these topics because, under the present medical care system, they don't have enough time. But common sense dictates that they need to discuss the basis of these problems before just prescribing pharmaceutical relief.

Aging: Mental and Muscular

If one looks around, it is easy to observe that aging is an individual thing, many times without a direct relationship to chronological age. Mental stress is a big factor in developing what we call aging. When we get worse in associating names with faces, this might foretell a need to think about the gradual decline in physical and mental functions. We say, "He is losing his grip"; yes, in muscles but also in ability and often in attitude. It is easy to observe problems that derive from diminishing sex hormone levels: hot flashes in women and some rearrangement of body fat around the waist, and an overly-emphasized diminished libido in men. The less obvious, but more significant, effect in men is diminished muscle strength and muscle wasting when testosterone levels fall. A similar effect of muscle weakening with age exists in women.[1] But we know that using muscles is an excellent way to slow the wasting process.

Quads and Squats

What does this have to do with falling? When you begin to fall forward, you quickly and instinctively thrust a foot out in front in order to catch yourself. If your quadriceps (the big thigh muscle) is weak, you may not be able to catch yourself. I feel jealous watching a NFL running back who leaps high to complete a forward somersault – he can't put his hands down, because he has to hang on to the ball – and lands squarely on the back of his neck and upper thoracic spine, then pops up on his feet as if it never happened. So don't try this in your home. But maybe do some squats every day. A five- or ten-pound weight in each hand makes this exercise even better.

Nutrients Help

It has been shown that, with age, one has a diminished ability to make creatinine, a precursor of ATP, responsible for muscle strength. Fortunately, there is creatinine in supplement form; so it can be used in conjunction with the "use it or lose it" principle.[2-5] Other supplements of essential nutrients may also help, including the B vitamins, vitamin D, and omega-3 fatty acids. "Postural sway is linked to increased risk of falls, and sway was more prevalent in those with serum 25(OH)D [vitamin D] concentrations below 30 nmol/L."[6] Excellent nutrition including adequate amounts of vitamins and essential nutrients is known to be important for maintaining weight, muscle mass, and cardiovascular health.[7-9] Vitamins C and E are necessary, especially in older people, to maintain skin, joints, muscles, blood vessels, and many organs including nerves and the brain.[10] And to get the most improvement with exercise, it's important to eat enough protein.

Muscle Sense

Proprioception is a kind of muscle sense through nerve endings in muscles that are stimulated by contraction. With age, we gradually lose the sense of proprioception. We have difficulty going down stairs while carrying a load that obscures our vision as we wonder "where did that next step go," or "just where is my foot?" In our youth, proprioception automatically did the "looking" for us. Just walking on an uneven surface now can cause confusion. A substitute for healthy proprioception is a must for those experiencing aging, and that is having – and using – a hand rail next to steps. With one hand on a railing, one can feel better oriented in space. The ease of negotiating steps may vary. There will be times in which we are only comfortable when taking baby steps. So be it. After all, we are in our second childhood.

The Eyes Have It

Cataract formation (opacity of the lens of the eye) is common in older folks. We have enjoyed eye-dominance – the brain's reliance on seeing the world around us – all our lives. When we change our focus from one object to the other, we almost instantaneously zero in with our dominant eye as the other eye follows. The greater the difference in visual acuity between the eyes, the longer the lag time that provides a moment of "where am I?" Proper depth perception depends on eyes, with similar acuity, working together. When vision is quite poor in one eye, we lose stereoscopic vision or depth perception. Again, an irregular surface can present a problem, as one might not detect the irregularity in time to avoid it. Adequate doses of essential nutrients from an excellent diet and supplements, including the B vitamins, and vitamins C, D, and E, omega-3 fatty acids, zinc, and magnesium, are essential to maintain health of the eyes as we age.[11]

One at a Time

Nobody performs their best with multitasking. Older folks are particularly affected. The old adage of "don't try to think and chew gum at the same time" has some merit. Just put your full attention on the task at hand. If you are smart enough

to operate a smart phone, don't do it while going downstairs, walking, or doing anything else. Even smart kids are having trouble with this.

Ears, Brain, and Balance

An easy test to demonstrate that balance "ain't what it used to be" is to try standing on just one leg. Since you might not do too well, try this in a place where you have something to grab onto if you start to fall. This deterioration of balance is made worse by a sudden change in position, probably due to deterioration of function of the semi-circular canals of the inner ear. These act like gyroscopes to tell you just where you are in space – something automatic that we often don't think about. There may be a connection between hearing loss and the workings of the inner ear. So if you have hearing loss, it might be better to be checked out by an ENT doctor, who can also evaluate inner ear function, before being fitted with a hearing aid.

Blood Circulation

Arising from a sleeping position too quickly may cause hypotension or even fainting. There are sensors in the carotid arteries (in the neck) that are designed to immediately kick in to avoid even momentary inadequate blood supply to the brain. However, these sensors don't function as well in the elderly, and often the carotid arteries are not as open as they used to be. So make that position change more slowly. Take stock of what you safely can do and what you can't. If you feel hesitant to get on a ladder, don't.

Maybe you think like I do: I don't as much fear falling as I do landing. I might slip on the ice. But I would much rather fall forward and risk breaking a wrist, than backwards and hit my head which can produce a concussion or, more subtly, cause bleeding entrapped by the covering of the brain (cephalohematoma), which may amount to real neurological trouble soon after. This problem develops much more readily in those on a daily aspirin regimen. The rigid, boney skull, of course, stops suddenly as it hits the hard surface, but the brain inside moves abruptly, which might cause blood vessels to tear. The bleeding may rapidly come to a stop unless enhanced by aspirin, which inhibits the first step in coagulation of blood – clumping of platelets.

Vitamins Help

Vitamin E slows blood clotting but has fewer side effects than taking aspirin, so it tends to prevent ischemic strokes, the most common type.[12] Vitamin C helps to maintain collagen so it strengthens arteries and makes them more elastic, which tends to prevent high blood pressure and hemorrhagic strokes.[13] So taking vitamin C and E together is beneficial: they both help to keep blood vessels strong and the blood flowing.[12-14] Further, vitamin C can regenerate vitamin E after it completes its antioxidant function.[15,16]

Recommended Supplement Doses

Since the firing of nerves is what causes muscle contraction, the nervous system needs all the help it can get. Several of the B vitamins are necessary co-factors in the formation of vital neurotransmitters. So, I recommend that you work with your own physician and consider taking:

- B-complex preparation (containing at least 50 mg of B1, B2, B3, B5, B6; 50 mcg of biotin and B12, and 500 mcg of folate) twice a day.
- 500 mg additional B3 as niacin or niacinamide. Niacinamide does not cause flushing. With niacin, start with 50 mg and *gradually* increase over several weeks to 500 mg 2x/day to avoid the skin flush.[10,11]

Many multivitamins contain the B-complex vitamins and some magnesium, zinc, and other essential vitamins and minerals. But you'll want to take additional

- Vitamin C (1000 mg 3x/d, more when stressed or ill)
- Vitamin D (2000-5000 IU/d)
- Vitamin E (mixed tocopherols 400-800 IU/d)
- Additional magnesium 100-200 mxg 3x/d (in citrate, malate, or chloride form)
- Possibly additional zinc (50 mg with 2 mg copper).

Health of nerves is also aided by taking a fish oil supplement rich in omega-3 fatty acids, which makes a more favorable myelin nerve sheath and enhances the transmission of nerve impulses.

Dietary Recommendations

- Eat a lower-carb diet, which will prevent bone mineral loss from too high sugar intake.
- Try intermittent fasting to increase growth hormone levels.
- Do squats and other weight-bearing exercises.

Many elderly people fall because they've broken a brittle femur (the thigh bone), which is one more reason why eating right and taking supplements including vitamin D and magnesium, along with weight-bearing exercise, are so important.

Your balance will be better sometimes than at others. Don't worry about being slow, since the alternative spells trouble. Rather, just give full attention to the task at hand and be thankful for what you *can* do. You can focus on eating an excellent diet, which means eating colorful vegetables, nuts, unprocessed whole foods, moderate amounts of meat and fish, and adequate doses of supplements of essential nutrients. And you can get adequate, appropriate exercise.

"We get too soon old and too late smart," says the old proverb. Movement with healthy awareness and healthy nutrition can help us get smarter a lot sooner and older maybe a tad later.

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In this Issue

February/March 2019 | #427/428

ON THE COVER: Dr. Thierry Hertoghe – Hormone Therapy for Female Disorders (pg. 34); A New Look at Sleep Disorders (pg. 42); Melatonin Prevents Age-Related Disease (pg. 50); Herbal Support During Pregnancy (pg. 68); Treating Hyperandrogenism (pg. 58)

Shorts

briefed by Jule Klotter
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Cochrane Collaboration Update

Peter Gøtzsche, co-founder of the Cochrane Collaboration, was suspended from the Nordic Cochrane Centre and from his clinical professor position at the Rigshospitalet and University of Copenhagen by the Danish ministry of health on October 29, 2018. Dr. Gøtzsche had been elected to the Cochrane Governing Board in 2017. Disputes with Cochrane CEO Mark Wilson led to his removal from the board in September 2018 (See January 2019 "Shorts"). In his December *Politiken* article, Dr. Gøtzsche wrote: "Wilson has required that I shall no longer be allowed to work at the Cochrane Centre, and the Ministry and Rigshospitalet have pleased him, although, according to Cochrane rules, I can continue working as head of department or as chief physician."

David Hammerstein, one of the four Cochrane Governing Board members who resigned in protest of Gøtzsche's removal from the board, and Tom Jefferson, MD, a current member of Cochrane, have petitioned the Danish minister of health to reconsider the suspension. As of December 30, 2018, over 9200 signatures were on the petition (https://www.ipetitions.com), including that of Cochrane co-founder Sir Iain Chalmers; *BMJ*'s editor Fiona Godlee, and John Ioannidis, a highly-cited health researcher from Stanford University (California).

Although Ioannidis does not necessarily agree with Peter Gøtzsche's positions regarding psychiatric drugs, the HPV vaccine, and the pharmaceutical industry, he deeply respects him as a scientist and defends "his right to provide dissenting views, hopefully with data and evidence." In a *European Journal of Clinical Investigation* editorial, Dr. Ioannidis praises Gøtzsche's "major contributions to evidence-based medicine," his advocacy for transparency in clinical research, and his fight against conflicts-of-interest.

While he acknowledges that "Gøtzsche is a well-known firebrand," Dr. Ioannidis condemns the secrecy, lack of transparency, and questionable reasons that shroud Gøtzsche's dismissal from the Cochrane Collaboration: "The position that the alleged bad behaviour needs to remain undisclosed has become entirely untenable, given this evolution.... If they have solid evidence against PG, they should be transparent about declaring it." Moreover, Ioannidis voices concern for the future of this heretofore respected scientific body:

> It is worrisome that neither the remaining Board members nor the Cochrane CEO have a particularly strong track record in what Cochrane became famous for: evidence-based medicine and high-quality, independent systematic reviews. None of them have published as key authors any pivotal, highly influential paper on systematic reviews and evidence-based methods.

He would like to see all remaining members of the governing board to resign after elections have filled the empty positions to "safeguard their integrity, accountability, and leadership."

"If you can easily get rid of inconvenient people and thus their research and participation in the academic debate, it can have serious consequences both for community health and economics." – Peter Gøtzsche.

Gøtzsche P. It is a full-blown scandal that Rigshospitalet will dismiss me. *Politiken.* December 11, 2018.
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Epigenetic Effects of Herbicides

Laboratory research is showing that widely used agricultural chemicals, such as the herbicide atrazine, can have epigenetic effects that affect the health of future generations. Atrazine, commonly used on soy and corn crops in the US, acts as an endocrine disrupter and has been linked to increased incidence of birth defects. The European Union banned atrazine in 2003 because of its prevalence in drinking water. The US Environment Protection Agency, however, allows its use. A 2017 rat study, led by Margaux McBirney, indicates that atrazine causes epigenetic changes resulting in testis disease, hyperactivity, and increased susceptibility to multiple diseases. Presently, chemicals are evaluated for immediate toxicity with lethal dose testing (i.e., LD50); epigenetic changes are not considered by government regulatory agencies.

In the 2017 lab study, McBirney et al injected gestating rats with 25 mg/kg body weight atrazine (days 8 to 14) intraperitoneally. This amount is 4% of the rat oral LD50 and considered a "putative high dose environmental exposure." The gestating females (generation F0) showed no indication of toxicity or pathology from the injections during three to six months of monitoring. The researchers evaluated the next three generations of rats, in control and atrazine lineages, for pathology at age one year. In the

atrazine lineage, F1 generation were the offspring of the injected rats (F0); F2 came from the egg/sperm of the rats exposed in utero (grandchildren); and F3 were considered transgenerational (great-grandchildren), as they had no direct germline (egg or sperm cells) exposure to atrazine.

The results for kidney disease, prostate disease, and ovarian disease were the same for controls and atrazine-lineage rats in F1, F2, and F3 generations at one year. While testis disease was similar between the F1 controls and F1 atrazine-lineage rats, the F2 and F3 atrazine rats had more testis disease that their controls, with about 25% of the F3 generation ("a five-fold increase in disease risk") affected. Tumor development was higher in the F2 generation, but not the F1 or F3 generations. Tumors were generally adenomas or sarcomas, and mammary tumors were most common.

What I found most troubling was the number of atrazine lineage rats in the F3 generation with two or more health issues. While the researchers found no statistical difference in disease incidence between the control lineage rats and the corresponding F1 or F2 atrazine lineage animals, over 50% of the F3 atrazine lineage males (2.7-fold increase) and females (4.6-fold increase) showed multiple disorders, including tumors, testicular disease, emotional and physical problems, hyperactivity, abnormal sperm, and premature puberty, compared to F3 controls. In addition, F3 atrazine males exhibited higher risk-taking behavior during testing.

McBirney et al found epigenetic alterations in the sperm of all three generations of the atrazine lineage males. They also found unique groups of DNA methylation regions for testis disease and lean phenotype found in F3 generation males: "This provides a preliminary proof of concept that epigenetic biomarkers for disease can be identified and potentially used in the future to diagnose disease and disease susceptibility."

Atrazine is not the only agricultural chemical with epigenetic effects, say McBirney et al. DDT exposure promoted testis disease, polycystic ovarian disease, immune abnormalities, kidney disease, and obesity in later generations. Vinclozolin, a common fungicide used on grapes and other fruits and vegetables, stimulated an increased incidence of prostate disease, kidney disease, immune system abnormalities, testis abnormalities, and tumors in transgenerational rats. The authors urge government regulators to include transgenerational effects in their chemical safety evaluations. Paul Winchester, MD, one of the co-authors of this study told GMO Free USA "...in the current paradigm, which is definitely pro-business, the only thing companies have to prove is that it doesn't kill you if you drink it or take a big dose of it."

If environmental factors can produce infertility and more disease through epigenetic changes, environmental factors can also increase health; but, I doubt that future generations can experience increased health so long as outdated safety tests permit widespread use of harmful chemicals.

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Shorts

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Human Breast Milk and the Infant GI Tract

"Human milk oligosaccharides (HMOs) are the third largest solid component of human milk (after lactose and fat) even in times of famine, and yet these free glycans are not digestible by the infant as the human gut does not produce the glycosidases necessary to cleave the HMO linkages," say Mark A. Underwood and colleagues at University of California-Davis. In fact, only a few species of commensal bacteria in the gastrointestinal tract view HMOs as food. So, if a baby cannot digest HMOs, why does human breast milk contain so much? It turns out that HMOs are the staff of life for *Bifidobacterium longum* subspecies *infantis*. (*B. longum* has two subspecies: subspecies *infantis* and subspecies *longum.)*

Underwood et al report, "*Bifidobacterium longum* subspecies *infantis* (*B. infantis*) is unique among gut bacteria in its prodigious capacity to digest and consume any human milk oligosaccharide structure, the result of a large repertoire of bacterial genes encoding an array of glycosidases and oligosaccharide transporters not found in other bacterial species." The high HMO-content gives *B. infantis* a competitive advantage, discouraging the growth of other bacteria, including pathogens.

In addition to inhibiting pathogen colonization, *B. infantis* provides important protections for the baby's developing GI tract and immune system. *B. infantis,* in the presence of HMOs, suppresses the production of pro-inflammatory cytokines, helping to control inflammation, according to in vitro and in vivo studies. *B. infantis* also decreases intestinal permeability by increasing the expression of genes that direct the production of junction proteins. Moreover, *B. infantis,* in the presence of HMOs, appear to have "an increased ability to bind and colonize the intestinal mucus layer" – which makes me wonder if this bacteria has an on-going role in regulating immune response. High levels of *B. infantis* in babies' stool have been associated with better weight gain, increased thymic index, and greater response to some vaccines.

The benefits of *B. infantis* have led to testing supplemental probiotic strains in breastfed infants. Breast milk is key as supplementation without providing the food the bacteria needs (in this case human milk oligosaccharides)- will not provide ongoing effects; GI bacterial composition changes with food consumed – even in babies.

A 2017 study, led by Steven A. Frese, compared breastfed infants as a control (n=32) to breastfed infants given *B. infantis* EVC001 from day 7 to day 28 of life (n=34). Both groups included babies who were born vaginally and those born by caesarean section. Caesarean-born infants are known to develop a very different GI microbiome because they are not exposed to the commensal bacteria in the birth canal. The authors analyzed the bacterial content of the babies' stool by using 165 rRNA gene sequencing, quantitative PCR, mass spectrometry, and endotoxin measurement. At day 60, the breastfed infants – regardless of delivery type – in the supplement group still had high levels of bifidobacteria. The Bifidobacteria levels of the babies in the supplemented group were more than twice that of the control group: 85.56% relative abundance for vaginal-delivery supplemented and 78.99% for the caesarean supplemented vs. 36.57% for the vaginal delivery controls and 29.37% for the caesarean controls.

While probiotic supplementation may be helpful for babies, I question the wisdom of relying on just one species. From what little we know about the gut microbiome, diversity is a sign of health. Are these high levels of Bifidobacteria crowding out some other species that play a role in health? Children would need to be followed long-term to see if this type of supplementation has unintended effects.

Frese SA, et al. Persistence of Supplemented *Bifidobacterium longum* subsp. *infantis* EVC001 in Breastfed Infants. *mSphere.* November/December 2017;7(6).
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Vitamin C and Bone Health

We hear about the importance of calcium and vitamins D and K2 in the prevention of osteoporosis, but vitamin C may be as important – if not more. A blog post by Marc S. Micozzi, MD, PhD, points to vitamin C deficiency as the reason that osteoporosis is so common in the US and "virtually unknown in East and Southeast Asian women" – at least until recently. "Problems with low bone-mineral density have been surfacing in South Korean women as they become more westernized in their diet and lifestyle," he writes. "So Korean researchers decided to investigate what's really going on."

Dr. Micozzi refers to a 2016 Korean epidemiological study that looked at vitamin C intake, physical activity, and osteoporosis among 3,047 Korean adults age 50 and over. On the whole, those with osteoporosis (n=1212) were older, had lower BMI, less dietary energy intake, less vitamin C and calcium intake, and lower vitamin D levels than the normal group. Income, education level, smoking, and physical activity were also significantly different between the two. As the study authors note, the cause of osteoporosis is multi-factorial. They did, however, find a correlation between vitamin C intake and osteoporosis; the incidence of osteoporosis decreased as vitamin C intake increased. Vitamin C appeared to have a greater protective effect in those who did not engage in regular physical activity than in those who did. Physical activity encourages bone formation, increases bone density, and prevents age-related bone mass loss.

The interaction between physical activity, antioxidants, and bone mass needs further clarification. A 2010 double-blind, controlled clinical trial with 90 elderly people, lasting 12 months, found evidence that daily supplementation with vitamin C (1000 mg) and vitamin E (400 IU of alpha-tocopherol) helped prevent and improve age-related osteoporosis. A 2017 clinical trial, however, found that elderly men who took 1000 mg vitamin C and 235 mg of vitamin E daily in addition to three sessions of resistance training each week had *less* improvement in hip and lumbar spine bone mass density than men who simply engaged in resistance training. The authors say, "High doses of antioxidant supplementations may constrain the favorable skeletal benefits of 12 weeks of resistance exercise in healthy elderly men." Given that hormones also play a role in bone loss, I'm not sure if these findings would apply to women as well.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Comparing Folic Acid and 5-Methyltetrahydrofolate (5-MTHF) Supplements

One hundred forty-two healthy women (aged 20-45 years) living in Malaysia, where there is no mandatory folic acid fortification, were randomly assigned to receive, in double-blind fashion, 1 mg per day of folic acid, an equimolar amount of L-5-methyltetrahydrofolate (5-MTHF; 1.13 mg per day), or placebo for 12 weeks. At 12 weeks, the mean folate concentration in red blood cells and plasma was significantly higher in the 5-MTHF group than in the folic acid group. At 12 weeks, compared with baseline, the mean plasma homocysteine level was significantly lower by 17% in the folic acid group and by 15% in the 5-MTHF group, with no significant difference between folic acid and 5-MTHF.

Comment: In recent years, it has been argued 5-MTHF is preferable to folic acid as a nutritional supplement. Some manufacturers have replaced folic acid with 5-MTHF in their multivitamin products, and some practitioners are of the opinion that products containing folic acid should not be used. In my previous writings, I have concluded that the evidence is not sufficient to justify routinely using 5-MTHF instead of folic acid.[1] This conclusion was based on two main points. First, the vast majority of the research demonstrating clinical benefits of folates has used folic acid. While a biologically active form of folate such as 5-MTHF might theoretically be more effective than a precursor molecule, we do not know enough about how 5-MTHF as a supplement is transported and utilized in our cells and tissues to make assumptions about its comparative clinical efficacy. Preliminary evidence suggests that folic acid is at least as effective as, and may be more effective than, 5-MTHF for lowering homocysteine levels and for augmenting the antidepressant effect of selective serotonin-reuptake inhibitors (SSRIs). Second, 5-MTHF is less stable than folic acid. That fact could be particularly important when 5-MTHF is included in a multivitamin-multimineral preparation containing ingredients such as vitamin C, copper, and thiamine, which may chemically interact with other nutrients.

In the present study, 5-MTHF was more effective than folic acid for raising erythrocyte and plasma folate levels, an effect that is of uncertain clinical importance. A more clinically relevant outcome is the effect on homocysteine levels. With respect to that parameter, folic acid was at least as effective as 5-MTHF. That finding supports my previous conclusions regarding the inadvisability of routinely substituting folic acid with 5-MTHF. On the other hand, anecdotal reports from some practitioners suggest that 5-MTHF is sometimes more effective than folic acid for achieving various clinical outcomes. However, there does not appear to be any lab test (including the MTHFR C677T polymorphism) that can reliably predict who those patients might be.

Henderson AM, et al. L-5-Methyltetrahydrofolate supplementation increases blood folate concentrations to a greater extent than folic acid supplementation in Malaysian women. *J Nutr*. 2018;148:885-890.

Can Whole Grains Prevent Type 2 Diabetes?

The association between consumption of whole grains and risk of type 2 diabetes was examined in a prospective cohort study of 55,465 individuals (aged 50-65 years at baseline) participating in the Danish Diet, Cancer, and Health study. During a median follow-up period of 15 years, 7,417 participants were diagnosed with type 2 diabetes. After adjustment for age, physical activity, intake of processed meat, and other potential confounding variables, the incidence of type 2 diabetes was significantly lower by 11% for men and 7% for women for each serving (16 g) of whole grains consumed per day. For men, intakes of all whole-grain cereal types investigated (wheat, rye, and oats) were significantly associated with a lower risk of type 2 diabetes, but only wheat and oats intake were significantly associated for women.

Comment: In this study, increased consumption of whole grains was associated with a decreased risk of developing type 2 diabetes. While observational studies do not prove causation, there are several different mechanisms by which eating whole grains might help prevent diabetes. First, the relatively high fiber content of whole grains may slow the absorption of carbohydrates, thereby blunting the postprandial rise in plasma glucose levels and decreasing the amount of stress on the pancreas. Second, consumption of high-fiber foods may increase satiety from a meal, thereby decreasing the risk of overeating. Third, whole grains, as compared with refined grains, contain larger amounts of various micronutrients that play a role in regulating glucose levels, such as magnesium, zinc, copper, and chromium.

Kyro C, et al. Higher whole-grain intake is associated with lower risk of type 2 diabetes among middle-aged men and women: the Danish Diet, Cancer, and Health Cohort. *J Nutr*. 2018;148:1434-1444.

Unusual Case of Vitamin C Dependency

A three-year-old previously healthy Swiss girl without any history of poor dietary intake presented with persistent fever, purpura on the extensor sides of the extremities, refusal to bear weight, and gingival bleeding. Blood tests revealed a significant increase of inflammatory markers and hypoalbuminemia. Full-body MRI revealed symmetrical bone marrow edema consistent with childhood scurvy. Serum vitamin C was in the low-normal range. After starting 500 mg per day (36 mg/kg/day) of oral vitamin C, the child showed rapid clinical, laboratory, and radiologic improvement. Vitamin C was stopped after four months, and within two weeks she developed pronounced fatigue, refusal to walk, and hair loss. These symptoms resolved when oral vitamin C was resumed. Dietary vitamin C intake was considered adequate for a normal child. The cause of this apparent dependency on high-dose vitamin C was not determined.

Comment: This is thought to be the first case of scurvy symptoms that were not directly linked to deficient dietary intake of vitamin C. The reason for this unusually high vitamin C requirement was not determined. The findings from this case raise the possibility that milder forms of vitamin C dependency occur more commonly in the general population. Individuals with a higher-than-normal vitamin C requirement might experience symptoms such as fatigue, depression, poor wound healing, or increased susceptibility to infection that would respond to vitamin C supplementation, even if their dietary intake meets or exceeds the Recommended Dietary Allowance.

Vaezipour N, Leibundgut K. Nonalimental scurvy with relapse symptoms after stopping oral vitamin C supplementation. *Pediatrics*. 2018;142:e20172139.

Magnesium Deficiency Increases Susceptibility to Pain

Two patients with metastatic cancer and chronic pain were found to have hypomagnesemia. Treatment with intravenous magnesium resulted in improved pain control and decreased the need for opioid medication.

Comment: N-Methyl-D-aspartate (NMDA) activation is considered to be one of the mechanisms involved in pain. Magnesium is an NMDA antagonist and may therefore be of value for decreasing pain. Animal studies suggest that magnesium is involved in pain control and that magnesium deficiency can cause increased susceptibility to pain. Intravenous magnesium has been used with some success to decrease postoperative pain and to reduce analgesic requirements in surgical patients.[2]

Magnesium deficiency is common in cancer patients. It may result either from cancer-related malnutrition or from the administration of chemotherapy drugs such as cisplatin. The findings from the present case reports suggest that identifying and correcting magnesium deficiency can improve pain control in cancer patients.

Coyle S, Monnery D. Improved analgesia by correction of hypomagnesaemia? *BMJ Support Palliat Care*. 2018;8:294-296.

Melatonin for Delayed Sleep-Wake Phase Disorder

One hundred sixteen Australian volunteers (aged 17-64 years; mean age, 29 years) with delayed sleep-wake phase disorder and a delayed endogenous melatonin rhythm relative to the subject's desired bedtime (as determined by salivary melatonin levels) were randomly assigned to receive, in double-blind fashion, 0.5 mg of melatonin or placebo one hour before desired bedtime for at least five consecutive nights per week for four weeks. The mean time required to fall asleep decreased by 34 minutes more in the melatonin group than in the placebo group ($p = 0.01$). Mean sleep efficiency (defined as the ratio of total time asleep to total time in bed) improved to a significantly greater degree in the melatonin group than in the placebo group ($p = 0.03$).

Comment: Delayed sleep-wake phase disorder is characterized by difficulty falling asleep when attempting sleep at conventional times, and difficulty waking at the required time for daytime commitments. Published therapeutic guidelines recommend the use of melatonin for this disorder, but there have apparently

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been no randomized controlled trials to confirm its efficacy. The results of the present study demonstrate that a relatively low dose of melatonin (0.5 mg at night) can decrease sleep-onset time and improve sleep efficiency in people with delayed sleep-wake phase disorder associated with a delayed endogenous melatonin rhythm.

Sletten TL, et al. Efficacy of melatonin with behavioural sleep-wake scheduling for delayed sleep-wake phase disorder: A double-blind, randomised clinical trial. *PLoS Med*. 2018;15:e1002587.

Not All Saturated Fats Are the Same

Ninety-six healthy British men and women (mean age, 60 years) with no known history of cancer, cardiovascular disease, or diabetes, who were not on lipid-lowering medication, were randomly assigned to consume 50 g per day of extra-virgin coconut oil, butter, or extra-virgin olive oil for four weeks. Coconut oil and butter are both high in saturated fat, whereas olive oil is high in monounsaturated fat. The assigned fats were incorporated into the usual diet or were taken as a supplement. The mean LDL-cholesterol level decreased by 3.5 mg/dl with coconut oil, decreased by 2.3 mg/dl with olive oil, and increased by 12.7 mg/dl with butter ($p < 0.0001$ for coconut oil vs. butter and for olive oil vs. butter; the difference between coconut oil and olive oil was not significant). Changes in fasting plasma glucose, blood pressure, C-reactive protein, and body weight did not differ significantly between groups.

Comment: Coconut oil is high in saturated fat, but the main saturated fatty acid in coconut oil (lauric acid [c12:0]) is thought to have different metabolic effects than other saturated fatty acids such as palmitic acid (c16:0), which predominates in butter, palm oil, and animal fats. In the present study, coconut oil and butter had different effects on LDL-cholesterol levels, even though they both consist primarily of saturated fat. The effect of coconut oil on LDL-cholesterol levels was similar to that of olive oil, which consists mainly of monounsaturated fats. While it has been believed for decades that saturated fat is atherogenic, that belief has in recent years been called into question. A meta-analysis of 21 prospective cohort studies that included a total of 347,747 subjects found no significant association between saturated-fat consumption and incidence of cardiovascular disease.[3] The results of the present study suggest that, if saturated fat does indeed contribute to atherosclerosis, some food sources of saturated fat (i.e., coconut oil) are safer than others. That suggestion is supported by findings in a Polynesian population living near the equator. Saturated-fat intake in this population is very high (47% of total energy, chiefly from coconut), but vascular disease is uncommon.[4]

Khaw KT, et al. Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in healthy men and women. *BMJ Open*. 2018;8:e020167.

Experiences with Intravenous Vitamin C for Cancer

The authors of this report conducted a retrospective chart review of all cancer patients who had received intravenous vitamin C at Thomas Jefferson University Hospital over a seven-year period. Eighty-six patients received a total of 3,034 doses, ranging from 50 g to 150 g per dose. Thirty-two patients received only vitamin C for their cancer treatment (1,197 doses), whereas 54 patients received vitamin C (1,837 doses) in conjunction with chemotherapy. The most common adverse effects of vitamin C were temporary nausea and discomfort at the injection site. There were no serious adverse events that were clearly related to vitamin C treatment, and more than 97% of the infusions caused no side effects. Patients reported improvements in fatigue, pain, and mood while receiving vitamin C.

Comment: The findings from this retrospective chart review are consistent with previous anecdotal reports in which high-dose vitamin C (given orally or intravenously) was well tolerated and improved symptoms and quality of life in cancer patients. Some studies have found that high-dose vitamin C increased survival times in cancer patients, but other studies failed to confirm those observations.[5] High-dose vitamin C has the potential to interfere with certain chemotherapy drugs and with radiation therapy, so it should be given only by a practitioner familiar with these potential interactions. High-dose vitamin C is contraindicated in people with advanced renal disease and in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Bazzan AJ, et al. Retrospective evaluation of clinical experience with intravenous ascorbic acid in patients with cancer. *Integr Cancer Ther*. 2018;17:912-920.

Does a Fast-Food Diet Cause Heart Disease?

Rats were fed for 18 weeks a standard rodent diet or a "Western" diet comparable to a fast-food meal, including a sugar-sweetened beverage and dessert. The Western diet contained 61% sugars, 20% fat, and 19% protein. The specific contents of the diet were not stated. After 18 weeks, the rats fed the Western diet had hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and increased plasma concentrations of advanced glycation end products. Examination of the heart revealed left ventricular hypertrophy, increased end-diastolic pressure (suggestive of diastolic dysfunction) and increased cardiac fibrosis. These changes in the heart are similar to those seen in patients with diabetic cardiomyopathy. None of these abnormalities were observed in rats fed a standard rodent diet.

Comment: In this study, rats fed on a high-sugar, high-fat diet comparable to a fast-food diet developed features of type 2 diabetes and diabetic cardiomyopathy. These findings are reminiscent of the documentary film by Morgan Spurlock (*Super Size Me*), in which he developed marked elevation of liver enzymes after subjecting himself to a "McDonald's only" diet for 30 days.[6] While few humans, and even fewer rats, subsist exclusively on these types of foods, one should consider the possibility that regular consumption of lesser amounts of fast foods for many years could promote the development of various diseases of Western civilization including type 2 diabetes, nonalcoholic steatohepatitis, atherosclerosis, and congestive heart failure.

Verboven M, et al. Western diet given to healthy rats mimics the human phenotype of diabetic cardiomyopathy. *J Nutr Biochem*. 2018;61:140-146.

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How to Brew a Great Cup of Coffee

by Steven M. Helschien, DC

I didn't get the nickname Dr. Coffee because I like coffee – I love coffee! And when asked how I want it, I say "I take coffee with my coffee."

If I get to Heaven and they are not serving Purity coffee, then I'll know it's not heaven.

I hope you have enjoyed the series on the many health benefits of coffee. And now the question that remains is – how are you going to brew it?

Here's to your health!
Steve (aka Dr. Coffee)

P.S. My personal favorites are cold brew and espresso.

Introduction

We know that coffee can be a superfood and have tremendous health benefits, due to its unique compounds, high amounts of antioxidants and polyphenols, and caffeine. Research has shown that coffee contains hundreds of potentially bioactive compounds, including those with anti-inflammatory, anti-oxidative, and anti-cancer effects. It has been proven that coffee is beneficial for health, performance, and longevity. Some of the amazing health benefits from multiple studies on drinking coffee include the following:

- Enhances brain function,
- Reduces the risk of Alzheimer's, dementia and Parkinson's,
- Helps fight depression and enhances mood,
- Protects the heart and cardiovascular system,
- Fights cancer,
- Reduces the risk of type 2 diabetes,
- Protects the liver,
- Aids metabolism and weight loss,
- Improves sports performance,
- Reduces risk of retinal damage,
- Reduces risk of multiple sclerosis,
- Suppresses pain, and
- Extends your life.

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How to Brew a Great Cup of Coffee

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We also know that not all coffee is created equal. Studies show organic, premium Purity coffee is the best coffee available for your health. Special care goes into Purity coffee, as it is handled and tested every step of the way to produce the healthiest coffee available, including:

- The way the coffee is grown, handled and roasted,
- Where it's grown (high altitudes, which are best),
- How it's farmed (organic),
- Tested for mold or mycotoxins (toxins produced by mold) at every stage.

Because of this attention to health, Purity coffee is mold free and two to ten times higher in antioxidants than 49 other brands. Purity has the healthiest coffee available that can give you maximum health benefits, and also tastes great. The question is – how will you brew it?

Brew a Great Cup of Coffee

Storage. Coffee beans are best stored in an opaque, airtight container in your pantry. Avoid keeping your beans in the freezer or refrigerator, because it exposes them to odors and moisture through condensation (unopened bags of coffee are safe in the freezer for up to a month). Coffee beans are very absorbent, so it's best to keep them away from moisture, heat, direct sunlight, oxygen, and odors.

