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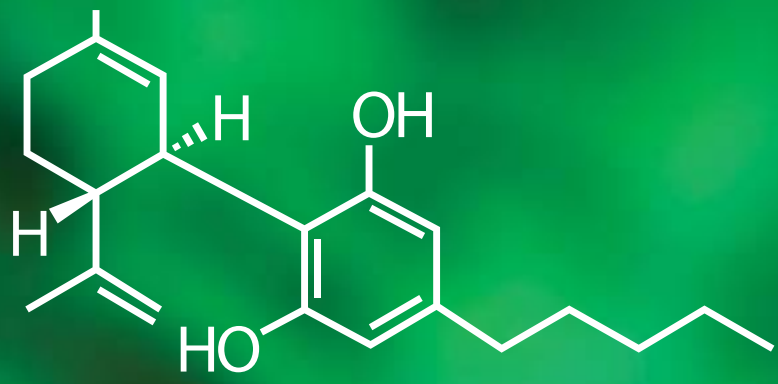

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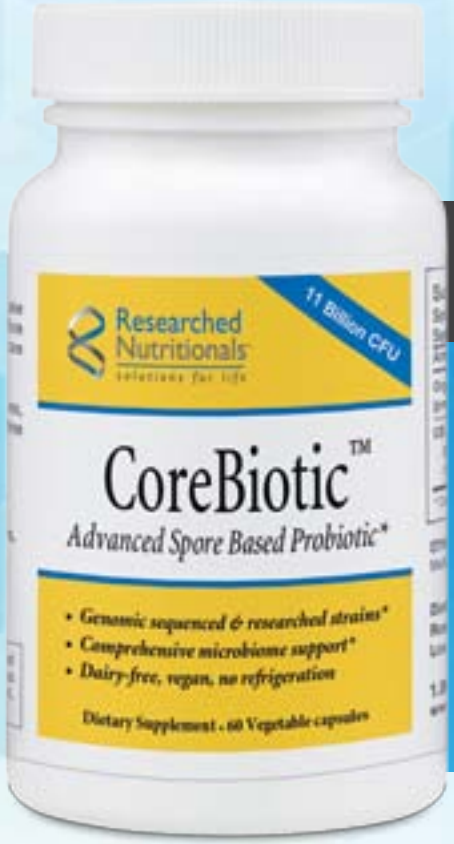

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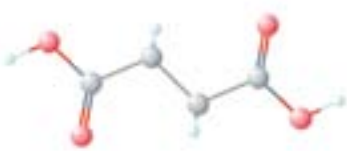

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From the Publisher

Dr. Joseph Pizzorno's *The Toxin Solution*

When I first started practicing integrative and functional medicine, we referred to it as alternative and holistic medicine. My introduction to this medical practice was riddled with controversy. There was chelation therapy, intravenous injections of vitamins and minerals, electroacupuncture, homeopathic medicine, herbal therapies, proprietary glandular supplements, environmental medicine desensitization, cancer vaccines and other unapproved therapies, colonic enemas, and more. From a diagnostic standpoint, we had hair analysis evaluation of trace and toxic elements, dark field microscopy, EAV and energetic diagnosis, kinesiology muscle testing, thermography, plethysmography, blood food allergy screening, and unproven cancer blood screening.

In the clinic in which I had been working, the hair analysis study of toxic elements brought us the greatest controversy with the medical board. We brought on board the great minds in

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nutritional medicine to defend why hair analysis offered a valid diagnosis of toxic metal burden. Concurrently, there was a number of skeptics, "quackbusters," who argued that hair analysis offered no acceptable understanding of toxic metal body burden. When we did do serum studies of toxic elements, there was generally little confirmation of the toxic element analysis. Moreover, toxic element studies performed on the same hair sample did not provide matching results in different labs; in fact, split specimens sent to the same lab sometimes provided contradictory results. This made an understanding of toxic element burden in patients difficult to accomplish. Practitioners developed their own "algorithms" (they didn't use that term) to understand hair analysis and make diagnoses. Still, despite the controversy, we were convinced that many if not most patients carried a toxic element burden and a chemical burden, even if these could not be diagnosed with 100% confidence. Moreover, we recognized that detoxification of toxic elements and chemicals was critical if we were to restore a patient's health. Despite its controversy, chelation was the right choice to unload toxic metals while sauna sweating was appropriate to excrete petrochemicals, pesticides, plasticizers, drugs, and other chemicals.

Several decades after my introduction to integrative medicine, detoxification or "detox" has become a process that is accepted as a regular health strategy by the general public. Detox kits offer herbals and absorptive clays to cleanse the digestive tract. Oral and intravenous chelation and infrared sauna use have become widely available. Herbal therapies are widely used in supplementation programs. But the rationale for why these treatments work has not been readily forthcoming. Despite the growing recognition that we are accumulating toxic chemicals and metals, medicine has largely ignored the problem, opting to only address the problem when poisoning is diagnosed. Dr. Joseph Pizzorno addresses "how hidden poisons in the air, water, food, and products we use are destroying our health – and what we can do to fix it." Pizzorno is co-author of *The Encyclopedia of Natural Medicine* and *The Textbook of Natural Medicine.* He founded and served as president of Bastyr University for 22 years. Pizzorno is the editor-in-chief of *Integrative Medicine A Clinician's Journal* and serves on the board of the Institute for Functional Medicine. In 2017 he authored *The Toxic Solution: An Eight-Week Program to Detox Your Life.*

Pizzorno's program offers a four-part program to detoxify over the course of two months; his program is backed by peer-review studies and is evidence-based. In the theory section, Pizzorno shows that there is a close correlation between the industrial production of chemicals and clinical prevalence of diabetes and metabolic syndrome. While we generally think that chemical and metal toxicity is associated with industrial, agricultural, and mining work, Pizzorno argues that these toxins are accumulating in individuals involved with office work and household activities. Toxic burden does not require a point source of major chemical exposure, although this would be a critical area requiring detoxification and elimination of ongoing exposure. Instead, toxic burden builds up slowly, accumulating with household and office use of cleaning products, pesticides, and plastic food and water containers. Additionally, the widespread use of hair and beauty products is contributory in chemical burden. The consumption of non-organic, GMO foods, that are processed, sugary, and loaded with trans fats, also burden one with chemicals and metals.

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From the Publisher

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Pizzorno's program is not for those who are addicted to their junk foods, hair products, and chemical cleansers. Nor is it appropriate for those who are unwilling to commit to the work of detoxification. The first phase of the program requires a two-week elimination of offending foods with an elimination of processed foods, gluten-containing foods, dairy products, beef and chicken, farmed fish, non-organic fruits and vegetables, soy, refined sweeteners, alcohol and recreational drugs, salt, and city/tap water. What does that leave to eat? Well, organic fruits, vegetables, beans, ocean fish, and gluten-free grains. Pizzorno offers a two-week menu with five meals per day, but it does take some preparation to cook these foods. Accompanying this restricted diet, Pizzorno wants one to give up using chemicals in the household and limit chemicals in hair-and-beauty-products. He offers patient-friendly programs to determine what chemical products are being used and what needs to be eliminated.

The second phase of the program focuses on "cleaning up the gut." The five steps require that 1) the bad bacteria in the gut are killed; 2) toxic chemicals released by the bacteria are bound; 3) good bacteria reseed the gut; 4) the gut is repaired; and 5) gut damage thereafter is avoided. For killing the bacteria, Pizzorno recommends the use of fiber, goldenseal root powder, and garlic supplementation. Repairing the gut requires probiotic, fresh cabbage juice, and quercetin. The third phase of the program "restores the liver," while the fourth phase "revives the kidney." Pizzorno states that the dietary and herbal detox for the kidney reduces kidney function abnormality. Although he offers some cases of individuals who normalized kidney functioning following the detox, there was no controlled study confirming the protocol's efficacy. The final phase of the detox employs the sauna but not chelation; Pizzorno cautions individuals not to do aggressive detox techniques before the initial phases of dietary modification, gut clean-up, liver detox, and kidney detox are completed.

The Toxin Solution is a systematic approach to detoxification that is well-documented and spelled out in detail. The book is easy to read for the patient and an excellent guide for the practitioner. When the patient is looking to do a detox program, Pizzorno's book is an important educational tool. Pizzorno makes the case that elimination of toxic chemical exposures and dietary modification must be undertaken before any detox program. The strategy of cleaning up the gut, and then detoxifying the liver, and then the kidneys makes sense. There is no reason to detox if the systems needed for detoxification are incapacitated and dysfunctional.

Shade and Decker on a "Push-Catch" System that Enables Effective Detoxification

Pizzorno's *Toxin Solution* book offers an overview of the problem with toxicity and a do-it-yourself detox program for the patient to undertake at home. Christopher Shade, PhD, and Carrie Decker, ND, examine the physiology of detoxification in this issue of the *Townsend Letter*. Pizzorno's premise that one needs to detoxify the gut, liver, and kidney makes sense, but what mechanisms are involved in these organ systems? Shade and Decker note that we generally talk about two states of detoxification: Phase

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From the Publisher

➤ *continued from page 10*

I is involved with biochemically metabolizing the toxins through the cytochrome P450 enzyme system. Phase II "conjugates" the toxin metabolites forming water-soluble chemicals. However, we often fail to discuss Phase III of detoxification concerned with the transport and elimination of these metabolites and chemicals though cell membranes. While there are important limiting steps in Phase I and Phase II aspects of detoxification, it is often Phase III where detoxification becomes severely impaired if not incapacitated.

Shade and Decker examine closely the proteins that are critical in Phase III detoxification. When these proteins are impaired, the ability to detoxify mold toxins, such as Ochratoxin A, a mycotoxin commonly found in food and water, is impaired and its accumulation shuts down Phase III detoxification. Endotoxins from gut bacteria enter the system because of leaky gut syndrome and further inhibit Phase III detoxification. Additionally, endotoxins contribute to the stasis of bile, inhibiting the transport of conjugated toxin metabolites from the liver into the intestines for elimination. Indeed, cholestasis may be the major factor why toxins are not effectively detoxified while also damaging kidney functioning. Shade and Deck refer to cholestasis as toxistasis.

How do we experience cholestasis/toxistasis? We recognize the right upper quadrant abdominal pain or epigastric tenderness. Pruritus and stool changes are not uncommon. Lab testing not infrequently reveals abnormalities in AST, ALT, and GGTP. What can be done to enable liver detoxification. Shade and Decker offer a "push-catch" strategy to enhance liver detox. The "push" part refers to employing nutraceuticals to support Phase I,II, and III detoxification as well as stimulating bile flow. The "catch" part is done 30 minutes (!) later with toxin binders sequestering the toxin metabolites before they are able to reenter the body from the gut.