Water. Use pure water to brew your coffee. (A great brand of purifier is Vitev; see www.level1therapeutics.com for more information on Vitev.)

Grind the beans. Use a good burr grinder.

- Only grind the amount of coffee that you need, and brew within 15 minutes of grinding.
- Determine the grind you need based on your brewing method. For longer brewing times, use coarse grinds (like a French press), while shorter brewing methods use finer grinds (like espresso).
- Changing the size of the grind can largely influence the taste of your coffee, so feel free to experiment to find your preferred taste.

Filters. Use a chemical-free paper filter if cholesterol is a concern of yours. Studies have shown that diterpenes in coffee oils (that are present when brewing with a French press) may increase LDL cholesterol (but may also have health benefits). But, using a paper filter traps the oils.

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

General brewing guidelines.

- Use the correct amount of coffee for the amount of water in your brewing method, the broad standard ratio is 1:16 – adjusting the ratio will give you either weaker or stronger coffee depending on how you change it. (With a 1:16 ratio, for every 1 gram of coffee, use 16 grams of water. When using tablespoons and ounces to measure, follow the ratio of 1:4: 1 tablespoon of coffee for every 4 ounces of water.)
- Use water between 195-205 degrees, i.e. just below boiling temperature.
- Take care of your equipment; keep it clean and dry when not in use.

Brewing Methods

When it comes to brewing a great cup of coffee, there are many options available, and which method produces the best coffee is entirely up to you. Here are a few popular options:

- *Drip brews***:** For drip brews, use medium ground coffee. Be sure to use a fresh dry filter for every use and swirl the thermos after it has brewed and before you pour a cup. Enjoy within one hour of brewing.
- *Keurig*: The Keurig brewing system has created quite a revolution and a big problem. While it is convenient, Keurig is responsible for polluting our world with non-recyclable K-cups. Purity makes a recyclable, PBA-free K-cup.
- *French press*: To brew your coffee with a French press use coarsely ground coffee. The entire brewing process takes about 4 minutes, give or take 30 seconds.
  - Preheat your French press by rinsing it with hot water, and be sure to have a separate serving device ready (or a large mug) ready to transfer the coffee to as soon as it's finished brewing.
  - Add the ground coffee and start your timer. Add all the water from beginning to the 30 second mark.
  - Stir with a spoon to saturate all of the grounds and place the plunger on top, let it sit for three minutes.
  - At 3:30 slowly start to sink the plunger down over 30 seconds.
  - At 4:00 minutes pour the brewed coffee into a separate service vessel, swirl and enjoy.
- *Steam method – Espresso machine*: Use finely ground coffee for steam methods. Espresso is obtained by pushing hot water, slightly under boiling temperature, with pressure, through coffee grinds. An espresso shot has an extremely strong flavor, although it doesn't contain as much caffeine as a cup of drip coffee. Your coffee will be finished when you hear a bubbling or hissing sound. Enjoy within an hour of brewing.
- *Cold brew*: A method growing in popularity is cold brew. Cold brew methods are used by those who want the low-acid coffee it produces. Done right, proper cold brew has a sweet taste that's rich, complex and never bitter. The overnight process of steeping coffee in water at room temperature yields a gentle-on-the-stomach concentrate that you can use again and again.

The idea behind cold brew is that you brew it cold — at room temperature. Instead of using heat to extract the coffee, it relies on immersion over time.

To make, set aside a good amount of time. Most people leave their cold brew to extract overnight. The coffee will be ready about 12 – 24 hours after you mix the water and coffee.

You can use a container, French press, or a manufactured cold brew coffee maker.

- Measure out a ratio of **one part coffee to 4.5 parts water** to make a concentrate (e.g., if you're using a 64 ounce, or 8 cup, container, you›ll want to measure out about 1.5 cups of medium-coarse ground coffee).
- Gently mix the coffee into the water, making sure all the grounds are saturated, and set the mixture to steep for the next 12 – 24 hours**.**
- Once your coffee has steeped, you can filter it through your French press or kitchen sieve and into another vessel to keep in the refrigerator.

Now you've got a base concentrate that you dilute. Try a ratio of one part concentrate to three parts water, and add or subtract to your taste. You can keep your cold brew concentrate in the refrigerator for up to two weeks. Drink it at fridge-temperature, over ice, or heat it for hot coffee.

Conclusion

Coffee has been enjoyed by people all over the world for generations. For many years it was believed that coffee was not healthy, but recent studies have shown that coffee has numerous health benefits. The only medicinal-grade coffee you can buy is Purity.

To make a great cup of coffee, there are many different brewing options, including drip brew, French press, steam method (espresso), and cold brew. Pick the one that's right for you or have several different brewing methods to choose from, depending on your mood, company, or the time of day. Enjoy brewed coffee and all the health benefits it offers.

If you would like a copy of the Level 1 Therapeutics book, "Your Guide to the Health Benefits of Coffee: What the Science Shows," email Dr. Steven Helschien at doc@level1diagnostics.com to request a copy.

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Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Chamomile Reduces Testosterone Levels in Women with Polycystic Ovary Syndrome (PCOS)

Polycystic ovarian syndrome (PCOS) is not really classified as a disease because it is not a specific and constant set of symptoms and physical characteristics. Rather, it is better described as a syndrome with a collection of symptoms, physical characteristics, and laboratory findings. There are two consistent aspects of PCOS: hyper-androgenism and insulin resistance, causing a lack of or infrequent ovulation. The most common characteristics of PCOS are obesity, hirsutism, and irregular/infrequent/lack of ovulation and thus irregular menses and poor fertility. Over 95% of women who have all three of the classic signs of obesity, hirsutism, and/or irregular menses have PCOS.

One of the problems with PCOS is that many women have this syndrome but don't have all three of the classic signs. Not all women with PCOS are obese, in fact, not even 50%. Many PCOS women are of normal weight or even underweight, have no excess hair growth on the face or chest or legs, and may even have pretty regular menses.

The current diagnostic criteria from the 2003 Rotterdam PCOS consensus workshop is that at least two of the following three features must exist (and exclusion of other etiologies for their hyperandrogenism and/or amenorrhea/oligomenorrhea):

- Oligo- or anovulation,
- Clinical and/or biochemical signs of hyperandrogenism,
- Polycystic ovaries ($\geq$ 12 follicles, 2-9 mm or volume > 10 ml).

Some symptoms of PCOS can be managed with weight loss and conventional pharmaceuticals such as oral contraceptives, antidiabetic drugs, and drugs that suppress androgen activity. Chamomile flowers are commonly used to treat anxiety, insomnia, digestive ailments, hay fever, and painful menstruation. Chamomile does contain phytoestrogen compounds that have metabolic and hormonal effects. The purpose of this randomized, placebo-controlled clinical trial was to investigate the effect of chamomile supplementation on lipid and hormone levels in women who have PCOS.

A total of 90 women in Iran, ages 15-45, with a diagnosis of PCOS were recruited. Women were randomly assigned to chamomile or placebo capsules three times daily for 12 weeks. Each chamomile capsule contained 370 mg of dried flower material.

Testosterone levels decreased significantly from baseline to 12 weeks in the chamomile group compared to the placebo group, but there were no statistically significant differences between the groups for changes in triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, and DHEAS or for the LH/FSH ratio.

Commentary: It was clear that chamomile in these doses did reduce testosterone in women with PCOS, but there was no report on whether this decrease resulted in clinical significance – such as less acne, or less hirsutism or more regular menstrual cycles. Unfortunately, the composition or active components present in the chamomile were not described. Any future research on chamomile and PCOS should include evaluating effect on ovulation, menstrual cycle length and androgenic clinical features. Other botanicals with a small amount of research in lowering androgens include spearmint tea and licorice root.

Heidary M, et al. Effect of chamomile capsule on lipid- and hormonal-related parameters among women of reproductive age with polycystic ovary syndrome. *J Res Med Sci*. April 2018;23:33.

Reducing Breast Density and Possibly Breast Cancer Risk with Green Tea

Breast cancer is the most commonly diagnosed cancer in women. The five-year cure rate with conventional medicine has become quite good; but even so, at least 40,000 women die each year. While most breast cancers have no known cause, there are some modifiable risk factors that include alcohol intake, exercise, weight, and breast density, as assessed on a mammogram. It has been reported that there is a 2% higher

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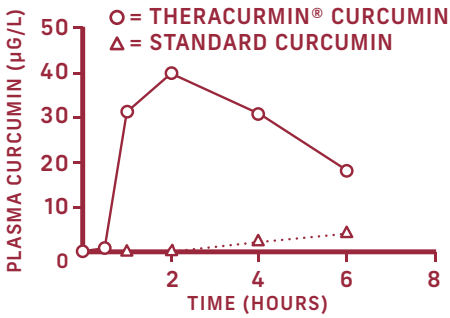

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risk of breast cancer associated with every 1% increase in mammographic density.

Green tea extract is one potential therapy for reducing breast density in those women who show significant breast density on the mammogram.

In the current study, 1,075 healthy postmenopausal women between the ages of 50 and 70 had heterogeneously dense or extremely dense breast tissue on the screening mammogram. These women were randomized to receive either green tea extract (538 women) or placebo (537 women). In the end, 462 women in the green tea group were analyzed. A decaffeinated green tea extract capsule containing 328.8 mg of total catechins, 210.7 mg epigallocatechin-3-gallate (EGCG), and less than 4 mg caffeine was taken at a dose of four capsules per day for 12 months. That's a total of 1,315 mg catechins, 843 mg EGCG, and less than 16 mg caffeine per day.

Each woman had a mammogram at baseline and after 12 months to assess mammogram breast density. Numerous other parameters were done including health questionnaires, some genotyping, and select blood tests (plasma insulin-like growth factor 1, IGF binding protein, estrone, estradiol, androstenedione, sex hormone-binding globulin, urinary estrogen metabolites and plasma F2-isoprostanes).

Daily green tea capsules did not significantly reduce percentage mammographic density or absolute mammographic density compared to placebo after adjusting for age and body mass index at 12 months. However, for the women, aged 50 to 55, the 12 months of green tea extract did significantly reduce the percentage mammographic density by 4.4% compared to placebo. Other factors, such as body mass index, years since menopause, alcohol, pregnancy history and tea drinking showed no effect on percentage mammographic density with green tea intake. This 4.4% decrease in density with one year of green tea extract in women, aged 50 to 55, could potentially translate to an 8.8% reduction in the risk of breast cancer.

Turns out, that a study on tamoxifen (used as an estrogen receptor blocker in specific breast cancers) had a similar 4.4% reduction in breast density over 18 months. This same study reported that after 54 months of treatment, tamoxifen reduced mammographic density by 13.4% in women, aged 45 or younger, while those older than 55 had only a 1.1% decrease in mammographic density over the same period of time.

In a 2007 study, women with greater than 75% mammographic density had an increased risk of breast cancer compared to women with less than 10% mammographic density; and the risk was especially greater for women younger than 56 years. For these women younger than 56 years old, 26% of the breast cancer cases and 50% of cancers detected within 12 months of a normal screening mammogram were thought to be due to a mammographic density of 50% or more.

Commentary: About three-fourths of women in their 30s have increased breast density vs about one fourth of women in their 70s. Causes of increased breast density include many potential factors such as genetic, neonatal, reproductive, hormonal, lifestyle, dietary and environmental factors. Some select details on these causes of increased breast density:

- Genetic: Ashkenazi Jewish women are more likely to have increased breast density compared to other Caucasians.
- Neonatal factors cause increased breast density later in life: e.g., higher birth weight > 4000 gms (or 8 lbs, 13 oz).
- Hormonal: Birth control pills (with some particulars regarding age of initiation of use, duration of use, doses), hormone replacement therapy (again with some particulars regarding duration, dose and age), increased weight gain in adult years, increased blood levels of estrogens.
- Reproductive: Onset of menses < 11 years old; a cycle length of < 25 days; age of menopause after age 53, not having birthed children.
- Dietary factors: increased red meat consumption (especially in adolescence), alcohol use, saturated fats, high glycemic load diets.
- Environmental: bisphenol A (hard plastics), mono-ethyl phthalate (soft plastics).

Providers and women should consider strategies to reduce breast density as a part of reducing the risk of breast cancer; and as for green tea extract, it is particularly important for women ages 50 to 55 who have heterogeneously dense or extremely dense breasts. Other natural strategies that have been shown to reduce breast density include the lifestyle changes implicated above (less saturated fats/high glycemic load diets, red meats, less alcohol, higher fiber, reducing endocrine disruptor plastics exposures), N-acetyl cysteine, gamma linolenic acid, selenium, and iodine.

Samavat H, et al. A randomized controlled trial of green tea extract supplementation and mammographic density in postmenopausal women at increased risk of breast cancer. *Cancer Prev Res (Phila)*. 2017;10(12):710-718.

Marijuana in Pregnancy – Please Don't

I live in a Oregon where recreational and medical marijuana is legal and, from small towns to urban streets, store fronts are as common as coffee shops. As such, it is highly accessible to anyone over the age of 21, and like smoking and alcohol, there are important possible risks to pregnant women. In addition to the pregnant woman who chooses to continue behaviors that present risk to her, customers are also seeking medical advice from the person behind the counter, asking the question, can I use these products for nausea of pregnancy?

A team of investigators from the University of Colorado decided to find out what type of information was being provided by staff members of marijuana dispensaries. The investigators posed as eight-week-pregnant patients and called 465 dispensaries which resulted in useful information from 400. They asked the employees if they had products that were "recommended for morning sickness." They also asked about any known fetal or maternal risks and whether they should check with their own health care provider.

continued on page 33 ➤

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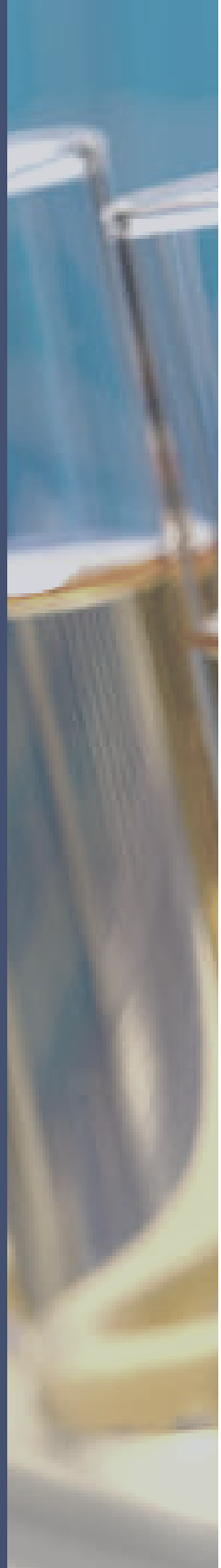

Recent research has determined toxins affecting the endocrine system are responsible for: low testosterone in men, infertility, autism, attention-deficit hyperactivity disorder, childhood obesity, adult obesity, and adult diabetes.

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➤ *continued from page 30*

Sixty-nine percent of dispensary staff members recommended marijuana products for morning sickness, and 36% said it was safe to use in pregnancy. Only 32% initially recommended that the caller check with their doctors, but after prompting, 81% eventually recommended that.

Commentary: Unfortunately, the majority of women who are using marijuana recreationally, and now during pregnancy, are likely not asking their provider for advice on the topic of use for morning sickness. Thus, they are seeking medical advice from marijuana sales people, who have not only a conflict of interest but also lack of medical knowledge, and according to this study, lack of a cautionary approach on the topic. Cannabis, the marijuana plant, contains up to 100 cannabinoids, with the two that we know the most about being tetrahydrocannabinol (THC) and cannabidiol (CBD). THC acts on CB1 receptors that then yield the psychotropic effects. CBD acts through its effect on serotonin and not CB1 receptors for the most part. We currently have only a small but growing amount of evidence for the medicinal properties of cannabinoids, including nausea and vomiting due to chemotherapy, some pain relief effects, anti-seizure activity in select seizure disorders, and anti-inflammatory properties.

Current marijuana products contain from 0.3% THC up to 15% and, now, even some concentrations up to more than 50% THC. There is a plethora of products with varying ratios of CBD/THC. In addition, there is a risk of marijuana dependence and addiction with currently an estimate of 2.7 million US individuals, affecting about 9% of users. This is compared to 15% of the population addicted to alcohol. And then there is the risk of addiction to the newborn, let alone other potential

Women's Health Update

consequences of cannabinoid exposure in utero. It will be very difficult to determine the true impact of cannabis on the fetus, as there are too often other confounding variables such as cigarette smoke, alcohol, other recreational drugs, socioeconomic influences, and nutritional habits. There have been some studies that have shown that children exposed in utero to cannabis performed more poorly in visual problem solving, motor coordination, and attention deficits compared to unexposed children. Other possible effects include increased risk of stillbirth, low birth weight (if mother used cannabis more than once per week), preterm birth (mostly in those who used cannabis and were cigarette smokers). To be fair, a few older studies have not shown any differences in adverse outcomes with pregnant users vs nonusers.

One thing for sure, marijuana use of any kind has not been proven to be safe in pregnancy. And since there is even any evidence of possible harm, we should recommend to our patients that they not use cannabis products during pregnancy – whether for recreational or medical purposes. For most women with nausea/vomiting of pregnancy, there are numerous natural and pharmaceutical options, ginger being my most favorite. That said, there are those women with serious, even dangerous, nausea/vomiting (hyperemesis). If she has tried all other options and cannabis does relieve her debilitating condition, I will be in a quandary about how to advise her.

Dicson B, et al. Recommendations from cannabis dispensaries about first-trimester cannabis use. *Obstet Gynecol*. 2018;131:1031-1038.

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

On the cover

Hormone Therapies to Cure Female-Related Disorders: Practical Tips

by Thierry Hertoghe, MD

Prevention and cure of breast cysts, under- and overdeveloped breasts, breast ptosis, amenorrhea, hypomenorrhea, and menorrhagia, poly- and spaniomenorrhea, irregular menstrual cycles, ovulatory pains, spasmodic and constant dysmenorrhea, premenstrual and menstrual migraines, ovarian cysts and polycystic ovarian syndrome, vaginal dryness, dyspareunia, endometriosis, lichen sclerosis, hirsutism, etc.

Most female-related disorders are caused by deficiencies, excesses, or imbalances of the two important types of female hormones – estrogens and progesterone. In this article, we will review the most typical female-related disorders and suggest how to correct them with hormone supplements.

To determine which female hormone deficiencies and excesses are causing female-related disorders, and which hormone supplements to provide as a treatment, I recommend physicians train their skills in recognizing the differences in actions and deficiency signs and symptoms between estrogens and progesterone.

Estrogens increase progesterone production by stimulating ovulation through the production of a high preovulatory peak that stimulates a peak secretion of LH, the pituitary hormone that triggers ovulation.

- Estrogens stimulate the (ortho)sympathetic nervous system directly and through conversion into catechol estrogens, making women **excited and enthusiastic**, but excess estrogens render women nervous, aggressive, and anxious.
- Estrogens also cause a person to **retain fluid** and benefit from adequate hydration of the skin and mucosa, but in excess they lead to painful swelling of breasts and lower abdomen.
- Estrogens also stimulate **healthy epithelial cell proliferation**, particularly in the genital areas (breasts, ovaries, and endometrium), however, at excessive levels, they stimulate excessive cell proliferation in these areas producing enlarged breasts or breast cysts, ovarian cysts, endometrial glandulocystic hyperplasia, and fibroids.

Progesterone has in these domains opposite actions that protect against estrogen excess. Progesterone reduces estrogen activity by reducing the levels of estradiol, the most potent estrogen, through a stimulation of the conversion of estradiol into the three to 10 times less active estrone.

- Progesterone stimulates the parasympathetic nervous system, making women **calm and in control**.
- Progesterone is **diuretic**, increases water excretion through urine, protecting in this manner against excessive fluid retention. This diuretic action is not shared by all progestogens. High doses of synthetic derivatives of bioidentical progesterone can cause fluid retention, particularly when they derive from androgens.
- Progesterone also stops estrogen-induced epithelial cell proliferation and **differentiates epithelial cells** into more functional cells. For example, progesterone stops estrogen-induced anarchic proliferation in the endometrium, differentiating these cells so that the endometrium of the uterus can accept implantation of a fertilized egg cell and nourish it.

Table 1 shows the differences in actions of the two types of female hormones.

Excesses (predominance) in these female hormones will accentuate these effects. **Estrogen predominance** produces nervousness, water retention, and excessive cell-proliferation.

Estrogen predominance is frequently encountered in premenopausal women who are not supplemented with female hormones. In contrast, postmenopausal women usually show estrogen predominance only when taking an imbalanced female hormone treatment (e.g., the medically unsafe, treatment with estrogen alone without progesterone) usually prescribed to women after hysterectomy.

Table 1. Estrogens and progesterone: Differences in actions

Affected areas	Estrogens	Progesterone
Sympathetic nervous system	Stimulates	Calms down
Body water in genital areas	Water retention	Water excretion in urine
Epithelial cell proliferation	Stimulates	Inhibits and differentiates
Hormone levels	Tend to increase progesterone levels	Reduces estradiol levels, increases estrone levels

Progesterone supplementation is necessary to keep not only the uterus tissues but also the ovarian, breast, and brain tissues well-balanced and safe. **Progesterone dominance** with depression and dehydration is rarely encountered, generally only when excessive doses of progesterone or progestogen derivatives are given.

Deficiencies in female hormones will provide opposite effects to their actions. In **estrogen deficiency**, low mood and energy, dehydration, and atrophy prevails. In cases of **progesterone deficiency** associated to adequate estrogen levels, nervousness predominates; and, in the genital areas, swelling and excessive epithelial cell proliferation. Table 2 reviews the most typical and pathognomonic signs and symptoms of each female hormone deficiency, enabling physicians to quickly detect which female hormone deficit(s) a patient is suffering from.

At what time of the day are female hormone deficiency complaints the worst? Contrary to hypothyroidism and cortisol deficiencies where symptoms are more severe at specific times in the day (upon awakening for hypothyroidism and in stressful moments for adrenal deficiency), women with estrogen and progesterone deficiencies find that most complaints appear at the same intensity at any time of the day, with the exception of vasomotor disorders (hot flushes and

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Table 2. Sex hormone deficiencies: Typical signs and symptoms in women

Effect factors	Estrogen deficiency	Progesterone deficiency	Testosterone deficiency
Complaints	Fatigue	Nervous	
	Low mood, depressed	Anxious, aggressive	
	Hot flushes	Insomnia	
	Lack of sexual desire		Lack of sexual desire
	Vaginal dryness	Vaginal leucorrhea	
	Menstrual syndrome (with fatigue, depression, spasmodic dysmenorrhea, and migraine during periods)	Premenstrual syndrome (with irritability, ovulatory pain, constant dysmenorrhea, migraine, insomnia before the periods)	
	Hypo- and amenorrhea	Menorrhagia	
	Changes in menstrual cycle length: poly- and spaniomenorrhea		
Time of worse complaints	Follicular phase, especially menstruation	Luteal phase, particularly during the 5 to 14 days before menstruation	
Physical signs	Flat hair		
	Pale face		Muscle atrophy
	Dry eyes		
	Droopy breasts, insufficient breast volume and tone	Swollen breast, mastalgia	
	Vaginal atrophy		
Long-term adverse consequences		Breast cysts	
	Small, underdeveloped breasts	Enlarged breasts	Nipple atrophy
		Ovarian cysts	Clitoris atrophy
		Fibroids	
		Endometriosis	Lichen sclerosis

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sweats), which tend to occur more at night and in stressful conditions. In premenopausal women, estrogen deficiency symptoms are worse during menstruation and in the follicular phase, whereas progesterone deficiency symptoms predominate in the luteal phase, during the 5 to 14 days before the period.

What are the most efficient and safest female hormone treatments? The **most efficient and safest treatment** consists, in my experience, of transdermal estradiol and oral or vaginal progesterone, in accordance with the current scientific literature. Estriol is interesting as an estrogen but does not absorb well through the transdermal route and has insufficient effects for the brain, bones, and cardiovascular system. The data are not all conclusive about its cancer safety or protection (the risk of endometrial cancer is several times higher in women taking estriol alone without progesterone). It is efficient for the vaginal mucosa and reduces ocular dryness. For this reason, I consider 1-2 mg/day oral estriol as a worthwhile adjuvant estrogen, but it does not replace the essential estradiol.

From what age do women need female hormone supplements? As soon as female hormone deficiency is diagnosed. Some women with weak ovaries may already need female hormones **at the end of puberty** because their ovaries never succeed in producing sufficient amounts of female hormones to be fully healthy. In most women, however, the need for estrogen and progesterone supplementation starts **between 30 and 35 years old**, as confirmed by research that shows that the levels of both hormones start progressively and significantly to decline at these ages.[1-2]

Which conditions can accelerate the natural age-related decline in female hormone production long before menopause? Pregnancies also weaken the ovaries. Research demonstrates that women who have been pregnant have significantly lower serum levels and urinary excretion rates of estrogen metabolites than women of the same age who have never been pregnant.[3] In my experience, most women after pregnancy show premature signs of estrogen and progesterone deficiencies and look like older mothers rather than the energetic and young-looking ladies they were before. To keep their health and good looks, they need small doses of estrogen and progesterone. Practice of intensive sport (reduced estrogen and progesterone metabolites),[4-5] stress (estrogen and progesterone deficits),[5] malnutrition,[5] overweight (decreased progesterone and its metabolites), smoking (decreased estradiol),[6] a history of induced abortion,[3] uterine tubal ligation[7-8] also reduce production of female hormones and their metabolites. These deficits make it necessary for women to get additional estrogen and progesterone therapies to correct the hormone deficits long before menopause.

Female-Related Disorders That Can Quickly Be Corrected in Days or Weeks

Droopy breasts (breast ptosis) are signs of significant estrogen deficiency. For this reason, in **premenopausal women** add estrogen daily during most of the menstrual cycle (follicular and luteal phases) but administer the protective progesterone only in the second half of the cycle, the luteal phase. In **postmenopausal women**, I usually prescribe both transdermal estradiol and oral or vaginal progesterone on the same days: from the 1st to the 25th day of the month. This usually and safely blocks menstruation, a relief for most older women.

The estradiol should be taken upon awakening because it increases energy, and progesterone at bedtime because it induces sleep. An efficient dose to bring back the breast volume and tone is 1.5 to 3 mg/day of transdermal estradiol (upon awakening) and 100 mg/day of oral or vaginal progesterone (at bedtime). If the breasts remain droopy, increase the estradiol dose further until the breasts regain their normal tone and volume.

Tip: The patient should **avoid consuming (unsprouted) whole grains** as the fiber contained in grains prevents intestinal reabsorption of female hormones. About 60% of the female hormones are attached (conjugated) by the liver to a glucuronate or a sulfate. These glucuron- and sulfo-hormone conjugates are secreted then by the liver into the bile, which flows into the small intestine. In the gut, bacteria break off the bonds between the glucuronates and sulfates and the estrogen and progesterone, permitting reabsorption of the latter through the intestinal wall and reutilization as hormones. This enterohepatic cycle is interrupted by the non-absorbable cereal fiber that strongly binds to the hormones and drags them into the stools, almost tripling the net loss of these hormones in the stools and lowering the female hormone levels 20 to 40% in the serum.

Amenorrhea and hypomenorrhea in **premenopausal women** who are not yet menopausal (FSH is still well below the 30 mIU/ml threshold for menopause) and still have healthy egg cells result from severe estrogen deficiency. Normal menstruation is restored by adding estradiol and progesterone as mentioned above (usually 2 to 3 mg/day of transdermal estradiol gel from the 5th to the 25th day of the menstrual cycle) and 100 mg (usually not more) progesterone from the 15th to the 25th day of the cycle. In **postmenopausal women** treated with both estradiol and progesterone on the same days (typically from the 1st to the 25th day of the month), amenorrhea is generally the rule and is safe because the progesterone blocks the proliferation of endometrium by estradiol and the possibility of having periods. I recommend stopping the treatment during 3-5 days at the end of the month as the interruption decreases the breast cancer risk and permits an abnormal endometrial cell that might have developed to die during the estrogen-free interval.

Tip: Amenorrhea and estrogen deficiency may be caused by low-protein and low-fat intakes as in low-calorie diets, for example. Recommend the patient eat at least 200 g/day (a little less than a half pound/day) of meat or fish and take a daily soupspoon of butter (preferably ghee, butter that has been clarified (cleaned) from its proteins) or an egg yolk. Eating more animal protein and fat boosts female hormone production.

Menorrhagia: How to reduce heavy menstrual bleeding by adding progesterone. Progesterone deficiency allows

excessive menstrual bleeding by permitting an excessive proliferation of the endometrium under impulse of estrogens. Once progesterone treatment is administered at a sufficient dose, it stops any further production of endometrium. By this inhibition, it reduces the material for bleeding as endometrium is what bleeds away during periods. In case of mild menorrhagia, 100 to 150 mg/day from the 18th to the 25th day of the cycle should be sufficient to reduce the bleeding back to normal. In case of heavier bleeding, 150 mg to 200 mg/day from the 15th to the 25th day of the cycle may be necessary. In extreme cases of severe menorrhagia, 50 mg/day from the 5th or the 10th day to the 14th day and then 150 mg to 200 mg/day from the 15th to the 25th day of the menstrual cycle can be required.

Tip: Check for hypothyroidism or adrenal (cortisol) deficiency as they both can cause insufficient ovulation, which results in progesterone deficiency. Check also for vitamin K, B3, etc., as well as thyroid (again), as these deficiencies are associated with insufficient production of coagulation factors and treat those deficits whenever they are confirmed.

Polymenorrhea, spaniomenorrhea, and irregular menstrual cycles: How to restore a 28-day menstrual cycle. Short (26 or less days), prolonged (30 or more days), and irregular (mixing of short and long) menstrual cycles are mainly due to estrogen deficiency. To treat them, a higher estrogen dose is useful (e.g., 2-4 mg/day of transdermal estradiol with a moderate 100 mg/day dose of progesterone given in premenopausal and postmenopausal women on the same days of the menstrual cycle or month, respectively) as suggested above.

In some premenopausal women with short menstrual cycles, progesterone deficiency symptoms, and not symptoms of estrogen deficit, predominate with severe premenstrual syndrome and tension, mastalgia, etc. In this case, I recommend treating with slightly lower doses of transdermal estradiol (1.5 - 3 mg/day) and higher doses of progesterone 150 to 200 mg/day.

Tip: Recommend the patient eat **sufficient animal protein-rich foods (> 200 g/day)** to support female hormone production and **avoid whole grain foods** to avoid hormone loss in the stools. There is a fivefold higher risk of irregular menstrual cycles in women regularly eating whole grain bread.

Spasmodic dysmenorrhea, menstrual migraine, and **hot flushes:** How to get rid of severe cramps, hot flushes and migraines. Heavy cramps in the lower abdomen alternated with pain-free periods during the day and hot flushes in premenopausal women occur generally during menstruation when estrogen levels are at their lowest levels. As for menstrual migraine, these menstrual abdominal cramps are due to estrogen deficiency and relieved by estrogen supplementation. In case one of these three complaints is the only bothersome complaint, the estrogen deficiency is probably only present during menstruation and 0.75 to 1 mg/day of transdermal estradiol during the first four days of the menstrual cycle may be sufficient as a therapy.

When a patient suffers from other estrogen deficiency complaints appearing at other times of the menstrual cycle, then a typical premenopausal female hormone treatment is required to relieve the patient from all her symptoms. It typically consists of 2-4 mg/day of transdermal estradiol gel from the 5th to the 25th day of the menstrual cycle with progesterone from the 15th or 18th day to the 25th day. If some spasmodic dysmenorrhea would persist, add a smaller (0.75 to 1 mg/day) dose of transdermal estradiol during the first 4 days of the menstrual cycle.

Tip: Avoid smoking and caffeinated beverages because even if they may help relieve some of the spasmodic dysmenorrhea or migraine, they usually accelerate the upcoming next painful period and increase its intensity. Note that for migraines, thyroid therapy may help, too, as it eliminates the myxedema, which compresses brain structures inside the non-extendable skull. Thyroid therapy also increases estrogen production, another way by which it can reduce migraine.

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Ovulatory pains, **constant dysmenorrhea**, and **premenstrual migraine**: All three symptoms are due to progesterone deficiency and require progesterone for treatment during the luteal phase, the second part of the menstrual cycle. To prevent **ovulatory pains**, progesterone treatment should start at a smaller dose of 50 mg/day before the normal time of ovulation (from the 10th to the 14th day of the cycle), usually from the 10th to the 14th day of the menstrual cycle, and then continue at higher doses of 100 to 200 mg/day from the 15th or 18th day to the 25th day of the cycle as there are usually many other complaints of progesterone deficiency when ovulatory pains occur.

The ovaries in hypothyroid women produce insufficient amounts of progesterone because of a lack of thyroid hormone stimulation.

When a patient suffers from **permanent lower abdominal pain** and **recurrent migraine** in the premenstrual period, starting progesterone from the 15th or 18th day of the menstrual cycle to the 25th day of the cycle may suffice and deliver the patient from her pain. However, frequently estrogen deficiency complaints may also be found in these premenopausal women and require small (not high) doses of 0.75-2 mg transdermal estradiol from the 5th to the 25th day of the menstrual cycle. Whatever the case, a relatively higher progesterone dose than the estrogen dose should be given when constant dysmenorrhea and premenstrual migraine are the predominant complaints, otherwise there is a risk of aggravating these stressful complaints with estrogen supplementation.

Tip: Check for **hypothyroidism** whenever progesterone deficiency complaints predominate, particularly in young women (below age 30). The ovaries in hypothyroid women produce insufficient amounts of progesterone because of a lack of thyroid hormone stimulation. In young women, thyroid therapy usually restores ovulation and progesterone levels and may make the complaints of progesterone deficiency disappear on their own without exogenous female hormone supplements. In hypothyroid women above age 35-40, the number of functional oocytes has dropped to levels that are too low, and progesterone supplementation is almost always necessary next to thyroid therapy.

Vaginal dryness and dyspareunia: The dryness and atrophy of the vaginal mucosa and its almost inevitable consequence of pain at penis penetration during intercourse are due to estrogen deficiency.

In most women, correcting the underlying estrogen deficiency with a typical pre- or postmenopausal treatment consisting of **transdermal estradiol and oral or vaginal progesterone** such as explained above is efficient. In some women, the vagina has remained in estrogen deficiency for too long a time and addition of **a vaginal gel or tablets of estriol** is necessary the first six months to make the symptoms completely disappear. In rare cases, the adjuvant vaginal estriol treatment should be continued for a longer time, perhaps indefinitely.

Female-Related Disorders That Need Months and (for some) 1-2 Years for Correction

Breast cysts: How to make breast cysts disappear naturally. It takes approximately six to 15 months to make cysts totally disappear in women, regardless of the age or severity of the breast cyst, even in Reclus disease. The main treatment here is not hormonal but nutritional: iodine. One to three drops per breast of a 5% iodine-containing **Lugol's solution** daily applied (no interruption) on the area overlapping the breast cysts permits 12% penetration of the iodine into the skin and cysts. The solution stains the skin yellow-brown, but this is transitory. After 20 to 30 minutes almost all iodine that has remained on the skin has outgassed into the atmosphere. Iodine blocks proliferation of tumor cells so that in the cysts drenched with iodine no new cells appear while the old cells die and disappear one after the other. In severe fibrocystic breast disease, I recommend reinforcing the efficacy of the topical iodine treatment by having the patient take an additional 3-5 drops/day orally of the same Lugol's solution mixed with water to reach cystic areas within the breast that are poorly accessible topically. As progesterone also helps to prevent and reduce breast cysts, I also prescribe the patient a **progesterone gel 1%** to apply daily on the breast before placing the iodine solution.