How this is accomplished is for you to read about in this issue.

What's New in Women's Health?

In addition to detoxification, this issue focuses on women's health. One of the surprising medical reports in 2017 was a large population study of women using birth control pills in Denmark. The December 6th study, published in the *NEJM* and written by lead author Lina S. Morch, found that the use of birth control pills (BCP) had a small but significant increase in the incidence of breast cancer.[1] The researchers examined national prescription and cancer registries of 1.8 million females in Denmark following them for more than one decade. Compared to women who have never used birth control pills, users experienced a 20% increased risk of developing breast cancer. Like most adult cancers, breast cancer incidence increases with increasing age. Statistically, it is estimated that for 100,000 women, birth control pill users experienced 13 additional cases of breast cancer compared to non-users; among contraceptive users there were 68 cases of breast cancer annually compared to 55 cases in non-users. The study did not find protective benefit from lower dose birth control pills; furthermore, the use of IUD delivery system of hormone did not reduce risk. On a positive note, the use of BCP decreased the risk of ovarian and endometrial cancer. The study did find there is a corresponding increase in risk in women above age 40 who used contraceptives as a younger adult. Also of note, progestins, synthetic progesterone compounds, also yield an increased risk of developing breast cancer.

The US Preventive Services Task Force published a recommendation statement for the use of hormone therapy for the primary prevention of chronic conditions in postmenopausal women in *JAMA* on December 12, 2017.[2] Although the task force did find 18 studies considered to be of fair-good quality, the Women's Health Initiative was the only study considered to be large enough to adequately assess the effectiveness of hormone therapy for primary prevention of chronic conditions. Unfortunately, the WHI based its results on women using Premarin/Provera (equine estrogen/progestin) combined or Premarin alone (equine estrogen). As expected, the task force found very limited benefit in prevention of fracture, diabetes, colorectal cancer but no benefit for prevention of breast cancer, pulmonary embolism, stroke, cognitive impairment, gall bladder disease, urinary incontinence, and all-cause mortality. The US Preventive Services Task Force concluded that there is no justification for the use of estrogen/progestin or estrogen alone treatment as a primary prevention for chronic conditions. Of course, the task force did not assess the use of bio-identical estrogen or progesterone.

Corina Dunlap, ND, on PCOS in Disguise

Think you know all you need to know about PCOS? Not so fast. Yes, our antennae come up when we see a woman who is not ovulating and shows evidence of excess testosterone. But what about a lean individual who is anovulatory with low testosterone? Indeed, such an individual may have PCOS. Another scenario that is frequently seen is the individual who has quit using birth control pills and does not resume normal menstrual cycles. If this woman is not ovulating, she may very well have PCOS, even though she is not showing evidence of hyperandrogenism. In this issue, Dr. Corina Dunlap discusses these variations of PCOS.

Bonnie Nedrow, ND, on Endocrine Disruptors: Our Cover Story

Much of this publisher letter has been devoted to our exposure and accumulation of toxins and how we should go about detoxifying. One of the unfortunate consequences of elevated toxins is male and female infertility. In this issue, Bonnie Nedrow, ND, focuses on infertility in the woman and why metal and chemical toxins play an outsized role in its cause. The reason that toxins are so problematic with fertility is that they mimic hormones and activate hormone receptor sites. This activity leads to endocrine disruption, a definite interference in successful reproduction.

Discovering the sources of toxin exposure and eliminating those exposures is fundamental to the detoxification process. As discussed earlier removing the chemicals, "depuration," is key to undertaking detoxification and vital to removing the endocrine disruption inhibiting a successful pregnancy.

Jonathan Collin, MD

1. Morch SL, et al. Contemporary hormonal contraception and the risk of breast cancer. *NEJM.* 2017; 377: 2228-2239.
2. US Preventive Services Task Force. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women. *JAMA*. 2017; 318 (22): 2224-2233.

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New Mexico Integrative Practitioners Dodge a Bullet

(with Shirley MacLaine's help)

But There's Still Work to Be Done

Awhile back, I reported that the New Mexico Medical Board was going after a prominent integrative medical practitioner because she was prescribing and selling herbal protocols as primary therapy for the treatment of various environmentally caused neurological conditions, supposedly in violation of the AMA ethical guidelines. (Published in *Townsend Letter*, December 2017 and at http://rickjaffeesq.com/2017/03/22/can-cam-docs-legally-prescribe-and-sell-herbals-and-nutritional-supplements-as-therapy-without-bad-things-happening-prescribe-yes-sell-well-see/)

New Mexico is one of a handful of states that incorporates the AMA's ethical guidelines as rules of practice, the violation of which are disciplinable offenses. Ironically, the AMA never intended its ethical precepts to be used as practice guidelines to discipline doctors. How do I know this? Easy, after each general ethical precept, the AMA places the following cautionary language: "The Opinions in this chapter are offered as ethics guidance for physicians and are not intended to establish standards of clinical practice or rules of law." So why have some states like New Mexico decided to disregard the very limitations placed on these precepts by the AMA? Good question.

Shirley MacLaine, Bill Wolfe, DDS, Rick Jaffe, and Pamela Costello, MD

Ethical precept 9.6.4 puts severe restrictions on the sale and even the use of nutritional supplements. The effect of the rule is to make it basically AMA unethical and New Mexico disciplinable for a physician to sell supplements out of his/her office or via a web site. Previously, when the New Mexico Medical Board found out about a physician's sale of supplements via a Board complaint, the doc has been forced to stop, which apparently prompted a few to quit the state.

I got involved after the case was presented to a panel of the Board to see if there was a violation. Based on the AMA "guideline," the panel gave the doctor the same ultimatum as it had to other docs: stop selling supplements or face formal charges. That didn't make sense to me for a few reasons, not the least of which was that she wasn't just selling supplements for general health or immune purposes. Rather, she was using natural remedies as primary therapy, which because of training requirement set by the manufacturer, the products were only sold to company-trained practitioners for dispensing to their patients.

The AMA seems to cover this type of practice in precept 9.6.6 which allows the sale of drugs, devices and "other treatments." That seemed like a better fit and it didn't have all the anti-supplement nonsense contained in 9.6.4. So, after I came into the case, we asked the prosecutor to re-present the case to the board panel. Because the Board's statute of limitation to file the case was fast approaching, we suggested we would be agreeable to waive the limitation period in the hopes he would ask the panel to change its mind based on this new information.

And then a funny thing happened…. Actually, nothing happened. We didn't hear back from the prosecutor for over a month. We had expected to receive a formal waiver of the statute of limitations, to be signed by the doctor, and we would have advised her to sign it. The proposed settlement had contained such a waiver, and we expected to get a proposed written waiver. But we never got it. Instead, over a month later, we got basically the same settlement agreement with the same prohibition against the sale of supplements, and the same waiver of the statute of limitations as in the original settlement proposal, but this second settlement proposal was over a month after the statute of limitations had expired. Hmmm.

I decided to take another run at the prosecutor to change his mind about the case. I gave him case studies showing the miraculous results achieved by the doctor on non-functioning patients who tried and failed many conventional modalities. We also showed him that almost all New Mexico integrative practitioners were selling supplements for general health, in direct violation of the AMA rules. I even showed him that the University of New Mexico's Integrative Medicine Clinic was selling supplements to patients, and the University was teaching medical students about the use of herbal remedies.

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NM Integrative Practitioners Dodge a Bullet

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This case against the doctor arose because her office staff did not timely respond to the patient's request for medical records. So, I had the doctor take a medical records-keeping course (which the board requested in the two settlement proposals) and offered that she would accept responsibility for the oversight, as a full settlement of the case.

But the prosecutor was a tough guy and insisted that she comply with the AMA supplement guideline, the way the other doctors faced with board action had done. As incentive (read threat), after he sent the first settlement proposal, he said that if she didn't take the deal, he'd go after her license. When he finally filed the case, he made good on his threat by throwing in a charge of incompetence for using herbal remedies, which could result in license revocation.

Despite all my efforts at persuasion, I couldn't get him to back-off. I started to think about an appropriate time to file a motion to dismiss based on his failure to timely file the case. Filing the motion wouldn't make dealing with him or the Board any easier. But frankly, I was tired of all his crap about supplements and how he was going to take out my client for being a supplement distributor.

Maybe I was waiting for a sign, and I got it. On a routine email exchange on a Monday, he announced that he was leaving the Board on Friday and going into private practice. That was good enough for me. The following Monday I filed a short motion to dismiss based on the fact that the complaint (called a "Notice of Contemplated Action" in New Mexico) was filed more than two years after the Board had notice of the patient complaint, which makes the case dismissible under New Mexico law. I'd let the new prosecutor figure out how to deal with the fact that his predecessor never presented us with a written waiver of the statute of limitations even though we offered to enter into such an agreement.

Turns out the Board didn't have a replacement for him, so he ended up responding to our motion. Awkward! I didn't think much of his responding papers.

The motion was to be heard by the full Board. I figured they wouldn't be too fond of me or my client for trying to dismiss a case on a technicality, based on its mission to protect the public and considering the fact I did offer to enter into a waiver of the statute of limitations. I also didn't think I had much of a chance to have the Board make a public finding that its own prosecutor screwed the pooch. Hmm. What to do?

I have a saying or rule which I try to follow: You have to give a board/judge the will and the way to rule for you. But even though my motion was legally correct, I had given the Board neither. After more thought, I figured it out. I filed another motion to dismiss in the interests of justice, and argued that the supplement issue was a matter of great public interest that was better addressed in a rule-making rather than a disciplinary process, in part because all integrative practitioners, including the University of New Mexico's own clinic were already selling supplements. I also showed the Board the doctor's truly impressive case studies. My goal was to go to the hearing and immediately pivot to the interest of justice motion, so as not to have to deal with the unpleasantness of the Board's own prosecutor's screw-up. It was a good plan, but it was not to be.

Things got really interesting right before the hearing. The prosecutor recused himself from the case because he was going to have to be a witness explaining why he didn't obtain a written wavier of the statute of limitations from the doctor. (The irony was that Mr. Tough Prosecutor charged the doctor with incompetence, and yet he was the one going before the Board testifying about his conduct and competence. Who says the universe doesn't have a sense of humor and karma?)

The other super interesting thing was that one of the patients whom the doctor was dramatically helping is Shirley MacLaine. She lives part-time in New Mexico. As luck would have it, she was going to be in town on the day of the hearing. I insisted that the doctor contact her and try to have Shirley come to the hearing. It was going to be a very tough day with personal attacks directed my way, so some star power wouldn't hurt. More metaphysically, based on her life and books, she seemed to be a very powerful force, (as in "the force is strong with that one"), and I really needed all the help on that front/dimension I could get.