Tip: Recommend the patient **avoid drinking coffee, tea, and alcohol** as the caffeine or ethanol these drinks contain promotes breast cysts formation. Make them also take progesterone orally or vaginally in the second phase of the menstrual cycle in case the breasts swell painfully.

Small breasts: How to stimulate underdeveloped breasts (micromastia) to grow to a normal adult size. In **young women** using female hormone treatment, it takes about 12 to 15 months to fully develop breasts from one of the lower Tanner puberty stages (stages 2 to 4) to a full adult stage 5 breast development. The typical treatment consists of administering upon awakening 2 to 4 mg/day of a transdermal estradiol gel from the 5th to the 25th day of the menstrual cycle and at bedtime 100 to 150 mg/day of progesterone from the 15th to the 25th day of the cycle. The higher the estradiol levels are, the bigger the breasts become.

In **older peri- and postmenopausal women**, growth hormone therapy may be necessary in addition to estrogens (and progesterone) to make the breasts grow.

Tip: Breast enlargement requires sufficient animal protein intake. Suggest the patient eat at least 200 grams/day of meat, fish, or chicken.

Enlarged breasts: How to prevent and treat over-sized breasts. Prevention of over-sized breasts is simple: Treat any progesterone deficiency as soon as possible as it is long-term progesterone deficiency that allows excessive mammary cell proliferation to make the breasts too big. In general, the treatment consists of administering 100 to 200 mg/day of micronized progesterone from the 15th or 18th day to the 25th day of the menstrual cycle.

Once the breasts have become excessively enlarged (macromastia), further enlargement can be hindered by administering progesterone alone in the same manner and at the same doses used for prevention of breast enlargement. Reduction of breast size is usually not very efficient with progesterone or other hormone therapies without surgery, and if so, it results in breast ptosis rather than breast reduction.

Tip: **Avoid coffee, tea and alcohol** as they increase breast epithelial cell proliferation.

Ovarian cysts, polycystic ovarian syndrome, and hirsutism: How to make ovarian cysts disappear. **Ovarian cysts** are facilitated by one of the following deficiencies: iodine, thyroid, cortisol, or progesterone deficiencies. Toxins (chlorine, etc.) may facilitate the development of cysts, but it is usually by producing one or more of these four deficiencies. Correction of one or two of these deficits is generally sufficient to correct the problem.

In case of iodine deficiency, 3 to 5 drops a day of a **5% Lugol's solution** may be sufficient to make the ovarian cysts disappear in 3-6 months. Hypothyroidism is, in my experience, best corrected with 30 to 150 mg/day of **desiccated thyroid extracts** from pork origin as they contain not only T4 (thyroxine, four iodine atoms), but also T3 (three iodine atoms, by far the most active thyroid hormone), T2 (two iodine atoms), T1 (one iodine atom), and T0 (zero iodine atoms), which all may have some additional benefit. These different T0 to T4 hormones are delivered by thyroid extracts imbedded in a big thyroglobulin protein. Absorption and digestion of this protein is slow and progressive, permitting progressive release of the different thyroid hormones out of this long protein. In this way, a more persistent 24-hour thyroid activity is achieved and, thus, better correction of the hypothyroidism than treatments containing only purified T4 or T3.

Cortisol deficiency is best corrected by hydrocortisone (bioidentical cortisol) 10 to 15 mg in the morning and 10 mg at midday. Remember to always supplement DHEA in equivalent doses (15 to 25 mg/day) whenever cortisol is given as the DHEA protects against any excessive catabolic effects of cortisol.

In **polycystic ovarian syndrome** with typical hyperandrogenism and hirsutism, the treatment is more complex as, in my experience, all of the aforementioned thyroid, cortisol, and progesterone deficiencies exist simultaneously with some degree of estrogen deficiency. These deficits trigger a compensatory increase in production of testosterone and adrenal androgens. Correction of these aforementioned deficiencies usually reduces and normalizes the androgen excesses and associated hirsutism, although slowly. After confirmation of the deficiencies by laboratory tests, administer to your patient hydrocortisone, desiccated thyroid, and a combination of 2-4 mg/day of transdermal estradiol from the 5th to the 25th day of the menstrual cycle and a maximum of 100 mg/day (not too high) of oral progesterone from the 15th to the 25th day of the cycle.

How do these hormones reduce **hirsutism**? The **hydrocortisone** reduces the secretion of ACTH, the pituitary hormone that stimulates the adrenal cortex to produce cortisol and adrenal androgens, thereby reducing the secretion of DHEA, androstenedione, and other adrenal androgens. In case of severe adrenal hyperandrogenism with important hirsutism, correct in the first six to nine months the cortisol deficiency with a potent synthetic derivative such as 0.25 to 0.35 mg/day of dexamethasone, which lowers the adrenal androgen levels more than the bioidentical cortisol. However, it is important not to lower the adrenal androgens too much, so regular control of the 17-ketosteroids, the metabolites of the adrenal androgens, in a 24-hour urine collection is recommended every six months. If a hirsute patient wishes only to take bioidentical hormones, then provide hydrocortisone in four divided doses of 5 mg taken at regular four-to-five-hour intervals: upon awakening, at lunch, at 4 PM, and before bedtime. The spreading of the dose permits better suppression of excessive adrenal androgen production. **Thyroid therapy** increases the conversion of testosterone into estradiol rather than into the masculinizing dihydrotestosterone. **Estradiol** blocks the masculinizing effects of androgens and progesterone amongst others by inhibiting the conversion of the harmless testosterone into the body hair-promoting dihydrotestosterone.

Without aesthetic hair removal, it takes 2-4 years after normalization of androgen levels for slow disappearance of the excessive body hair. For this reason, I suggest women with hirsutism get their excess body hair removed. After hair removal, the hirsutism should not grow back if all hormone levels are in the meantime normalized.

Endometriosis: Can a patient get rid of endometriosis without surgery? The development of endometrial mucosa inside the abdominal cavity is also, in my experience, due to a multiple hormone deficiency syndrome with thyroid, cortisol, and progesterone deficiencies. Hypothyroidism and cortisol deficiency do not allow good ovulation, resulting in progesterone deficiency. One of progesterone's roles is to relax the uterine wall and prevent unwanted uterine contractions. It is very useful during a pregnancy, for example, as otherwise excessive contractions could lead to a miscarriage. It is also useful to avoid endometriosis. With progesterone deficiency, the uterine body and tubes contract too frequently and anarchically so that islets of endometrium detach from the inner wall of the uterus, penetrate the fallopian tubes, and from there enter into the abdomen and implant themselves in places where they do not belong. Additionally, cortisol deficiency increases the inflammation around the endometrial islets inside the abdominal cavity, increasing pain and suffering.

In my experience, the best treatment is to correct the hormone deficiencies in the same way as for polycystic ovarian syndrome by using hydrocortisone, desiccated thyroid, and progesterone. If pain and inflammation predominate, I prefer using a synthetic cortisol derivative such as prednisolone (5 mg/day) with 15-20 mg/day of DHEA for the first six to nine months of treatment and then later switch to bioidentical hydrocortisone.

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Table 3. Female-related disorders requiring as treatment a relatively **higher estrogen** and **lower progesterone dose**

Female-related disorders	Treatment	Type of Patient	Doses	Days
• Menstrual migraine • Spasmodic dysmenorrhea • Hot flushes as **sole symptoms** during menstruation only	**Transdermal estradiol** alone	Pre-menopausal women	0.75-1 mg/ day of estradiol	1st - 4th day of the menstrual cycle
• Menstrual migraine • Spasmodic dysmenorrhea • Amenorrhea and hypomenorrhea • Poly- or spaniomenorrhea, irregular cycles • Droopy breasts • Underdeveloped breasts • Vaginal dryness, dyspareunia + Many **other symptoms of estrogen deficiency** appearing at other times than the periods	**Combination** of: • **Trans-dermal estradiol** gel • **Oral or vaginal proges-terone** capsules	Pre-menopausal women	2-4 mg/day of estradiol	5th - 25th day (+ possibly 0.75-1 mg/day estradiol 1st - 4th day) of the menstrual cycle
			100 mg/day of progesterone	15th or 18th day - 25th day of the menstrual cycle
		Post-menopausal women	2-3 mg/day of estradiol	1st - 25th day of the month
			100 mg/day of progesterone	

Female-related disorders requiring as treatment a **lower or no estrogen dose** and a relatively **higher progesterone dose**

Female-related disorders	Treatment	Women	Doses		Days
• Premenstrual migraine • Ovulatory pains, constant dysmenorrhea • Menorrhagia • Breast cysts • Ovarian cysts, polycystic ovarian syndrome • Fibroids • Endometriosis • Enlarged breasts + **No estrogen deficiency signs or symptoms**	**Oral or vaginal pro-gesterone** capsules alone	Pre-menopausal women	100-200 mg/ day of pro-gesterone		15th or 18th day - 26th day of the menstrual cycle
• Premenstrual migraine • Ovulatory pains, constant dysmenorrhea • Menorrhagia • Breast cysts • Ovarian cysts, polycystic ovarian syndrome • Fibroids • Endometriosis • Enlarged breasts + **Estrogen deficiency signs and symptoms**	**Combina-tion** of • **Trans-dermal estradiol** gel • **Oral or vaginal proges-terone** capsules	Pre-menopausal women	1-2 mg/day of estradiol		5th - 25th day of the cycle
			Moderate	100-200 mg/ day of proges-terone	15th - 25th day of cycle
			Important	50 mg/day	10th - 14th day
				150-mg/day	15th - 25th day of cycle
			Severe symptoms	50-100 mg/day	5th - 14th day
				150-200 mg/ day of proges-terone	15th - 25th day of the men-strual cycle
		Post-menopausal women	1-2 mg/day of estradiol		1st - 25th day of the month
			100-200 mg/ day of pro-gesterone		

Female-related disorders requiring as treatment **testosterone** under protection of an estroprogestative treatment

Female-related disorders	Treatment	Women	Doses	Days
Clitoris atrophy	Topical testos-terone cream in very thin layer	0.5% cream	1x/day on the clitoris	For 6-15 weeks
Lichen sclerosis			2x/day on the vulvar lips	For 2-6 months

Tip: Insist that the patient follow a healthy diet that makes her have a flat belly free of bloating and inflammation and does not irritate the gastrointestinal system. A bloating abdomen is sick, inflamed, and aggravates the endometriosis. Suggest that the patient eat boiled vegetables and ripe fruits. Make her eat fruits in the first half of the day at a distance from the meals (1/2 an hour before or 3 hours after meals). Suggest she consume protein-rich foods such as meat and fish as early as possible in the day so that with gravity and movement the foods go down in the gut quicker and get digested in the different parts of the gastrointestinal system. Proteins should not be consumed in the evening as they then unnecessarily stagnate the whole night in the stomach, overloading the gastrointestinal system and causing inflammation in the same abdominal cavity where the islets of endometriosis are located. The patient should also avoid junk foods: not only fast foods, sweets and soft drinks, but also unsprouted grains (bread, muesli, porridge, pasta, and rice) and dairy products (milk, yoghurt, and cheese) that are too irritating for the human digestive tract.

Fibroids are mainly due to progesterone deficiency, by allowing excessive tumor cell proliferation, although iodine deficiency (hypothyroidism) by causing progesterone deficiency may contribute to fibroid formation. The best treatment is to **prevent fibroid** development by correcting progesterone deficiency on time (100 to 200 mg/day from the 15th or 18th day to the 25th day of the menstrual cycle).

What to do when **major fibroids** are already developed? Prevent further aggravation. In premenopausal women, further aggravation can be prevented by providing 50 (to rarely 100) mg/day of micronized progesterone from the 5th to the 14th day of the menstrual cycle, and then 100 to often 200 mg/day from the 15th to the 25th day of the cycle. If a patient needs estradiol, too, then do not exceed 1.5 mg/day of transdermal estradiol. In postmenopausal women, a smaller dose of estradiol is recommended such as 0.75 to 1.5 mg/day and a relatively higher progesterone dose such as 150 mg/day. It works better with synthetic derivatives of progesterone because of their more prolonged 24-hour action (whereas bioidentical progesterone has an average 16-hour action). Dydrogesterone (Duphaston®) is the only safe one I know of, but is, to my knowledge, not available in North America.

An alternative is to apply transdermally a 10% progesterone liposomal cream in the morning and evening on the skin areas with the highest hormone absorption such as the zones rich in blood vessels where we flush – the upper chest and the face. One gram of a 10% liposomal cream corresponds to progesterone caps of 100 mg. Liposomal creams are better absorbed than other forms. High-dosed progesterone treatments may also partially reduce the fibroids, but a near-total cure is generally only obtained by using gonadotropin agonists for six months, which put the ovaries in menopause. This artificial menopause can be partially compensated by adding the synthetic tibolone, which relieves menopausal symptoms and does not stimulate fibroid development.

Vulvar lichen sclerosis: This type of inflammation of the vulvar lips is very painful and can lead to a fusion of the vulvar lips and an impossibility of having intercourse. It is mainly due to androgen deficiency. If it is in a not too advanced stage, then the lichen sclerosis may be cured by applying on the vulvar lips a topical testosterone cream. Avoid using gels as the alcohol may irritate the skin of the vulvar lips. Testosterone is a potent anti-inflammatory hormone for genital, muscular, and tendon tissues, not in other areas. A 0.5% testosterone cream twice a day applied in a very thin layer on the vulvar lips may suffice. If the inflammation is very active, addition of a 1% hydrocortisone cream may be necessary. Ideal is even to use the more potent dihydrotestosterone creams, but they are to my knowledge no longer on the market. Studies have also shown that progesterone creams may help improve lichen sclerosis to a lesser degree than androgens, but this is likely due to its conversion into testosterone, and from the testosterone to dihydrotestosterone. After curing the lichen sclerosis, a systemic testosterone treatment should be continued to avoid recurrence (of course, combined with female hormone treatment to avoid virilization)

Tip: Recommend the patient wear **lose underwear made of natural fiber** such as cotton. She should avoid wearing underwear made of synthetic fiber to avoid excessive sweating and irritation that would aggravate the vulvar inflammation. Daily application of a **topical vitamin A solution** (e.g., the patient can open and use high-dosed 25,000 IU caps) may help, too, as it reduces lichen sclerosis.

Table 3 reviews the sex hormone treatments of the most important female-related disorders.

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

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

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New Whys and Ways to Sleep Better, Especially After 40

by Dr. Devaki Lindsey Berkson

There are two planets. One where you get a great night's sleep and feel phenomenal the next day. And a second where you can't get a good night's sleep, and your tomorrow feels like trudging through molasses.

In modern life, it's easier to end up on planet number two. Healthy sleep is under continual attack, and threats against achieving a restorative night's sleep keep mounting.

Today's sleep gets mugged in many ways:

- *By chronic daily stressors*, like tending aging parents or having kids who announce they want to change their genders, or from single severe traumas – such as tornadoes and wildfires to anything like betrayal, getting fired, or receiving a serious diagnosis.
- *By night-shift* work schedules.[1]
- *By excessive electromagnetic field exposures*[2] that occur regularly in towns across an America dotted with electrical and Wi-Fi towers.
- *Unhealthy food habits*. Magnesium lives inside red blood cells where it nudges healthy enzymes for sleep. Regularly consuming junk food[3] creates nutrient deficiencies, especially magnesium deficiencies.[4] Late night eating syndrome[5] – lying down too much, eating too much, all too soon before bed (unfortunately normal for life in the good ole USA) – dings sleep.
- *Sugary foods* – like candies, colas, pastas, and pastries – disrupt the sugar hormone insulin, derailing sleep. And vice versa: chronic insomnia creates chronic blood sugar issues.[6]
- *Hormonal swings* can disrupt both genders.
  - Women wake from hot flashes[7] urgently flinging off their sheets, and sleep is disrupted. Today's toxic planet is rife with endocrine-disrupting pollutants. These hormone-altering chemicals are making some younger women develop hot flashes earlier, with sleeping issues earlier, too.
  - As middle-aged males go through "andropause," lower levels of testosterone[8] can worsen sleep. Again, our toxic planet and diets are promoting an epidemic of lower testosterone levels in American males,[9] which can ruin sleep.
- *Even climate change*[10] is being linked to worsening sleep through disasters such as hurricanes, floods, wildfires and higher temperature levels.

What Does Sleep Loss Do to Us?

Insomnia – the inability to achieve restorative sleep – gives you a worse tomorrow. You have a greater likelihood of being *exhausted* the next day, as well a greater risk of feeling anxious and depressed. By the way, this is also true the other way around[11]; mood issues can worsen sleep.

"Perimenopausal insomnia"[12] is one of the most common complaints of midlife women. The perimenopause is when hormone levels yoyo as eggs age and regular ovulation becomes harder to achieve. During this time, women typically require *more sleep* to feel better the next day. Yet they often don't get it. Bone-curdling exhaustion manifests. Life feels harder. Up to forty percent of perimenopausal women complain of serious sleep and fatigue issues. Much more so than same-aged men. Female hormones nosedive much faster in middle-age, compared to male hormones that typically decline more slowly. Though with today's pollution, this appears to be changing.

Of note is that the age of perimenopause[13] is *lowering.* This is due to hormone-altering chemicals in today's dirty world along with today's dirtier diets. Perimenopause historically occurred in a woman's mid-to-late 40s. Now some women are starting their perimenopause in their late twenties and more in their thirties. As menstruation milestones wane, so does sleep.

Without adequate sleep, we're not only tired and wired, but we also can't think as clearly, get any job done as well, plus we are more accident-prone. Inadequate sleep promotes errors in judgment, even more neuroticism, and less mindful conscientiousness[14] (no matter how much you try to sit and shut off your thoughts).

Lack of restorative sleep raises stress hormones[15] (epinephrine and cortisol) that shrink the hippocampus (hippocampal atrophy). The hippocampus is the area deep inside your brain where your sense of "self" lives. I call it the seat of your 3 M's (me-ness, memories, and motivation). Lack of sleep causes poor memory retrieval, overwhelm, and self-doubt as hippocampal function[16] degrades. Maybe you're seeing a psychotherapist when you need to address your sleep.

Excessive levels of cortisol are linked to increased belly fat that is not easy to lose.[17]

Excess cortisol can ding sex hormones. Higher levels of cortisol do this by "competitive inhibition." Excessive cortisol swims inside and

binds into the estrogen, testosterone, or progesterone receptors and clogs them (competes with the parent hormone). Even if your blood and saliva levels of hormones look *normal* on testing, these blocked sex steroid receptors can't deliver their signals optimally.[18] You feel tired, bloated, fat, and slow. No matter how many green drinks you down. No matter how much your gynecologist or endocrinologist insist that your hormone levels look normal.

Excessive cortisol can increase an adrenal and brain hormone called *dehydroepiandrosterone*, nicknamed DHEA. Excess DHEA can make estrogen or testosterone levels soar.[19] Thus, too little sleep causes too much stress hormone, which can *lower* or *amplify* sex hormone signals, depending on lots of individual factors that make up individual physiologies, all which ups your risk of various health issues such as hormonally driven cancers.

Too high levels of stress hormones for too long depress your immune system. This puts you more at risk of diverse diseases and infections, for example, greater risks of heart disease, type-2 diabetes, and even eye diseases.

Did you know that eye doctors are now required to learn about sleep disorders, as sleep is becoming known as a major influencer on eye health?[20] Any person with absolutely any kind of eye disease must have their sleep tested and improved to protect their vision.

Sleep disturbances are strongly associated with "impaired" release of factors called growth or trophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1).[21] Optimal functioning of growth factors protects mood, staves off depression, and maintains neuroplasticity.

Sleep is a huge contributor to psychology. Sleep is a portal to help you sort out the things you learned and endured all day long. Studies have linked a nightly battle with insomnia to anxiety, depression, memory loss, dementia, socialization issues and even Alzheimer's and other brain disorders, including Parkinson's.[22]

Why You Can't Sleep

- *Too much caffeine.* Excess caffeine consumption has now been shown to suppress the production of melatonin in *pinealocytes* (cells in the pineal gland) through competitive inhibition of adenosine A2 receptors by caffeine.
  - Higher cumulative lifetime coffee consumption has been shown to reduce the size (volume) of the pineal gland! This gland makes the sleep hormone melatonin. The size of the pineal gland is referred to as the VPP (volume of pineal "parenchyma" – term for pinealocyte cells). When you regularly drink "excessive" amounts of coffee, the volume of the pineal gland shrinks. Too many cups of Joe over too many years makes your pineal gland shrink!
  - A squattier pineal gland releases less melatonin. Less sleep hormone means impaired quality of sleep, especially in later life from the long-term effects of a "life well-caffeinated."[23] Of course, what constitutes too much caffeine and a smaller pineal gland probably depends on genetics and SNPs. It's all individual. There are significant health benefits from coffee, so it's a "Goldilocks" kind of thing, drinking the just right amount for your physiology.
  - Less melatonin also means more risk of cancer, as melatonin is a major anti-cancer fighting hormone.
  - *How much coffee is okay?* Moderation is the key. One to several cups of coffee, rather than numerous shots of espresso all day long, seems to be the healthiest for most of us.
- *Too much alcohol*. With advertisements on TV making alcohol look as safe as water and trendy and cool as heck, too many are drinking too much. Especially young adults. This is linked with harming sleep.[24]
  - Each of us metabolizes alcohol differently due to various liver capabilities, body size, organ size, and genetics. Some folks can drink more and still get their Z's, but some women will have insomnia from just one nightly glass of wine.
  - Alcohol blocks REM sleep, the most *restorative* type of sleep, so you wake up feeling groggy. Alcohol also reduces anti-diuretic hormone (ADH) so you may have to get up to urinate during the night, which also is sleep disruptive.
  - Women literally have smaller livers than men, so women are more vulnerable to these potential adverse effects of alcohol than males. *Gender unfairness but "is-ness!"*
  - Studies yoyo on how much alcohol is healthy or harmful, but most female bodies cannot handle alcohol on a daily basis, and often, those several glasses of wine at night are the enemy of your sleep.

Did you know that eye doctors are now required to learn about sleep disorders, as sleep is becoming known as a major influencer on eye health?

- *Too little exercise*. Exercise improves your sleep; there is no doubt about it.[25]

  Adding just 15 to twenty minutes a day of getting your circulation going, allows your body to wind down more successfully during night time hours.
- *Not being outside*. Even just 20 minutes a day in nature enhances well-being and sleep.[26] Even just looking out the window at nature, or at pictures of nature, help promote wellbeing and sleep.[27]
- *Hormone yoyo-ing*. In both women and men, hormones out of balance cause sleep out of balance. From hot flashes and night sweats caused by peri- and post-menopause in ladies, to too little T (testosterone) in ratio to too much E (estrogen) in gents (especially chubby dudes), all dent sleep.
- *Growth hormone insufficiency*. Human growth hormone is released in the first deep-sleep episode of the night. When adequate levels are released, this phase of sleep is associated with "deep" body/mind *rejuvenation*. Thus, growth hormone is essential for restorative sleep and vice versa; healthy sleep promotes healthier blood levels of your growth hormone (so does digesting healthy protein and exercising). When you sleep less well and exercise too little,

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you produce less growth hormone. A growth-hormone-deficient body becomes less efficient at *falling* and *staying* asleep. Growth hormone naturally lowers as we age, unless we eat and digest optimally, and continue to regularly work out.

- By the way, the 24-hr urine hormone test (by Meridian Laboratories) easily measures *growth hormone* (GH) levels along with other hormones and their metabolites. This is my favorite GH test.
- The insulin-like growth factor-1 (IGF-1) test is an indirect measure of your average blood levels of growth hormone. Low blood levels of IGF-1, less than 160, are typical in severe fatigue states and elevated levels can also occur from poor sleep, worsening cancer risk or progression.
- A Belgium double-blind, placebo-controlled study found that women who took 300 mg of oral progesterone before bed, got to sleep faster, slept better, had higher levels of growth hormone and even more stable blood levels of thyroid hormone.[28] Did you know that progesterone helps thyroid hormone enter the thyroid receptor to deliver its signal?

- *Unresolved emotions*. Emotions of sadness, fear, regret, perfectionism, and even guilt[29] disrupt sleep. Unfinished emotional business promotes unfinished sleep. And vice versa.
  - Chronic insomnia makes you feel more insecure and anxious and these feelings then sabotage sleep. Emotions can get more chaotic in mid-life as circumstances become more demanding. Your parents get older and need help, your kids get into shockingly more trouble, close friends or family start to get ill, and you can't believe that your own work life, relationship life, money life, etc., aren't yet stable. Who knew that growing up doesn't automatically make life or sleep, easier?
- *Non-dippers.* Healthy blood pressure is supposed to gently lower during the night (compared to pressures during the day) by approximately 10–20%. "Non-dippers" are people whose blood pressure doesn't lower adequately during sleep. This damages restorative sleep. Make sure to turn the TV off, get the phone off the table, those ear-buds out of your ears, and have your doc check your blood pressures, sometimes with a 24-hr pressure monitor.
- *Nocturnal hypertension.*

I had one patient that kept waking at 2:30 AM with rapid heartbeats. Once awake he couldn't easily fall back asleep. In contrast, during the day his blood pressure was perfect. Heart physicals by several heart docs found nothing wrong. After three years, and after several cardiac work-ups found nothing abnormal, he continued to feel worse and worse from disturbed sleep. Finally, a functional cardiologist, I referred him to, ran a 24-hr. blood pressure test. This demonstrated that at 2:30 AM, when he'd consistently woken up with arrhythmias, his blood pressure soared to 190 over 120, even though multiple day-time pressures were continually normal and perfect. When this patient got a small dose of an anti-hypertension drug before bed; sleep immediately normalized. He slept like a baby.

It's critical to mention, that "nocturnal hypertension" was not the "root cause" but rather a sign of a deeper issue that had to be found and addressed. It turned out that one of his heart chambers was *hardened,* and also one valve had a leak, none of which was found by the many other heart docs he had seen. It was early enough to use sophisticated nutrition intervention, to ward off fatal congestive heart failure. But the point is that his insomnia and arrhythmias had been flashing red lights for deeper heart issues that were not easily identified by multiple of well-respected specialists!

Natural Ways to Help You Sleep

Before taking any sleep aids, even over-the-counter or natural, it's best to work with a practitioner that understands your personal physiology and medical history. Sometimes relentless insomnia occurs due to a hidden disease. For example, excess calcium blood levels from primary hyperparathyroidism (a benign tumor on a parathyroid gland) can adversely affect the brain and manifest as insomnia. Sleep apnea, trouble breathing during sleep, can cause insomnia. Chronic hidden infections can cause insomnia.

Once disease is ruled out, natural sleep aids can be very helpful for midlife sleep issues. Some of these natural sleep aids bind to the same places in the brain as prescription sleep meds (sleep hypnotics) and may lose their effectiveness over time, just like those drugs do. Thus, it's good to have lots of sleep-promoting tools, especially ones that work by mechanisms that do not lose their effectiveness, such as hormones, nutrients, and lifestyle improvements.

- **Hormone Hacking.** A healthy brain produces *progesterone* right inside the brain.[30] This is because progesterone is a brain-protective hormone in both men and women. Progesterone is also one of Nature's chief sleep protectors.
  - Progesterone binds to the GABA[31] receptors in the brain and calms the brain to help it turn off and promote *restorative* sleep.
  - Progesterone regulates a member of the neurotrophin family, *brain-derived neurotrophic factor*, which keeps your brain healthy. A healthier brain turns off easier at night as well as being more protected from neurodegeneration.[32]
  - As we age, both genders' brains produce less progesterone, and this contributes to poorer sleep. Progesterone therapy usually improves it. In fact, perimenopausal insomnia is often a woman's body "screaming" for additional progesterone.[33] But sometimes males need some progesterone replacement, too.
  - *Oral* progesterone is a better tool to improve sleep, most of the time, than topical. This is because progesterone's major sleep-promoting metabolite, *pregnenolone*, is only produced if progesterone is taken *orally.* When swallowed, progesterone goes from the gut into the liver (called *the first hepatic pass*) where liver cells morph the *progesterone* into sleep-promoting *pregnenolone*. This progesterone metabolite acts very similarly to Valium™,[34] but without the adverse and potentially dangerous side effects.[35]

- Progesterone reduces "brain on fire" or excessive inflammation in the brain. In this way, progesterone also fights depression and possibly small vessel ischemic brain disease.[36]
- If men are recommended progesterone, it's usually prescribed in much lower dosages than women and can be given orally from 30 to 50 mg, or sometimes is prescribed in *facial creams* (Key Pharmacy in Federal Way, WA, has been making a male hormone face cream for many years).
- Sometimes men and women need other hormones. Estrogen therapy in ladies or T replacement in gents can help achieve deeper and healthier sleep.

- **Less caffeine.** Too much caffeine is a commonly overlooked problem in too many insomniacs. This is because there is a lot of individuality in the "caffeine sensitivity" effect on sleep.[37] Some persons can drink espresso all day long and right before bed, and still sleep like a baby. Other people may be extremely sensitive to caffeine (usually due to how genetics affects the speed at which they rinse caffeine out of their bodies). These people may become insomniacs from just one caffeinated beverage a day, sometimes even in the morning. Many caffeine-sensitive folks find that not consuming caffeine after 3 PM does the trick. But sometimes any caffeine may be too much for you. We don't appreciate that what we sip, can sap sleep.
  - Make sure you aren't suffering sleep issues because you are hitting Starbucks too often for your physiology. Also, as crazy as it seems, *caffeine can promote sleep apnea*, even in kids.[38] There is a lot of caffeine in many sodas.
  - There are gender differences, too. Women are typically more sensitive to caffeine than gents. Women metabolize caffeine much more slowly than men.[39] This is why many men can down a cup of coffee right before bed, while if a woman did this, she would spend the night staring at the ceiling.
- **Melatonin.** Melatonin is secreted by the brain's pineal gland in response to cycles of light and darkness. Melatonin regulates your ability to stay "in sync" with light and dark, in sync with Mother Earth. Melatonin is thus often helpful for traveling across time zones, to keep you in sync with new light and dark cycles. When you are more in sync with light and dark, you are tired at night and sleep deeply, and are more awake and energized during the day. When melatonin production or metabolism is dysregulated, this gets reversed; you can't sleep at night and are tired throughout the day. You're out of sync with Nature's light and dark cycles
  - Natural melatonin secretion is dys-regulated by light at night, depression, shift work, seasonal affective disorder, and as you read above, excessive caffeine intake over a long period of time.
  - Melatonin is a major antioxidant and protector of estrogen, keeping it from acting less as a cancer-causing molecule in both men and women. Melatonin, in combination with omega-3 fatty acids, especially does its estrogen and cancer fighting actions *while you sleep*, if your levels of melatonin are high and healthy enough (PS Meridian 24-hr hormone test assesses melatonin levels. Excessively high melatonin levels can suggest health issues such as cancers. This test has helped me ID cancers on several patients.)
  - The usual dose is 0.5–3.0 mg, taken one-half hour before bedtime. (I have found it works best as a non-time-released tablet chewed and held under the tongue for 30 seconds)
  - For some recent cancer patients, the dosage can go up to 20 mg, but this must be done in conjunction with an in-the-know doctor.
  - Melatonin can safely be used with aromatase inhibitors[40] and estrogen blockers, as it has been shown to reduce some of their adverse side effects.
  - Melatonin itself acts as a *natural aromatase inhibitor* and also limits cancer growth by additional helpful mechanisms other than aromatase blocking. Melatonin is one of the cancer patient's best friends.
- **Magnesium-rich foods and supplementation**. Magnesium is Nature's Valium. It relaxes the body and mind. Magnesium deficiency is linked to causing insomnia.[41] It's easy to become deficient in magnesium. Magnesium is deficient in the Standard American Diet (often referred to as SAD). This diet is typically low in green vegetables. Magnesium "lives" inside the center of the chlorophyll molecule that gives veggies their green color. In essence, magnesium is "captured sunlight." Sufficient magnesium inside your red blood cells, where magnesium does most of its magic, makes you feel relaxed and calm, like lying outside under the sun.
  - However, healthy magnesium levels are not easy to maintain inside red blood cells, no matter how normal blood (serum) levels appear.
  - Why? Magnesium is constantly "rinsed out" of the body during times of chronic or severe stress. And today, who's not stressed?

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- To make magnesium matters even more confusing, many magnesium supplements don't contain the "elemental" levels that the label says will be in there, which are necessary for keeping your red blood levels healthy.
- Thus, there are a lot of magnesium insufficiencies and misunderstandings.
- Magnesium supplementation before bed may help you sleep more soundly. Sometimes taking taurine[42] helps keep magnesium more anchored inside the red blood cell and less at risk of being rinsed out. You could refer to taurine as a "magnesium-sparing nutrient" (coined by Berkson).

- **GABA.** Gamma-Aminobutyric acid, or γ-aminobutyric acid, or GABA, is the chief "inhibitory" neurotransmitter that "quiets" down the central nervous system. Some people do well taking 500 mg of GABA one half hour before bed. Some require more. But it's not easy for GABA to pass the blood brain barrier, whereas the progesterone metabolite does and also signals GABA receptors.
- **CBD oil.** *Cannabidiol* (CBD) is a major "non-intoxicating" component of cannabis and possesses anti-epileptic, anxiolytic, anti-hyperalgesic and sleep-promoting properties. CBD signals $GABA_A$ receptors. It works in both capsule or drop form, but the dose varies greatly depending on the individual and the cause of insomnia. The CBD signals the cannabinoid system, which relaxes the central nervous system and by the way, overlaps with oxytocin signals.[43]
- **Magnolia bark.** This herb is especially helpful for sleep, if the cause of insomnia is due to elevated nighttime levels of the stress hormone cortisol. This herb lowers both stress hormones (cortisol and adrenaline) and keeps these lower all night to allow you to sleep.
  - Magnolia bark reduces the time it takes you to fall asleep and increases the amount of time you spend in both REM sleep and non-REM sleep.
  - Magnolia acts like an "herbal magnesium." It reduces anxiety. For some people, magnolia bark can be as effective as diazepam (valium) without the risks of dependency or adverse side effects. The typical dosage is 250-500 mg taken with dinner and also before bed.[44] Severe insomniacs may need much more at the beginning but can taper down after sleep improves for at least two weeks.
- **Moon Drops.** This is a pleasant vanilla-flavored homeopathic that works for a lot of my patients when slowly dissolved in the mouth half an hour before bed. It comes in such a cool-designed small box, tastes delicious, and works so well that it's a real go-to natural sleep aid, if your progesterone replacement is not doing the trick or you want to try to fix your issues sans hormones.
- **L-Theanine.** This amino acid increases the levels of the three neurotransmitter musketeers – GABA, serotonin, and dopamine – calming neurotransmitters that "live" inside the brain and regulate emotions, mood, concentration, alertness, energy, and sleep.
  - L-theanine promotes healthier daytime emotions and nighttime sleep, helps with menopause- and andropause-related mood swings, difficulty concentrating, and it even helps some people regulate portion control.
  - If you're a caffeine junkie, L-theanine may even help counteract the anti-sleep effects of caffeine.[45]
- **5–HTP.** 5-HTP (5–hydroxytryptophan) increases serotonin, which is then converted to melatonin. 5-HTP is, thus, a *melatonin-booster*. Start at 100 mg, three times per day. Gradually increase to 200 mg, three times per day. Some cases of IBS (irritable bowel syndrome) are worsened by excessive levels of serotonin so don't take this without working with a smart doc, especially if you have gut issues.
- **Herbal helpers.**
  - **Valerian.** (*Valeriana officinalis*) in capsule form – the liquid has a bitter taste though some of my patients think the liquid works better/faster – at 150–300 mg standardized to 0.8% valerenic acid. Take one hour before pulling the covers up. **Dormeasan®** drops are an organic valerian and hop tincture mixture that doesn't have a severe bitter taste. The dosage is 30 drops half an hour before bed. Putting the drops in a half cup of your favorite nighttime tea is a effective sleep-promoting routine.
  - **Traditional Chinese medicines.** One is called ***Suan Zao Ren***.[46] The formal name is *Semen Ziziphi spinosae*. It is the dried ripe seed of the sour jujube or spiny date. It has been used for hundreds of years in China to treat insomnia as well as reducing severe sleep disruptive dreams.[47] This herb is especially helpful for patients trying to take *low dose naltrexone* (a super immune booster) but who begin having overwhelming dreams or insomnia as an adverse side-effect. Dosage varies depending on the product.
  - Another standard Chinese formula is called **Gui Pi Tang**.[48] Again, dosage varies depending on the product.
  - ***Pueraria mirifica*.** An herb[49] from Thailand used for hundreds of years to promote sleep by helping your body's natural estrogen reduce hot flashes or nasty sensations of dysphoria. **Boron** is a mineral that also helps bodies utilize estrogen in both ladies and gents.[50] Estrogen is produced in six places inside a healthy brain and promotes sleep in both genders, although males, of course, have less estrogen than females. Sometimes I recommend the herb and boron together.
  - **Pregnancy insomnia: Lettuce Seed** (*Lactuca sativa* L. seeds) has been shown, in a human pregnancy study, to promote better sleep in insomniacs and found *safe to take during pregnancy.*[51] The dose is one 1000 mg capsule of lettuce seed a half-hour before bed.

Avoid Sleep Hypnotics Like the Plague

Regular use of sleeping pills, prescription sleep hypnotics, are linked to making you die prematurely from diverse causes.[52] Even taking less than 18 sleep hypnotics in one single year has been linked to dying prematurely from all-cause mortality.[53] By the way, the authors of this study pointed out that this was the 19th scientific investigation linking sleep hypnotics to premature death. This means that the link between taking sleeping pills and

decreasing your time on earth is well established! The sleeping pill fix is not worth it. If you take them, use them for the shortest time possible while you fix the root issues causing your insomnia.

Also, these meds are habit forming. Plus, they lose their effectiveness over time as the brain builds up tolerance.

Sometimes doctors say that since sleeping pills are dangerous why not take allergy *antihistamine* drugs as they cause less dangerous drowsiness. Not true. Antihistamine meds block *acetylcholine*, which lubes neurotransmitters and is crucial for memory. The use of antihistamines, either pharmaceutical or over-the-counter, is now reproducibly linked to increased risk of cognitive decline and dementias[54] as well as premature death and increased risk of cancer.[55]

For every three years on regular use of anti-histamines, the increased risk of dementias increases significantly. Stay away!

Sleep medications can cause other issues. More car accidents. Poorer job performance. Addiction. When you try to stop taking these meds, you get "rebound-worsened insomnia,"[56] which makes them very difficult to stop. And… you risk late night atypical behaviors or food binges that you can't even remember when you wake up the next morning.

You Gotta Laugh

I love the scene in *Grace and Frankie* where Jane Fonda (Grace) gathers up her courage and energy to break up with her beau when he comes down at night to raid the fridge. But the next morning he acts like it never happened.

Lily Tomlin (Frankie) queries to Jane, "Did you break up in English? Was he even in the room?"

But the truth comes out – it was an Ambien break-up!

Now Jane Fonda has to break up with him again when the Ambien is out of his bloodstream, and he is vertical and conscious.

I have had some patients admit to me that when on Ambien, they wake up in the morning to 10 empty tuna cans strewn throughout the kitchen and a mouth that tastes of fish!

Too Much Sleep Isn't Better

Both excessive longer and shorter sleep hours are associated with increased mortality.[57] Sleeping more than you need, it turns out, can be just as detrimental as sleeping too little. Just like Goldilocks, you need to find the optimal "just right" amount of sleep that works best for you.

Keep in mind, though; this may not be *truth* for all. There was a book by an anthropologist (it's out of print now and I can't find the name) who traveled the world assessing cultural differences in sleep. Some indigenous tribes did well sleeping with full light, chickens in the room, and 15 people on top of each other. Perhaps they did not have the constant barrage of electromagnetic fields that US towns and citizens now have.

Some people with severe adrenal fatigue and cortisol dysregulation have to wake up many times during the night to urinate and suffer with severe sleep issues.

Sleep-Boosting Lifestyle

- **Eat less junk foods,** especially high glycemic ones that spike your blood insulin. Excessive blood sugar and insulin levels ding sleep.
- **Drink less alcohol and limit caffeine intake.**
- **Limit IT exposure before bed and during sleep.** Many people are sleeping with their phones under their covers or on their nightstands. This can disrupt sleep[58] as the *blue light* that comes off screens mimics the light of full daylight. This can disrupt sleep as well as promote insulin resistance and keep you fat!
- **Get regular exercise. Especially outside.** Or work out at a gym, but stand outside in front of the gym for a bit of time to get sunlight, even on cloudy days. Or just look outside the window and let the vision of nature inside your body/mind and spirit.
- **Try to find your most sleep-promoting mattress.** Science now shows that many memory foam mattresses and pillows outgas dangerous solvents. For years. *When will the bad news stop?*
- **Sleep in as a dark room as possible.** Excess artificial light emitted from lights on in the bathroom or from street lights, televisions, monitors, smartphones and other devices can suppress melatonin production and sleep quality. Some very sensitive and ill people even need to "turn off" their electronics several hours before bed to start winding their brain and nervous systems down adequately to achieve restorative sleep.
- **Clean up.** Creating orderly spaces in your bedroom and home reduces cortisol levels, which then soothes spirits and sleep.
- **Resolve your emotions as best as you can**. Unhealthy emotions make for unhealthy sleep, and vice versa. Emotional house-cleaning soothes spirits and sleep.
- **Don't eat before bed, for most of us.** It takes approximately three hours for your stomach to empty after a meal. Thus, it's an ideal practice to stop eating at least three hours before bed. Part of insomnia is the American habit of snacking while lying down in front of the TV late at night. But we are all different. Some people sleep better with a light snack before bed, one that is high in protein but low in refined carbs.
- **Deal with grinding your teeth**. Sleep is harmed by *bruxism* (teeth grinding). The combination of insomnia and tooth grinding is considered a primary sleep-related movement disorder.[59] Bruxism can be helped by mouth guards, and sometimes by identifying and avoiding *intolerant foods*. Adverse food reactions can cause any ongoing issue. Food is powerful!
- **Getting up to pee.** Drinking excess fluid before bed may cause you to wake up in the middle of the night

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➤ to urinate and this then disrupts your sleep cycle. If you don't drink too much before bed, yet you wake up to pee, this suggests *cortisol dysregulation*. Appropriate lower nighttime levels of cortisol are supposed to keep you sound asleep, even if your bladder starts to fill up. Some people with severe adrenal fatigue and cortisol dysregulation have to wake up many times during the night to urinate and suffer with severe sleep issues. *Fluid intake, adrenal health, and cortisol issues all overlap* in affecting urination and ability to achieve deep restorative sleep.

- **Regular wind-down routines** help signal your mind and body that it's time for sleep. Even changing your sheets more often can contribute to a healthier sleep and be part of this ritual. If I were super wealthy, I'd have someone change my sheets nightly!
- **Mindfulness.** I often suggest mindfulness exercises to my patients. I am seeing more and more patients, especially women, who are so chaotic during the day that they have abandoned congruency with their bodies and can't turn off their minds during sleep. If they do achieve hours of sleep, those hours still seem less restorative. Most of my patients are already rushing to fit in yoga, meditation, or workouts (so oxymoronic), so I recommend unique focused exercises that I learned while living with Swami Satchitananda at Yogaville East in the 1970s. *Acupuncture* is also a physical way to achieve more physiologic and emotional balance that contributes to better sleep.[60]
- **A message from your deeper self… is your sleep issue trying to tell you something?** Persistent sleep problems may be flashing red lights on your physiological dashboard saying that something is off in your life that needs attention and healing. If true for you, try to gently fix these issues. Put some *intention* and/or *prayer* onto these issues to inform your higher self that they need recovery. Sometimes repeating healing *affirmations* or *requesting guidance* (by repeating a simple inquiry over and over again) – before falling asleep – helps your unconscious take over and heal ongoing woes while you count sheep. You may be surprised to wake up to obvious restorative answers!

Sleep Performance Anxiety… Go to Bed Without It

We tell patients you "must" have eight hours of sleep or your toes will fall off. But some tribes around the world sleep for four hours, wake up and dine and party, and then go back to sleep for four hours, and are healthy and happy. My mother lived to 96 years of age and was never ill till her early 90s. She had infinite energy and only slept four hours a night. So did Einstein.

Even though practitioners make recommendations, everything ultimately has to be *individualized* to you… even sleep.

Maybe you do better on less sleep than the average bear. I used to sleep four or five hours a night, like my mother, and did great. But once I had a kidney removed, those short beneficial sleep nights were a thing of the past. I then had to sleep more and sleep better to have happier tomorrows. Need for optimal hours of sleep morphs with your personal life circumstances. Tune in and try to sense how many hours of sleep work best for you. You may need more hours of sleep when healing from illness or moving through tragedy than when all of your hours are humming healthfully.

The healthiest body is one you listen to.

If All Else Fails…*Gabapentin*

I had a number of patients that tried everything but still couldn't sleep, and thus were miserable. I did my geeky thing and sleuthed the peer review literature. Science-based articles showed that the old-time safe medication, gabapentin,[61] lubes the sleep pathways to "retrain" the brain for healthier sleep. This is an off-label use of this medication that is typically used to treat nerve root pain. But it's an amazing helper for some people with severe non-responsive insomnia.

Gabapentin, 100 to 300 mg, taken one-half hour before bed for a few months helps brain cells *retrain* themselves for a good night's sleep. I've been recommending this for about a decade. It is not 100 percent foolproof. One patient told me it made her more jittery and less able to sleep. But most start sleeping that very night.

Presently, many medical sleep centers are recommending gabapentin because it's so effective for so many insomniacs.

Remember, integrative medicine is a combination of both sides of the healing coin. It's okay to use drugs for a while when they work, and you can eventually get off them once your brain has re-learned to sleep deep. After using gabapentin for four to nine months, you'll start responding to simple melatonin and magnesium one-half hour prior to bedtime, when before these didn't work. You need to *slowly* taper off this medication. Adding more magnesium helps you do so in a shorter period of time.[62]

Don't use this medication if you have kidney disease without working with a physician in-the-know.

May the therapeutic sleep force be with you!

- If you want me to help you with your sleep issues, contact me via my consult section at drlindseyberkson.com.
- Check out my podcast on sleep at Dr. Berkson's Best Health Radio.

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Melatonin Isn't Just for Sleeping – From Cardiovascular Disease and Cancer to Aging and Macular Degeneration the Research Will Shock You

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Hormones become deficient as our bodies get older. And these deficiencies are one of the root causes of all of the diseases and symptoms of aging. So, treating these deficiencies along with a healthy lifestyle is fundamental to living long and well. But of all the hormones that our bodies depend on, there is one particular hormone that stands out above all the others.

The surprising thing is that almost nobody fully appreciates how important this hormone is. I'm talking about melatonin. And when you hear about all of the things that researchers are discovering about melatonin, you're going to be absolutely amazed.

Everybody knows that melatonin is important for sleep. But it's my opinion that even if you sleep like a baby, if you are over the age of 40, you should be taking melatonin. This information is too significant to quickly gloss over. So, in this article I'm going to present you with 19 recent research papers that will tell you why it is so important that we all supplement with this very special hormone no matter how well we sleep. Specifically, I am going to show how this one hormone promotes all of these unexpected effects:

- Protects against viral and bacterial infections,
- Prevents cardiovascular disease and high blood pressure,
- Reduces oxidant stress and inflammation and slows aging,
- Prevents neurodegenerative diseases such as Parkinson's and Alzheimer's,
- Improves menopause therapy,
- Protects against ionizing radiation,
- Prevents macular degeneration, and
- Prevents and treats cancer.

First of all, some people may have a hard time understanding how melatonin can be so important for so many different aspects of the body. After all, isn't it produced only in the brain? That is one of the first misunderstandings that needs to be cleared up. No, melatonin is not produced only in the brain. It is produced all over the body in larger amounts than it's produced in the brain. The largest production of melatonin is in the intestines. Researchers have also discovered that it's produced in the retina, the bone marrow, the skin, the thymus, and the white cells of the immune system. The fact that it's made in the thymus, which is an important regulator of the immune system, and in the immune cells themselves is why melatonin is so important for preventing and treating infections and cancer.

Infections

Let me just quote for you from a recent review of the infection-fighting potential of melatonin. "Melatonin has also been found to be effective in combating various bacterial and viral infections. Its administration has been shown to be effective in controlling chlamydial infections, infections induced by Mycobacterium tuberculosis, and also in many viral infections."[1] The researchers go on to explain that melatonin is such an efficient anti-infectious supplement for several reasons.

For one, it can directly decrease bacteria's ability to reproduce. If bacteria cannot reproduce, they cannot infect. Secondly, it sets up an environment in our tissues that bacteria cannot survive in. And third, it acts to decrease the inflammatory effects of bacterial infections. This is why it's so effective in animal models of septic (infectious) shock.

Amazingly, the authors go on to say, "Use of melatonin has been beneficial in treating premature infants suffering from severe respiratory distress syndrome and septic shock." And, "It has a potential therapeutic value in treating septic shock and associated multi-organ failure in critically ill patients in addition to its antimicrobial and antiviral actions."

One of the real battles we have these days is the constant exposure to new viruses and antibiotic-resistant bacteria. Along with ozone therapy, melatonin could be just the answer we need. Both of these therapies not only strengthen our immune systems, but also have a direct effect on these infections.[2] I am sure that the reason we hear of old people dying from flu infections every year is because they are deficient in melatonin.

Cardiovascular Disease

Another effect of melatonin is in preventing and treating heart disease and high blood pressure. A brand-new review article on the effects of melatonin on cardiovascular disease points out that "the major contributor for morbidity and mortality of the impaired cardiovascular system" is not cholesterol or stress. It's getting older! The risks for coronary disease, high blood pressure, heart failure, and stroke increase with age more than any other risk factor. Why? The authors state that one of the reasons is because as we get older, our levels of melatonin decline to almost nothing. These researchers produced a number of remarkable studies on senescence-accelerated mice to make their point.

Senescence-accelerated mice are a special breed of mice that age much faster than regular mice. Compared to normal mice, these senescence-accelerated mice have much more inflammation and oxidative stress and die earlier. They also have much lower amounts of nitric oxide. Nitric oxide is critical for cardiovascular health and maintaining a healthy blood pressure.

So, the researchers gave the senescence-accelerated mice melatonin. They discovered, "Melatonin treatment prevented the age-dependent cardiac alterations observed in the senescence-accelerated prone group." In fact, when they were taking melatonin, the senescence-accelerated mice had the same level of cardiac function as normal mice![3] Why did they get these results? Because, as you will see in a moment, melatonin has remarkable anti-inflammatory and antioxidant properties. So, mice do better with melatonin, but what about people?

Researchers recently looked at 16 men with high blood pressure. First, they measured their blood pressures using a 24-hour blood-pressure monitoring device. Then they gave each of the men a placebo pill to take before bed every night and re-measured their blood pressures. Then they repeated the experiment, but the second time they gave the men 2.5 mg of melatonin. They only did this for three weeks. But even in that short a period of time and with that low a dose, their systolic blood pressures dropped an average of six points, and the diastolic dropped an average of four points.[4]

Another characteristic of melatonin is that it acts directly on the DNA and mitochondria in our cells, causing them to behave more like they did when we were younger.

Aging, Inflammation, Oxidant Stress

So, melatonin is protective for infections and cardiovascular disease. But what about aging and the diseases of aging? Everybody agrees that the two major causes of degenerative disease and the aging process are oxidant stress and inflammation. So, does melatonin have an effect on these?

A recent article on melatonin, aging, and the nervous system looked at the effect of melatonin on NF-kB. NF-kB is the protein complex that causes inflammation. One of the ways that NF-kB causes inflammation is by stimulating the pro-inflammatory enzyme COX-2. COX-2 is the enzyme that many of the anti-inflammatory drugs interfere with. These researchers found out that not only does melatonin inhibit NF-kB, it also suppresses COX-2. So, melatonin does have a strong anti-inflammatory action. By the way, another effect of the COX-2 enzyme is that it stimulates tumor development.[5] Remember this when I discuss the role of melatonin to prevent and treat cancer. But that's not all.

Through many of the same mechanisms in which melatonin prevents inflammation it also stimulates Nrf2. Nrf2 is the main transcription factor that stimulates the production of all of the antioxidant enzymes that the body uses to control oxidant stress. One of the reasons that ozone therapy is so effective for so many age-related diseases is because it is a potent Nrf2 stimulator. Nrf2 levels are directly related to how long you will live and what your risks are of becoming sick from anything. By decreasing inflammation and oxidant stress through the suppression of COX-2 and of NFkB and the stimulation Nrf2, melatonin may be the most effective anti-aging supplement you can take.

Another characteristic of melatonin is that it acts directly on the DNA and mitochondria in our cells, causing them to behave more like they did when we were younger. Studies have shown that aging rats supplemented with melatonin are healthier and live 20% longer than their deficient friends. That's why researchers at the Menopause Center in the Madonna delle Grazie Health Institute in Rome decided that the way melatonin functions in the body of women as they near menopause might provide some clues for the aging process in both men and women.

They set up a double blinded, placebo-controlled study in a group of peri and post-menopausal women between the ages of 45 to 60. First, they measured their thyroid hormones, T4 and T3, and their melatonin levels. The researchers knew that as we get older our levels of thyroid hormones decrease. This leads not only to increased weight gain and decreased energy levels, but it also results in high cholesterol and a shorter life span. All of these symptoms are very common in the over-fifty crowd. Then they gave half of the women 3 mg of melatonin, and the other half a placebo. Three and six months later the same tests were repeated. Here's what they found out. Every single one of the women who had lowered levels of melatonin at ➤

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the beginning of the study showed a significant increase in the levels of both thyroid hormones.

According to the authors, "These findings seem to show a recovery of pituitary and thyroid functions in melatonin-treated women, towards a more youthful pattern of regulation."[6]

Anti-infectious, preventing cardio-vascular disease, and anti-aging – so far so good. But what else? How about brain function?

Alzheimer's and Neurodegenerative Diseases

The data on melatonin and brain and nervous system function is astounding. Many of the problems that we face as we get older are directly related to nervous system aging. This includes declines in cognition and memory, impairments in vision and hearing, chronic constipation and other stomach and intestinal tract problems, decreased coordination, decreased balance, and falls. Studies say melatonin is effective for all of these problems.

In one recent study, the researchers looked at the levels of 6-sulfatoxymelatonin in the urine of 1,105 men and women between the ages of 64-78. This is a metabolite of melatonin that shows up in the urine. The more 6-sulfatoxymelatonin in your urine, the higher your levels of melatonin are. Then they measured their MMSE scores. The MMSE test is an easy to do test that I use in the office all the time to measure and monitor memory and cognitive function.

The men and women with the higher levels of 6-sulfatoxymelatonin and hence had the highest levels of melatonin also had the highest scores on the test. The researchers concluded that the higher your melatonin levels are, the less likely you are to have any kind of cognitive impairment.[7] But why? What's going on?

First of all, melatonin is by far the major antioxidant in the brain and nervous system. Since oxidant stress is the primary destructive force on our brain's cells, having enough melatonin is absolutely vital for preserving optimal brain function in the over-60 crew. Animal studies clearly show that melatonin protects brain cells as we get older more effectively than any other antioxidant supplement.

Here's a powerful example of how effective melatonin is at protecting the brain. Methamphetamine is a street drug that destroys brain cells. When researchers give animals melatonin supplements along with high doses of methamphetamine, they are completely protected from the damaging effects of the drug. But melatonin does much more than just protect the cells from degeneration. It also acts to stimulate brain stem-cell activity.[8]

You might not know this, but unlike all the other cells in the body, many brain cells do not divide and replace themselves before they die. You have these cells when you are young. But since they do not breed new daughter cells, when they die, they are gone for good. Don't worry, though. That's because we have brain stem cells. Brain stem cells are special cells that can magically turn into any one of the many cells that the brain has. So, when our non-multiplying brain cells die, our brain stem cells can come along and replace them. The process is called neurogenesis. That's great news, right? Not so fast.

Stem cells are amazing, but their activity decreases as we get older. As that happens, neurogenesis decreases. And that's another reason melatonin levels are so important. Because studies show that when researchers give animals melatonin supplements as they age, the process of neurogenesis goes the other way – it actually increases! But animals aren't the only ones who benefit.

In humans, scientists have found that giving melatonin supplements "potentiates hippocampal neurogenesis in elderly populations." Why is this so important? The hippocampus is the area in the brain that regulates short-term memory and spatial orientation. Spatial orientation refers to knowing where you are and how to get to where you want to go. In Alzheimer's disease, the hippocampus is one of the first regions of the brain to suffer damage. And that's why memory loss and disorientation are two of the early symptoms.

A recent study looked at 80 men and women with mild to moderate Alzheimer's disease. The researchers gave half of them 3 mg of melatonin every night for four months. The other half got the placebo pill. According to the authors, "Melatonin treatment resulted in significant and clinically meaningful effects versus the placebo in mean IADL and MMSE scores."[9] IADL refers to activities of daily living and scores how well patients are able to get around and take care of their basic needs. The MMSE I mentioned above. If melatonin can have this effect on patients with such a severe disorder as Alzheimer's, imagine what it can do for those without the disease.

Another study looked at the effect of taking melatonin to prevent Parkinson's disease. The researchers gave a group of mice the drug MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). This drug selectively destroys the dopaminergic cells in an area in the brain called the substantia nigra and causes Parkinson's disease. When the mice were pretreated with melatonin before being exposed to the drug, their brain cells were protected, and none of them developed the disease.[10]

Menopause

Melatonin is also important for women going through menopause. Just this past year researchers looked at the effects of melatonin on 240 menopausal women between the ages of 40-60 years. They divided the group in half and gave half of the women 3 mg of melatonin every night. The other half got the placebo. After three months the symptom scores in the melatonin group were cut in half. As expected, the symptoms in the placebo group did not change.[11]

In the study I mentioned above from the Menopause Center in the Madonna delle Grazie Health Institute in Rome, the researchers also measured the luteinizing hormone and follicle stimulating hormone levels in the group of peri- and post-menopausal women. Luteinizing hormone and follicle

stimulating hormone are pituitary hormones that regulate a woman's production of the ovarian hormones. Here's what they found.

The women with the lowest levels of melatonin had the highest levels of both luteinizing hormone and follicle stimulating hormone. This finding indicates that lower levels of melatonin are likely a trigger for menopause, since elevated levels of luteinizing hormone and follicle stimulating hormone are what happens to women as they enter menopause. This conclusion is further strengthened by the fact that within six months of receiving the 3 mg melatonin supplement, the younger women (43-49) showed a decrease in their levels of luteinizing hormone and follicle stimulating hormone to levels more typical of younger women. In addition, most of the melatonin-treated women reported a general improvement of mood and a significant decrease in symptoms of depression. Here's why this is important.

I see a lot of women for hormone replacement. Many of them come to see me because their doctors have been unable to effectively rid them of their menopausal symptoms using the customary combinations of bio-identical hormones. And I have learned over the years that what often makes the difference for these women is melatonin. So, whenever I am working to balance the hormones in either a peri- or post-menopausal women I always make sure to prescribe melatonin. It makes both of our lives a lot easier!

Ionizing Radiation

Here is an especially important role for melatonin. It has to do with ionizing radiation. Ionizing radiation causes cancer. Children are especially at risk. One of the most potent sources of ionizing radiation is doctors – specifically the x-rays we order. And x-rays are only a minor source of ionizing radiation compared to CT and PET scans. Just one CT scan exposes you to the same amount of ionizing radiation as 70 chest x-rays. And a combined CT/PET scan has almost two times the amount of radiation as a plain CT. And it is not uncommon for me to see patients getting 2-4 CT/PET scans a year. That is an incredibly high amount of radiation and is sure to be unsafe. But not to worry. There is a simple, natural substance that you can get that can cancel the potentially damaging effects of ionizing radiation.

Researchers took blood samples from several men and women. Then they gave them a single dose of 300 mg of melatonin. One and two hours later they collected a second and third blood specimen. Then they exposed all of the blood specimens to a whopping dose of radiation (150 Gy) that was roughly the equivalent of 1000 CT scans. After the blood was irradiated, they tested the white blood cells to determine the extent of radiation-induced genetic damage.[12] Here's what they found.

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The lymphocytes in all of the blood samples had a degree of genetic damage from the radiation. But the cells that were taken an hour after the melatonin dosing had significantly less genetic damage. And the ones taken at the two-hour mark had the least damage. The authors concluded that the data had important implications for the protection of our immune cells from the genetic damage induced by ionizing radiation. So, what does this mean for you? It means that if you are ever told that you need a CT scan or CT/PET scan, be sure to take 300 mg of melatonin about two hours before the procedure. You will basically eliminate any negative effects of the ionizing radiation.

Macular Degeneration

Several animal experiments have shown that melatonin protects against macular degeneration. This should not be too surprising for several reasons. One, studies have shown the both blood levels of melatonin and urine levels of 6-sulphatoxymelatonin, the metabolic breakdown product of melatonin are lower in people with macular degeneration than they are in people with healthy eyes. Two, melatonin is produced in the retina, the part of the eye that is affected by macular degeneration. Three, melatonin is the most powerful anti-oxidant in the eyes. And four, oxidative stress is the primary cause of macular degeneration.

One study looked at the effect of melatonin supplementation on rats that have been bred to develop macular degeneration. The researchers gave the animals a dose of melatonin that was equivalent to a 3 mg dose for humans. When they examined the eyes of the animals, they discovered that the melatonin decreased the incidence and severity of the damage to the retina, improved microscopic abnormalities associated with macular degeneration, prevented the structural and functional changes in retinal cells associated with macular degeneration, reduced the severity of microcirculatory disorders in the retina, and prevented the destruction of neurosensory cells, associative and ganglionic neurons in the retina. According to the authors, "Taken together, our data suggest the therapeutic potential of Melatonin for treatment and prevention of macular degeneration."[13]

Another study reported on the effect of a melatonin supplement in 55 patients with either dry or wet macular degeneration. The natural history of macular degeneration is that it gets worse over time. But in this study, the melatonin supplement stopped the progression of the disease.[14]

Cancer

The last thing I want to share with you about melatonin is truly remarkable. Who would have guessed? Melatonin is one of the best supplements you could ever take for cancer. I treat a lot of patients with cancer. I believe one of the most important things I can give them is melatonin. Here's why.

Researchers looked at all of the controlled studies published on the use of melatonin in patients with cancer from 1993 to 2004. They were specifically looking at the rates of survival during the first year of treatment. They included trials that used melatonin as either the only treatment given or when it was given along with other treatments such as chemotherapy or radiation. The results were astounding.

The researchers reported that melatonin not only has been shown to have a direct anticancer action, but it also activates the body's immune reaction against cancer. Additionally. melatonin has been found to protect healthy cells from the negative effects of chemotherapy and radiation. All of this from a safe, inexpensive, natural substance. The authors also mentioned that there were no significant side effects reported in any of the studies. And here's the best news.

On average melatonin reduced the risk of dying by 44%! That's astounding. If results one-tenth this good happened from the use of a $20,000 per month drug, Big Pharma would be touting it as the next great thing. But that's not all. The effects were consistent no matter what dose they used. And none of the patients had any significant side effects from the melatonin. The authors put it this way, "The substantial reduction in risk of death, low adverse events reported, and low costs related to this intervention suggest great potential for melatonin in treating cancer."[15]

Despite incredible data like this, oncologists continue to be suspicious of using a natural substance along with their chemo or radiation. For reasons that always prove to be false, they keep suggesting that natural substances will somehow interfere with these therapies. That's why a brand-new animal study is so important.

The researchers took a group of rats who had estrogen positive breast cancer and divided them into four groups. One group received no treatment at all. They gave the second group melatonin. The third group got a chemo drug called adriamycin. And they gave the fourth group a combination of adriamycin and melatonin. Then they measured the amount of tumor growth, the microscopic changes in the tumors, and the survival rate of the animals after one month. Once again, the results are incredible.

Did the melatonin interfere with the chemo drug? Absolutely not. In fact, the tumors were smaller, and the amount of microscopic tumor cell injury was higher in the group that had the combination of melatonin and chemo than they were in the chemo-only group. Melatonin not only did not interfere with the drug, it actually improved the results. This is what I see 100% of the time when I combine natural therapies with conventional therapy for cancer.

But that's not all the researchers found. The group that had the highest one-month survival was the group that got the melatonin all by itself. And the one that had the most side effects and were the sickest was the one that had the drug by itself. The researchers concluded that adding melatonin to chemotherapy enhanced the treatment effect of the drug while at the same time decreased the side effects. But why?

In their words, it's because, "Melatonin has been shown to play a fundamental part in neuro-

immunomodulation." This means that it improves the way the immune system is able to kill the tumor. This is critical because chemo agents are immune suppressive drugs. Melatonin seems to protect the immune system from this effect. They also found that melatonin has its own direct action on tumor cells that kills them just like chemo does. Once again, in their own words, "A number of studies have documented that when given in combination with chemotherapy to patients with disseminated disease [stage 3 and 4 cancer], melatonin increases the overall one-year survival and reduces toxic side effects."[16]

One of the most important things that this study points out is that melatonin works well when it is used in combination with chemotherapy. According to another paper, "Because of its SERM (selective estrogen receptor modulators) and SEEM (selective estrogen enzyme modulators) properties, and its virtual absence of contraindications, melatonin could be an excellent adjuvant with the drugs currently used for breast cancer prevention (antiestrogens and antiaromatases). The antioxidant actions also make melatonin a suitable treatment to reduce oxidative stress associated with chemotherapy, especially with anthracyclines, and radiotherapy."[17]

If you are fighting cancer, or if you know anybody who is fighting it, this information is critical. It is critical for two reasons. One, as you have seen melatonin therapy will not only extend your life, but it will also improve the quality of your life. And two, although the information has been out for over 17 years you will still not hear it from any oncologist including the ones at the supposed great cancer centers. The next study was published in the *European Journal of Cancer* way back in 1999.[18]

The authors begin their report by stating that the hormone melatonin "…has been proven to counteract chemotherapy toxicity, by acting as an anti-oxidant agent, and to promote apoptosis of cancer cells, so enhancing chemotherapy cytotoxicity." Just to be clear, what they are saying here is that melatonin decreases the toxicity of chemotherapy while at the same time increasing its ability to kill cancer cells. If that doesn't sound like the most perfect natural addition to conventional chemotherapy, then I don't know what does. So, based on this fact, the researchers set out to evaluate the effects of giving melatonin along with chemotherapy in several different cancers.

The researchers looked at a total of 250 men and women who had advanced, metastatic cancer: 104 had lung cancer, 77 had breast cancer, 42 had gastrointestinal tract cancer, and 27 had head and neck cancers. They gave some of the patients in each group 20 mg per day of melatonin in addition to their regular chemotherapy. The rest did not get the melatonin supplement. The following chemotherapy drugs were used: cisplatin, etoposide, gemcitabine, doxorubicin, mitoxantrone, paclitaxel, and 5-FU. Here's what happened.

According to the authors, "The 1-year survival rate and the objective tumor regression rate were significantly higher in patients concomitantly treated with melatonin than in those who received chemotherapy alone." Specifically, the chemotherapy was effective in killing the tumors in 34% of the patients taking the melatonin compared to only 15% in the non-melatonin group. That's more than a 100% improvement over chemo alone! Clearly, the melatonin dramatically improved the efficiency of the chemo drugs. And that's not all.

In terms of survival, the melatonin group had a 51% survival rate after one year compared to a 23% survival rate for the patients not getting the melatonin. The results mean that if you take melatonin along with your chemotherapy your treatments will be more than twice as effective, and you will be more than twice as likely to be alive a year later. Dear readers, if there was any drug out there right

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now that was anywhere close to being this effective it would be all over the news, and every oncologist would be prescribing it. And once again, that's not all.

The melatonin also reduced side effects and improved the quality of life. Listen to the researchers once again:

> Moreover, the concomitant administration of melatonin significantly reduced the frequency of thrombocytopenia [platelet destruction], neurotoxicity [nerve damage], cardiotoxicity [heart damage], stomatitis [mouth sores], and asthenia [weakness and poor appetite]. This study indicates that the pineal hormone melatonin may enhance the efficacy of chemotherapy and reduce its toxicity, at least in advanced cancer patients of poor clinical status.

Researchers in the Department of Cellular and Structural Biology, at the University of Texas Health Science Center in San Antonio studied the effects of the hormone melatonin on prostate cancer cells. They used two different cell lines. One was the LnCaP cells, and the other the PC3 cells. Both of these cell lines are human prostate cancer cells. The LnCaP cells are prostate cancer cells that are hormone sensitive. That means that their growth is stimulated by the hormone testosterone. The PC3 cells are not hormone sensitive. What they found should make us older guys sleep a little better.

The study looked at what happened to the growth rate of both kinds of cells when they were exposed to varying doses of melatonin. According to the researchers, "Melatonin treatment dramatically reduced the number of prostate cancer cells and stopped cell cycle progression in both LNCaP and PC3 cells." That means that no matter whether the prostate cancer cells were sensitive to testosterone or not, they were all stopped with melatonin.[19]

One study, entitled, "Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis" summarizes the known anti-cancer effects of melatonin. The researchers stated that, "Melatonin has oncostatic [anti-cancer] properties in a wide variety of tumors."[15] This includes colorectal, breast, prostate, pancreas, liver, and brain cancer. It is particularly effective in estrogen receptor positive breast cancer because it regulates estrogen receptor expression and transactivation, and modulates the enzymes involved in the synthesis of estrogen. Melatonin also stimulates apoptosis.

Apoptosis is the mechanism that causes heathy cells to eventually die. It is how the body maintains a normal, healthy growth rate. The reason cancers are so lethal is because they finds ways to avoid apoptosis. That allows them to continue to grow and spread without any restraint. As I mentioned above, melatonin activates the process of apoptosis in cancer cells, and thus limits the malignancy potential of cancer cells. Keep this in mind. The only problem with cancers is that they don't stop growing and spreading. If you have a cancer in your body that for some reason is not growing in size or spreading, it will never be a problem for you. I am convinced that many of you who have an as yet undiscovered cancer right now while reading this report can prevent that cancer from ever being a problem for you simply by taking a melatonin supplement.

Telomerase is another reason cancer cells don't stop growing and multiplying. Telomerase is an enzyme that can cause a cell to live way beyond its normal life expectancy. Unlike heathy cells, cancers cells can activate this enzyme, and just like with decreased apoptosis, activated telomerase can result in unrestricted cancer growth. That's the bad news. The good news is that melatonin inhibits telomerase activity in cancer cells. But increasing apoptosis and decreasing telomerase activity are not the only ways that melatonin stunts cancer growth.

Melatonin also inhibits angiogenesis. Angiogenesis is the mechanism that cancers use to grow new blood vessels. They use the newly developed blood vessels to increase the delivery of the sugar and other nutrients they need to grow. The result is that they grow faster. There are drugs that oncologists use to decrease angiogenesis, but these drugs are so strong that they can create problems by inhibiting angiogenesis not only in cancers but also in healthy tissues. Unlike these drugs, melatonin is selective. It does not affect angiogenesis in heathy tissues.