We all showed-up at the hearing. My plan to pivot to the interest of justice motion failed. The Board insisted on focusing on the statute of limitations motion, despite my repeated efforts to talk about how the public would be better served by the Board considering the supplement issue in a rulemaking capacity and to dismiss the case to allow that process to take place.

As expected, as I argued that the prosecutor missed the deadline under the law, he as a witness and some of the Board members went after me, questioning my professionalism honesty and integrity. But zealous advocacy is the job, and taking some incoming is sometimes a part of it.

We went at it for over an hour and a half. The former prosecutor testified in effect that I was a sleaze ball, and me arguing that he didn't do the one thing he had to do, get a written waiver, while imploring the Board we should really be talking about creating a public forum for input on the supplement issue.

For over an hour I got nowhere, or so it seemed, but then one Board member asked me a question which suggested that the former prosecutor should have gotten a written waiver, and I ran with it. Then the chairman of the Board asked me how important a right it was for someone to have statute of limitation protection, and how would that right best be protected. Terrific question! From then it was all downhill. Some of the other members started asking similar questions, then the Board said they heard enough and excused us to go into executive session.

We waited almost half an hour. In the lobby, some Board employees came out from their offices to meet Shirley. She

was gracious and engaging. We both chatted-up the new prosecutor, whom I'd be dealing with if the Board denied our motion. Shirley was apparently fascinated by the proceeding. She had never been to a board hearing or seen the kind of legal back and forth. She told the prosecutor she was going to do a feature film about the case, and asked the prosecutor – a fit and attractive woman of Hispanic decent, who she wanted to play her in the movie. The prosecutor loved it. They had a lengthy discussion about different actresses, and they decided that Jennifer Lopez would be offered the part. We had a great time waiting, laughing so loud at times that the Board members inside must have wondered what was going on.

Finally, we were called back into the room. The chairman announced that they were going to vote on two motions. Ok, I had only argued one, but I had put in strong papers on my interest of justice motion. The first motion was the limitations motion. One-by-one they voted. We lost that vote by a wide margin.

Then the chairman called a vote on a motion to terminate the proceedings against the doctor. No interests of justice, no nothing, just a motion to end the case. We won that motion by a wide margin. And so, the case against the doctor ended. It took a while for it to sink in. We thanked the Board profusely.

You know the saying "when you make the sale, sit down." Well I don't subscribe to it. I wasn't done. I told the Board members that I hoped they would consider the physician sale of supplements issue because integrative physicians and the people of New Mexico deserved to have input. In response, the Board chairman told us that the Board had decided to address the issue at an upcoming meeting; and, he invited me to return and make a presentation to the Board. I immediately accepted.

Finally, I told the Board members that I was giving them all homework. They had to decide who they wanted to play them in the movie. Everyone got a good laugh, and I'm sure they left the meeting amused and had a good story to tell their families.

I'm hoping to enlist some of the American College of Nutrition luminaries and other of my high-profile integrative physician friends to take a trip to Santa Fe and help make the case for rescinding that idiotic AMA "guideline." Any takers?

And finally, the one burning question which I'm sure is on everyone's mind:

Who's going to play me? George, Brad, or Ben.

Happy Independence Day to you, Dr. Pamela Costello, holistic neurologist extraordinaire, and thank you, Shirley MacLaine.

Richard Jaffe, Esq.
rickjaffeesquire@gmail.com

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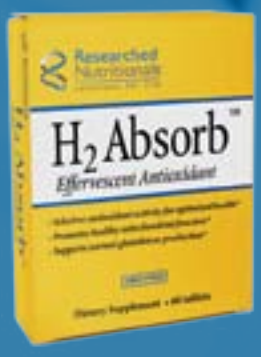

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IN THIS ISSUE February/March 2018 | #415/416

ON THE COVER: Bonnie Nedrow, ND Infertility and Environmental Chemicals (pg. 48); Vaginal Health and Microbiota (pg. 31); Cholestasis and the Three Phases of Detoxification (pg. 22); Treating the Many Symptoms of Cortisol Deficiency (pg. 60); Estrogen and the Gut (pg. 51)

International College of Integrative Medicine Conference

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Resource people – Jeffrey Dach, MD; Karen von Merveldt-Guevara, MD; Phyllis Bronson, PhD; Hal Blatman, MD; Barrie Tan, PhD; Lou Diorio, RPh; Dan Nelson, MD; Elizabeth Vaughan, MD; and Bryan J. Treacy, MD – are on the agenda to present evidence about what works for hormone balance, manual medicine, controversies in nutritional supplementation, office compounding, and opioid addiction recovery.

Plus, we'll hear updates on ozone with Frank Shallenburger, MD; cord blood live cell therapies with A.J Farshchian, MD; and an exciting lecture from Joel E. Mortensen, MD, Director of Diagnostic Infectious Diseases Testing Laboratory, at the Cincinnati Children's Hospital Medical Center. ◆

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Lead in workshops:

Robban Sica MD
IV Therapy for First-Timers

Karen von Merveldt-Guevara MD
Radical New Treatment Options: Routine Lab Panels Cross-Referenced with Hair Analysis

Ellie Campbell DO and Natalie Patierno
Revolution Practice Management

A.J Farshchian MD
What's New in Cord Blood Live Cells

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Integrative Medicine for Mental Health (IMMH) Conference 2017

Ira L. Goodman, MD, FACS, ABIHM, FAARM

I had the pleasure of attending the Integrative Medicine for Mental Health (IMMH) annual conference recently. I have been to two of them in the past few years. There are about 400 attendees and it occurs over a four-day period. The philosophy of the group is that mental health, just as physical health, deserves a holistic approach involving multiple organ systems, physiology, nutrition, hormones, detoxification, and biochemistry. The unfortunate truth is that the brain is fully integrated into the rest of the body, which is a fact that conventional psychiatry has apparently missed with their simplistic reductionist approach: the idea that all you need to do to treat depression is an "anti-depressant" or all you need to treat anxiety is an anxiolytic, or all you need to treat psychosis is an anti-psychotic pill. A pill for every ill. Could it get any simpler? As Einstein said: "Everything should be made as simple as possible but not simpler." Conventional psychiatry has made these problems way too simple and they have achieved the expected results, which for the most part are horrible.

L to R:
Kat Toups, MD, Integrative Psychiatry
Felice Gersh MD, Integrative OBGYN
Ira Goodman MD, Integrative Ophthalmologist

Any objective look into the effects of psychotropic drugs used long term shows the same thing - a worsening of symptoms and quality of life. Not good news for the quick fix mentality of our population. Robert Whitaker's book, *Anatomy of an Epidemic* shows how psychotropic drugs re-set the receptor sensitivity and density of whatever neurotransmitter is being targeted, so either a lifetime dependence on these drugs results or increased susceptibility to the same symptom occurs if the drugs are withdrawn (which is almost impossible to do). Schizophrenia was usually a one-time event treated with hospitalization or frontal lobotomy (as horrible as that sounds and was) before the advent of thorazine. Once the easy fix was in with the dopamine blocker, thorazine, the natural history of schizophrenia was changed from being 95% a one-time event to being 95% a lifelong recurrent process requiring anti-psychotics. It's the receptors. Irving Kirsh in his book, *The Emperor's New Drugs* proves without a doubt that psychotropic drugs perform no better than placebos in most cases. There are many other writers who agree. Of course, they can't stand up to Big Pharma and their control of the medical schools, journals, advertising, and lobbying.

Eventually, however, the public and some courageous physicians see that we are losing the war against mental illness and many of the battles, so an alternative approach has evolved. This is what the IMMH Conference is about. There were lectures on detoxification, diet, exercise, organic acids, a multi-modal approach to Alzheimer's and dementia, sauna, infectious diseases, etc. There is no question that this approach consumes a lot of time, money, and energy; but there is one difference between it and the conventional approach. It works. Small detail.

Dr. William Shaw from The Great Plains Laboratory gave several talks as did Dr. James Greenblatt, Dr. Dale Bredesen, Dr. Felice Gersh, and many others. There are people thinking about this deeply, which is a refreshing change from the pill pushers. Dr. Bredesen's new book, *The End of Alzheimer's* seems to be getting some traction. I fear the level of care required will be too high for most people to understand or comply with; but for the motivated few, it will work if applied early enough. It's a basic functional medicine approach for the most part, but there are some specific nuances taught at this conference as well. I have to acknowledge the practitioners who have patients willing to try regimens like this and the patience to explain them, follow them, and study the results. It's truly groundbreaking. The good thing though is that this approach will have side benefits instead of side effects, which could include cancer prevention, cardiovascular disease prevention, and longevity. I truly hope the IMMH Conference can become more mainstream and increase its popularity among the front-line mental health practitioners.

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A Push-Catch System That Enables Effective Detoxification

by Christopher Shade, PhD, and Carrie Decker, ND

The human body is exposed to environmental toxins every day from a wide array of sources: particulate matter and diesel fumes in the air,[1,2] heavy metals and other contaminants in the water,[3,4] pesticide and herbicide residues found on foods,[5,6] and even substances like bisphenol A (BPA) via contact with the skin.[7] On a continuous basis, the body must work to eliminate toxic substances that are taken in. If intake exceeds removal, the toxins accumulate within the tissues and cells. These toxins tax our antioxidant systems, which must be upregulated in attempts to reduce cellular damage and death.[8] But even with upregulation, the antioxidant protection system is often depleted by repeated insults and toxin exposure, and this depletion may contribute to disease processes.[9] Chronic exposure to environmental toxins and toxic heavy metals is associated with the development of many types of cancer, respiratory disease, cardiovascular disease, diabetes, infertility, allergies, autoimmune disease, and many other conditions.[10,11,12,13]

Detoxification is the process by which the body eliminates substances that are both endogenous (such as hormones) and exogenous (such as medications, pollutants, metals, and other substances). In addition to cleaning up the diet and eliminating sources of toxicity, the use of chelating substances, antioxidant support, and therapeutic sweating are often the mainstays of detoxification protocols. However, these basic strategies, despite being crucial, lack consideration for other factors such as chronic infections, cholestasis, and enterohepatic recirculation of toxic substances that significantly impair the body's ability to detoxify. To comprehensively support detoxification, one must consider and address not only the glutathione system and its enzymes; liver, kidney, and gastrointestinal function; but also infections or dysbiosis, cholestasis, and the removal of toxins from circulation.