Summation

Collectively, all of these effects – direct anticancer action, enhanced immune reaction against cancer, preventing the negative side effects of chemotherapy and radiation, apoptosis stimulation, telomerase inhibition, and angiogenesis inhibition – help to explain why melatonin should always be prescribed to both prevent cancer and as part of the overall treatment of cancer.

Melatonin Facts

Melatonin is produced and released in the pineal gland in the brain in darkness while you are sleeping. The release of all this wonderful melatonin is immediately suppressed by all colors of light except red light. These two facts help to explain why people who work at night and sleep during the day, and people who live in metropolitan areas where nighttime darkness is diminished are more prone to cancer. So, when you are sleeping, no matter whether it is in the day or the night, be sure that your bedroom is completely dark. Ideally, you should not be able to see your hand in front of your face. Any light, except red light, needs to be eliminated. This includes light from LEDs, night lights, your clock radio, etc. One simple approach is just to cover the lights with a black cloth or tape. And be sure to buy some red night lights, so that you don't kill yourself going to the bathroom. That would completely negate the whole plan.

Unlike what is commonly taught, melatonin is not a soporific. That means that it doesn't make you sleepy. What makes you sleepy is darkness. When it is dark, your brain releases melatonin, and the melatonin sensitizes you to this effect of darkness. This is why older people, with melatonin levels close to

zero, have all kinds of sleep disorders. It's also explains why you can take it during the day and not get sleepy. I routinely prescribe my patients with stage four cancer 60 mg of melatonin four times a day – breakfast, lunch, dinner, and before bed. And only rarely does anyone tell me that it makes them sleepy during the day.

Melatonin is completely free of any significant side effects. Even after 50 years of study, scientists still cannot find an LD50 dose for melatonin. That means that it has no observable toxicity at any dose. Dr. Pierpaoli, one of the world's leading melatonin researchers, has successfully used daily dosages of melatonin in patients ranging from 0.1 to 200 mg. That's a 2,000-fold difference between the lowest dose and the highest. Studies on mice show that even at astronomical doses of 300 mg per day for two years there were no side effects. This is a dose equivalent to 45,000 mg per day in humans! Occasionally, a patient will report sleep disturbances or drowsiness in the morning, but more often than not, that is due to contaminated melatonin. Melatonin is a very delicate molecule. It must be carefully processed. Pressing it into a tablet and other methods of supplement manufacturing often destroys or alters the molecule. I recommend that you only use either pure melatonin powder or melatonin capsules that are free of additives.

One of the concerns that some people have about taking high doses of melatonin is that it can cause the body to stop its own production of the hormone. This concept is called negative feedback inhibition, and it is true of most hormones. But unlike other hormones, there is no negative feedback inhibition with melatonin. You can take as much as you want, and it will not interfere with your own production of melatonin. Additionally, melatonin supplements do not alter the levels of any other hormones.

In my conversations with Russell Reiter, PhD, the world's leading melatonin researcher, I learned that he has been taking 180 mg of melatonin every night for the past 18 years. At age 83, he is still running a laboratory and working as a fulltime researcher. He has boundless energy and a brain that is as sharp as ever. When I asked him why he took so much melatonin he gave me two answers. First, 180 mg is the dose for a human that is equivalent to the dose that is so effective in animals. The other reason is that there is absolutely no down side to taking even these large doses.

Conclusion

So, should you be taking melatonin even if you sleep well? If you are older than 40, I say yes. The data that I have presented to you from 19 different papers on melatonin speaks for itself and is just the tip of the iceberg. But don't you need to check blood levels? Not if you're older than a teenager. The body peaks out in melatonin production during puberty. After then, it's all downhill. By the time you hit 20, you're already becoming deficient in the hormone. Studies on the urinary metabolite of melatonin, 6-sulfatoxymelatonin, a good indicator of how much melatonin your body is making, show that it decreases steadily with age. By the time you're 50, your levels of production are seriously low. So, if you want to have all of the benefits of melatonin, you're just going to have to take it as a supplement.

There are two sources of high-quality melatonin that I recommend. One is the pure bulk powder. You can get this at www.purebulk.com. They also sell a scale that will allow you to measure out the amount that you want. The other source and the one that I prescribe to my patients is called Melatonin Max. You can get it at www.perfectvitaminproducts.com. At 60 mg per capsule, it is the most powerful melatonin on the market. If you are over fifty, I recommend that you do as Dr. Reiter and I do, take 180 mg every night before bed.

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Non-Pharmaceutical Androgen-Lowering Agents in the Treatment of Hormonal Acne, Hirsute, and Male-Pattern Balding

by Corina Dunlap, ND, MS

Hirsutism, acne, and male-pattern balding are all common signs of hyper-androgenism. Many suffering from these symptoms are increasingly seeking non-pharmaceutical options. Conventional care guidelines recommend combined oral contraceptives (COCs) as monotherapy, or COCs with an antiandrogen, such as spironolactone or finasteride, as combination therapy.[1] Natural alternatives are becoming increasingly in demand due to the potential side effects of these options, which include weight fluctuation, emotional lability, depression, and lowered libido (for COCs), and potential reproductive harm, gastrointestinal discomfort, and irregular menstrual bleeding (for spironolactone and finasteride). There is also increasing awareness that effective natural treatment options exist without complications of these undesirable side effects. This article serves as a resource for non-pharmaceutical, androgen-lowering, evidence-based updates for the effective management of hormonal acne, hirsute, and male-pattern balding.

Androgen-excess leads to an increased rate of terminal (i.e. course) hair growth in androgen-sensitive tissues such as the upper lip, chin, mid-sternum, upper abdomen, back, and buttocks, and hair loss on the scalp, particularly along the temporal region.[2] Although acne is in many cases multi-factorial, hyperandrogenism can contribute to the development of acne through its impact on increased production of sebum in the sebaceous glands.[3]

Clinical history goes a long way in determining if someone has hyperandrogenism, but it is also important to test biomarkers in order to 1) confirm clinical suspicion, and 2) identify cause. Based on the 2018 Endocrine Society Clinical Guidelines on hirsutism, serum total testosterone is a mainstay for workup.[4] Additional testing may be added if the patient has additional menstrual irregularities (i.e. oligomenorrhea or amenorrhea).

- *First line* (for all women with signs of hyperandrogenism): **serum total testosterone** with liquid chromatography-tandem mass spectroscopy (LC-MS/MS) for accuracy.
  - Upper limit of normal is 45 to 60 ng/dL range (1.6 to 2.1 nmol/L).
  - If elevated, but <150 ng/dL (5.2 nmol/L), most likely PCOS, however, may consider testing 17-hydroxyprogesterone to rule-out nonclassic congenital adrenal hyperplasia (NCCAH) due to 21-hydroxylase deficiency (see below).
  - If >150 ng/dL (5.2 nmol/L), consider possible androgen-secreting tumor and refer to endocrinology specialty.
- *Second line* (for women with hyperandrogenism + menstrual irregularities (i.e. oligomenorrhea or amenorrhea), add:
  - **17-hydroxyprogesterone** (at 8 am early in follicular phase). A value of 200 ng/dL is a strong indicator for NCCAH.
  - **Human chorionic gonadotropin [hCG]** to rule out pregnancy or hCG producing adenoma.
  - **Prolactin** to rule out hyperprolactinemia.
  - **Follicle-stimulating hormone [FSH]** to rule out primary ovarian insufficiency.
  - **Thyroid-stimulating hormone [TSH]), fT4, fT3, and Thyroid Abs** to rule out thyroid disease.

The following summaries highlight the natural medicine modalities (e.g. techniques, botanicals, and nutrients) that have been explored in recent human research to lower hyperandrogenism as an alternative, or in addition to pharmaceuticals such as COC and anti-androgenics.

Acupuncture and PCOS

In a meta-analysis of 31 articles and N = 2,321 with PCOS:[5]

- Results (significant; all for acupuncture group)
  - Total testosterone decreased.
  - Reduction in Day 3 FSH, insulin resistance, and BMI.

Resveratrol and PCOS

In an RCT, N = 34 with PCOS; randomized to 12 weeks of 1) resveratrol (1.5 g/day) or 2) placebo:[6]

- Results (significant; all for resveratrol group)
  - Total testosterone decreased (by 23.1%).
  - DHEAS decreased (by 22.2%).
  - Fasting insulin decreased in the resveratrol group (by 31.8%).

Myo-Inositol (MI) plus Combined Oral Contraceptive Pill (OCP) vs OCP alone in PCOS

In an RCT, N = 155 with PCOS; randomized to 1) MI 4 g/day used alongside OCP (estradiol 30 mg/gestodene 75 mg) or 2) OCP alone for 12 months:[7]

- Results (significant; for Myo-Inositol group)
  - Fasting insulin decreased.
  - Androgens decreased.
  - Lipid profile improved.

Myo-Inositol (MI) alone in PCOS

In a prospective cohort trial, N= 46 with PCOS and hirsute received myo-inositol 2 g/2x daily for six months:[8]

- Results (significant)
  - Hirsutism decreased.
  - Androgens decreased.
  - Lipid profile improved (specifically, HDL increased and LDL decreased).

Myo-Inositol (MI) plus Folic Acid in PCOS

In a prospective cohort trial, N= 50 with PCOS received myo-inositol 2 g/2x daily plus folic acid 200 mcg/2x daily for six months:[9]

- Results (significant)
  - Hirsutism and acne decreased after six months.

Myo-Inositol (MI) plus Alpha Lipoic Acid (ALA) in PCOS

In a prospective cohort trial, N= 50 with PCOS received myo-inositol 2 g/daily plus ALA 800 mg/daily for six months:[10]

- Results (significant)
  - Free androgen index (FAI), mean androstenedione, and DHEAS levels decreased.
  - Mean SHBG levels raised.
  - Improvement in mean Ferriman–Gallwey score.
  - Reduction of BMI.
  - Reduction of AMH levels, ovarian volume and total antral follicular.

Melatonin alone in PCOS

In a prospective cohort trial, N= 40 with PCOS received melatonin 2 g/daily at night for six months:[11]

- Results (significant)
  - Total testosterone decreased.
  - Free androgen index decreased.
  - AMH decreased.

Omega 3s

In a double-blind, randomized, controlled trial, N=78 overweight and obese women with PCOS, randomized to eight weeks of 1) omega 3s (3gr/day total) or 2) placebo:[12]

- Results (significant; for omega 3s group)
  - Reduction in serum concentrations of total testosterone.
  - Regulation of cycles.

Although this article is focused on human research, there are many animal studies investigating natural modalities to lower hyperandrogenism, including use of ashwaganda, chrysin, berberine, green tea, and *Moringa oleifera*. Keep an eye out for follow-up human trials examining these agents.

As always, it is extremely important to figure out etiology of hyperandrogenism in order to treat effectively. Many factors such as blood sugar, weight, blood pressure, smoking, alcohol, diet, exercise, and sleep can all play into endocrine dysfunction. There may also be structural endogenous and/or exogenous causes such as an androgen-producing adenoma, or a partner's use of testosterone cream. The importance of addressing these factors is not to be underestimated in order to identify and remove route of potential cause and support the whole person.

As an added note to the treatment of acne, a multi-modal approach may be a more efficient treatment approach vs targeted anti-androgenic therapies alone, especially since most patients with acne have normal androgen levels.[13] There are effective research implications for use of diet, microbiome optimization, stress and insulin-resistance lowering lifestyle recommendations, and hypoallergenic topical treatments.

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Lichen Sclerosus – A Roadmap to Treatment Beyond Steroids

by Sara Wood, ND

Since her husband passed away six years ago and she wasn't dating, Sheila hadn't given much thought to her vulva until her gynecologist mentioned, during a routine exam, that her lichen sclerosus had progressed and her clitoral hood was starting to fuse. She didn't even remember being told that she had lichen sclerosus, but apparently it was in her chart, observed and "diagnosed" years prior. Sheila was alarmed, though her clitoris had been admittedly underused over the past few years, she certainly didn't want it sealed away! Her doctor told her that the diagnosis may not have been emphasized to her at the time it was originally observed because she wasn't experiencing any symptoms. Bewildered and confused, Sheila returned home to process this new information and to do some research, and she found that she wasn't alone. Online forums were filled with stories like hers, or worse. Many women who were symptomatic, experiencing severe itching or pain, who were still undertreated or told that there wasn't much that could be done. Those that were treated were primarily given steroid creams of varying strengths that sometimes helped, but often they weren't advised on a long-term management strategy. Reasons for this shortcoming in treatment are multifaceted but include the sensitive nature of the subject and the counseling required to fully address it. Unfortunately, many physicians don't have the luxury of time required to discuss the emotional impact of labial fusion, let alone the time needed to discuss underlying causes and possible lifestyle changes.

It's not a household word, but lichen sclerosus isn't exactly rare; one study found a prevalence of 1.7% in a general gynecology practice,[1] although many women have never heard of it until they read it on a pathology report or their doctor prescribes them a steroid cream. For some, like Sheila, the symptoms are mild or even absent and the condition is discovered upon routine exam; for others, itching or pain with sex are what lead them to investigate the problem. Since tissue changes can lead to labial fusion, narrowing of the vaginal opening and even carcinoma (in approximately 3% of cases), **even the mildest of cases should be treated and monitored**.

Lichen sclerosus (LS) is a chronic inflammatory disease that may initially manifest as white patches on the skin. The tissue becomes fragile and itchy; and because LS is most commonly found on genital tissues, pain with sex is a frequent presenting complaint. LS occurs in women approximately 10 times more often than men and is most common during phases of life with relatively low reproductive hormones (pre-pubertal and post-menopausal).[2] Since men make up such a small percentage of LS patients, they are often overlooked in the conversation, although the same general therapies are used for both sexes with the exception of circumcision, which is often an effective treatment in uncircumcised men.[3]

A diagnosis of lichen sclerosus typically requires a biopsy of the tissue, and the steroid creams that are the standard of care are effective at slowing tissue damage. Unfortunately, many treatment plans stop there, using a combination of different strength steroids to halt the progression of the disease. An important part in truly treating any condition is trying to understand what causes it; and while the definitive etiology of lichen sclerosus isn't known, there is increasing evidence of an autoimmune component. Restoration of hormones, repletion of important nutrients, elimination of inflammatory foods as well as mechanical or chemical irritation and employment of immune modulating agents can have a significant impact. Beyond that, there are new studies on injection treatments that are proving to be very effective for some patients.

What Is Autoimmunity?

The immune system is an invaluable component to health, as it identifies and targets infectious organisms including bacteria, viruses, and fungi as well as eradicates random mutations in our own tissues that may lead to malignancy. This is happening behind the scenes, all the time, in every tissue in the body. But occasionally something goes wrong and the immune system targets tissue that is not foreign and is otherwise perfectly healthy. Like friendly fire, the body

incorrectly attacks itself for reasons that are largely unknown, although evidence is mounting that one of the initial triggers may be gut dysfunction.[4] There are approximately 80 identified autoimmune diseases, some of which are diagnosed with a specific test for an antibody to a target tissue. Others are thought to be autoimmune but do not have an identified "marker." Lichen sclerosus generally falls into this latter category, and there is a high rate of comorbidity with LS and autoimmunity; between 20 and 30% of women with LS have also been diagnosed with another autoimmune disease,[5,6] autoimmune thyroiditis is the most common.[7] When it comes to long-term treatment of lichen sclerosus, there are many effective ways of addressing underlying immune dysfunction that are often overlooked and can have a profound effect on symptoms as well as the overall progression of the disease.

Hormones

There is a clear pattern to the demographic of lichen sclerosus patients: women who have low circulating levels of reproductive hormones are more likely to be affected.[8] When discussing changing hormone levels in peri and postmenopausal women, estrogen is invariably the first name to come to mind, and a low estrogen state does exacerbate almost all vulvovaginal disorders. Additionally, we know that estrogen helps to modulate the inflammatory response and cytokine expression,[9] as well as work to counteract the tissue thinning caused by the primary treatment with topical steroids.[10] For these reasons, topical estrogen creams are often prescribed to LS patients, although the literature actually better supports the use of testosterone. It has been observed that lichen sclerosus patients have decreased serum testosterone levels,[11] and treatment with topical testosterone is nearly as effective as clobetasol (a high potency steroid) in both establishing remission, and to prevent reoccurrence.[12]

Sex hormones are only part of the picture. As stated above, there is a close connection between hypothyroidism and LS, and stress hormones have a significant impact as well. Thyroid hormone levels should be evaluated in all patients who have received a diagnosis of lichen sclerosus, or any other autoimmune disease for that matter, as thyroid hormones have a bidirectional relationship with the immune system and can serve as a modulator of immune function and inflammatory processes.[13] Repletion of thyroid hormones, if deficient, may play a key role in improving general immune function.

Stress hormones, including cortisol, also have a very direct impact on inflammation and immune processes. Chronic stress has been implicated in increasing the risk of autoimmune disease.[14] While cortisol is ordinarily a potent anti-inflammatory agent in the body, chronic overproduction of the hormone can lead to resistance in the immune system and result in an increase in inflammatory markers.[15] Furthermore, continued chronic stress can lead to a general state of hypocortisolism through a number of mechanisms, further disrupting control over immune function.[16] As with many conditions, the symptoms and treatment of lichen sclerosus itself greatly contribute to chronic stress on top of any additional stressors the patient may be experiencing. Modulating and managing stress is a very complex and difficult task for many people, although it is important to note that the perception of stress is key in its power. Recurring negative thoughts, perseveration, and feelings of helplessness are maladaptive responses that may exaggerate the stress hormones effects on immune tissues.[17] In additionally to the emotional or psychological input, physical stressors including genital piercings, sexual trauma, chronic mechanical irritation from tight clothing or ongoing chemical irritation from compounds found in soaps or detergents can lead to inflammation and tissue changes.[18] The development of inflammatory tissue changes following trauma or irritation is often referred to as the Koebner phenomenon.[19]

Diet and Nutrients

While tissue biopsy for diagnosis, laboratory testing to identify hormone deficiency, and prescriptions for steroids, thyroid medication or testosterone require a physician, there are many things that any patient with a diagnosis of lichen sclerosus can do on their own that can greatly improve symptoms. Just the act of taking control can be empowering and reduce some of the negative impact of stress hormones,[20] adding additional benefit.

There are few published studies on the influence of diet on lichen sclerosus specifically; however there is an abundance of empirical evidence that supports this approach in autoimmunity in general and we can extrapolate data from studies done on other autoimmune diseases that illustrate the anti-inflammatory benefits of certain foods[21] and the role that foods play in triggering a leaky gut and subsequent immune dysfunction.[22] When it comes to diet changes, there are several approaches that may be worthwhile for LS patients including the avoidance of individual food sensitivities that are identified through testing and the broader elimination/challenge of foods that have been implicated in compromising intestinal barrier function and stimulating inflammation. ➤

What to eat	What to avoid
Quality meat - preferably grass-fed, pasture raised	Processed foods - especially refined and processed sugars and oils
Fish and shellfish - preferably wild	Grains
Vegetables - in as much variety and as many colors as possible	Legumes
Organ meats	Dairy
Quality fats - grass fed butter, coconut, olive oil, avocados, fatty fish	Nightshade vegetables - white potatoes, tomatoes, eggplants, sweet and hot peppers, paprika
Fruit	Alcohol
Fermented foods - fermented vegetables, kefir, kombucha, coconut milk yogurt	Eggs (especially the whites)
Bone broth	Nuts and Seeds - including cocoa, coffee and seed based spices
Herbs and spices	Sweeteners - natural and artificial, all of them
	Emulsifiers and thickeners

Table 1

Lichen Sclerosus

➤

The autoimmune paleo diet (AIP) is a modified version of a pre-agricultural diet that promotes gut healing and eliminates inflammatory foods including grains (both gluten and non-gluten containing), dairy, sugar, alcohol, legumes, nuts and seeds, nightshade vegetables, eggs and processed oils.[23] While some patients need to be extremely restrictive, others may see significant benefit by eliminating just one or two of the greatest offenders. When inflammatory foods are removed, chronic immune stimulation is reduced which leads to an improvement in symptoms. The gold standard for identification of which foods may be of individual concern is an elimination period followed by provocation. The elimination period should be done for at least 30 days, although in many cases will be done for up to a year. Foods are then re-introduced in a systematic fashion, which enables the patient to identify what the biggest culprits are.

Compromised intestinal function doesn't just lead to immune stimulation directly but can also affect absorption of essential nutrients, which in turn can further disturb immune function. Even in people without autoimmune disease, insufficient levels of vitamin D are remarkably common due to inadequate sun exposure, lack of vitamin D-rich foods and malabsorption. Low serum vitamin D levels have been linked to several autoimmune diseases[24-27] as vitamin D plays an important role in establishing and maintaining self-tolerance by stimulating T-regulatory cells. These important immune cells (as their name suggests) work to regulate the immune system, neither stimulating or suppressing it. Recommended dosing of vitamin D varies tremendously. The recommended daily allowance (RDA) is relatively low and was generally established to prevent osteomalacia, a bone density disease that results from frank vitamin D deficiency.[28] Supplemental dosages are frequently 3-10 times the RDA and many patients are prescribed large bolus weekly doses. Regardless of how it is supplemented, target serum levels should be 75 nmol/l (30 ng/ml)[29] at a minimum and potentially twice that for autoimmune patients.

Low Dose Naltrexone

Naltrexone is a medication that blocks opioid receptors. It was first developed to treat addiction, although it was subsequently discovered that when used in very small doses (approximately 1/10th of the amount using with addicts) it stimulates the immune system. This therapy is referred to as low dose naltrexone or LDN. The temporary blocking of receptors causes an upregulation in the production of endorphins and enkephalins, which act on the immune system directly.[30] Though the use of LDN hasn't been researched with lichen sclerosus specifically, it has been shown to improve inflammatory markers and disease outcomes in autoimmune diseases including multiple sclerosis and Crohn's disease.[31-33] Doses of LDN are typically 3.0-4.5 mg and dosed before bed to coincide with the increase in natural endorphin production overnight. In addition to the boosting of immune modulating endorphins, LDN has also been shown to influence glial cell activation, which decreases inflammatory cascades in the central nervous system and has a dramatic effect on pain.[34]

Platelet Rich Plasma

Platelet rich plasma (PRP) is prepared by concentrating the growth factors found in the blood. These factors, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), and epithelial growth factor (EGF), are involved in the phagocytosis of fibrotic tissue, reduction in inflammation, angiogenesis stimulation, and collagen synthesis. Though most frequently used (and studied) in orthopedic medicine, healing sports injuries and torn ligaments and tendons, there are broad applications for PRP in medicine as it stimulates healing and regeneration of whatever tissue it is applied to. New studies have illustrated the use of PRP to halt the progression of lichen sclerosus and restore tissue integrity.[35] In this application, the patient's blood is collected through routine venipuncture and then processed to specifically concentrate the platelets and growth factors. There are a number of FDA-approved, closed systems that do this effectively. The PRP is then injected into the affected tissue following the application of a topical anesthetic. Preliminary clinical trials found that half of patients were completely free of symptoms a year following treatment and nearly one-third no longer had any visible evidence of tissue changes.[36]

Conclusion

The internet age has provided patients more access to healthcare information than ever before in history; and while this can sometimes work to fuel health anxieties or promote dangerous home remedies, it can also provide supportive social networks and allow for learning beyond what is

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Outside of the clinic, Dr. Wood can be found keeping up with her two little boys, cuddling with her dog and always searching for a spot in the sun.

possible in a brief physician visit. Patients who are experiencing vulvar itching, pain with sex or visible labial fusion should absolutely seek medical care for a proper diagnosis and begin treatment that will preserve the integrity of their tissue. For patients like Sheila who are asymptomatic, or stable on steroid creams but are interested in preventing their immune system from causing additional damage to their tissues, diet changes, stress management techniques, and vitamin supplements are something they can do to augment their treatment. For hormone replacement, an LDN prescription, or PRP therapy, an informed physician will be needed; and there are an increasing number of doctors around the country who are integrating these services.

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Lichen Sclerosus

Preconception Optimization – Investing in the Next Generation

by Bonnie Nedrow, ND

Preconception Care

Preconception care supports the health of both parents-to-be and begins at least six months prior to a planned conception. The focus on parental health is based on the growing understanding that healthy parents are more likely to have healthy children. The desired outcome of preparing for conception is to optimize biomarkers and reduce medical complications. When an individual has a health challenge that cannot be fully resolved prior to conceiving a baby, focus is on minimally invasive management with medications and supplements shown to be safer for reproduction.

Care begins with a complete health history, an environmental health history, a full physical and a biomarker assessment. Biomarkers for all preconception patients include body composition, CBC, lipid panel, glucose, hemoglobin A1C (HgA1C), homocysteine, vitamin D, TSH, C-reactive protein (CRP) and the liver enzymes ALT, AST and GGT. Additional markers may be indicated for specific health concerns or when nutritional deficiencies are suspected. Areas of concern are identified and a course of treatment with a specific time-line is negotiated.

Preconception planning can be emotionally challenging and financially daunting for many patients. This is particularly true when working with healthy, presumably fertile young people who do not anticipate any complications with getting pregnant and having a healthy baby. However, parents-to-be are often very motivated to invest in their own health prior to conception when they understand the life-long health benefits for their future child. Educational topics include nutritional counseling, endocrine disruptive and oxidative damaging chemical exposures, and genetic and epigenetic effects on reproduction. For the clinician offering preconception care, there is a delicate balance of honestly outlining the risks while at the same time empowering patients to choose healthful interventions that are both manageable and prudent.

The preconception period begins with the maturation of the gametes from both parents and ends with the successful union of the sperm and egg. Gamete restructuring with demethylation and remethylation prior to conception marks this window as one of the most genetically vulnerable. Nutritional deficiencies, nutritional excess, stress and environmental toxicants can all negatively affect the genetic material of the baby-to-be during this time of rapid development. Because of this susceptibility, optimizing preconception health may be viewed as equally important as pregnancy and early childhood healthcare. In light of the expanding research on paternal epigenetic programming of both children and grandchildren, fathers-to-be should be considered equally important participants in preconception optimization.

For sperm, the preconception window is the three months prior to conception. Spermatogenesis occurs when a sperm stem cell divides through mitosis to create a haploid spermatocyte with 23 chromosomes and a new diploid stem cell capable of repeating the process. The haploid spermatocytes become mature spermatozoa and are then transported to the epididymis in preparation for ejaculation. Oocytes, on the other hand begin mitosis in the developing female fetus in-utero in the fifth month of her mother's pregnancy. At this time, a female's lifetime supply of ovum is produced and stored as primordial follicles, also known as primary oocytes. The primary oocytes remain in this relatively protected dormant state until the young woman reaches puberty. Each month from puberty until the supply of eggs is exhausted at menopause, luteinizing hormone stimulates resumption of meiosis producing a secondary haploid oocyte from the primordial follicle. It takes roughly four months for maturation of the female gamete.

Developmental Origins of Health and Disease

Most people are aware that the pregnancy environment can significantly impact the health of the newborn baby and young child. Pregnant women generally strive to eat healthy food, get plenty of rest, avoid stressors and take their prenatal vitamins, all with the goal of having a healthy baby. Parents often give a sigh of relief and believe they have dodged a genetic bullet once the baby is born, takes its first breath, responds to stimuli and appears normal and healthy. However, research has demonstrated that chronic disease processes not overtly observed until later in life can be initiated during early development. This phenomenon is referred to as the developmental origin of health and disease (DOHaD). DOHaD maternal

factors include infections, nutritional status, maternal stress, medications and exposure to environmental toxicants during the preconception window, throughout pregnancy and during the lactation period. Poor outcomes include congenital defects noted at birth, neurobehavioral disorders diagnosed in childhood, cancer at any age, and metabolic disease including obesity, cardiovascular disease, and insulin resistance.[1]

Male Epigenetics

The majority of studies on the DOHaD have, to date, focused on the mother-child dyad. However, both epidemiological and animal studies indicate that the paternal contribution to birth defects and chronic illnesses in offspring is not insubstantial. Nutritional factors, environmental toxicant exposures, and ionizing radiation have all been shown to epigenetically alter the paternal genome and can have lasting effects on the health of the next generation. There are four critical windows when the paternal germ-line is vulnerable to these gene alterations: the father's embryonic stage, prior to puberty, preconception spermatogenesis and post-conception embryo development. These insults are not due to changes in DNA sequencing, but to epigenomic alterations of DNA methylation, histone modifications, and transcription of non-coding RNAs.[2]

A 2011 study of 242 babies with birth defects as compared to 270 children with no defects examined environmental toxicant exposures of parents in the preconception window. They found a positive correlation with preconception paternal occupational exposure to pesticides, solvents, and welding fumes.[3]

In a review of the next generation health impact of paternal preconception smoking, multiple animal and human studies demonstrated both genetic and epigenetic negative effects. Cigarettes contain more than 7,000 chemicals including 69 polycyclic aromatic hydrocarbons that are proven carcinogens and mutagens. Studies link paternal preconception smoking to birth defects including cardiovascular anomalies, congenital heart disease, cleft palate, hydrocephalus and spina bifida. Some of the genetic mechanisms that were discovered include DNA oxidation, sperm DNA strand breaks and chromosomal abnormalities. A mouse study further revealed the epigenetic effect of hypomethylation of testicular DNA when exposed to benzo(a)pyrene, a compound in cigarettes.[4]

Information gleaned from the afore mentioned studies indicates that paternal avoidance of chemicals in the three months prior to pregnancy has the potential to positively impact outcomes not only for the newborn but extending to life-long wellbeing. Because avoidance of toxic compounds is not always possible, measures to mitigate toxicant effects on sperm should be employed. Unfortunately, intervention studies to counter the negative effects of unavoidable toxicant exposure for fathers-to-be are extremely limited. Hypothetically, supplementation with folate and additional methylation support may reverse insults leading to hypomethylation. While there are no studies currently on treating sperm, studies on repletion of cellular hypomethylation with folate supplementation in adults is promising.[5]

…paternal avoidance of chemicals in the three months prior to pregnancy has the potential to positively impact outcomes not only for the newborn but extending to life-long wellbeing.

Zinc is frequently found to be effective in treating male infertility where poor sperm quality due to oxidative stress has been identified. Since sperm DNA damage has also been linked to oxidative stress, zinc has a potential role as a nutrient in male preconception care. In sperm studies, zinc is thought to act as an antioxidant via direct scavenging of superoxide radicals and protection of sulfhydryl proteins from oxidation.[6] Selenium as a co-factor of glutathione peroxidase is another important trace mineral with antioxidant properties. While copper and iron are essential for sperm function, the balance of trace mineral ratios suggests that excess copper and iron with low zinc and selenium lead to increased sperm oxidative stress.[7]

Paternal Inheritance of Metabolic Syndrome

Undoubtedly one of the most concerning trends in human health is the exponential rise in all age groups of overweight and obesity with metabolic co-morbidities including diabetes, cardiovascular disease and hepatic steatorrhea. Optimizing body composition in the preconception window is a safe strategy to reduce the risk of metabolic syndrome in the next generation. It is well recognized that the uterine environment of obese and diabetic mothers increases the risk of offspring metabolic disease. More recent research points to the additive impact of paternal epigenetic programming of offspring metabolism.

In a rare analysis of life-style modifications on paternal epigenetics, an animal study found that nutrition and exercise reduce paternally inheritable metabolic syndrome. Overweight male mice were found to program their female offspring for insulin resistance and enlarged adipocytes, leading to an increased risk for obesity and associated metabolic diseases. The study used a short-term eight-week intervention of exercise and balanced macronutrient diet on obese male mice that had been sedentary and eating a high-fat diet. This intervention was shown to improve the male mice's metabolic health and significantly decrease metabolic disease in their female offspring even when there was no change in paternal weight. This study not only demonstrates that preconception exercise and nutrition can improve reproductive outcomes, it also provides us with measurable biomarkers. Paternal preconception biomarkers that correlated in this study with offspring metabolic disease include fasting glucose, cholesterol, triglycerides, CRP, insulin, and leptin.[8]

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Endocrine Disruptors and Female Reproduction

An endocrine disruptor is defined as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action."[9] These chemicals can bind to the body's endocrine receptors to activate, block, or alter natural hormone synthesis and degradation. Over 1,000 man-made chemicals have been identified as endocrine disruptors including plasticisers, flame-retardants, metals, dioxins, air pollutants and pesticides. One of the best-studied and most ubiquitous endocrine disrupters is the estrogenic plasticizer bisphenol A (BPA).[10] BPA alters DNA methylation in the developmental stage where the primary oocyte returns to meiosis to develop into the secondary haploid oocyte in preparation for conception. This has been shown to either block maternal imprinting or affect the imprint stability. Such alterations are associated with both infertility and offspring defects. Disturbances of maternal imprinting have been linked to infertility, cancer and neurodevelopmental diseases such as Angleman, Prader-Willi, and Russell-Silver syndromes.[11]

In a mouse study, BPA at physiologically relevant doses poorly impacted placental implantation. Inadequate implantation caused poor oxygen perfusion leading to increase sequelae of preterm birth and intrauterine growth retardation (IUGR).[12] This is an important finding because IUGR is one of the causative factors of gestational induction of metabolic syndrome.

The general public is increasingly knowledgeable about the ill health effects of BPA. Industry has responded by creating a line of BPA-free products using alternate bisphenols including BPS. This is an example of what has been termed a "regrettable substitution" of one toxic chemical for another less understood but equally damaging compound. In a study on pig oocytes, BPS was found to both slow and block maturation of the secondary oocyte by interfering with both estrogen and aromatase metabolism. Pig oocytes are frequently utilized for maturation studies due to their similarity to human oocytes, particularly when compared to the more common mouse and rat studies, animals whose oocytes mature in a relatively rapid time frame.[13]

It is often discovered that chemicals negatively impact health by operating on multiple systems. Mancozeb, one of the most commonly used fungicides on golf courses and produce, acts both as an oocyte endocrine disruptor and a contributor to oxidative stress. In a 2017 mouse study, resveratrol was shown to reduce apoptosis and suboptimal formation of mature oocytes. The study authors attributed the positive effects of resveratrol not only to enhance mitochondrial performance through redox pathway, but also protection from mancozeb-induced histone methylation, an epigenetic affect.[14]

Maternal Programming of Metabolic Syndrome

As mentioned earlier, metabolic syndrome (MetS) is perhaps the greatest health concern of our times. MetS is a constellation of medical conditions including obesity, dyslipidemia, diabetes, non-alcoholic fatty liver disease and cardiovascular disease. Parents-to-be who have MetS are more likely to pass on the condition to their children. While the paternal line has been shown to epigenetically induce metabolic syndrome in the next generation, maternal developmental programing is much more complex. In addition to the developing oocyte, we need to take into consideration the intrauterine environment and post-natal lactation.

Mothers who exhibit MetS features of obesity, gestational diabetes, and gestational hypertension are at increased risk of programming MetS in their children. Additional risk factors include malnutrition associated with IUGR, maternal smoking exposure, and in-utero exposure to endocrine-disrupting chemicals.[15] An obvious health goal is to reduce or eliminate features of MetS in the mother prior to conception. However, additional protective measures are warranted when full recovery is not attainable. A 2012 review article cites a number of potential maternal dietary interventions to prevent MetS in offspring. The use of vitamin C, vitamin E, folate, zinc, multivitamins and iron appeared beneficial only when a specific nutrient was found to be deficient in the maternal diet and was repleted. As a word of caution, studies on high doses of nutrients in the conception and gestation windows have been conversely shown to exhibit health risks including IUGR. Therefore, treatment with these nutrients should be conservative and take into account maternal diet. In this literature review the two agents that were found to have the most positive risk-benefit ratio were melatonin and resveratrol.[16]

Melatonin plays a significantly protective role in a healthy pregnancy through regulation of the circadian rhythm, antioxidant-free radical scavenging, and immune modulation. Additionally, melatonin impacts both fetal growth and organogenesis. An interesting finding that warrants more research is the ability of melatonin to act epigenetically by inhibiting DNA methyltransferase and histone deacetylase. In this review, multiple studies demonstrated gestation reprogramming by melatonin that prevented adult onset of disease in offspring. While this is an exciting finding, more research is needed to determine the timing and dosage that will produce a positive effect.[17] In the meantime, preconception optimization can safely include establishment of circadian rhythms with sleep during the hours of darkness to enhance natural production of melatonin.

Resveratrol is a powerful antioxidant found to be highly effective for the treatment of MetS. Mechanisms include inhibition of platelet aggregation, improvement of endothelial function, restoration of nitric oxide bioavailability, and increased activity of superoxide dismutase and glutathione peroxidase. In a small human study of 110 obese women, resveratrol combined with inositol positively affected lipid and

blood glucose levels; however, effects on the next generation of the intervention were not reported.[18] Other studies on the long-term impacts of resveratrol are animal models and offer interesting yet limited applications for the prevention of developmental programming of MetS in humans.

Neuroinflammation

One of the most challenging pediatric conditions that parents are most interested in reducing the risk for is autism spectrum disorder (ASD), which occurs in roughly 1 in 100 births. The cause is complex and multifactorial and includes both genetic susceptibility and environmental insults, particularly in fetal and early-life development. One hypothesized mechanism for an in-utero initiation of ASD is maternal inflammation secondary to infection including viral, bacterial and parasitic. Maternal immune activation in response to infection could plausibly initiate fetal cytokine upregulation. Cytokines, generally considered immune modulators, are also essential for fetal and neonatal brain remodeling.[19] When maternal immune cytokines increase, alterations in fetal brain cytokines can become imbalanced causing neuroinflammation. Potential interventions in the preconception window include optimization of maternal microbiota and repletion of omega-3 fatty acids.[20]

In addition to infection, inflammatory maternal health conditions including gestational diabetes and obesity are associated with a higher risk of having a child with ASD. It has been hypothesized that CRP, which is elevated in cases of metabolic syndrome, may be the initiator of fetal neuroinflammation and could therefore be an important biomarker for ASD risk. However, research on this association is conflicting. A 2014 cohort of over a million pregnancies in Finland demonstrated a linear association of elevated CRP in pregnant mothers who then had children diagnosed with ASD. In this study the highest measurements of CRP were associated with a 43% increase in incidence in ASD.[21] Two years later a second case-control study including 500 children with ASD and 580 general population controls demonstrated the exact opposite finding. In the 2016 study the highest mid-pregnancy levels of CRP were associated with the lowest incidence of ASD. The study author's interpretation was that CRP was not a marker for ASD.[22] A third 2016 study of over 4,000 mother-baby pairs measured CRP in early pregnancy prior to week 18 and found no association of CRP with pervasive developmental problems.[23] More studies on biomarkers for ASD are needed to support earlier clinical intervention. Because CRP is a plausible marker, it deserves more scrutiny in future studies with additional data points in preconception and throughout pregnancy. Studies of other plausible biomarkers should also be considered. Potential measurable elements would include BMI, fasting and postprandial blood sugars, insulin and HgA1C. In the meanwhile, weight reduction for obese and overweight preconception patients would theoretically reduce the risk of having a child with ASD.

In Summary

It is evident that preconception health of both parents has a life-long impact on the wellbeing of their children, especially when we consider the DOHaD. Chronic illnesses such as MetS and ASD are affecting the quality of life for an increasing number of humans and exponentially inflating health-care cost worldwide. Preconception interventions allow time to optimize nutrition, reduce toxicant exposure and chemical body burden and help parents-to-be achieve ideal body weight: all factors that can program life-long health and disease. Optimizing preconception presents an opportunity to reduce developmental disorders in future child and adult populations.

Bonnie Nedrow, ND, lectures nationally on environmental medicine and reproductive health, preconception optimization, and the ketogenic diet for metabolic flexibility. She is currently located in Santa Rosa, California, at Farmacopia, where she has a private practice and teaches classes on her programs to the public. In addition, she offers coaching for her ketogenic detoxification program to patients in Oregon and California. She has co-published two books, *The Seasonal Cleanse Workbook* and *The Cleanse Companion Cookbook*. Dr. Nedrow is available for case consultations on the ketogenic diet, single nucleotide polymorphisms, and detoxification. For more about her programs and publications, or to contact Dr. Nedrow, go to keto-cleanse.com.

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Herbs for an Easier Labor

by Aviva Romm, MD

If you're freaking out a little (or a lot) at the thought of pushing a small cantaloupe-sized head out of your vagina and also want to do everything you can to avoid unnecessary medical interventions at your birth, including cesarean, you're probably here because you're doing your homework ahead of time to learn what to do to make this upcoming passage into motherhood as short, easy, empowering, and as safe as possible for yourself – and your baby. I'm here to help!

Thirty-five years of practice initially as a home-birth midwife, and then as an MD specializing in women's health, including obstetrics, as well as being a momma of four, has shown me that labor and birth can be – yes – hard work – but beautiful, powerful events in our lives. While there should be absolutely no judgment over what type of birth experience you prefer or ultimately require, it's worthwhile considering what natural tools we have that can help us avoid the speed bumps that often lead to preventable birth interventions – the most common being not going into labor within a reasonable amount of time after your due date (this is hotly debated – most obstetricians think within a week after, however normal human gestation actually goes up to two weeks after, which most midwives support), having a long labor, or needing pain medication, which often becomes the case when labor is long.

Support Your Body's Innate Wisdom

Fortunately, our bodies know exactly what to do to bring our babies into the world – but we have to support this with the following:

- A healthy diet,
- Daily walking or other movement,
- Regular yoga for flexibility, strength, and supplements,
- Getting educated about birth,
- Being around birth-positive women and care providers during pregnancy,
- Doing the deep inner work of unlearning patriarchal beliefs about birth – particularly that it's inevitably a catastrophe waiting to happen, and
- Having a plan for working with and through labor's intense sensations.

A few of my favorite books on preparing for birth include S*piritual Midwifery*, *Birthing from Within*, *Ina May's Guide to Childbirth*, and for a deeper understanding of which medical inventions are necessary and which are overused, Henci Goer's *The Thinking Woman's Guide to a Better Birth*.

The support of another woman in labor – whether a midwife in a hospital or at home or a doula who is supportive of you, knows the 'tricks of the trade' like nipple stimulation (I know, doesn't sound sexy but it really works), and also knows how to kickass to protect your space if you're birthing in hospital – has been shown to dramatically reduce the need for medications, forceps, and cesareans, with happier, healthier moms and babies, too, at the end of the day.

There's also some good science – and safety – behind two of my go-to natural remedies that can give you that little bit of extra assurance you'd like to know you're doing everything possible to help your body get ready for birth: tried, true, and tested red raspberry leaf, and the red date.

Drink Raspberry Tea

Red raspberry leaf (RRL), literally the leaves of the plant that provides us with delicious raspberry fruits, has been used for at least centuries in Europe and amongst North American native tribes as a mineral-rich tonic tea, to support a healthy pregnancy and "tone" the uterus to help women prepare for birth. It remains popular, with about 63% of US midwives recommending it.

Red raspberry leaf is high in vitamins C, E, A, B and has significant amounts of major minerals like magnesium, potassium, calcium, and phosphorus that not only nourish the uterus, but provides minerals it needs to contract and relax – which is exactly the combination you need for labor to work effectively for the powerful muscles of your uterus to push your baby out. It's also rich in a naturally plant constituent called fragarine, which is thought to also tonify and stimulate uterine muscle.

While RRL doesn't actually appear to be very effective at stimulating or shortening labor, research has found that drinking RRL tea or taking capsules can have a number of benefits.

The results of a double-blind, randomized, placebo-controlled trial, led by Simpson, consisting of 192 low-risk, first-time moms found that RRL tablets, taken daily starting at 32 weeks' pregnancy until labor, reduced the rate of forceps deliveries while another study (Parsons et al) found that raspberry leaf was associated with the following:

- Decreased likelihood of preterm labor,
- Decreased likelihood of going too far past your due date,

- Decreased need for having your bag of waters artificially ruptured to stimulate labor, and
- Lower overall rates of caesarean section, forceps delivery, and vacuum extraction.

While RRL has been used practically since time immemorial with no evidence of harm, two rat studies did find some curious results that I want you to at least be aware of. In one study, RRL tea and capsules at typical doses were found to have the effect of stimulating uterine contractions – as we'd expect them to do to support healthy labor (Jing Zheng et al). However, in very high concentrations, contractions were inhibited – quite the opposite effect we'd be looking for. In another study also conducted on rats, the authors observed that pregnancy seemed to last longer, and there were was some changes in the rat offspring – they appeared to go into puberty early (Johnson J, et al). Now these are not problems that have been observed in humans, in spite of literally centuries of use, and the rat mommas in both studies consumed RRL products in doses far higher than humans would normally ingest. And the bottom line is there are a lot of differences between rats and humans (most of the time!).

As a pregnant midwife-herbal-momma, I drank it daily starting about halfway into my pregnancy – always carrying my mason jar of tea with me. This was in the 1980s, long before the days of green juice – so I got some strange looks when I was out and about, having a swig! While some recommend starting it in the first trimester, I generally recommend avoiding it then because, while there are no studies associating it with miscarriage, there is some evidence that it increases uterine contractility. Herbalists and midwives consider raspberry leaf to be a gentle, effective, nutritious herb to use in the second and third trimesters – and I concur.

Two cups of tea daily is known to be safe in pregnancy, and several studies have now shown that taking 1-2 cups, regularly in the last trimester, can make labor easier. You can also use capsules or tablets, 1.5-5 grams daily.

Since it doesn't have the most pleasant taste when taken as a tea by itself, I generally recommend mixing it with some spearmint and rose hips for a delicious tea that can be taken daily, 1-2 cups throughout the second and third trimesters. (See Sidebar)

Red Dates

Date fruits are perhaps one of our most ancient 'sweets.' Delicious, they are also nutrient-rich, loaded with fats, proteins, carbohydrates, a variety of vitamins, and minerals, and fiber. They also turn out to be a common remedy for preparing for labor in certain parts of the world. In a study of 919 Iranian women, asked what natural remedies they used in pregnancy for labor preparation, 26% said they ate red dates as part of their preparation at the end of pregnancy. Talk about food as medicine!

While we still don't fully know how dates work to, it appears they might have an impact on the oxytocin we need for labor to start and progress on time and effectively.

Three scientific studies have shown that red dates are associated with the following:

- Increased cervical "ripening,"
- Less need for labor induction,
- Greater likelihood of being more dilated when arriving at the hospital, and
- Less need for Pitocin to stimulate labor and greater likelihood of induction working if it's needed.

A 2011 study found that women who ate six dates a day for the four weeks leading up to their due date were significantly more dilated when they got to the hospital, had a significantly higher rate of intact membranes, were significantly more likely to go into labor spontaneously (i.e. without induction), and had nearly half the length of first stage of labor (Al-Kuran et al).

A 2014 study found that women who ate dates from 37 weeks on had greater cervical dilatation at admission and higher success rates of labor induction when needed (Kordi et al).

A 2017 study (Razali et al) concluded that all the above was accurate and yet another study (Khadem et al) found that eating dates in pregnancy led to less bleeding immediately after birth.

Any Risks?

Studies that have looked at blood sugar levels in women eating dates this way have found no changes, however, this has not been studied in women with diabetes, so if you do have gestational,

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Mama Aviva's Pregnancy Tea

Many of the popular pregnancy teas you see on the market came from one of my original blends published in my now classic book *The Natural Pregnancy Book*. This is a simple, delicious version you can drink hot or iced. For use as a "Labor Day" tea, I actually use 4 Tbsp. of RRL and make the whole thing in a quart of water for sipping throughout labor and after the baby is born. You can even make popsicles to enjoy during labor.

Mix together

- 1 Tbsp. red raspberry leaf
- 2 tsp. spearmint leaf
- 1 tsp. rose hips

Place into a tea bag or teapot strainer.

Steep in 8 oz. of boiling water for 20 minutes. Strain and drink 1-2 cups daily.

Will keep in the fridge for two days.

Make sure any herbal tea products you purchase contain actual RRL because raspberry flavored teas don't have any of the RRL benefits.

(Mountain Rose Herbs is a great online source for purchasing bulk organic herbs – I have no financial relationship to the company.)

Herbs for an Easier Labor

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Type 2, or Type 1 diabetes, do discuss their use with your midwife or doctor.

Based on the studies that have shown some effectiveness, it's recommended to eat about 70-80 grams (about 2.5 ounces) of red dates daily starting at about 36 or 37 weeks of pregnancy and continuing until labor begins. The 2007 study I mentioned specifies deglet noor dates and suggests that about six to eight per day is the magic number. Medjool dates are likely fine as well, but typically are twice as large, so maybe keep it to three to four of those.

FYI: An Herbal Don't

There's an herb called blue cohosh that's been used historically in late pregnancy and in labor to get – and keep – labor going. While it's very effective, it's not without its risks. These are rare – but do include an increased risk of baby going into distress in utero, and even more serious consequences for baby than that. As a midwife-MD I do use it, but only when there's a medical need to induce, and a natural approach is within reason, and with personal guidance and with proper monitoring of baby's well-being. I have particular expertise in this herb as I wrote my medical school senior thesis on it over the course of two years and conducted extensive surveys of contemporary midwives and an exhaustive search of the pharmacologic and historical literature. Like so many herbs, it does work – but it's more like an herbal medication – and as with any medications, can have unintended consequences.

If you're a midwife or other birth care provider, my senior thesis is published in the form of an official botanical monograph, can be obtained from the American Herbal Pharmacopoeia (I did not get paid to write this beyond a small institution research stipend in 2006 by Yale, nor do I get paid for the sale of this book, not even a royalty, nor was I salaried as AHP Medical Director) or can be read as the thesis itself online for free.

Intention and Surrender

Each baby and momma have their own story that they create together – and we don't have total control over how it all happens in the end. Our bodies are beautifully wise and know how to birth our babies. However, complex, cultural factors and changes in how we live in modern times, along with over-medicalization, mean that we do need to put some intention and conscious effort into creating the birthing experience we hope for – and natural remedies, along with a healthy pregnancy and doula or midwife support (or both) can make this all the more likely

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Dr. Aviva Romm is a midwife, herbalist, and Yale-trained MD, board-certified in family medicine with obstetrics, who has been bridging the best of traditional medicine with good science for over three decades. Her focus is on what she calls our total health ecology, utilizing exposome medicine to identify and reverse the root causes of chronic health conditions, particularly hormonal problems in women and common children's health problems. She is considered one of the world's leaders in botanical medicine and is the author of seven books on natural medicine, including the textbook *Botanical Medicine for Women's Health* (Elsevier) and *The Adrenal Thyroid Revolution* (Harper One).

Dr. Romm is the author of the integrative medicine curriculum for the Yale Internal Medicine and Pediatric Residencies, is on numerous scientific advisory and editorial boards, and is a widely sought and highly engaging speaker. Her online programs for women are wildly popular and successful, helping women take back their health, affordably, and her innovative professional programs are educating a next generation of health practitioners. Her non-profit organization, DharmaMoms, provides funding for midwifery education and salaries in high risk obstetric, low resource countries. Dr. Romm lives and practices medicine in the Berkshires and New York City. You can learn how to study with Aviva at https://avivaromm.com/online-courses/

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Sample Treatment Strategies in Women's Health

by Tori Hudson, ND

This issue of the journal is intended to offer some of the best of what natural medicine has to offer in the area of women's health. Because of that, I decided to offer some of my best sample treatment plans for some select women's health issues. It is assumed that we treat the individual patient, but with diagnosed medical conditions. We have the advantage of using long-standing historical therapies, reliable empirical medicine, and modern evidence-based therapies for condition specific issues with some expectation of reproducible results. We can individualize our overall treatment approach based on the multitude of considerations for each patient.

I offer these core sample treatment plans as an optimistic option for endometriosis, perimenopausal/menopausal symptoms, and polycystic ovary syndrome. Individuals with multiple health care problems and important individual subjective and objective findings can then be addressed with the insight and experience of each practitioner.

Endometriosis Therapeutic Priorities

- Acute pain,
- Chronic pain,
- Fatigue,
- Constipation,
- Infertility, and
- Medications-side effects and risks.

Tori Hudson, ND, graduated from the National College of Naturopathic Medicine (NCNM), now National University of Natural Medicine (NUNM), in 1984 and has served the college in several capacities. She is currently a clinical professor at NUNM, Southwest College of Naturopathic Medicine, and Bastyr University. Dr Hudson has been in practice for more than 34 years, is the medical director of her clinic, A Woman's Time (Portland, Oregon), is co-owner and director of product research and education for VITANICA, and is the program director for the Institute of Women's Health and Integrative Medicine. She is also the founder and co-director of NERC (Naturopathic Education and Research Consortium), a non-profit organization for accredited naturopathic residencies.

Dr. Hudson has received numerous awards, including the 1990 President's Award from the American Association of Naturopathic Physicians, the 1999 prestigious Naturopathic Physician of the Year Award, the 2009 Natural Products Association NW Pioneer Award, and in 2012 was inducted into the NUNM Hall of Fame.

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

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www.instituteofwomenshealth.com

Sample Natural Medicine Treatment Plan for Endometriosis

Diet

- Garlic, onions, curries, cold water fish, fruits, veggies, nuts/seeds
- Decrease saturated fats, sugar, salt, caffeine

EPA (1,000 mg or more daily)
Antioxidant combinations= robust dosing
NAC (600 mg tid)
Melatonin (10 mg h.s./day)
Pycnogenol (30 mg bid)
Curcumin (1,000 mg bid)

Conventional Treatments to Consider for Endometriosis

Oral micronized progesterone (200 mg daily, days 15-26) *or*
Norethindrone Acetate (5-10 mg/day) *or*
Medroxyprogesterone acetate (10-20 mg/day) *or*
Other hormonal contraceptive pills *or*
Progestin IUD;
Pain medications;
Surgery.

Therapeutic Options for Perimenopause/Menopause Symptoms

- Diet, exercise, lifestyle, stress management
- Nutritional supplementation
- Botanical supplementation
- Compounded bioidentical hormone preparations
- Bioidentical conventional pharmacy available HT
- Non-bioidentical conventional HT
- Nonhormonal OTC and prescription medications

Interventions are based on published evidence – either few or many, large or small – are presented below.

Diet/Lifestyle

- Soy: modestly helpful for vasomotor symptoms; (Associated with modest effects on bone density and lipid lowering.)
- Flax seeds: modestly effective in reducing vasomotor symptoms.

Exercise

- Whether exercise can reduce incidence and/or severity of hot flashes during menopause is not clear. Can improve depression.

Psychological Support

- A meta-analysis of psychological interventions such as mindfulness-based, cognitive-behavioral, and behavior-based therapies found a modest but statistically significant short- term benefit of less than 20 weeks for bothersome hot flashes and

general menopause symptoms, but no short- or medium-term benefit for the frequency of hot flashes.

Supplements

- Vasomotor symptoms: bioflavonoids, soy supplements, vitamin E, gamma-oryzonol, grape seed extract, pine bark, fish oils. In general, the research does not show regular effectiveness, as do some of the botanicals.
- Anxiety: L-theanine, GABA
- Insomnia: L-tryptophan, 5-HTP, glycine, melatonin
- Depression: SAMe, folate, B12, magnesium, phenylalanine, tryptophan, tyrosine, high-EPA fish oil

Botanicals

- Vasomotor symptoms: black cohosh, hops, kava, kudzu, maca (especially *Lepidium peruvianum*), Panax ginseng, pine bark, red clover, St. John's wort (SJW), schisandra, Sibiric rhubarb, valerian; Combinations: SJW/black cohosh; select proprietary combinations have been the subject of published studies.
- Vasomotor symptoms plus mood and sleep*:* black cohosh, black cohosh/SJW, hops, kava, SJW, valerian; likely combination of two or more of the above
- Depression: lemon balm, SJW, rhodiola
- Anxiety*:* Ashwaghanda, chamomile, hops, kava, lavender, magnolia, skullcap, valerian
- Insomnia: hops, valerian; combinations: passion flower/hops/valerian

Hormone Therapy

Assessing the benefits and the risks and prescribing hormone therapy in perimenopausal/menopausal women requires studious and ongoing/updated efforts. Timing of initiation, dose, duration, route of administration, and type of hormone are all related to benefits and risks. Each type of estrogen and progestogen, route of administration, timing of initiation, and duration of use have distinct benefits and adverse effects. For a current comprehensive review of the benefits and risks of hormone therapy for menopausal women, consider the 2017 position statement from the North American Menopause Society and the 2015 Endocrine Society of the US, guidelines.

Research continues to review the literature in the areas of the potential benefits (vasomotor symptoms, mood, quality of life, sleep, osteoporosis, fractures, type 2 diabetes and more) and potential risks (breast cancer, cardiovascular disease, strokes, deep vein thrombosis, dementia, gall bladder disease, ovarian cancer, lung cancer.

Non-Hormonal Pharmaceuticals

- Vasomotor symptoms: non-hormonal options for hot flashes include clonidine, Neurontin, venlafaxine, and paroxetine.
- Sleep: numerous commercial OTC and prescription options
- Anxiety: numerous prescription anxiolytics
- Depression: SSRIs, SNRIs, MAO inhibitors

Polycystic Ovary Syndrome (PCOS)

This sample treatment plan is based on two primary goals: to address insulin resistance and hyperandrogenism in women with PCOS. Some strategies will need to be additionally utilized when specific clinical issues also need targeting: infertility, hirsutism, acne vulgaris, hair loss, overweight, secondary amenorrhea. The following is based on the published research and my clinical experience.

Fundamental Treatment for PCOS

- High protein/low carb diet for 60 days, then modified Whole 30 diet; ground flax seeds (1-2 tbsp/day); cinnamon
- Frequent exercise 6x/week (cardio-60 minutes); strength train 2x/week
- Soy powder (30 gm protein/30-90 mg isoflavones)
- NAC (600 mg tid)
- Chromium (1,000 mcg/day)

Top Add-Ons

- Black cohosh (40 mg/day, 10 days/month (day 2-9))
- Myoinositol (4 gm/day)
- Spearmint tea (2 cups per day)
- Green tea extract (1-2 caps per day)
- Fish oils (3 gm/day)
- Licorice extract (3.5 gm/day)
- Fenugreek (25 gm/day)
- Saw palmetto (s.e. 85-95% f.a./sterols 160 mg bid)

Considerations

- Cyclic OMP (100-200 mg bid x 12 days/month)
- Calcium, cinnamon, fish oil, vitamin D, berberine
- Antioxidants, anti-inflammatories, detoxification support
- Meds: Metformin (1-2 gm/day), spironolactone, Vaniqa, OCPs (with drosperinone)

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A Doctor's Journey to the End – Looking Death Straight in the Face

by Gabrielle Duebendorfer, ND

Having practiced as a naturopathic physician for over 20 years, I felt quite equipped, when my mom asked me to come and take care of her. She had decided to not treat her newly diagnosed stage IV ovarian cancer and wanted to die at home. I hadn't lived in Germany, my home country, for almost 40 years, still had a 17-year-old at home, and had a part-time practice, but there was something about this request that I couldn't refuse.

What my mom was really asking of me was to accompany her during this last phase of her life. As a family physician, fully engaged in her small community and vibrantly alive into her 80s, she had had a very full life and didn't quite know how to deal with a body that didn't serve her anymore. She had always wondered about my yoga and meditation practice and had thought of it more of a luxury that she didn't have time for. But now she sensed that I had access to something that she needed during this last stretch, which she couldn't penetrate with her brilliant mind. She was a philosopher at heart, having studied all the major German and French philosophers, with an emphasis on existentialism. She knew I would love to have philosophical discussions, but there was this something else that we both knew was more important here.

With her as a physician, me as a naturopathic physician, and one of my sisters a palliative oncologist, we made an interesting team together with the local palliative care doctor. It wasn't easy for the latter to always have herself being questioned. My sister's knowledge and experience were invaluable, but made care-taking for me and being a daughter for her difficult at times. My mom had a hard time giving up her doctor role all the way to the end, especially as she had never liked taking medication. And as much as I deliberately tried to not wear my doctor hat in order to be fully available to her, it did keep slipping on. Honestly, I very much admired the palliative doctor's patience with all of us!

It was a very rich experience to witness my mom's cancer journey in this context from beginning to end. We, maybe even more so as physicians, generally think that death is something that happens to other people. Pema Chödrön, a prominent Buddhist teacher, says that we tend to grasp for certainty, solid ground, something predictable to stand on, especially when facing the stress of a cancer diagnosis: "How can we live wholeheartedly in the face of impermanence, knowing that one day we're going to die?"[1] My mom took on this journey fully facing this uncertainty.

The basic question that arose for me was what healing really means. Is it remission and/or extension of life? Is it simply relief of symptoms for better quality of life? Is it holding the space to allow suffering to experience itself to make it meaningful and allow for post-traumatic growth (PTG)? Dr Shani Fox in her lecture "PTG: An Organizing Principle for Cancer Recovery" at the recent OnCANP Conference defines trauma as resulting "when our assumptions about the world, and our place in it, are shattered."[2] Both certainly got shattered for my mom as her body gradually withdrew its service from her.

Rainer Maria Rilke describes the regular dying process in *The Notebooks of Malte Laurids Brigge*, which we read together with great curiosity and joy: "… the different fatal endings belong to the sickness and not to the people who are sick…the death which is died is one that is utilized by the institution; everyone approves."[3] My mom was determined to live her own death and not follow conventional treatment for the purpose of extending her life. She was intensely interested in what this process of dying would entail and did not want to interfere with it in any way. I had to ask myself how often I focus on the sickness and how to best treat it with my patients and in the process ignore this deeper unfolding – covered up by complicated protocols.

What I observed in her was the unfolding of PTG, which Dr Fox describes as "perceived positive changes resulting from personal coping efforts with traumatic events."[2] It was a nine-month process that started out quite difficult.

Besides the ever-increasing tumor fatigue, which she fought all the way to the end, the pressure from the ascites caused most of her symptoms. The biggest was the resulting dyspnea, which ended up in disabling anxiety. Being a certified instructor in iRest (www.irest.us), a proactive mindfulness approach based on ancient meditation techniques, I was quite cocky, thinking that I could help my mom deal with this without medication. At the beginning, using a basic herbal relaxation formula and experimenting with some breathing techniques worked quite well.

Focusing that much on her body, however, was a big challenge, as it always had just functioned for her without much thought. Therefore, my efforts of guided mindful body-scans and breath awareness were quickly abandoned. Deeper inquiry and listening from my perspective eventually led to a simple reminder to breathe into her heart, with all the love she had felt for her kids and received from my dad, and then allowing her outbreath to gradually breath itself out into the pause at the end. This was a beautiful way for her to establish a personal inner resource that was always available.

However, when the constantly changing symptoms came on more suddenly and more frequently, her inability to deal with being out of control caused ever-increasing anxiety. Lorazepam at that point was a lifesaver. Anxiety was not an emotion that was accepted in a family that prided itself as being strong and together. A simple explanation of the body just going into a physiological flight-and-fight response with sudden physical changes such as sudden onset of leg edema, normalized that process, making it ok to take the prescription. Pride at not taking medications gradually soften into a surrender to her failing body.

My willingness and ability to stay calm and present when she went into one of the panic attacks, made the biggest difference until the medication kicked in. Sitting behind her and breathing with her gave her a sense of safety. Holding her feet at the ankles and putting gentle traction on them relieved the dyspnea. It is common knowledge that physical closeness releases oxytocin, stimulates the vagus nerve, and causes relaxation. In fact, touch, like brushing her hair, rubbing special oils into her swollen legs, or massaging her belly, including the protruding tumors, helped her make friends with the cancer itself. Less known might be the fact that cold water or air movement across the face, like from a little fan or walking outdoors also relieves breathing and induces the relaxation response.

In fact, wheelchair rides, once resistance to being cuddled up like a little child and paraded through town was overcome, became an exquisite pleasure. As the months wore on we went out for hours at a time in the balmy late spring, early summer warmth, watching the fields sprout and blossom: few words, just the felt sense of air and warmth on the skin, the beauty of the poppies and waving barley fields, the delight of wild rose fragrance, the sweet scent of linden flowers. In fact, my mom finally understood meditation in a way, as she was gathering the rose petals in her lap that I was picking from wild rose bushes along the path. It was quite a sight to see the town doctor with a lap full of herbs! Trifolium, Achillea, Urtica, Hypericum, Equisitum, Viburnum, and others grow profusely there as well and made delightfully nutritious and calming teas. An opportunity for my mom to connect with life in a different way, being wheelchair bound at that time.

Dispelling false hope by giving facts and prefacing them with "in my experience…" allowed me to acknowledge her will to live.

As we wheeled through the little hamlets that she used to make house visits in, we kept encountering former patients. I gained a whole new respect for my mom as I witnessed countless tears of gratitude. I had had no idea how much impact she and my dad, also a physician, had had on this small rural community. Story after story emerged about the good old times when my parents were available at all times, as the practice was in our home. A mother recounted how she felt so grateful for having been welcomed on the weekends when her child with a cleft palate had had frequent ear infections. A young man shared how my mom had saved his life by normalizing his mental disability in the community. Another woman remembered how my mom left a full practice to help the local midwife with her breech delivery, which my dad usually did. Based on a procedure she had learned in medical school, she saved the baby.

Not all the tears were of gratitude. Many were due to grief and sadness. As we kept going for "rides" through town, despite my mom's deteriorating condition, some people had difficulty seeing their former doctor obviously close to dying. My former elementary school teacher, over 90 and still vibrantly alive, couldn't stop chatting about this and that. When I met her later, she broke down in tears and explained that she couldn't bear seeing my mom like that. She had helped her so much throughout her life; she didn't know what to say.

The importance of stories lies in discovering one's life value. It was incredibly uplifting for my mom to still be seen as the "doctor" while one capacity after the other was rapidly disappearing. The inability to be productive or useful was agonizing at times – probably more problematic for her than the physical symptoms. Particularly when her mental capacity started to be impaired and she couldn't read her beloved books anymore, her depression got worse. That's when playing Canasta became very important as the game gave her an opportunity to check on her mental capacity, provide welcome distraction by focusing on the

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game, and afforded a good laugh at exasperated losers, which in itself was very uplifting.

Asking about certain events from her past provided another opportunity to process old unfinished business and make the dying process meaningful. As Rilke says so poetically: "One must be able to think back to roads in unfamiliar regions, unexpected encounters…. to think back to those days in one's childhood that are still unexplained…."[3]

For example, she recalled having to get firewood out in the woods, when she came to a meadow where she felt called to drop everything and just run down the hill with arms wide spread – letting completely go of all the burdens put upon her by her proverbial stepmother. Rilke describes an indifference of the heart that arises when one rests in pure Being and the mind is not involved in its usual conditioned reactivity: "For no reason he would quit the footpath and go on through the fields...and then he would fling himself down somewhere out of sight and no one would care a jot about him."[3] Having that memory confirmed by a poet allowed her access to an inner resource she didn't know she had.

"But one must also have … sat in a room with the dead…. For the memories are not what's essential. It's only when they become blood within us …. does it happen …."[3] It's this integration of the past that happened for both of us as I sat with my mom over the nine months, facing and embodying the potential and reality of illness and death. Moreover, as a doctor, developing the capacity to just stay with suffering has helped me guide my patients in a more open, helpful way to allow the healing process to unfold by facilitating inherent meaning and purpose to emerge.

Hope is a difficult subject we had to deal with during this process. Dispelling false hope by giving facts and prefacing them with "in my experience…" allowed me to acknowledge her will to live. Even accepting coping strategies that are based on irrational hope and denial was necessary at times, as it allowed me to be with her in her entirety.

For example, I was surprised to hear her, a life-long physician, want to see a new cancer marker value to make sure that she really did have cancer! At some point she said: "I want to fall asleep by myself in the room and see what happens when I wake up - maybe everything will be fine and I can go into the garden and feel great – everything like normal." The longing to survive is strong!

Mostly, however, the danger with terminal disease is of falling into the delusion of, what Frank Ostaseski describes as ordinary, blind hope. In his book *The Five Invitations*,[4] he explains that often we are afraid of the potential outcome and try to control that fear by action based on an expectation of a fixed outcome, i.e. cure. This is a set up for disappointment.

On the other hand, he describes mature hope as allowing one to open to

"the potential for new life that exists in every moment." My mom fully trusted her capacity to meet every challenge along the way, even though she was consumed with fear and confusion at times. At the end, her curiosity and openness, her willingness to step fully into life even as it was being sapped out of her, allowed her to open into this naked presence where love just bubbled out of her: "Gaby, When I am dead, you don't need to cry because the trees will continue to whisper, the river will continue to flow." I experienced the truth of what Frank has found to be the two most important questions at the end of life: have I loved well and am I loved?

In the last chapter of his book, Rilke poetically describes the old biblical story of the prodigal son in a very unique way. Rather than putting the emphasis on the father being all-forgiving, he sees the lost son as having gone off to try on a variety of masks, fulfilling his and others' expectations, or just plain wasting life, but eventually returning home changed: "What art has scope enough to simultaneously describe his thin cloaked form and the vast space of his colossal nights?"[3]

That's how I experienced my mom at that final time. A different wisdom emerged now; a wisdom that didn't come from the rational mind but rather from direct experience: "The garden is so beautiful…good that you can scream as loud as one wants, one can be how one is…" and "Fighting is like family cinema – bigger and bigger and one doesn't really even want it."

At times it became quite comical despite the seriousness of the situation, causing us to laugh and cry at the same time: "I don't want to do anything wrong – that would be very bad for my life," she said as she distributed her jewelry. Having some last sips of beer brought forth some quite hilarious statements: "People actually are quite stupid if they get drunk, it is quite enough to rinse your mouth out with beer – you don't even have to swallow it" as she toasted to "nothing or better everything – to life and the cosmos that doesn't know a moment." No more separation of what should or should not be – emotions freely flowing from one into the other.

This all might induce a kind of, in Frank's terms, romantic hope of a "good death" for our loved ones or ourselves. In fact, very few walk towards this immense challenge of dying and find peace and beauty like my mom did. There actually was a time earlier on in this process where she got very mad at me as we watched a program by a dying meditation teacher, who said that she found this dying process exhilarating. "Dying is a very ugly and messy affair" my mom asserted. Indeed it is!

Frank explains that many people go down fighting, like it is a badge of honor. Others fearfully fight to keep a lifetime of unquestioned habits in place. Still others even turn away from loved ones. The one thing I learned is that we have no right to say how anyone else should die. That would place a tremendous burden on the dying. What we can do is be open to and support the other's unique process without letting our own preferences get in the way. Simultaneously we can take the opportunity to fully dive into each moment of life ourselves.

Healing doesn't necessarily mean remission or cure. It might just mean making the cancer process or pain meaningful, which in itself is healing beyond measure. Tedeschi describes PTG's positive changes to include deeper relationships; greater sense of empathy, personal resiliency, wisdom and strength; and a deeper appreciation of life and what really matters.[5] Even though my mom died of her cancer, the manifestation of all of these changes made the whole process like the ultimate birthing process into death.