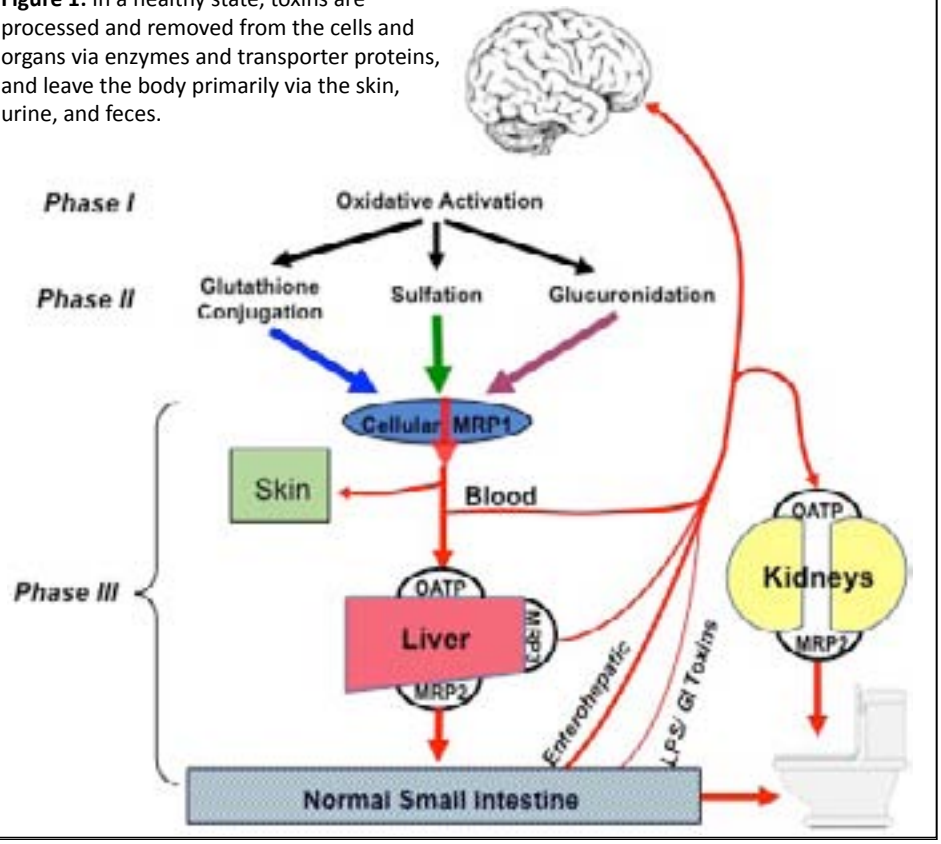
Stages of Detoxification

The process of detoxification consists of three phases, although many people are only familiar with the first two of these. Phase I reactions involve the oxidation, reduction and hydrolysis of substances via enzymes from the cytochrome P450 (CYP450) family.[14] It is Phase I metabolism that converts many drugs into their active compounds, and converts some chemicals into more toxic metabolites. Phase II metabolism involves the conjugation of toxins, creating larger, inactive, water-soluble molecules. Phase II reactions include sulfation, glucuronidation, and glutathione conjugation (see Figure 1).[15]

Phase III is often neglected in discussions of detoxification. However, it is critical. Phase III involves the process of transport and elimination of toxic substances through cellular membranes. The primary proteins that play a role in Phase III are multidrug resistance protein (MRP) 1, 2, 3, and 4, organic anion transport proteins (OATP), and P-glycoprotein (P-gp).[16] These proteins also regulate the movement of molecules through barrier tissues, such as the blood-brain barrier.[17]

The work horses for detoxification are 1) MRP1, the transmembrane transporter serving most cells in the body for exporting toxins to circulation, 2) OATP, the basolateral membrane transporter which moves toxin conjugates from the

Figure 1: In a healthy state, toxins are processed and removed from the cells and organs via enzymes and transporter proteins, and leave the body primarily via the skin, urine, and feces.



blood into the hepatocytes or renal tubule epithelial cells, and 3) MRP2, the apical transporter that moves toxin conjugates (and some bile salts) into the bile canaliculus or renal proximal tubule lumen. MRP3 and MRP4 are basolateral transporters that move toxin conjugates and bile salts from hepatocytes into the blood. All of the enzymes and transporters required for detoxification are present at a basal level, but many have increased expression in a coordinated fashion when stimulated by drug or toxin exposure.[18,19]

Although the process of detoxification occurs in every cell of the body, the liver, kidneys, and intestines are primary tissues in which higher levels of detoxification occur.[20] Many are familiar with the importance of the liver and kidneys as organs of detoxification, yet neglect awareness of the role of the intestines, the mucosal lining of which expresses high levels of the proteins important for all phases of detoxification.[21,22] When any of these systems are impaired, a backup in processing of toxins will occur, with a greater burden being placed on other organs.

Nrf2: The Cellular Detoxification On-Switch

Nrf2 (short for nuclear factor E2-related factor) is a cellular switch that orchestrates antioxidant, detoxification, and cellular defenses. Nrf2 is present in the cytosol of the cell (see Figure 2), and responds to oxidative stress by translocating to the nucleus and binding to the promoter region of genes that encode the transcription of critical components of detoxification known as the antioxidant response element (ARE).[23] In addition to elevated levels of reactive oxygen species (ROS), the Nrf2/ARE pathway is activated by a reduced cellular antioxidant capacity, and by exposure to toxic substances like air pollution and heavy metals.[24,25]

When activated, the Nrf2/ARE pathway can switch on over 200 genes that help the cell generate protective molecules (see Figure 2).[26] This includes antioxidant elements, detoxification enzymes, and proteins required for glutathione synthesis and recycling such as glutathione S-transferase (GST), glutathione reductase (GSR), and glutathione peroxidase (GPX).[27–30] Nrf2 also upregulates proteins responsible for Phase III detoxification (P-gp, BCRP, and MRP2) and the transfer of toxic substances out of the cell and central nervous system.

Factors that Impede Detoxification

Nrf2/ARE Pathway. Studies have shown that the ability to upregulate Nrf2 and its antioxidant-supporting action declines with age, which may be one reason the elderly are more susceptible to damage from environmental pollutants.[31] Ochratoxin A, one of the most common mycotoxins found in foods and water-damaged houses, acts as a Nrf2 inhibitor (see Figure 2).[32] Indoxyl sulfate, a uremic toxin that is increased in the blood with chronic kidney disease and exposure to toxic heavy metals such as cadmium, also acts as a Nrf2 inhibitor, further contributing to accelerated renal damage at the level of the tubules.[33–35]

Endotoxin. Lipopolysaccharide (LPS), also known as endotoxin, is associated with the outer membrane of gram-negative bacteria. Increased intestinal permeability, aka "leaky gut," allows for increased translocation of LPS from the gut into circulation. Damage to the intestinal barrier is common and can occur with infection, surgery, stress, intense exercise, celiac disease, food allergies, non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol use (see Figure 3).[36–38] Toxins, including heavy metals, pesticides, and herbicides such as glyphosate, also have

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Figure 2: Oxidative stress causes Nrf2 to dissociate from binding protein (Keap1) in the cytosol and translocate to the nucleus where it binds the promoter region (ARE), leading to transcription of detoxification enzymes and proteins. Various substances have been shown to have an inhibitory or inducing effect on the Nrf2/ARE pathway.

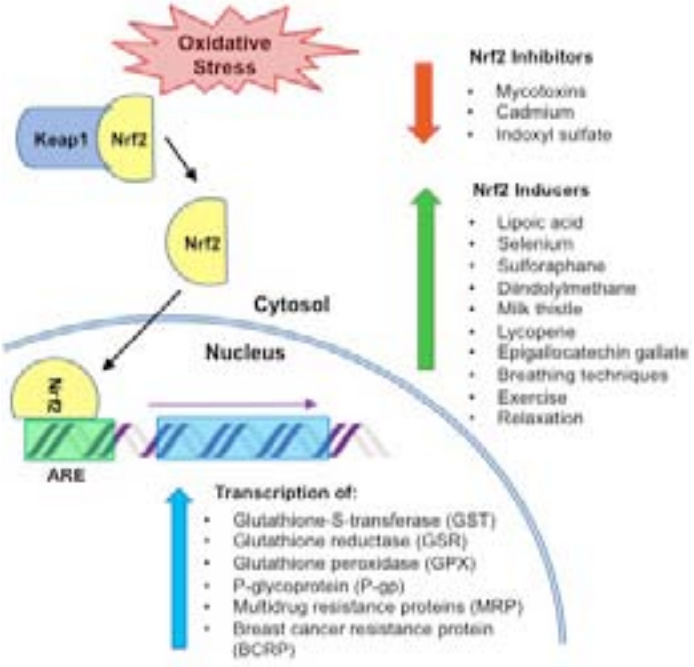

Figure 3: Gastrointestinal inflammation and increased intestinal permeability allow for endotoxin (LPS) to be released from bacteria in the gut into circulation. Endotoxin and related inflammatory cytokines block detoxification pathways by downregulating the detoxification enzymes and Phase III transporters, as well as contributing to cholestasis and kidney damage.

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been shown to lead to inflammation and/or increased permeability.[39–43] With exposure to mercury, inflammation and increased intestinal permeability may occur due to oxidative stress and glutathione depletion.[44]

Endotoxin and the associated inflammation leads to glutathione depletion, further contributing to cellular damage as toxins are no longer efficiently transported out of the cells, or protected from oxidative stress.[45,46] Exposure to endotoxin and the cascade of inflammatory cytokines it triggers also has the effect of downregulating expression of some of the important CYP enzymes and Phase III transporters.[47,48] Endotoxin exposure has a dramatic effect on the urinary elimination of mercury, acting synergistically with the heavy metal to further induce kidney damage.[49] Endotoxin also has an effect of rapidly and dramatically reducing bile flow by suppressing expression and function of hepatobiliary transporters (Figure 4b).[50]

Cholestasis. Bile plays a role in the human body not only for the emulsification and digestion of fatty substances, but also regulates many critical facets of physiology including glucose and cholesterol metabolism as well as thyroid hormone activation.[51,52] Along with bile salts, the body secretes cholesterol and phospholipids *as well as toxins* out of the liver and into the intestines, where they either move out of the body or are reabsorbed via enterohepatic circulation. Bile salts have an impact on the gastrointestinal flora and promote normal gastrointestinal motility.[53,54] Because of these many important functions, diminished bile flow can have a serious and broad ranging impact on health.