Pema Chödrön mentions the "… essential choice that confronts us all: whether to cling to the false security of our fixed ideas and tribal views, even though they bring us only momentary satisfaction, or to overcome our fear and make the leap to living an authentic life."[1] Even though my mom had lived a very authentic life, towards the end of those last nine months there was a different authenticity that emerged – an authenticity not dependent on her accomplishments. She had consciously navigated into this final transition filled with an exuberant aliveness where joy and grief were present simultaneously. What an honor to have been a witness to that! What a challenge to be available to my patients to facilitate the same or be open to an entirely different process.

Dr. Gabrielle Duebendorfer has practiced as a licensed naturopathic physician for over 20 years. As a long-term meditator, yoga practitioner, and certified iRest instructor, she weaves meditation and mindfulness-based tools into evidence-based naturopathic protocols to help patients navigate the journey of chronic disease. She offers long distance consults, seminars, and talks.

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The Sweet Potato Story

by Sue Visser

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Many herbal concoctions, supplements, and hormone creams claim to work better than hormone replacement therapy (HRT), but no magic bullet can whip away a hot flush within minutes – why not? I am one of the "do it now" Baby Boomers and enjoy such a challenge, even though it was ten years prior to my own menopause. I was experimenting with natural ways to help alleviate menopausal symptoms. By chewing a chunk of raw red-skinned sweet potato, I stumbled upon a completely natural progesterone-boosting phenomenon. Unbelievable, unscientific you may be thinking, but curiosity and serendipity are strange bedfellows. Within a few months I produced solid evidence – the manifestation of a dramatic rise in progesterone levels. For over twenty years my sweet potato story and those who have tried it out themselves bear testimony to the efficacy of this low-tech breakthrough. Hot flashes went away, and babies were born – against all odds – to mothers, even in their forties, who chewed the red sweet potato. How did it all begin?

In 1998 I was asked by a top Cape Town gynaecologist to develop herbal alternatives to HRT to relieve symptoms like moodiness, bloating, fatigue, and hot flashes. Doctor Lee was already making great claims about wild yam cream, but the progesterone panacea was being shed in a dim light by Dr. Marilyn Glenville, who preferred to correct hormonal issues at a more causative level. She recommended better nutrition and using herbs like *agnus castus* or black cohosh to improve hormonal output. I enjoyed the lectures she presented during her visit to Cape Town and read her book, *Natural Alternatives to Menopause*.[1]

Dr. Glenville's opinion about taking any replacement form of estrogen or progesterone (synthetic or bioidentical HRT) was: "Use it or lose it." She maintained that if you take these hormones, you will no longer be able to make them in the long-term. She explained that the body gets used to an external supply of the hormone and then the signal to generate the hormone shuts down. I like to add: "Don't take it if you can still make it." The cause of a hormonal shortfall, she explained, may just be a micronutrient deficiency, such as boron or a few vitamins and essential fatty acids. These are easy enough to correct, she said.

Being the ever-curious health researcher, I went to look for some yams to experiment with. But instead of yams, I bought some red-skinned sweet potatoes that had been mistakenly labelled as yams from the supermarket. In structure, yams are very close to progesterone, but so is the red sweet potato, I found out. My "yam" was identified as a sweet potato (*Ipomoea batatas*) at our university.[2] Could this reddish, plum-colored tuber hold the key to relieving hot flashes? The liver breaks down the chemical structure of yams and sweet potatoes, as does cooking them. So, eating them to relieve hot flashes was not an option. At least raw sweet potatoes are not toxic, like the Mexican yam.

There was no reason why the bloodstream could not absorb the raw, fresh active substances within the sweet potato. One of my doctor friends told me, "Go ahead, the body will somehow manipulate it – or not!" Sublingual absorption is the key delivery system used by homeopaths to introduce their remedies into the bloodstream. I started to chew a small fistful of the raw, peeled sweet potato every day to see if the active substances could be absorbed via the blood vessels under the tongue. I slowly chewed and "mouth absorbed" my daily ration of raw, peeled *Ipomoea batatas*, wondering if anything would ever happen.

Skipping the Menstrual Cycle

After a few weeks, I skipped my menstrual period that usually arrived like clockwork. The late Professor Serfontein, who was a nutritional expert at Pretoria University, was intrigued. He said he would really be impressed if I could intentionally "suppress the follicle stimulating hormone." He doubted that I could spike up my progesterone levels that easily. His research team was developing a progesterone-based yam cream at the time. I preferred the challenge of introducing a progesterone precursor into my bloodstream to see if it could affect hormone levels. I continued with the same dose of sweet potato every day for six months to really prove the point, and menstruation ceased throughout the trial run. I was told that a high dose of progesterone fools the body into thinking it is pregnant and that is how some birth control pills work. I was definitely not pregnant – no thanks!

Normal menstruation with no adverse effects resumed when I stopped my daily sweet potato chewing ritual, to the relief of Dr Zeelenberg, the gynecologist for whom I had already developed a range of personal hygiene products. He could not prescribe fresh sweet potatoes to his patients and asked me to develop a remedy instead. I produced a tincture from the grated flesh of the sweet potato and tested the potion at twice the estimated regular dose of 10 drops a day under the tongue for another six months. It worked as well as the original experiment. What a year – skipping another six menstrual cycles!

A number of older women, including many of the doctor's patients, took part in these trials using a normal dose of the tincture; or they chewed the original sweet potato so we could compare the effects. The ladies experienced a degree of improvement in some cases, especially with their hot flashes, fatigue, and depression. Red sweet potato was added to our range of hormone-balancing tinctures that included red clover, black cohosh and *agnus castus*. As a completely safe and natural way of skipping a menstrual cycle or two, the sweet potato tincture at twice the normal dose of 10 drops a day (or chewing a golf-ball size of the sweet potato) helped many ladies take part in religious or sporting events that they would otherwise have missed out on. I advise them to try it out for a month or two beforehand for a

more reliable result. The sweet potato trick produced the same effect as the newly developed menstrual-skipping patent drugs that were beginning to emerge on the market at the time.

Balancing Menstruation and Bringing on the Babies!

As with progesterone, the sweet potato is dose-dependent. The ladies who needed to conceive by gently raising progesterone have done so successfully by chewing a piece of it the size of a finger. The first of these babies was accidentally conceived by Zelma, a 38-year-old friend of mine who was suffering from very heavy menstrual bleeding at the time. After seeing me nibble at my chunk of sweet potato in the laboratory, she asked for an explanation. I was unaware that she had also started chewing a secret chunk of sweet potato until her next menstrual cycle was unusually late. She really did fall pregnant! A beautiful new daughter was added to her brood of two teenage boys.

In a neighboring country, a lady naturopath heard about this new fertility stunt and decided to give it a try. I received the joyous news that she had become pregnant at last, after batting for over 10 years. She had all but given up after trying the best of treatments and was already forty-something years old. She had faithfully chewed her finger-sized piece of sweet potato, much to the amusement of the family. When her son was born, he was nicknamed "Patat." Two years later, his sister arrived – another "Patat" phenomenon. I still hear about babies who are born as a result of using our herbal tinctures and am happy that people are keen to try natural remedies, even if some of the results are unexpected. Black cohosh, for instance, is the nickname of the fourth son of Miriam who was in her early forties. Not exactly a cure for menopausal symptoms! According to some of the letters I have received over the years, red clover and *agnus castus* are herbal remedies that have also helped women to fall pregnant.

In smaller doses, five to ten drops of the "Sweet Potato Tincture" have helped women to conceive or to resume menstruation that had ceased due to anorexia or excessive marathon running. A lot of the feedback was provided by Dr. Zeelenberg, who used all four of the tinctures in his practice. His initial request for a hormone balancer resulted in a range of remedies because I explained that women are not alike. I told him that although we do morph into premenstrual or menopausal monsters, we still differ and need individual remedies! The sweet potato tincture became his favourite alternative for patients who refused to take HRT to treat fibroids or progesterone-related complications.

My Own Menopause

For ten years after the sweet potato experiment, I had maintained strict control over my diet, supplementation, and lifestyle factors and used to encourage ladies to do likewise on countless radio shows. "Train for the menopause, be prepared and sort out your niggly health issues – before you make the transition" was the general message I broadcasted. Then the time came for me to personally experience the menopause, after many years of writing and talking about it. I stopped ovulating, eventually at the age of 54. For me it was a great challenge, to finally take my own medicine!

I thought I was too good for hot flashes, but they arrived. Ovulation was coming to an end, and I presumed that the follicle stimulating hormone was calling up eggs that were no longer waiting in line. The heat waves were trying to tell me something. I listened to my body and not to the regular solution – the call for hormone replacement. I did not want any more estrogen – no thanks because my childbearing years had officially ended.

No progesterone cream – nada![3] Three of my close friends, all staunch supporters of alternative medicine had used wild yam (progesterone) cream before and during their menopause. They had sold these products and believed in them – yet they developed breast cancer. They continued to use the cream till the day they died. Progesterone is a precursor to estrogen, so I do not understand why people take it to lower estrogen. After a few days of chewing my good old sweet potato, the hot flashes went away. Whenever the creeping heat threatened to broil me, I chewed the sweet potato and after 5 – 15 minutes I generally cooled down. Who was to know that I too, could now personally lay claim to this kitchen cure for hot flashes!

During the nights, I got hotter and hotter; and contrary to popular belief, I began to embrace and appreciate them, suspecting they had a purpose. Hyperthermia is not something going wrong! Now cancer treatments make use of high temperatures. The affected areas of the cancer patient are exposed to very high temperatures, combined with spells of intense sauna treatments to increase the overall body temperature. Artificially induced hot flashes and night sweats? Aha! Would this be an explanation at last, as to why the body heats up during the menopause? Hyperthermia or raising the body temperature is also a natural way of dealing with certain infections. As we know, some forms of cancer are caused by bacteria and mycotoxins. My hot spells were intense, and I kept on telling myself they must get hotter and hotter until they have done their job. Kill the bugs, knock out the gremlins!

After a month or two of observing and voluntarily experiencing the hot spells of night sweats, they finally abated. No hormone replacement was required – what you could call elegant medicine. I stepped out of my cocoon, free from the burden of menopausal mythology. My hormones have rearranged themselves without the need for any replacing. Sound supplementation and the odd dose of black cohosh or sweet potato have sufficed. Menopause = metamorphosis. So why resist or try to interfere with the change of life? Now whenever I prepare sweet potato for dinner, I nibble some – just for good measure. They grow just about anywhere in the world and the hormonal magic that lies within them is truly a gift from nature. They cost so little and can do so much.

Trusting in nature means just that – to allow things to work out the way they were originally designed to.

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Sue Visser is a natural health researcher, product developer, writer, and Agony Aunt. She specialises in nutrition and herbal medicine with a working knowledge of most of the popular modalities of natural/alternative medicine. She has contributed to the world of radio, television and journalism for over 20 years. Sue wrote, illustrated and published her popular book: *Healthy Happy Eating* for all blood types followed by *The Holistic Guide to a Healthy Happy Heart.* The second book was co-authored by Dr James Liddell. Sue is also a product developer and has formulated a wide range of alternative health products based on her unique insight and research. www.naturefresh.co.za

Letters to the Editor

Re: GABA as a Neuroinhibitor

I wish to comment on my reaction to the overall interesting article by psychotherapist Julia Ross: "The Nutritional Solution to our Worldwide Dietary Crisis." There are some good points here.

As a biochemist, I have studied amino acid impacts connected to hormones, notably extensive work on the GABA-A receptor (GABA-AR).

My area is molecular aspects of bioidentical hormones, and how these gender molecules form a container for the moods of women as we age: testosterone and progesterone, specifically, are protective against the oxidative neurological stress of aging, for men too!

There are significant interfaces between neurosteroid-hormonal impact on the brain and specific amino acids. For example, GABA is the most abundant neuroinhibitory neurotransmitter in the body, AND it is unusual in that it is also an amino acid. It is also not chiral; it has no asymmetric center and is not rotatory.

What happens in the connection is that progesterone breaks down to allopregnanolone in both women and men. This is a crucial interface with the alpha-4 subunit on the GABA-AR as, if there is none of this molecule present or if insufficiently present, then GABA has the inverse effect; it can become excitatory rather than inhibitory.

We often have both women and men rub varying amounts of compounded progesterone cream into their wrists (15 mg for men, 50-100 mg for women) to stop a panic attack, along with sipping GABA – sometimes at those times more is needed, but not on an empty stomach.

Further we have for many, many years found that using sufficient GABA and co-factors (average 400 mg/dose) is important to interface with the GABA-AR and with the progesterone metabolites, and everyone is different. Rarely have we seen good results with lesser amounts having any enduring significant impact. (We do like Anxiety Control™ by Metabolic Maintenance.)

There is a paper on my website (http://phyllisbronsonphd.com/) on GABA that was peer reviewed and published, and my book also explains the hormone/mood/amino acid connection in more depth: *Moods, Emotions, and Aging: Hormones and the Mind Body Connection* (Rowman and Littlefield, NY).

Sincerely,
Phyllis J. Bronson, PhD
Biochemical Consulting Company
Biochemical Research Foundation
(Aspen, Colorado)

BRAIN CONNECTION

Estrogen is most important for cognition, but progesterone also serves the brain, decreasing anxiety and mood swings.

Progesterone enhances dendritic activity, so that neuro-inhibitory molecules are more readily up-regulated.

Natural progesterone from your ovaries or transdermally applied in sufficient quantity affects $GABA_A$ and $GABA_C$ receptors.

Oral Progesterone such as Prometrium or compounded goes through liver first pass, and after being metabolized affects GABA receptors in a more potent BDZ drug like manner.

5-alpha pregnandione is made in upper GI from oral progesterone: this has 12x the potency of Phenobarbital.

Re: Dr. Gaby's August/September Editorial

Dr. Gaby got it wrong in his 1998 book review, and he is wrong again in 2018. His editorial "Blood-Type Diet Not Supported by Research" is inflammatory, and his interpretation of the one and only study mentioned is careless at best. Reviewing and interpreting research studies is supposed to be his forte, yet he failed or refused to acknowledge the flaws of the El-Sohemy et al, PLOS One study. Dr. D'Adamo summarizes that "this study conclusively proved that if young, healthy research subjects self-report eating potato chips, sandwiches, pizza, 'beans', mac-and-cheese, French fries and processed meat products, all the while doing 13.7% of the Blood Type Diet for six weeks, their final cardiometabolic markers will probably not vary much by blood type." An average compliance rate of 13.7% is insufficient to prove anything.

The title of his editorial should read "There is no scientific research that proves the Blood Type Diet is ineffective." There is a lot of 'fake' science out there with questionable research practices, falsification, bias, fraud, undisclosed conflict of interest, and professional jealousy. Many of us, until now, have relied on 'experts' like Gaby to help interpret the data to find the truth. Dr. Gaby 'dropped the ball' on this one.

The ABO blood typing system is only one of many, but it is the main typing system in use and one with fatal outcomes if an incorrect blood transfusion is given. The ABO and FUT polymorphisms create many distinct differences and need to be factored into all research. Isn't it important to know for example that non-O blood types have 11% greater risk of coronary heart disease compared to O blood types?

I am not a research scientist. I am a naturopathic physician in my fourth decade of practice. In this time I have prescribed the appropriate blood type diet (BTD) to thousands of patients with consistently good results. 'Physician heal thy self...follow the BTD in earnest for two months and prove to yourself the benefit. Dr. D'Adamo's diet book *Eat Right for Your Type* is now published in 75 languages and is available in every corner of the world. It is still only available in hard-cover after over 20 years. The continued and immense world-wide interest in this book should tell you that there is something to the BTD.

Dr. Peter D'Adamo is one of our greatest scientific minds and it is shameful that his work is so under-recognized. Read his *Fundamentals of Generative Medicine* textbook, and check out his computer programs, SWAMI (epigenetics) and OPUS23 (genetic interpretation) and his other sophisticated analytics. He is the leader in precision medicine, and editorials like Gaby's unfortunately do humanity a huge disservice. It seems we are doomed to suffer another Semmelweis effect. Semmelweis was the fellow that first suggested doctors wash their hands; he was ridiculed and persecuted until decades later we realized that he was right.

Sincerely,
Dr. Loren Kozak, ND, MIFHI

Dr. Gaby's Response:

As I mentioned in my editorial, I have no doubt that people who follow the blood-type diet experience various improvements in their health. Every one of the four diets recommends the avoidance of refined sugar and processed foods. In addition, three of the most frequently allergenic foods – wheat, corn, and dairy products – are restricted (3 of the 4 diets prohibit wheat, 3 prohibit corn, and 1 prohibits dairy products). It is legitimate to ask whether the improvements that people experience are related to blood type or are merely nonspecific benefits of avoiding junk food and common allergens.

More than 20 years ago, I invited proponents of the blood-type diet to conduct a simple clinical trial that could answer this question. Participants would be randomly assigned to follow one of the four diets, and the investigators would determine whether people assigned to the "appropriate" diet fared better than those assigned to one of the three "inappropriate" diets. To my knowledge, no such trial has ever been conducted. Providing a definitive answer to this question would be more than just an academic exercise, because the dietary requirements for some of the blood types (e.g., eat a lot of animal foods; permanently avoid common foods such as wheat, dairy products, and corn that one might not really need to avoid; and restrict cruciferous vegetables) could have adverse health consequences. If such a study failed to demonstrate the importance of blood type for making dietary recommendations, then people would be freed to follow a potentially more effective approach, such as avoiding junk food and identifying hidden food allergens by means of an elimination diet followed by individual food testing.

The study I cited by Wang and coworkers was not the same study that Dr. Kozak mentioned, in which young subjects apparently ate a bunch of unhealthful foods. The study I cited was a follow-up study by the same research group, in which middle-aged overweight individuals were assigned to one of two diets that emphasized fruits, vegetables, whole grains, and other healthful foods and recommended avoidance of refined sugar. The researchers found that greater adherence to any of the four blood-type diets was associated with significant clinical improvement, but these improvements occurred independently of whether the diet did or did not conform to the person's blood type.[1] To be sure, the study I cited was not a definitive test of the blood-type theory and, as Dr. Kozak noted, it does not prove the theory is invalid. However, the failure of the study to provide any support at all for the blood-type theory reemphasizes the need for its proponents to conduct a clinical trial.

1 Wang J, et al. ABO genotype does not modify the association between the "blood-type" diet and biomarkers of cardiometabolic disease in overweight adults. *J Nutr*. 2018;148:518-525.

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Is Your Body Out Of Tune

review by Jim Cross, ND, LAc

Tuning the Human Biofield: Healing With Vibrational Sound Therapy by Eileen Day McKusick; www.eileenmckusick.com
Healing Arts Press; www.HealingArtsPress.com
2014; 252 pages; 16.95 (US)

After reading this wonderfully eclectic and extremely thorough book on vibrational sound therapy by Eileen McKusick, the first thought that came to my mind was a song from my youth: "Good Vibrations" by The Beach Boys. This is what I gleaned from her book: how to restore good vibrations in our bodies with tuning forks, and much more, which I will try to summarize in this way-too-short book review.

Ms. McKusick is the originator of Biofield Tuning or Sound Balancing, which is a therapeutic modality utilizing tuning forks. She is also the founder of the Biofield Tuning Institute, which currently partners with the Consciousness and Healing Initiative and the Institute of Noetic Sciences to apply the scientific method to her biofield anatomy hypothesis. The Institute also offers classes training people to utilize her theories on sound and tuning forks in the treatment of disease all over the United States and in various countries around the world.

I really enjoyed the comment that her vibrational journey to her hypothesis progressed like a trail of crumbs from one book/seminar to another. This trail of accumulated knowledge led her to writing a master's thesis that explains what she has learned about vibrational sound therapy: "Exploring the Effects of Audible Sound on the Human Body and Its Biofield."

Her biofield anatomy hypothesis states that sound balancing makes use of frequencies produced by tuning forks to detect and correct distortions and imbalances within the biomagnetic energy field or biofield of a person that surrounds every person's body.

Why should we believe her? She quotes the illustrious Max Planck in her book: "There is no such thing as matter. It is all just different rates of vibration designed by an unseen intelligence." She then goes on to hypothesize that treating vibration with vibration is logical and elegant, which makes incredibly good sense to me and hopefully you also.

She also incorporates an incredible foreword by Karl Maret, MD, who also holds electrical and biomedical engineering degrees. Amazingly, the foreword is also copyrighted, probably because it contains very useful information.

Maret posits that we should consider a new medical paradigm: we're fundamentally energetic and informational beings who possess sophisticated, high speed communication channels in our living extracellular matrix capable of rapidly affecting tissues, cellular processes, and nuclear expression.

In addition, Maret claims that quantum physicists like James Oschman are showing humans exist in a sea of almost infinite energy in which matter and mass manifest and disappear continuously. Humans are constantly immersed in this invisible, energetic ocean. This basically appears to be the Zero Point Field that Lynn McTaggart writes so eloquently about in her informative book, *The Field.*

Essentially, Maret and McKusick are theorizing that, as sound emanates from the tuning fork striking the skin's surface, complex electrical and phonon interactions take place that can alter tissue bioelectrical properties. This then can produce a coherent frequency that travels through the body and opens up energetic blockages. Removing these blockages then allows blood, lymph, and electricity to flow with greater efficiency.

This vibrational energy of the tuning forks can reawaken various tissues around the body that have become energetically blocked from various environmental stimuli such as heavy metals, various chemicals, EMFs, or emotional trauma. This potentially then leads to a healing response in the part(s) of the body where the blockage had occurred.

What she states regarding emotional trauma really resonated with me and my clinical experiences with clients treating the real mental/emotional/spiritual root cause of their various illnesses. She states that trauma can live as a charged incoherence within the human biofield and can exert a non-beneficial frequency pattern within the person's biofield, which leads to a breakdown in order, structure, and function of their body. She next posits that the tuning forks can create a vibration that manipulates the subtle energy of the body to restore order, structure, and function to the body by neutralizing the dissonant emotional energy fields that were created.

I always want to reach to the root cause of a person's health issue. Otherwise you are just putting a band-aid onto the problem, whether it's a pharmaceutical, herbal, or nutritional band-aid. She is attempting to actually enact a change at a fundamentally deep level of the body. In many of our patients, the same pattern just keeps repeating itself over and over because the biophotons in their fields lack coherence. By correcting the incoherence, people should be energetically free to put their lives back on a healthy track again.

Utilizing sound is just one of many clinical choices that we have to affect change at a deep level in a person's body. Homeopathy, nutrition, etc. can all achieve a similar result. Finding which modality really vibes with each patient is, for me, the true magical part of the equation. As my friend Eric Gordon, MD, so eloquently states: do we use door numbers 1, 2, 3, 4, or 5 to get the healing ball rolling?

Her book also delves into talking about the types of tuning forks she uses and why. Even if you don't like physics, her scientific explanations of sound and frequency are brief but to the point and leave you with a comfortable understanding of the topics.

Finally, she makes a comment that totally hits home with me. She thinks that humans are both spiritual beings having a physical experience and physical beings having a spiritual experience. Wow, insightful comment integrating true balance/homeostasis into the health equation. Truthfully, I never bought the concept of a mind/body connection. To me, all that is present is you: the physical you and the energetic you, which are as tightly interwoven as the moss growing on the north side of a giant white fir.

So, she is asking you to buy into a novel system of healing that is both simplistic and holistic at the same time. I, for one, intend to find out more about her use of tuning forks by taking her beginning foundations class in Portland, Oregon. I'm basically following that little voice in my enteric nervous system that has reliably led me to various wonderful places in my life such as naturopathic school and working in Northern Europe. It is telling me to go for it! I think I'll listen. ◆

Patient-Focused Medicine

by Dickson Thom, DDS, ND; James Paul Maffitt Odell, OMD, ND, L.Ac.; Jeoffrey Drobot, NMD; Frank Pleus, MD, DDS, OMFS; and Jess Higgins Kelley, MNT

The following excerpt is from *Bioregulatory Medicine: An Innovative Holistic Approach to Self-Healing* (Chelsea Green Publishing, 2018) and is printed with permission from the publisher.

Today, over half of the world's population is afflicted with some form of chronic or degenerative illness – heart disease, diabetes, dementia – the list is long. Arthritis is now the most common cause of disability, and one in four people struggle with normal activities because of joint pain. Half of all people will be diagnosed with cancer in their lifetime. One in five people have an autoimmune disease. And these are just a few of the diagnosable diseases. Currently, an estimated one in ten people have a rare, undiagnosable, or medically indefinable condition. Passed like a hot potato from specialist to specialist, these tired, frustrated, and debilitated patients often spend years – not to mention significant financial resources – seeking answers, relief, and eventual cure. And the Western, conventional, allopathic, suppress-the-symptoms-with-pharmaceutical-drugs model is rapidly falling out of favor as more patients desire a nontoxic, noninvasive prevention and healing medical model that identifies and addresses the root cause of illness and elicits true healing. *Bioregulatory Medicine* (Chelsea Green Publishing, 2018), authored by five experts in the field of natural health, introduces a model that has been alive and well in Europe for decades. In countries such as Switzerland, Germany, India, China, Canada, and France – all ranking far higher in health care than the United States – *bioregulatory medicine* is a household term.

Bioregulatory medicine, or *BioMed*, is a comprehensive, evidence-based, and holistic medical model that has been used and refined for over five thousand years by some of the brightest minds in medicine, science, and philosophy. A total body (and mind) approach to health and healing, the scope of BioMed extends into disease prevention, optimizing performance, and chronic and degenerative illness treatment. Using a sophisticated synthesis of a wide range of natural and technologically advanced diagnostic and treatment equipment, BioMed aims to help facilitate and restore natural human biological processes. It is a proven, safe, gentle, highly effective, drugless, and side-effect-free medical model designed to naturally support the body to regulate, adapt, regenerate, and self-heal. Repairing and restoring your body's systematic natural biological processes is the *only* way to prevent, reverse, and correct the deepest roots of chronic and degenerative disease. And this restoration is achieved by placing the focus on the interconnections among all the regulating systems of the body, while simultaneously facilitating detoxification, deep nutrition, oral health, and nervous system calibration.

What exactly is bioregulation? For starters, the human body is comprised of approximately one hundred thousand billion cells that carry out over one hundred thousand biochemical reactions per second. Humans have dozens of bioregulating systems, including the nervous, endocrine, neurological, cardiovascular, digestive, and many more. Every bio-regulating system is intimately related on both an electrical basis and a biochemical basis to another. When communication either within or between these systems fails, dysregulation and symptoms will follow. The human body is a wondrously designed, self-regulating system that sustains all life processes, such as heart rate, blood sugar levels, hormone production, respiratory rate, detoxification, immune function, and blood pressure. Processes most of us aren't even aware are happening. Each of these systems seeks a state of balance, called homeostasis. One example of a system balancing itself is thermoregulation, where if we get too hot, we perspire. Another example is a feedback system called blood sugar regulation, where if our blood glucose gets too high, insulin is released to lower it. And if a toxin enters your system, your immune system reacts to disarm it. Breathing is regulated, blood pressure is regulated, digestion is regulated, circulation is regulated, and on and on. Consider of all the things your body is doing without you even thinking about it!

"Dis-*ease*" happens when one or more of these systems is pushed out of balance. That said, there is rarely ever a single cause of disease. Modern chronic and degenerative illnesses usually have at least five regulatory systems that are out of balance. This complexity is why there are no – and can be no – "specialists" in bioregulatory medicine, the body is interconnected. As soon as systems are viewed in isolation, we lose the whole.

Each bioregulatory system has an innate ability to self-repair or self-heal if injured. Think about it: A cast doesn't heal a broken arm; the biological process of bone formation called *ossification* does. A cast only creates one single preferred precondition – static immobilization – for a broken arm to heal. We've known about this self-healing ability for a long time. Hippocrates stated during the fifth century BC, the body has the inherent ability – the vitality – not only to heal itself and restore itself to health, but also to ward off disease. But it does this only on the condition that it's given the right tools to do so. In bioregulatory medicine, disease is not seen as the enemy with which one needs to fight but is seen as a manifestation of the breakdown of mechanisms that maintain control and homeostasis. Symptoms are simply the body's way of expressing dysregulation, and the goal is to identify and remove these obstacles to cure.

BioMed is about supporting and restoring the body's bioregulating systems' ability to regenerate, repair, and self-heal through the use of natural and energetic therapies. And it's even more than that, too. BioMed is a multifaceted, multidisciplinary medical model that is patient-, health-, performance-, ecology-, biology-, spiritually, physiology-, and curatively centered. Bioregulatory medicine focuses on individuality, taking into account each person's unique biochemical, historical, energetic, structural, sociological, and psycho-emotional patterns. There's only one you, so there can be only one tailored medical approach that will best meet your needs. In this way, bioregulatory medicine offers entirely customized protocols that combine ancient health care wisdom with modern scientific technological advancements. Since there is no health care manual specific to you, there is no one case study that will be similar to your process. Everyone is unique. So while allopathic medicine has strived to become an exact science, working from the platform of "hard data," just the facts, irrefutable formulas, or proven double blind studies, bioregulatory medicine simply, artfully, and skillfully centers on the *patient*.

The Bioregulatory Medicine Institute is a non-profit program of the Marion Institute founded to promote the science and art of biological regulatory medicine, and to increase public knowledge and integration of bioregulatory medicine as a wholistic and evidence-based medical system. ◆

Ask Dr. J

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

Food: It's What Could/Should Be for Dinner

Really, how important is food. For me, in my practice and in my personal life, food forms the beginning, middle, and end of any health-related choices or treatments I choose. I appear to not be alone in this endeavor. In 2014, the Institute for Functional Medicine's annual international conference's entire focus was on food, which was reflected in the title of its conference: "Functional Perspectives on Food and Nutrition: The Ultimate Upstream Medicine."

What a novel concept: upstream medicine. At UC Davis in 1971, I was first introduced to the concept of upstream medicine or what I was taught then: preventative medicine. This began my odyssey of searching for the ways and means to lead a lifestyle that would constitute *an effective anti-aging strategy* to prevent disease later in life. This naturally led me to naturopathic school, albeit in an unusual place, Monte Rio California on the lovely Russian River, in a state where naturopathy wasn't legal yet, and to a school that was in its first year of existence, Pacific College of Naturopathic Medicine, which would fold two years later. The Grateful Dead sing "what a long strange trip it's been," which for me appears to be how I lucked into my present place in medicine.

I like the writer Michael Pollan. Like the Institute for Functional Medicine, Pollan appears to place food in an equally lofty place in his life. On the cover of his entertaining book, In Defense of Food, are his seven words of wisdom to follow in choosing which foods to place in our mouths: eat food, not too much, mostly plants. In his book, he explains why those seven words. I have modified those seven words into lucky 13: *eat local, photon-rich, nutrient-dense food, not too much, according to your genetic make-up*. This article will explain my modifications.

Before I delve deeper into my 13 words of hopeful wisdom, I want to emphasize the fact that I consider food to be information. I tell my patients the information/food they are eating will have an epigenetic effect on which of their inherited genes are expressed. This epigenetic effect in turn will have a positive or negative impact on their overall health and what diseases will/will not manifest during their lifetime. In other words, food is not random information. It is turning genes on or off which have the downstream effects of releasing transcription factors and signaling cascades that can lead to a long, healthy life or one fraught with dysfunction and disease.

Unfortunately, most humans have what can be termed a "termite lifestyle." In a building, a termite lifestyle means you don't see any damage being perpetrated by the termites until the building collapses. In a human being, a termite lifestyle means you don't diagnose the obvious chronic diseases like cancer until an organ system has basically become so structurally dysfunctional that it is ready to collapse, and symptoms/signs finally present themselves. Eating food with the proper information can prevent a person's foundational deterioration. This would be analogous to using Raid to kill the termites and prevent the building's eventual collapse.

Eat Local

Let's begin with the local phenomenon. Why encourage our patients and us to eat a local diet? For me, this boils down to two areas: people and pollution. I have been buying food from the Chico Farmer's Market in Chico, California, for almost 30 years. I buy from one Hmong vendor whose son was age ten 25 years ago and is now a grown-up California Highway Patrol officer who can't wait to issue me a ticket for the bad time I used to give him when he was the money taker for his older brother's veggies. I buy from another vendor where four generations of family are working the farm. In other words, I'm buying from actual people, not corporations, and am also supporting local families, not corporations. I see basically two reasons for the degradation of American society: the loss of the family unit and the almost total control of our state and federal governments by corporations. I can positively affect both of these factors by buying from a local farmer's market.

With regards to pollution, the California Air Resources Board estimates that in 2005 alone, 2,400 people died prematurely; and there were 2,800 hospital admissions for diseases such as asthma which could be linked both to direct and indirect exposure to the extremely fine particles in diesel exhaust

that bypass our cilia's filtering apparatus in our respiratory system. One significant source of these very fine exhaust particles stems from the transport of our food via trucks.[1] Diesel pollution from freight transport activities then directly contributes to these premature deaths and pollution-related diseases. By choosing to shop at local farmer's markets we can dramatically reduce fuel consumption and the pollution associated with transporting our food long distances and protect our air from these dangerous microparticles.

Photon-Rich Food

What's a photon? According to freedictionary.com, a photon is the smallest unit of light or other electromagnetic energy. It has been shown that virtually all living organisms emit extremely weak light spontaneously without any outside stimulus which also occurs in photosynthesis due to sunlight hitting the plant's leaves.[2] This weak photon emission appears to be a by-product of the 100,000 or so biochemical reactions happening constantly in all of our cells.[3] Our cells are actually emitting light at about 1/1,000 the strength of the naked eye.[4,5] The researchers found that the photon emission wasn't constant but rose and fell over the day, with the peak at 4 PM and the lowest point at 10 AM, which suggests that these light emissions are linked to the body's daily biorhythms.[4]

Fritz Albert Popp, a biophysicist in Germany, and his postdoctoral fellow Bernard Ruth solved the problem of how to measure this weak light emitted by human beings when they constructed a machine which used a photomultiplier to count light one photon at a time. Dr. Popp later proved that light in your body is stored by and emitted from your DNA. He also believed that these types of biophoton emissions were a type of information [6]

Fortunately, Popp's mind is similar to the late MD Nicholas Gonzalez's mind: one thought begins a chain reaction that takes them into more new thoughts and previously uncharted clinical territory. If light was used in photosynthesis to grow plants, we must be taking in and storing these photons when we eat plant foods. Popp theorized that these biophoton emissions provided an ideal communication system for the transfer of information to cells all across our bodies and also were a driving force for all the molecular biochemical reactions occurring in the body.

Next Popp theorized that different sources of food may contain more and more coherent biophotons than others. In one experiment he compared the light from free-range eggs with eggs from hens which remained in cages. The photons in the former were far more coherent than those in the latter. After performing this experiment on other foods, he found the foods closest to their natural state had the most coherent intensity of light.[7]

So, our farmer's market's fresh, organic/biodynamic food appears to contain more light. This extra added light could help fuel a more efficient and greater energy-generating biochemical milieu in the trillions of cells in our body. More light, this is what we hopefully want from our food.

Nutrient-Dense Food

Unfortunately, calories are invisible and devoid of taste. This also pertains to phytonutrients, minerals, and vitamins. If you couple this with the pleasure you get from consuming high calorie, nutrient-inadequate food that overrides the physiological regulatory signals by rewiring your brain to desire these junk foods, you have created a perfect storm. At least you've created the perfect storm for the food industry who has taken full advantage of this vulnerability that they have created. They have fashioned a conditioned overeater who overconsumes their products because these overeaters are blissfully unaware of how their food environment influences what they wish to place into their mouths.

The standard American diet/SAD could not have been designed more optimally to alter our body's homeostasis and eventually lead to various chronic diseases and death. Processed foods provide us with macronutrients, most prominently sugar, and have virtually no micronutrients or phytochemicals. In 2000, the Center for Disease Control and Prevention's Behavioral Risk Factor Surveillance Survey showed that less than 25% of Americans consumed the recommended amount of fruits and vegetables.[8] Plus, French fries and ketchup make up the bulk of many Americans' vegetable intake. What are we to do?