Bile acids are normally secreted from hepatocytes across the canalicular membrane via the bile salt export protein (BSEP), as well as the Phase III transporter MRP2.[55] BSEP and MRP2 are from the same superfamily of transporters known as ATP-binding cassette (ABC) transporters, which also includes the Phase III transporters MRP1, MRP3, MRP4, BCRP, and P-gp. *Very importantly, BSEP and MRP2 have an **interdependent** expression, and under normal conditions are colocalized in the apical membrane of the hepatocytes lining the bile canaliculi* (see Figure 4a).[56] The binding of bile salts to nuclear bile salt receptors, including farnesoid X receptor (FXR),[57] pregnane X receptor (PXR),[58] the vitamin D receptor (VDR),[59] and possibly the xenobiotic receptor, constitutive androstane receptor (CAR),[60] increases the expression of transporters for their efflux from the cell, and also regulates their uptake and biosynthesis (see Figure 4a).[61]

The rate limiting step in bile salt excretion is transport at the canalicular membrane, as there is a high concentration gradient to overcome in order to excrete bile salts into the bile acid pool.[62] There are many factors which can inhibit or limit bile acid production and secretion. Substances such as estrogen (in excess), certain medications (including antidepressants), endotoxin, and related inflammatory cytokines are capable of inducing cholestasis by impairing the function of the bile acid transport proteins.[63–66] Though often triggered by inflammatory responses, cholestasis also *induces* an inflammatory response, leading to ROS- and surfactant-induced hepatocyte damage and death due to intracellular bile sale accumulation.[67,68] This failure to move bile salts into the bile canaliculus is termed intrahepatic cholestasis.

Cholestasis is toxistasis. With cholestasis, not only is there reduced

Figure 4a: Normal functioning hepatocyte. FXR remains in the cytosol until activated by bile acids. Oxidative stress causes Nrf2 to dissociate from Keap1 in the cytosol and bind ARE in the nucleus, increasing transcription of detoxification-related enzymes and proteins.

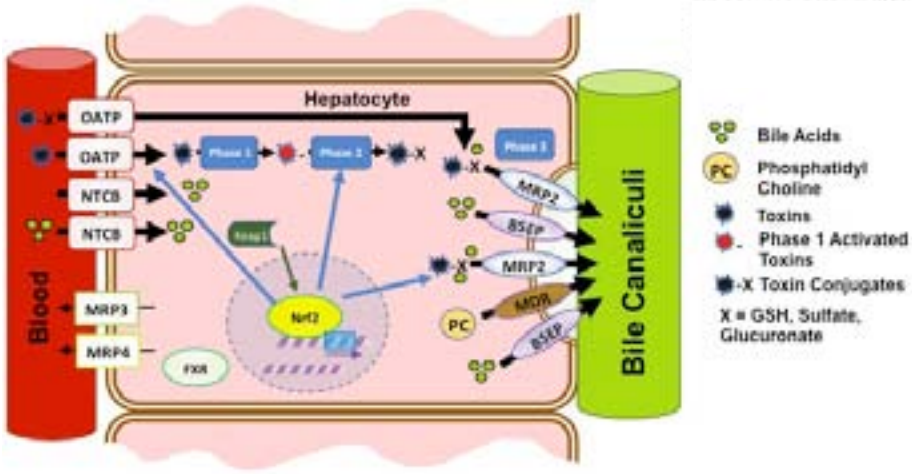
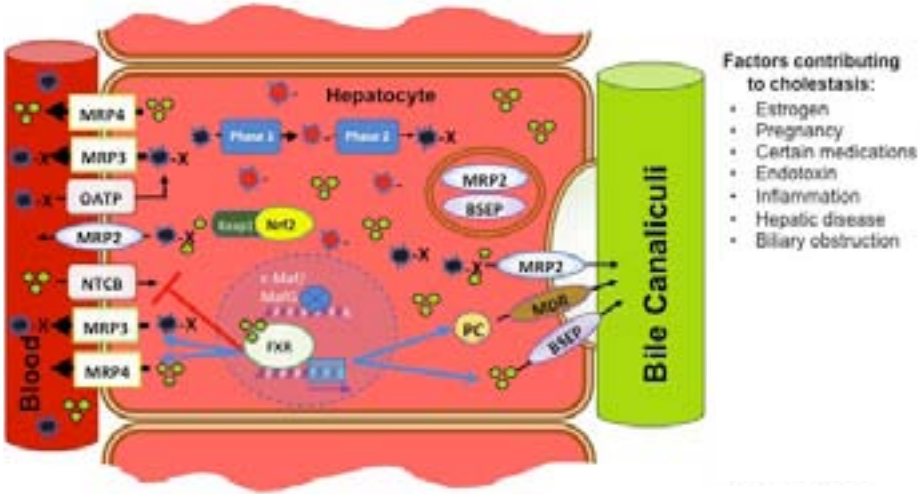


Figure 4b: In cholestasis, there are reduced levels of BSEP and MRP2 at the canalicular membrane due to internalization and relocation. Binding of bile salts to FXR inhibits NTCB transport of bile acids into the cell and increases transcription of BSEP and MRP3 and 4 to lower intracellular bile acid concentration. Nrf2 is blocked from binding ARE by c-Maf/MafG, leading to reduced Phase II inactivation of toxins as well as diminished glutathione synthesis.



biliary excretion of bile, but, due to coregulation of BSEP and MRP2, detoxification is impaired as well. There is a reduction of transport of toxins out of the cell by the Phase III proteins, a reduction of Phase II metabolism, and decreased hepatocellular synthesis of GSH, in part due to the blocking of Nrf2 binding to ARE (see Figure 4b).[69–71] In cholestasis, a decreased expression of BSEP and the Phase III transporter MRP2 is seen at the canalicular membrane.[72] The Phase II estrogen metabolite, estradiol-17β-d-glucuronide (E217βG), triggers internalization of both BSEP and MRP2,[73] while LPS causes relocation of MRP2 to the basolateral membrane.[74] Each of these factors negatively impacts the ability of the hepatocyte to transport toxins out into the bile. OATP, which serves to transport bile acids and toxins from the blood into the hepatocyte, decreases. An additional protein in the ABC transporter family, MRP3, upregulates in cholestasis, protecting the hepatocytes from toxin-related damage and death.[75] However, rather than serving to transport toxins out into the bile canaliculi as MRP2 does, it eliminates them from the cell back into the blood and neighboring cells (see Figure 4b).[76] With the additional relocation of MRP2 to the basolateral membrane there are now two pumps moving toxins and toxin conjugates back into the blood during cholestasis. *This is likely the mechanism of "detox reactions" or "Herxheimer reactions" experienced during unbalanced detoxification protocols and points to therapeutic interventions to remedy those reactions or prevent them in the first place.*

The kidney reflexively adapts in attempts to support bile salt removal from the blood in cholestasis by a variety of mechanisms.[77] Passive glomerular filtration increases, while at the level of the tubules, active secretion of bile increases, and tubular reabsorption of bile acids is repressed.[78] MRP2 is one of the specific proteins that have increased expression in the kidney, protecting the organism by increasing renal bile salt and toxin elimination.[79] In severe biliary obstruction, acute renal failure may occur.[80] In the intestines, with biliary obstruction, the expression of MRP2 in the enterocytes, where it also serves to transport toxins out, is dramatically reduced.[81] The intestinal reabsorption of bile also adapts in cholestasis, as a bile acid transporter that contributes substantially to enterohepatic reabsorption in the duodenum is also downregulated.[82]

Clinical Manifestations of Cholestasis/ Toxistasis

A range of conditions including biliary obstruction, pregnancy, chronic viral hepatitis, cirrhosis, primary biliary cholangitis, and primary sclerosing cholangitis may lead to cholestasis. Cholestasis related to extrahepatic or intrahepatic biliary obstruction is suggested by gastrointestinal symptoms including right upper quadrant pain or tenderness which may be prolonged, epigastric tenderness, discomfort or nausea after meals, and stool changes possibly including evidence of gross fat malabsorption (see Table 1a). Symptoms often are exaggerated with consumption of meals containing a high amount of fat. General or isolated pruritis, localized to the palms or soles of feet, is common, and often worse at night or pre-menstrually in women.[83] Depending on the cause of cholestasis, there also may be symptoms of fatigue and impaired memory and concentration.[84,85] These symptoms, however, mirror those of toxemia and point to the liver "backfire" (basolateral toxin transport dominating over canalicular transport, Figure 4b) described previously as being causal. Laboratory findings and imaging which may suggest cholestasis are found in Table 1b.

Table 1a: Signs and Symptoms of Cholestasis

Right upper quadrant pain or tenderness
Discomfort or nausea after meals
Pruritis, often worse at night
Epigastric tenderness
Fat malabsorption
Stool changes, especially pale stool
Jaundice
Fatigue
Impaired memory and concentration

Table 1b: Labs and Imaging Suggestive of Cholestasis

Elevated serum aminotransferases[86]
Elevated alkaline phosphatase, particularly if marked elevation with respect to aminotransferases[87]
Elevated gamma-glutamyl transpeptidase[88]
Elevated bilirubin
Elevated 5'-nucleotidase[89,90]
Elevated serum bile acids[91]
Biliary sludge or gallstones shown on imaging

A "Push-Catch" Strategy to Maximize Liver Detoxification Pathways

Successful and effective detoxification requires not just support for the phases of detoxification, but also the implementation of a proper directionality to progressively mobilize and eliminate toxins from the cells and tissues, and then from the body as a larger entity. As described previously, much of this is controlled at the canalicular membrane of the hepatocyte; however, it also involves the efficient binding of toxins in the upper GI tract. With a rapid delivery system, such as nanoscale lipid-based deliveries, it is possible to supplement nutraceuticals to support detoxification phases and stimulate bile flow (the "push") and then, within 30 minutes, follow with solid-phase toxin binders (the "catch"). This Push-Catch strategy creates an efficient and discreet detoxification cycle that can be done once per day or can be repeated multiple times per day for more rapid detoxification. Importantly, because of the focus on directionality, "detoxification symptoms" are minimized or eliminated. Though many combinations of compounds can be used, the following are core concepts.

Glutathione Support

Glutathione is central to multiple cell functions, such as detoxification, free-radical control, immune balance, and cell growth. Because glutathione is lost during removal and elimination of mercury and other toxins from the cell, it also can become chronically depleted in settings of toxicity.[92] Many conditions such as autoimmune disease,[93] chronic infections,[94,95] and autism[96] are also associated with lower levels of glutathione, which sheds light on why individuals who experience one of these are often extremely vulnerable to additional insults and toxicants.[97] Furthermore, liver concentrations of glutathione are five-fold higher than other cells in the body. Glutathione support is thus a cornerstone of detoxification protocols.

Typical oral supplementation of glutathione has low bioavailability, and minimally impacts intracellular levels.[98] N-acetylcysteine (NAC), which supports the production of glutathione by providing

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the precursor L-cysteine, also has limited ability to support intracellular glutathione levels as the conversion of L-cysteine to glutathione is often poor.[99–101] Because of this, intravenous glutathione, and alternate oral glutathione delivery forms, such as liposomes and S-acetylglutathione, are often utilized.[102,103]

Another important mechanism to consider in detoxification protocols is inducing the endogenous cellular production of glutathione and the related antioxidant-supporting and chemoprotective (detoxifying) enzymes and proteins via the Nrf2/ARE pathway (see Figure 2). Sustained activation of Nrf2 has been shown to counteract hepatic injury and bilirubin elevation associated with cholestasis.[104] Although Nrf2 is maintained at a basal level, it has a half-life of approximately 15 minutes and is constantly degraded in cells not experiencing stress.[105,106] Natural substances that have been shown to induce Nrf2 include lipoic acid (especially the R-form), selenium, diindolylmethane (DIM), sulforaphane, lycopene, milk thistle, and epigallocatechin gallate (EGCG).[107–111] Importantly, lifestyle factors also have the ability to affect Nrf2 induction. Activities such as relaxation, breathing techniques, and exercise have the effect of inducing Nrf2.[112–114]

Hepatoprotection and Biliary Support

Some of the medications which improve symptoms and biochemical markers of liver injury in settings of cholestasis have mechanisms that include supporting the detoxification pathways. Ursodeoxycholic acid (UDCA), a primary medication used in settings of cholestasis, may have a protective effect via co-regulation of Phase III transporter expression. UDCA stimulates hepatic BSEP, and also co-stimulates hepatic, intestinal, and renal MRP2.[115] UDCA, as well as S-adenosylmethionine (SAMe), prevents the cholestasis-induced blockage to Nrf2/ARE binding, increasing synthesis of detoxification-related enzymes and glutathione.[71,116] Rifampicin, a medication that is used primarily as an antibiotic, but also for pruritis associated with cholestatic liver disease,[117] enhances bile acid detoxification by increasing expression of CYP3A4 (Phase 1), UDP-glucuronosyltransferases (Phase 2), and MRP2 (Phase 3).[118]

Many natural substances support detoxification by improving biliary elimination of toxins. Phosphatidylcholine, the predominant phospholipid building block of cellular membranes, is a crucial constituent of bile. As phosphatidylcholine comprises over 90% of the total bile phospholipids content,[119] inadequate intake contributes to impaired biliary excretion of bile and toxins, and promotes cholesterol crystallization and gallstone formation.[120] This further promotes liver damage by obstruction of the small bile ducts. Increased intake of phosphatidylcholine has been shown to enhance biliary lipid secretion, preventing cholestasis and subsequent liver damage.[121,122] Although small amounts of choline can be synthesized from methionine or serine, it is considered an essential nutrient and must be obtained from the diet.[123] A recent study showed that only 8% of US adults meet the recommended adequate intake (AI) of choline, with vegetarians, postmenopausal women, and men at greater risk of inadequacy.[124, 125]

Bitter Herbs

Well known for their generally stimulating effect on digestive system function, bitter herbs play an important role in promoting adequate biliary secretion. Digestive bitters which have hepatoprotective effects and/or support the formation and elimination of bile include gentian, dandelion, myrrh, and milk thistle. Some of these botanicals also have specific mechanisms by which they have been shown to support detoxification pathways.

Gentian (*Gentiana lutea*) is one of the strongest herbal bitters that is often utilized in digestive bitter formulations. Gentian has been shown to have a choleretic effect, normalizing bile volume in the setting of liver injury.[126] As a liver protective agent, gentian has been observed to increase levels of GSH, GSR, GPX, and superoxide dismutase which were otherwise reduced by alcohol or acetaminophen-induced oxidative damage.[127,128]

Dandelion (*Taraxacum officinale*) simultaneously stimulates the production of bile by the liver (choleretic), the flow of bile into the small intestine (cholagogue), and also has hepatoprotective effects.[129] In the setting of alcohol-induced oxidative stress, supplementation with dandelion root extract has also been observed to increase hepatic antioxidant activity, including GSH, GST, GPX, and GSR.[130]

Myrrh (*Commiphora myrrha*) has a complex profile of use and is perhaps most recognized for its antimicrobial effect.[131,132] Myrrh also acts as an anesthetic, anti-inflammatory, antioxidant, and cholesterol-lowering agent.[133] In Ayurvedic medicine, myrrh is used as a detoxifier and female reproductive tonifying agent, helping to move stagnant blood.[134] Myrrh, and its close relative guggul (*Commiphora mukul*), contain molecules known as guggulsterones that have diverse biological activities. The guggulsterones are the bioactive agents responsible for the cholesterol-lowering effect, as well as anti-inflammatory and anti-oxidative properties.[135] Guggulsterones have been shown to increase the transcription of BSEP as well as induction of the detoxification-promoting nuclear transcription factor PXR.

Milk thistle (*Silybum marianum)* has been vastly studied for its anti-oxidative, anti-inflammatory, and hepatoprotective effects.[136] Silymarin is the active complex extracted from the seeds of the plant, with the flavonolignan silybin, also known as silibinin, being the most biologically active moiety comprising 50% to 70% of silymarin. One of the most important mechanisms by which milk thistle supports detoxification, in addition to its antioxidant effects, is via its anti-cholestatic properties.[137] Silibinin stabilizes BSEP in its hepatocyte membrane location, preventing cholestasis caused by BSEP internalization in the presence of substances like estrogen.[138] When co-administered with estrogen, silymarin was shown to prevent the estrogen-induced decrease in bile-salt dependent bile flow.[139] Silibinin and silymarin also have been shown to stimulate the nuclear bile salt receptor FXR in a dose dependent manner, which increases expression of BSEP and MRP2, and also may have other positive metabolic effects.[140]

Toxin Binders

Completing the process of detoxification requires intestinal binders for two reasons: 1) many toxins (methylmercury, cadmium, and mycotoxins being well-known, as well

as others with increased intestinal permeability) are reabsorbed after excretion into the bile, and 2) endotoxin and other dysbiotic toxins derived from the gut can be prophylactically bound with non-absorbed sorbent substances like activated carbon. As translocation of endotoxin from the gastrointestinal tract to circulation not only directly causes inflammation and oxidative damage but also has a dramatic negative effect on detoxification, it is imperative to bind and remove it from the body. Supporting reduction of intestinal permeability is also an important aspect of detoxification strategies. However, because there is no universal toxin binder that has an equal affinity for all toxins (heavy metals, molds, plastics, and more), a combination of binders that span a breadth of possible toxin chemistries is necessary (see Table 2).

Table 2: Toxic Substances Bound by Common Binders

Activated charcoal	Endotoxin, mycotoxins, pesticides and herbicides, volatile organic compounds (VOCs)
Bentonite clay	Mycotoxins, bisphenol A (BPA), pesticides and herbicides, some metal binding, also has antibacterial activity
Chitosan, a molecular mimic of Welchol	Ochratoxin, polychlorinated biphenyls (PCBs), phthalates, BPA, endotoxin, metals, also has prebiotic activity
Thiol-functionalized silica	Heavy metals specific binder including mercury, lead, arsenic, and cadmium

Activated charcoal is well known for its ability to adsorb a wide variety of toxic substances, and is used for this purpose in many emergency settings when poisonous substances or medication overdoses have been ingested.[141] One of the most important things about charcoal is that it is very effective at binding and removing endotoxin, a major contributor to blocked detoxification pathways.[142–144] Activated charcoal also effectively adsorbs pesticides and herbicides,[145] volatile organic compounds (VOCs) such as benzene,[146] mycotoxins,[147] and the intestinal precursor to indoxyl sulfate, a uremic toxin.[148] Charcoal has also been observed to reduce pro-inflammatory cytokine production in settings of infection.[149]

Bentonite clay is particularly good at absorbing mycotoxins, including food-borne aflatoxin; aflatoxin's precursor mycotoxin sterigmatocystin, commonly found in water-damaged buildings;[150,151] zearalenone, a mycotoxin with estrogenic effects commonly found on stored grains[152]; and fumonisin B1, a mycotoxin most often found on corn.[153] Bentonite clay also strongly binds bisphenol A (BPA),[154] as well as pesticides and herbicides,[155,156] and cyanotoxins, a product of harmful algal blooms that may be found in contaminated drinking water or food.[157] Bentonite clay has an affinity for some heavy metals such as lead,[158] cadmium,[159] and nickel,[160] and has been shown to reduce the cadmium-induced toxicity and pro-inflammatory response *in vivo* as well.[161,162] Bentonite clay also has intrinsic broad-spectrum antibacterial properties and has a healing effect on the gastrointestinal lining.[163]

Derived from shellfish, chitosan is the result of enzymatic treatment of chitin, a component of the shell. As a biomaterial with use in a variety of applications including as a vaccine adjuvant, chitosan has been observed to be safe for use in individuals with shellfish allergies.[164,165] Chitosan acts similarly to the bile acid sequestrants cholestyramine (Questran) and colesevelam (Welchol),[166] preventing the absorption of lipids by effectively binding to bile salts,[167] but most importantly where detoxification is concerned, removing the many conjugated toxins excreted in the bile. One extremely harmful and common toxin, ochratoxin, a mold toxin found in many foods as well as water-damaged buildings,[168,169] is very effectively bound and removed by chitosan.[170,171] Chitosan also binds metals including mercury[172,173] as well as polychlorinated biphenyls (PCBs), phthalates,[174] and BPA.[175] Chitosan, like charcoal, also is able to bind endotoxin.[176,177] Chitosan also has a prebiotic effect, promoting the growth of Bifidobacterium and Lactobacillus.[178] Like bentonite clay, chitosan also has been demonstrated to have an antimicrobial effect.[179]

Although chitosan and bentonite clay have an ability to bind some heavy metals, they are not the most effective tools for this purpose. Thiolated resins are substances with covalently attached thiolic metal-binding groups which very tightly bind metals including lead, mercury, cadmium, and arsenic.[180,181] The use of thiolated resins dates back to the 1970s when they were used to address methylmercury (MeHg) poisoning in Iraq, and were found to significantly reduce the half-life of MeHg from 61 to 20 days, performing even better than penicillamine, a medical metal-chelating agent.[182,183] The thiol-functionalized silica intercepts MeHg and other metals trapped in enterohepatic circulation, binding them and escorting them out of the intestines.[184]

Because binders act locally in the gastrointestinal tract, they allow tissue-bound toxins such as metals to safely drain into the blood at a natural rate. This contrasts with many blood metal chelating agents, which may increase circulatory levels of metals and place a greater burden on the kidneys and liver in the process of elimination.[185] With gastrointestinal binders, the work of the liver and kidneys to eliminate toxic substances including metals is diminished as enterohepatic reabsorption is interrupted. The ability of charcoal and chitosan to block initial absorption of endotoxin is an important aspect of the role of binders in effective detoxification protocols.