Basically, our industrial agricultural system has given us higher yields of plants that have lower nutritional value. Our middle Stone Age ancestors ate no foods that were, as Philip J. Goscienski, MD, says in his book *Health Secrets of the Stone Age*, nutrient-null. There are oodles of studies showing that nutrient-dense foods help prevent chronic diseases and help optimize the day-to-day functioning of the organelles in our cells, specifically our mitochondria. The vitamins and minerals are just small components of whole foods. They co-exist with hundreds of phytonutrient co-factors (flavonoids, carotenoids, phenols, etc.), which make these whole foods nutrient-dense and which lead to improved biochemical performance in our bodies.

We need to encourage our patients to visit farmer's markets and substitute the word foods of color/FOC for nutrient-dense food. They need to consume 10 servings/day of FOC's. This will help to make them a biochemical powerhouse or the equivalent of Michael Jordan at a cellular level.

Not Too Much

So now where is there evidence of long-term calorie restriction leading to an increased life expectancy? It appears this is the case on the Japanese islands of Okinawa. The islands of Okinawa, a lush archipelago southwest of the main island of Japan, are home to the largest number per capita and healthiest population of centenarians on Earth. The Japanese Ministry of Health and Welfare has been conducting large-scale and extremely accurate nutritional surveys yearly since 1946.[9] Legal birth certificates have been kept in Japan since 1872, so the number of centenarians is very reliably calculated. Today, Okinawa appears to have the highest number of centenarians per 100,000 people at 38.[10] The United States has more

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overall centenarians due to a larger population but only 22 centenarians per 100,000 people.[11]

Specifically, Okinawa has more people over 100 years of age per 100,000 population than anywhere else in the world, the lowest death rates from cancer, heart disease and stroke, which are the top three killers in the United States, and the highest life expectancy for males and females over 65. Females, in particular, have the highest life expectancy in all age groups.[12]

In the United States, we average approximately 3,770 calories/ day.[13] In Japan it is 2,810/day and on Okinawa it's 20% less than Japan only 2,248 calories/day.[14] They must not be eating at the fast food restaurants on the American military bases of Okinawa! On Okinawa they practice "*hara hachi bu*" which translates literally into 80% full.[15] Unfortunately the stretch receptors in our stomachs are a tad slow to signal their fullness to our brains. As a result, it takes about 20 minutes for our stomachs to signal the brain that there's no need for more food. *Hara hachi bu* gives the brain a chance to catch up before the calories spill over!

Elders on the island also claim that some of the centenarians still have active sex lives, which unfortunately hasn't been independently verified. There are though some Super Seniors who clearly are a cut above most seniors the world over. Ninety-six-year-old martial arts expert Seikichi Uehara defeated a 30-year-old ex-champion boxer several years ago. After the match Seikichi was quoted as saying his opponent had not yet matured enough to overpower him! Nabj Kinjo became a local legend when, at 105, she hunted down and killed a poisonous snake that invaded her home with a fly swatter![16]

Limiting calories may not be as much fun in the long run, as eating is physically, mentally, emotionally, and spiritually satisfying. Having functional health though is, I think, something that is more important than soothing my prefrontal cortex with extra, unneeded calories.

According To Your Genetic Make-Up

I have two basic sayings that I tell all my patients about food:

1. You are what your metabolism does with what you eat.
2. Your genes are smarter than you. Don't get in their way

Roger Williams, in his way-under-read book *Biochemical Individuality*, coined the term "genetrophic disease," which means that disease results from genetically determined nutritional or metabolic needs not being met by the individual's diet that result in poor gene expression and lead to common degenerative diseases over time. Genetics then determines the ability of organisms to achieve their optimal biochemical potentialities provided they are supplied with the raw materials of food that is genetically compatible to them. Basically, Williams proves my saying to patients that their genes are smarter than they are and to eat in a way that optimizes the expressions of those genes.[17]

With regards to what your metabolism does with what you eat, Vilhjalmur Stefansson is the best example. Stefansson was no armchair anthropologist. He lived 10 years with the Mackenzie River Inuit of the Canadian Arctic. These Inuit were still following their traditional hunter life. He calculated that their diet was approximately 80% fat and 20% protein. The Inuit told him that an all-meat diet with less fat would make them sick. What really impressed him about the Inuit was their personality as they lived in a cohesive and cooperative society centered on the family unit. They also didn't even have a word for depression.[18]

When Stefansson returned to the US, he lectured extensively. Armchair scientists, who had never been to the Arctic, refused to admit that humans could thrive and survive on an all-meat diet, especially one so high in fat. In response, Stefansson and a colleague went into a locked ward at Bellevue Hospital under the direction of a group of eminent scientists from Cornell University Medical College. Under this close supervision, they were fed an all-meat, 80% fat diet. After two months, the two men were in excellent physical condition and were allowed to return home where they continued to follow the diet. During this time, Stefansson's cholesterol levels ran in the range of 130-150.[18]

I would next like to offer up an example of someone who figured out 50 years ago that calorie restriction and eating according to your genetic make-up could be an incredible anti-aging tool. Johan Hultin was born in Sweden in 1925. He came to the United States in his early 20s as a graduate student at the University of Iowa where he was researching the 1918-19 influenza plague that killed some 50-200 million people worldwide. Fast forward to 1997 when Dr. Hultin returned to Brevig, Alaska, where the matriarch of the village remembered him from her youth when he had come there as a graduate student. She gave him two young males to help him dig in the graveyard where he found one obese Inuit who hadn't unfrozen that he named Lucy. He removed three samples from her lungs and sent one via UPS, one Fed Ex, and one USPS to the CDC. Remarkably, the virus was still intact, which Dr. Jeffrey Taubenberger used to map the base sequence of the 1918-19 virus.[19]

At the end of the February 17, 2002, *San Francisco Chronicle* article on Dr. Hultin, it talked about how approximately 50 years earlier Dr. Hultin had cut his calories in half and almost completely removed wheat from his diet and had emphasized protein and fat. He had delved into eating according to your blood type way before Dr. D'Adamo. He then used the rudimentary lab testing available to him at the time and found no changes in red blood cell count, hemoglobin, hematocrit, etc. with his calorie reduction.[19]

He was 77 at the time I met him. His grip would make Michael Jordan wince. He also walked around the hilly part of San Francisco for five miles every day. I went with him one day on his daily trek. I was astounded. Very few 20-30-year-olds could keep up with him! Basically, here was a living, breathing example exemplifying the long-term benefits of calorie restriction and eating according to your genetic make-up.

So, as Paul Harvey used to say, that was the rest of the story. Most of my patients relate to my 13 words of nutritional wisdom but some remain resistant for various reasons. I think JFK said it best with this quote: "The great enemy of the truth is very often not the lie… but the myth…. Belief in myth allows the comfort of opinion without the discomfort of thought."

Unfortunately, there are way too many myths about the perfect diet out there. Because of this people are completely confused as to which foods will make their bodies hum like a 1965 Rambler. I think my 13 words are a great place to start and make them realize eating is all about them, not Atkins, South Beach, or Pritikin. Only they can decide the types of food that maximize their particular biochemical and genetic make-up, which will comprise an effective anti-aging regimen. Hopefully they don't manifest the singer Paul Simon's magical words that I've altered so as not to be sexist: a person hears what they want to hear and disregards the rest!

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Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Our Infatuation with Human Studies

In recent years we have fallen in love with the idea that we can rely only on human studies to inform our practice decisions. All we want to think about, talk about, or consider is the information they reveal. Rats and mice have lost all of their charm. Some of our naturopathic journals go so far as to prohibit writers from even citing animal studies. We certainly no longer give the time of day to data strained from in vitro work; we have few if any qualms about ignoring it.

Having human papers on nutritional supplements is still such a novelty, so bright and so fresh to our experience that it is hard to resist the urge to fall into a myopic trance. Dredging up a paper on PubMed that is extracted from human data generates a tremor of excitement along some cerebral pathway that is near impossible to say no to: "Finally, we have 'real' information that supports what we do."

Granted as well that with the entire medical establishment going through a fascination with evidence-based medicine (EBM), our reaction to finding evidence that supports what we alternative sorts do that fits into this framework is something of a relief. It gives us a chance to keep up and pretend to be like the MDs

The trouble is that sometimes we may have gone too far, too quickly, seduced by this newfound attraction and cease thinking rationally. What brings all this to mind was a simple question a patient brought me: "Does eating soy affect my prognosis if I am taking tamoxifen to prevent breast cancer recurrence?"

Given that tamoxifen has been on the market since 1979, there should be nearly 40 years of data to inform my answer. Tamoxifen, as I explain to my patient, gums up the estrogen receptors on breast cancer cells so that estrogen can't stimulate cell growth. Our assumption is that the isoflavones in soy bind onto these same receptors blocking estrogen stimulation. In theory, soy and tamoxifen together might work better than either alone. Or just as possible, the isoflavones might interfere with tamoxifen blocking estrogen, or while we are listing possibilities, the soy components might bind to the estrogen receptors and stimulate growth on their own. Our best guesses remain only guesses; we need data to inform an answer.

When we turn to the in vitro data, a definitive answer evades us. Some studies suggest a synergistic benefit when genistein is added to tamoxifen while others suggest the opposite, that soy negates tamoxifen's benefit in protecting against breast cancer recurrence.

In 1999 Shen et al reported that the combination of tamoxifen and soy "synergistically down-regulate signal transduction and proliferation in estrogen receptor-negative human breast carcinoma."[1] This is interesting but, for the moment, of little relevance; as the perceptive reader will notice, they were looking at women with a history of estrogen receptor negative breast cancer who are rarely if ever treated with a hormone therapy such as tamoxifen. So, let's put this tidbit aside for the moment.

More relevant is a study by Tanos published in 2002 that reported that when either dysplastic or malignant breast cancer cells, being grown in a monolayer, were treated with a combination of tamoxifen and genistein, the growth inhibitory effects were far stronger than with either agent alone.[2] Obviously cancer cells do not grow in monolayers, rather they proliferate in complex 3-dimensional structures. Also ignore the fact that the cells were being fed a diet of beef serum and l-glutamine, a combination that would make a bodybuilder exuberant. Tanos' bottom-line was that soy plus tamoxifen looks good for treating ER+ breast cancer.

On the other hand, two other studies from 2002, one by Jones et al and the second by Ju et al, attempted to more closely model clinical use; and both studies suggest that genistein negates the inhibitory effects of tamoxifen. Genistein's effect on breast cancer growth is concentration dependent. Apparently genistein "inhibits breast cancer cell growth in vitro at doses of 10 microM or above. At lower doses genistein may stimulate

cell growth and entry into the cell cycle." Thus when Jones used low doses in his research, "…genistein was able to inhibit the therapeutic effects of tamoxifen in this postmenopausal model of breast cancer." That earlier study by Tanos used genistein in doses of (1-10 microg/ml) 3.7 to 37 microM.[3,4]

Ju et al reported that genistein 'negated tamoxifen's inhibitory effects on breast cancer.' This study moved up a rung on the evidence-based scheme of things because it used animal models, in this case ovariectomized athymic mice with implanted breast tumors. The mice were divided into six groups each dosed with their own combination of estrogen, tamoxifen, and genistein. Dietary genistein negated or overwhelmed the inhibitory effect of tamoxifen on breast cancer growth in this experiment. The mice given genistein received 1000 ppm. The authors suggested that, "… caution is warranted for postmenopausal women consuming dietary genistein while on…" tamoxifen therapy for ER+ breast cancer.[5]

Yet in 2007, Mai reported seemingly opposite results in the journal *Carcinogenesis*. Again, using a model to predict behavior in humans, they found that the combination of tamoxifen and various soy isolates 'synergistically delayed the growth" of breast cancer tumors leading to their suggestion that this might be a useful therapy.[6]

We should mention in passing that a 2008 paper reported that soy also negated the cancer inhibitory effect of letrozole on ER+ breast cancer cells in another animal study with implanted tumors.[7] As this study isn't about tamoxifen, we'll just include the reference and drop the matter.

Another athymic mouse study appeared in 2012, and in this case low-dose genistein again negated the therapeutic effect of tamoxifen in a mice model.

Tamoxifen significantly reduced the estrogen-induced breast cancer tumor prevalence and size. Yet this inhibitory effect was significantly negated by the low doses of dietary genistein (250 and 500 ppm), whereas the 1000 ppm genistein did not have the same effect. This rather begs us to translate what ppm genistein means in terms of soy food consumption as it seems we need to keep concentrations above a certain threshold to have benefit.[8]

More recent studies on soy have singled out specific isoflavones. In a 2016 study, Johnson et al., reported that glycone-rich soy extracts promoted ER+ breast cancer growth and that "daidzin-rich isoflavone extracts antagonized tamoxifen."[9]

Thus, looking just at in vitro and ex vivo studies, the answer to our question about soy and tamoxifen is a bit murky, though the preponderance of data suggests that low-dose soy may be a problem but that high-dose soy could be useful. Leave tamoxifen out of the equation if we must and simply wonder about soy and breast cancer recurrence for the time being. Where is the dividing line between low and high doses of soy and how might this translate into servings of tofu or soy-milk lattes?

It is when we bring people into the equation that all this gets harder to define. So far human epidemiologic studies have solidly supported soy consumption post breast cancer diagnosis and treatment. Two human studies published in 2009 standout because they strongly argue in support of soy and turned the tide of opinion.

The first, published in February 2009, analyzed data from the Life After Cancer Epidemiology study (LACE). The results made using soy seem like a brilliant idea. The LACE cohort is made up of 1,954 female breast cancer survivors, diagnosed during 1997-2000, who were prospectively followed for 6.31 years. Comprehensive questionnaires allowed detailed analysis of a range of lifestyle factors seeking an association with eventual outcome, in particular recurrence and mortality. The data suggest a significant reduction in risk is associated with using tamoxifen in combination with higher intakes of soy isoflavones: "Among postmenopausal women treated with tamoxifen, there was an approximately 60% reduction in breast cancer recurrence comparing the highest to the lowest daidzein intakes (>1,453 vs. <7.7 microg/day; HR, 0.48; 95% CI, 0.21-0.79, P = 0.008). Soy isoflavones consumed at levels comparable to those in Asian populations may reduce the risk of cancer recurrence in women receiving tamoxifen therapy and moreover, appears not to interfere with tamoxifen efficacy."[10]

An analysis of data from the Shanghai Breast Cancer Survival Study, another large, population cohort, this one comprised of 5,042 female breast cancer survivors in China, gives further support to the idea that soy is beneficial. These women were initially diagnosed between 2002 and 2006 and were followed through 2009. Soy intake, measured by either soy protein or soy isoflavone intake, was inversely associated with mortality and recurrence. The hazard ratio associated with the highest quartile of soy protein intake was 0.71 (95% confidence interval [CI], 0.54-0.92) for total mortality and 0.68 (95% CI, 0.54-0.87) for recurrence compared with the lowest quartile of intake. The four-year mortality rates were 10.3% and 7.4%, and the four-year recurrence rates were 11.2% and 8.0%, respectively, for women in the lowest and highest quartiles of soy protein intake. The inverse association was evident among women with either estrogen receptor-positive or -negative breast cancer and was present in both users and nonusers of tamoxifen. This would suggest that the benefit of soy is not related to its impact on estrogen receptor sites as we have thought all along.[11]

A secondary analysis of the Women's Healthy Eating and Living Cohort (WHEL) study published in 2011 yielded similar findings suggesting the soy and tamoxifen combination was better than fine. Recall the WHEL study was the prospective dietary intervention in which 3,088 breast cancer survivors diagnosed in the 1990s were enrolled, half of them encouraged to follow a low-fat diet exceedingly high in vegetables and fruit. Recall that after seven-plus years, there was no significant difference in prognosis between groups. In this re-analysis of the data the women were divided into groups based on soy isoflavone intake reported on dietary questionnaires. The highest intake was typical of Asian populations (6.3–86.9 mg/d).

There was no increase in risk of recurrence seen with increasing soy intake for menopausal status, tamoxifen use, or ER or PR status. Women with the highest intake of isoflavones (>16.3 mg/day) had a non-statistically significant decrease in all-cause mortality.[12]

Kang et al's 2010 study also failed to find any lurking risk in eating a lot of soy even with estrogen therapies in breast cancer patients. This study included 524 Chinese women all of who had

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surgery and had stage I-III disease. All received tamoxifen (438) or anastrozole (86). After a median follow up of 5.1 years, risk of recurrence or mortality was not associated with soy intake in premenopausal women. Postmenopausal women had a significantly lower risk of recurrence in the highest versus the lowest quintiles of isoflavone intake (HR: 0.67; 95% CI: 0.54–0.85; *P*= 0.02). Postmenopausal women on anastrozole had a significant reduction in the risk of recurrence in the highest versus the lowest quintiles [13]

These publications prompted many of my colleagues to reach the conclusion that the matter was settled. One well respected colleague, Michael Uzick, ND, of Tucson, Arizona, wrote me:

> Regarding soy and tamoxifen…. The research to date is quite clear, there should be no confusion. The in vitro and animal data, which used levels of genistein that cannot be achieved through diet, have been proven to be deceptive and erroneous. That's because these pre-clinical studies are contradicted by a massive amount of human research, of which Tina Kaczor ND nicely reviewed a few years ago.[14]
>
> Since then even more research confirms the same thing, women with breast cancer taking tamoxifen who consume the largest amounts of soy dramatically delay relapse and have significant improvements in survival compared with low or no soy diets. That's the end of the story until prospective interventional trials are conducted and actually show something different, which seems highly unlikely given the number and consistency of epidemiological studies, which currently exist.

I just hate it when someone tells me there is 'no confusion' when all I feel is confusion.

Sometimes it feels as if a mist has filled my brain and memories from the past fade faster than they should. The alternating swings in opinion about soy bring this to mind. Soy is good, then it's bad, but now it's good again. I drift back to an old memory, to a 1970s undergraduate classroom, a speaker who is listing the anti-nutritional factors found in soybeans. My recollection is that we had to memorize a full dozen for the eventual test on the lecture. Soy was popular back then for all of us vegetarians inspired by *Diet for a Small Planet*. A classmate of mine was hard at work trying to turn tofu into French brie. It was hard to believe that soy could contain 'anti-nutritional factors' when we were thinking it was a perfect food, a solution to the world's hunger problems.

Most websites, including Wiki, tell us that tofu was invented about 2,000 years ago during the Han dynasty in China based on kitchen images incised on a stone slab that purportedly show soymilk and tofu being made. A more reliable source dates the invention a millennium later: "Tofu is first mentioned in the early Song [10-11th centuries AD] Dynasty. It was imported into Japan and first appears there in about 1183. It was used as a substitute for meat and fish in the Buddhist vegetarian cooking."[15]

Whatever the actual date for tofu, soy milk, though a necessary step in tofu manufacture is hardly mentioned in the history of soy until the early 1900s and becomes popularized by vegetarian Seventh Day Adventist missionaries in China, in particular during the Japanese invasion of China, when it used as a milk substitute for infants.[16]

Dr. Uzick's assurances all seem well and good. This isn't the first time that life has left me confused, yet some bug in my head continues to gnaw and nag at me. Why are all those in vitro studies so at odds with the human studies, or is it the other way around? What are these levels of genistein when translated into dietary intake? I have yet to convert parts-per-million (ppm) into microMolar concentrations or Starbucks concoctions. And of course, there's the assumption that multivariate analysis of complex data gathered via questionnaires is actually accurate. So many things impact breast cancer recurrence, could there not be some confounder associated with soy consumption that has yet to be factored into the calculations? I don't know what exactly, but one could rightly guess that higher soy consumption is associated with higher education, greater wealth, lower smoking, more exercise, more expensive olive oil, and a long list of other lifestyle and dietary choices that individually and perhaps synergistically have an influence on breast cancer recurrence?

Our brains so deeply want clear black and white realities. We demand clear yes or no rules that will simplify our decisions. (It seems we expect science to deliver answers the same way a religion does and take the uncertainties out of living.) We want human data to supersede other data. Based on these human epidemiological studies, we seem content to ignore prior conflicting information found in vitro and ex vivo studies.

We want to say, "Soy is good for breast cancer." Period.

Yet epidemiologic studies are far from fool proof. In fact, attempts to derive clear conclusions from observed patterns of behavior, diet, and associations with disease in free-living human populations is fraught with hazards for error. Life by its very definition is complicated, and to think we can distill simple answers is laughably simple minded.

I recall a lecture by Frank Meyskens, MD, at Society for Integrative Oncology (SIO) conference in Vancouver, British Columbia, a few years back. Much of Meysken's research has been in cancer chemoprevention. He was involved in the Caret Trial that reported beta-carotene increased rather than lowered risk of lung cancer in smokers.[17-19] He also worked on the SELECT trials that found that vitamin E and selenium rather than prevent prostate cancer increased risk of getting it.[20,21] He was also involved in a 2013 trial that reported omega-3 fats were associated with an increased risk for prostate cancer.[22]

According to Meyskens, cancer clinical trials have a disturbingly poor track record in supporting theories predicted by epidemiologic studies. Meyskens coauthored a 2013 report that compared meta-analyses of randomized controlled trials with the epidemiological data that the RCTs were initially meant to confirm. In only 23 out of 34 associations were the findings in the same direction. In only six of those 23 associations, were the findings statistically significant. In the remaining 11 out of 34 associations, meta-analyses of epidemiological studies and of RCTs had summaries pointing in opposite directions. The association between epidemiological observations and RCTs were statistically significant in only 12 of 34 associations: six were in same direction and six in opposite direction of what

was predicted by the epidemiologic observations.[23] There is poor correlation of what we think will work to prevent cancer based on epidemiology and what is eventually actually proven to work.[24]

So why are we in such a rush to believe that soy is useful in preventing breast cancer recurrence based on epidemiologic studies? The odds that such predictions will prove accurate are low, based on past performances. We should learn something from these failures.

I am willing to suspend my doubts about soy because a number of newer in vitro studies point to mechanisms of action that may explain soy's anticancer effects that are independent of estrogen receptor actions. In fact if we look at Zhang et al's 2017 paper, this lack of estrogen receptor effect becomes quite apparent. This study looked at the association between dietary intake of isoflavones and all-cause mortality in women with breast cancer in the United States. The participants in this study (n=6,235) were limited to women living in North America, thus eliminating the confusion that prior studies have had trying to untangle the possible confounding effects of Chinese diet and lifestyles.

In comparing the women in the highest quartile of isoflavone consumption per day (≥1.5 mg per day) vs. the lowest (<0.3 mg) there was a 21% reduced mortality (hazard ratio [HR]: 0.79; P trend=0.01). Further analysis showed this reduction was only seen in women who had estrogen receptor negative (ER-) tumors (HR: 0.49; P trend=0.005). This would suggest that isoflavones are helpful but not for the reasons we had thought.[25]

In recent commentary, Tina Kaczor, ND, suggests that the discrepancy in animal studies and human outcomes with soy and breast cancer is due to basic differences in isoflavone metabolism; humans do it differently, that is they metabolize soy isoflavones in a manner quite different from rats:

> … humans metabolize (ie, conjugate) nearly all of the isoflavones, leaving <1.0% unconjugated genistein in circulation. Rodents are comparatively poor metabolizers, with unconjugated genistein reaching levels up to 150 times that of humans. Conjugated and unconjugated genistein are different molecules, with different biological effects.

Her conclusion is that rodents are poor models for testing how isoflavones affect human biology.[7,26]

Davis Lamson, ND, recently pointed out to me another possible mechanism of soy action. Soy protein fractions it turns out are potent matrix metalloproteinase (MMP) inhibitors.[27] MMPs are zinc-containing, protein-digesting enzymes that cancer cells use to dissolve the extra cellular matrix so that tumors can grow and invade surrounding tissues. If these enzymes are inhibited, the tumor cells are held in check.[28] Thus if soy acts as a MMP inhibitor, then soy's anti-cancer actions may have nothing to do with estrogen-like effects. This goes a long way toward explaining the reported benefits in ER-negative breast cancers we have mentioned.

Thus, with an excuse to ignore in vitro studies that are cautionary and an alternative mechanism of action to explain soy's anticancer effect, we have an excuse, or might we say are at liberty, to believe the current human studies.

Thus, we do have reason to believe that soy will be beneficial for breast cancer patients, including those taking tamoxifen but also for those that have or had ER negative tumors. We can believe this not because of the quoted human trials, but because of the combination of in vitro and ex vivo data that unravel the complexity of the biochemistry. Life is complicated, and we must be on our guard to resist the desire that could reduce the fullness of the experience to black and white rules.

These and other explanations derived in the laboratory give us confirmation that soy may indeed have anticancer action. Someday we will have data from prospective RCT trials that either confirm or dispute our current thinking. Until then we should continue to look at all the relevant research, seeking direction in the complex journey that is life.

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HYPERCOAGULATION

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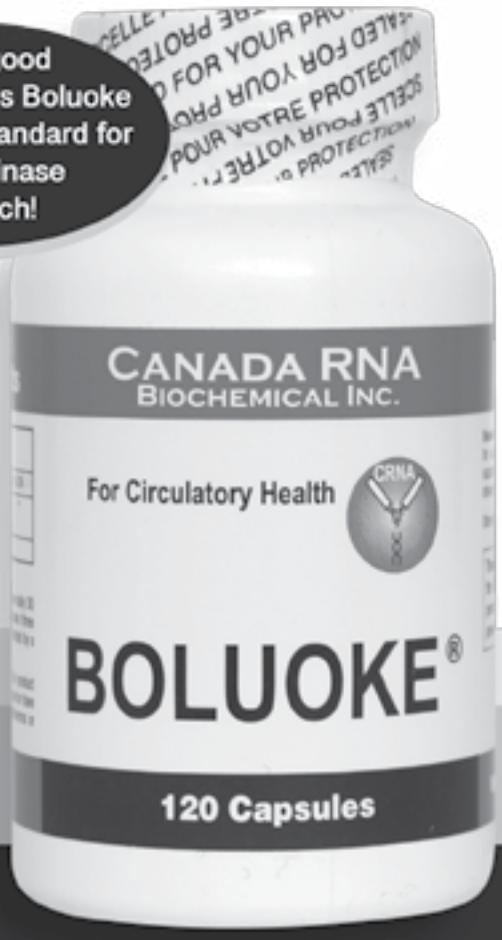

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the sun differ from those who do not, and those differences might influence a person's health. Moreover, if sun exposure per se is beneficial, the effect may not be due entirely (or even primarily) to vitamin D. Because of the limitations of observational studies, randomized controlled trials are needed to determine whether supplementing with enough vitamin D to achieve a purported optimal 25(OH)D level is beneficial or harmful.

In a 2014 paper, researchers reviewed 172 randomized intervention studies that examined the effect of vitamin D on non-skeletal health outcomes in adults. They found little or no evidence that vitamin D supplementation improved any of the non-skeletal health outcomes that had been examined in observational studies. Of note, among the 34 randomized controlled trials in which participants had a mean 25(OH)D level below 20 ng/ml at baseline, vitamin D supplementation was not more effective than placebo. Supplementation of elderly people with 800 IU per day did result in a slight decrease in all-cause mortality. The researchers concluded that the discrepancy between observational and intervention studies suggests that low 25(OH)D is a marker, rather than a cause, of ill health, particularly illnesses associated with inflammatory processes. They further concluded that in elderly people, correction of vitamin D deficiency resulting from aging and lifestyle changes induced by ill health could explain why low-dose supplementation led to a slight decrease in mortality.[3]

Fast-forward now to a couple of weeks before this editorial was written, when three studies that were damning to the vitamin D craze were published in such rapid succession as to invoke memories of the Saturday night massacre of the Richard Nixon presidency. In one of these studies, 25,871 US adults were randomly assigned to receive, in double-blind fashion, 2,000 IU per day of vitamin D or placebo for a median duration of 5.3 years (range, 3.8-6.1 years). Participants were required to limit the use of vitamin D from other supplements, including multivitamins, to 800 IU per day. The mean 25(OH)D level at baseline was 30.8 ng/ml; 12.7% of participants were below 20 ng/ml and 32.2% had a level of 20-30 ng/ml. Primary endpoints were invasive cancer of any type and major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes). Secondary endpoints included site-specific cancers, death from cancer, and additional cardiovascular events. Compared with placebo, vitamin D had no significant effect on any of the primary or secondary endpoints, or on all-cause mortality.[4]

The second study was a meta-analysis of 81 randomized controlled trials (including a total of 53,537 participants) that examined the effect of vitamin D on the incidence of fractures (42 trials), falls (37 trials), and bone mineral density (41 trials) in adults. In pooled analyses, vitamin D had no significant effect on the incidence of total fractures, hip fractures, or falls. Results were similar in trials of high-dose vs. low-dose vitamin D and in subgroup analyses of trials using more than 800 IU per day. Vitamin D supplementation also had no clinically relevant effect on bone mineral density at any site (lumbar spine, total hip, femoral neck, total body, or forearm). Further statistical analysis revealed "reliable evidence" that, if vitamin D does reduce the risk of fractures or falls, the effect is likely to be small (less than 5% relative risk reduction).[5]

In the third study, 132 postmenopausal women (mean age, 62 years) with a serum 25(OH)D level below 32 ng/ml (mean, 27.7 ng/ml) and no history of osteoporosis, hypercalcemia, hypercalciuria, or kidney stones were randomly assigned to receive, in double-blind fashion, 10,000 or 600 IU per day of supplemental vitamin D3 for one year. Analysis of the high-dose vitamin D capsules revealed that they actually provided 12,000 IU per day. (The excess potency was presumed to be due to recommendations by the United States Pharmacopoeia to provide 20% more vitamin D than stated on the label, in order to maintain shelf life.) All subjects received 600 mg of supplemental calcium twice a day. Participants were monitored for hypercalcemia and hypercalciuria at 3, 6, 9, and 12 months. If either of these abnormalities occurred, the dosage of calcium was cut in half. If the abnormality persisted at subsequent visits, the calcium supplement, and then three months later if necessary, the vitamin D supplement was discontinued. Fifty-two percent of women in the high-dose group and 29% of those in the low-dose group developed hypercalciuria at least once during the study. Eleven percent of the subjects in the high-dose group developed hypercalciuria that persisted for at least three months after the calcium and vitamin D supplements were discontinued. The proportion of women who developed hypercalcemia was nonsignificantly higher in the high-dose group than in the low-dose group (23% vs. 17%).[6] Proponents of high-dose vitamin D therapy claim that 10,000 IU per day is generally safe for long-term use. However, the present study demonstrated that hypercalciuria (a risk factor for kidney stones) occurs frequently at a dose slightly higher than that, and that the effect of this fat-soluble vitamin persists at least three months after treatment is discontinued.

There is no question that many people (such as the elderly, individuals who receive little or no sun exposure, and those who avoid vitamin D-fortified foods such as dairy products) could benefit from supplementing with vitamin D. Among people who are truly deficient, vitamin D supplementation probably does prevent falls and fractures and improve neuromuscular function. For most of those people, however (and I'm not talking about patients with malabsorption or certain other diseases), it seems that 800 IU per day would be sufficient to prevent problems related to vitamin D deficiency. Considering the repeatedly negative findings from randomized controlled trials (RCTs), the evidence from RCTs that high doses are not more effective than moderate doses,[2] the evidence that high-dose vitamin D may not be safe, and the likelihood that serum 25(OH)D is an unreliable indicator vitamin D status, it seems that we should abandon the idea that vitamin D should routinely be given in large doses, or that the dose should be titrated according to the results of lab tests. Supplementing empirically with moderate doses of vitamin D instead of ordering labs tests would save a lot of money and possibly prevent many kidney stones, and would be unlikely to have an adverse effect on the public health.

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More Bad News About Vitamin D

When I first began studying nutrition and orthomolecular medicine in the 1970s, vitamin D was not considered to be one of the nutrients with great therapeutic potential. While it was generally accepted that maintaining adequate sunlight exposure or adequate vitamin D intake was important for preventing rickets and osteomalacia and for promoting skeletal health, the idea that vitamin D could be useful for preventing and treating a wide array of non-skeletal conditions was not on anyone's radar screen. If people thought much about vitamin D back then, it was often about the possibility that even moderate vitamin D excess might increase the risk of developing atherosclerosis; an adverse effect had been reported in animal studies.[1] In the 1980s, many avant garde nutritional supplement companies limited the amount of vitamin D in their multivitamin products to 100-200 IU per day, because of concern that higher doses could cause problems.

In the ensuing years, the pendulum shifted 180 degrees, as some researchers and practitioners argued that there is an epidemic of vitamin D deficiency and that many people need relatively large doses of the vitamin to achieve "optimal" levels. Several factors contributed to this change of opinion. First, the reemergence in the 1990s of rickets among breastfed black children reminded us of the importance of vitamin D. Factors that predisposed these children to developing rickets included being breastfed (breast milk from black mothers tends to be particularly low in vitamin D) and living in an urban setting. The reemergence of rickets underscored the recommendation of the American Academy of Pediatrics that all breastfed infants receive 400 IU per day of supplemental vitamin D. Second, many laboratories changed the reference range for serum 25-hydroxyvitamin D (25[OH] D; the most commonly used indicator of vitamin D nutritional status). Whereas vitamin D deficiency had previously been defined as a level below 10 ng/ml or 15 ng/ml (depending on the assay method used), a level below 20 ng/ml was now considered to indicate a deficiency, and a level of 20-30 ng/ml was considered to indicate vitamin D "insufficiency" (a milder form of vitamin D deficiency). With the adoption of these new reference ranges, vitamin D deficiency went from being rather uncommon to being extremely common. Third, observational studies began to appear in which higher serum 25(OH)D levels were associated with a lower risk of developing a wide array of health conditions, including cardiovascular disease, serum lipid abnormalities, inflammation, diabetes, infectious diseases, mood disorders, and cognitive decline. Higher 25(OH)D levels were also associated with lower all-cause mortality. A protective association began at around 30 ng/ml and the best outcomes were seen at levels 36-40 ng/ml. Although observational studies do not prove causation, many researchers and practitioners leapt to the conclusion that we should be measuring everyone's 25(OH) D levels and supplementing with enough vitamin D to achieve a desired level.

In my lectures and writings over the past 10 years, I have repeatedly challenged many of the assumptions being made about vitamin D.[2] These challenges have been based on several points. First, serum 25(OH) D appears to be an unreliable indicator of vitamin D nutritional status unless a person has vitamin D toxicity or severe vitamin D deficiency. Second, the increase in the 25(OH)D laboratory reference range from its traditional 10-15 ng/ml was based on very weak evidence, and the new reference range may substantially overestimate the prevalence of vitamin D deficiency. Third, the idea that we should push serum 25(OH) D to a purported "optimal" level is also based on very weak evidence, and doing so may in some instances do more harm than good. And fourth, the safety of long-term use of high doses of vitamin D (such as more than 2,000 IU per day) has not been established.

It is beyond the scope of this editorial to review these points in detail, which have been discussed elsewhere.[2] I will mention, however, two of the reasons to suspect that the reported inverse associations between 25(OH)D levels and various diseases are spurious (i.e., they do not indicate causation). First, 25(OH)D levels decline in response to inflammation, and in people with one of the many chronic diseases that have an inflammatory component, serum 25(OH)D may not be a reliable indicator of vitamin D status. The association of higher 25(OH)D levels with a lower risk of many diseases might have nothing to do with vitamin D, and might simply mean that people with chronic inflammation are less healthy than people without chronic inflammation. Second, higher 25(OH)D levels in observational studies resulted mainly from sunlight exposure. People who spend time in

continued on page 95 ➤

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