Nanoscale Delivery Systems Optimize Detoxification

In order to appropriately time the cellular and hepatobiliary flushing of toxins with a gastrointestinal binder to properly bind and eliminate them, a nutritional delivery system with rapid uptake and cellular delivery is necessary. Lipid nanoparticle delivery systems pose a feasible solution, as appropriately designed lipid-based vesicles have the potential for rapid uptake into circulation and greatly increased cellular delivery.[186] However, not all liposomal and nanoemulsifed particles are able to deliver these benefits, as only appropriately sized particles with properly designed surface chemistry enable rapid intraoral absorption and enhanced cellular delivery.

Particle size has a dramatic effect on systemic and cellular absorption, the capacity of the vesicles to extravasate from blood vessels and permeate into tissues,

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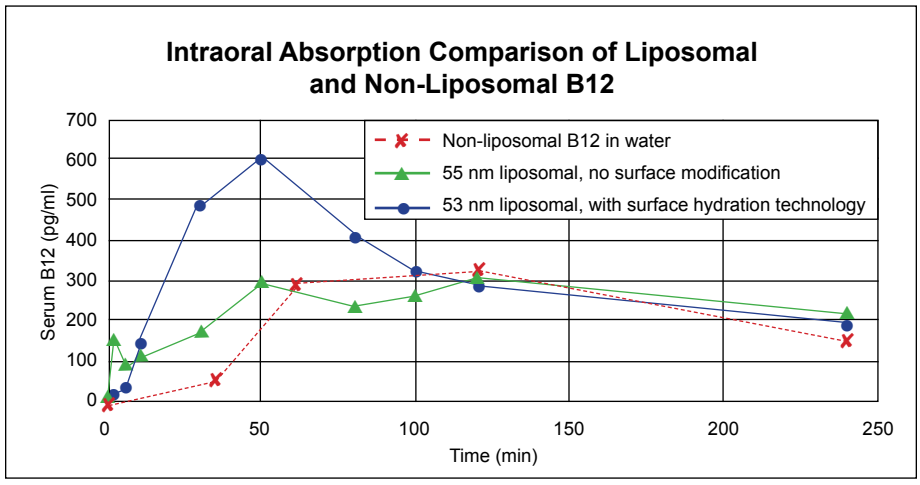
and the ability to evade immune system clearance.[187] The consideration of each of these factors has led to the optimal sizing of lipid nanoparticle delivery systems in the range of 50 to 100 nm. As capillary pore size ranges from only 6 to 12 nm in endocrine glands to 50 to 180 nm in the discontinuous leaky capillaries,[188] it is obvious that only the small liposomes will be able to permeate into the tissues through these openings.

Surface modifying techniques also can be used to improve the ability of lipid nanoparticles to traverse through the blood vessel endothelium and be absorbed by the tissues.[189] Particles utilizing surface hydration technology have been observed to dramatically increase intraoral absorption of liposomal particles, as shown in Figure 5, which compares delivery of B12 with and without surface modification to that of non-liposomal B12. Intelligently-designed surface modifications of lipid nanoparticles have also been shown to prolong the time a therapeutic agent is in circulation, reducing clearance by the mononuclear phagocyte system.[190]

Although absorption of the very small lipid nanovesicles primarily occurs intraorally, there always will be a percentage of the nanoparticle-containing liquid which is swallowed and experiences lower gastrointestinal absorption. In this setting, the lipid vesicle serves to protect the substances which it contains from degradation by the harsh gastric juices. These particles are absorbed via the lymphatics, which also allows for them to bypass first-pass hepatic metabolism, increasing bioavailability.[191]

Figure 5: Comparison of B12 absorption intraorally in human subject.



In addition to their use in clinical applications for the delivery of drugs including anti-cancer, anti-fungal, and anti-inflammatory medications,[192,193] lipid nanoparticle delivery systems have been shown to dramatically improve absorption of a variety of natural substances such as DIM and milk thistle, which otherwise have poor bioavailability.[194–196] Liposomal delivery systems are becoming increasingly popular for delivery of substances such as glutathione because they protect it from breakdown in the digestive system, and, in cell culture studies, have been shown to dramatically increase intracellular delivery 100-fold over non-liposomal formats.[197] Because optimally-sized liposomes with intelligent surface modifications prolong the time the therapeutic core remains in circulation, they are ideal for the delivery of many substances for which a prolonged systemic effect is desirable. Phosphatidylcholine, which forms the external membrane of lipid nanoparticles, also nourishes cellular membranes by providing necessary phospholipids for cellular repair.[198]

Although many products claim improved bioavailability via liposomal delivery, few are able to truly deliver the increased absorption these systems are capable of. However, with appropriately engineered lipid nanoparticle delivery systems, the rate of absorption, cellular delivery, and bioavailability of many medications and natural substances can be dramatically enhanced. ◆

Dr. Christopher Shade, PhD, founder and CEO of Quicksilver Scientific, specializes in the biological, environmental, and analytical chemistry of mercury in all its forms and their interactions with sulfur compounds, particularly glutathione and its enzyme system. He has patented analytical systems for mercury speciation (separation of different forms of mercury), founded the only clinical lab in the world offering mercury speciation in human samples, and has designed cutting edge systems of nutraceuticals for detoxification and antioxidant protection, including advanced phospholipid delivery systems for both water- and fat-soluble compounds. Dr. Shade is regularly sought out to speak as an educator on the topics of mercury, environmental toxicities, neuroinflammation, immune dysregulation, and the human detoxification system for practitioners and patients in the United States and internationally.

Dr. Carrie Decker, ND, graduated with honors from the National College of Natural Medicine (now the National University of Natural Medicine) in Portland, Oregon. Dr. Decker sees patients at her office in Portland, OR, as well as remotely, with a focus on gastrointestinal disease, mood imbalances, eating disorders, autoimmune disease, and chronic fatigue. Prior to becoming a naturopathic physician, Dr. Decker was an engineer and obtained graduate degrees in biomedical and mechanical engineering from the University of Wisconsin-Madison and University of Illinois at Urbana-Champaign respectively. Dr. Decker continues to enjoy academic research and writing, and uses these skills to support integrative medicine education as a writer and contributor to various resources.

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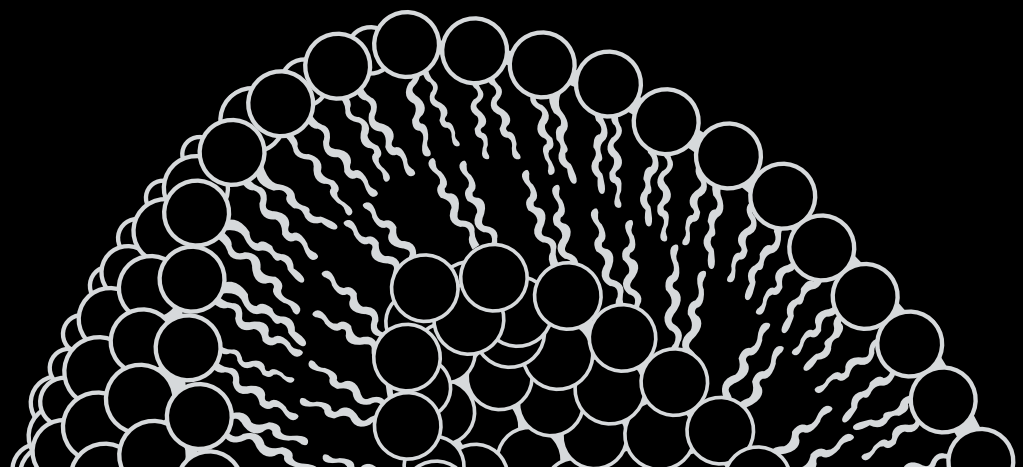

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The Vaginal Microbiota and Influence of Select Probiotic Lactobacilli Strains

by Anthony Thomas, PhD

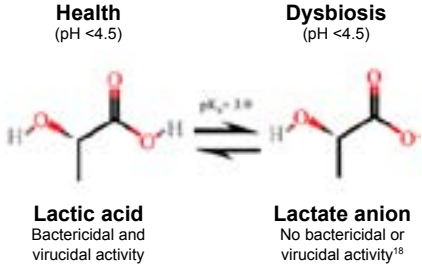
Specific, highly complex microbial communities (microbiota), including their collective genetic material (microbiome), differ between anatomic sites of an individual (e.g., intestinal, vaginal, oral, skin) as well as between people.[1] An increasing body of scientific evidence has demonstrated these microbial communities markedly influence human health. Furthermore, clinical research is demonstrating the targeted manipulation of these microbial communities with specific probiotic strains offers a promising strategy to improve and maintain health.

The vagina is a dynamic environment colonized by various microorganisms (microbes), thus, collectively referred to as the vaginal microbiota. The composition and function of the vaginal microbiota has been linked to women's health status. Microbes inhabiting the vagina are thought to provide the first line of defense in the urogenital tract. Although there is not a definitive "normal" vaginal microbiota, current scientific knowledge has revealed that lactobacilli predominance is generally the hallmark of a healthy vaginal microbiota as high lactobacilli abundance is associated with the promotion and maintenance of vaginal microbial ecosystem balance. In 1892, Albert Döderlein, a German obstetrician and gynecologist considered one of the founders of gynecological bacteriology, first described a Gram-positive vaginal bacillus (Döderlein's bacillus) occurring in normal vaginal secretions of asymptomatic pregnant women, which was later renamed *Lactobacillus*. He argued that in normal vaginal secretions, Döderlein's bacilli and lactic acid produced by the bacilli were essential to keep the vagina free of pathogenic bacteria. Low numbers or absence of vaginal lactobacilli is more often associated with increased risk of bacterial vaginosis (BV), yeast overgrowth ("yeast infection"), aerobic vaginitis (AV), urinary tract infections (UTIs), and adverse obstetric outcomes (e.g., miscarriage, premature rupture of membranes (PROM), preterm birth, ventilation/respiratory distress at birth, neonatal sepsis, neonatal intensive care unit admission).[2-6] Clinical research has established the therapeutic value of administering specific probiotic lactobacilli strains for the restoration and maintenance of a healthy vaginal microbiota.

Vaginal Acidification: Lactobacilli Production of D- and L-Lactic Acid

Lactobacilli are facultative anaerobic (aerotolerant) bacteria that produce lactic acid via the fermentation of glucose.[7] The vaginal lactic acid concentration is inversely associated with vaginal pH in women with a lactobacilli-dominated vaginal microbiota, indicating lactic acid is predominantly responsible for vaginal acidification.[8] Production of lactic acid and vaginal acidification plays a prominent role in imparting the broad protection against other microbes associated with a lactobacilli-dominated vaginal microbiota.[9] Furthermore, lactic acid reinforces lactobacilli predominance and maintenance of an acidic vaginal pH in support of a balanced microbial ecosystem with limited diversity.

Vaginal lactobacilli are the primary source of lactic acid in the vagina[10,11] and only source of the D-isomer as human cells can only produce L-lactic acid, with < 15% of L-lactic acid produced by vaginal mucosal epithelial cells.[11] The production of the D-lactic acid isomer by some Lactobacillus strains enhances protection against microbial invasion of the upper genital tract by supporting the integrity of the cervical external orifice of the uterus.[12] The majority of preterm births result from infections caused by bacteria from the vagina that have traversed the cervix. In addition to vaginal acidification, lactic acid has been shown to directly inactivate various reproductive and urinary tract pathogens.[13-15] The active microbicidal/viricidal form of lactic acid is the protonated (LAH) rather than the un-protonated lactate anion (LA^-),[16,17] with the latter form a function of both the concentration of total lactate (LAH + LA^-) and hydrogen ions (H^+)/pH.



Lactic acid may also regulate host immune responses to evoke protection against potentially pathogenic microbes within the vaginal microbiota. In the presence of a synthetic analogue of double-stranded viral RNA, lactic acid potentiates the production of protective pro-inflammatory cytokines (IL-8 and IL-1b) by vaginal epithelial cells.[19] Lactic acid was shown to potentiate interleukin-23 production from innate immune cells in response to lipopolysaccharide (endotoxin), which may promote activation of T-helper type 17 subclass of T-lymphocytes in response to Gram-negative bacteria.[20] Each of these activities exemplifies enhanced activation of host anti-microbial innate and acquired immunity.

continued on page 33 ➤

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Clinical Study #1 (1999)

In a study of 319 women visiting three medical clinics, most women's normal vaginal bacterial residents included *L. crispatus* (32%), followed by *L. jensenii* (23%), *L.* 1086V (15%), *L. gasseri* (5%), *L. fermentum* (0.3%), *L. oris* (0.3%), *L. reuteri* (0.3%), *L. ruminis* (0.3%), and *L. vaginalis* (0.3%).*

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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Other Potential Protective Mechanisms of Vaginal Lactobacilli

In addition to lactic acid production and vaginal acidification, Lactobacilli are thought to utilize several mechanisms to inhibit pathogen colonization of the vaginal tract: co-aggregation of non-pathogens and pathogens to interfere with the infectious capacity of pathogenic species, production of biosurfactants to disrupt adhesion to the vaginal mucosa by pathogenic species, production of antimicrobial bacteriocins and hydrogen peroxide, competitive exclusion of pathogenic species via competing for nutrients and host surfaces, reinforcing the integrity of the vaginal mucosal epithelial barrier (up-regulation of tight junction proteins to limit damage caused to vaginal epithelium by inflammatory processes or pathogens), and regulation of host immune responses (production of antimicrobial peptides/proteins such as defensins, lactoferrin and lysozyme, and alkaline phosphatases, which can bind to lipopolysaccharide/endotoxin to neutralize toxicity).[21]

Lactobacillus Species Predominance of Vaginal Microbiota

Unlike any other anatomical site of the human body, most vaginal microbial communities (>70%) are dominated by one or more species of *Lactobacillus* that constitute >50% of all genetic sequences obtained. Recent studies using high-throughput 16S rRNA gene sequencing studies have shown that composition and relative abundance of vaginal microbial communities in reproductive-aged women cluster into at least five core vaginal microbiota, termed community state types (CSTs).[22-24] Four of these CSTs, representing the majority (>70%) of women, are dominated by a different *Lactobacillus* species: *L. crispatus* (CSTI), *L. gasseri* (CSTII), *L. jensenii* (CSTV), and *L. iners* (CSTIII), whereas CSTIV is characterized by low proportions of lactobacilli and is composed of a diverse mixture of primarily strict anaerobic bacteria including species of the genera *Gardnerella*, *Atopobium*, *Mobiluncus*, *Prevotella* and other taxa in the order Clostridiales, as seen with states of BV.

Of note, *L. iners* is present in most women, including both healthy and those with dysbiosis/BV,[4] whereas *L. crispatus* is typically only observed in healthy women. Ravel et al.[22] observed that *L. crispatus*-dominated vaginal microbiota have lower vaginal pH compared to communities dominated by other species. Vaginal microbiotas dominated by *L. iners* have lower vaginal concentrations of D-lactic acid as *L. iners* lacks the gene coding for D-lactate dehydrogenase, so cannot produce this lactic acid isomer,[12] which may in part mediate the higher observed frequency of BV and preterm delivery in these women.[25] D-lactic acid levels were significantly higher when *L. crispatus* was the dominant vaginal bacterial species than when *L. iners* or *Gardnerella* dominated the vaginal microbiota.[12] It has been suggested that the increased proportion of *L. iners* in women with BV may be due to increased tolerance of this *Lactobacillus* species to an elevated pH, characteristic of BV, more than other *Lactobacillus* species.[26] In contrast, *L. crispatus*, *L. gasseri*, and *L. jensenii* are all producers of the D-lactic acid isomer as well as hydrogen peroxide. *L. iners* also does not produce antimicrobial hydrogen peroxide.

Hydrogen peroxide-producing lactobacilli are more likely to sustain long-term vaginal colonization, and women colonized by hydrogen peroxide-producing lactobacilli have decreased acquisition of human immunodeficiency virus (HIV) infection,[27] gonorrhea,[27] and BV.[28] Evidence supports a vaginal microbiota dominated by *Lactobacillus* species other than *L. iners* is optimal to support vaginal health (i.e., strains of *L. iners* have not been considered candidates as probiotics to support women's urogenital health).[29,30]

Ethnic Differences

Differences in the composition of these vaginal microbial communities have been observed between women of different ethnic backgrounds. Lactobacilli-dominated vaginal microbial communities (CST I, II, III, V) were observed in ~80% and ~90% of Asian and white women, respectively, but only ~60% and ~62% of Hispanic and black women, respectively.[22] Over-representation of CSTIV in Hispanic and black women was associated with a higher median pH in these ethnic groups as well. Such differences in vaginal microbial communities between women of different ethnic backgrounds have been observed in other studies as well.[24,31]

Although CSTIV can be observed in otherwise healthy women, asymptomatic for BV, it is associated with higher Nugent scores (a Gram stain scoring system from 0 – 10 for vaginal swabs reflecting abundance of Gram-positive rods [lactobacilli] and Gram-negative variable rods and cocci [*G. vaginalis, Prevotella*, etc.] to diagnose BV with 0 – 3 considered normal, 4 – 6 indicative of intermediate bacterial counts, and 7 – 10 diagnostic of BV) and may be a risk factor for adverse gynecologic and obstetric outcomes.[3,32,33]

Pregnancy and Estrogen Promotion of Vaginal Lactobacilli

Composition of the vaginal microbiota can be dynamic and capable of rapid shifts within a short period of time (e.g., < 24 hours), although more stable in many women and during different physiologic states such as pregnancy. Vaginal microbial communities of pregnant women are more stable and have higher relative abundance of lactobacilli than non-pregnant women.[34,35] The most common lactobacillus species of the vaginal microbiota observed in healthy pregnant women in the late first trimester were *L. crispatus* and *L. gasseri* (>50%), followed by *L. jensenii* (~20%) and *L. rhamnosus* (~10%), as well as combinations thereof (~10%).[36]

Estrogen is thought to play an important role in promoting a lactobacilli-dominated vaginal microbiota by stimulating accumulation of glycogen in the vaginal epithelial mucosa,[37,38] which is thought to contribute to the increased lactobacilli predominance and stability of the vaginal microbiota observed in healthy pregnant women. Nutrient-containing vaginal secretions and glycogen-containing (as a source of glucose) vaginal epithelial cells that are sloughed and subsequently lyse are thought to be primary nutrient sources for the vaginal microbiota. Estrogen increases the volume of vaginal secretions and induces thickening of the vaginal epithelium along with glycogen accumulation, thought to support growth of glucose-fermenting lactobacilli.[39] Changes in relative abundance of vaginal lactobacilli are associated with both estrogen levels and glycogen content across the various life-stages of women (e.g., pre-pubertal, pubertal/reproductive age, postmenopausal).[40] Additionally,

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use of oral hormonal contraceptives (i.e., estrogen) and a decreased prevalence of BV has been consistently observed in epidemiological studies.[41-44]

Loss of Vaginal Lactobacilli: Common Factors

Various common factors are thought to influence the vaginal microbiota and have been associated with dysbiosis/BV: hygiene/intravaginal practices (douching), sexual activity (e.g., increased frequency and number of partners, lack of male circumcision/condom use), stress, smoking, and use of antibiotics/anti-fungals.[3,45] Antimicrobials have been the primary therapeutic intervention utilized for the treatment of urogenital "infections" (overgrowth of potentially pathogenic microbes) for more than four decades. Unfortunately, antimicrobial treatment of urogenital infections is often ineffective, particularly for BV; and there is a high rate of recurrent infections without preventative continuation of antimicrobial therapies. Efficacy is also diminishing with increasing development of antimicrobial resistance. The antimicrobial, metronidazole, is the most commonly used treatment for BV; however, cure rates associated with this treatment are low (as low as 61% one month post-therapy[46]) with a high incidence of overgrowth of potentially pathogenic bacteria following treatment.[47]

Antibiotics

Antibiotics affect not only pathogenic microorganisms, but many human residential symbiotic and administered probiotic bacterial strains too. Many strains of the most prevalent vaginal lactobacilli species (*L. crispatus, L. iners, L. jensenii,* and *L. gasseri*) were all demonstrated to be susceptible to commonly used systemic antibiotics including ampicillin, cefazolin, cefotaxime, and vancomycin, but insensitive to metronidazole and trimethoprim/sulfamethoxazole along with differential sensitivity to others (gentamycin, clindamycin, erythromycin, ciprofloxacin, and tetracycline). For example, treatment with clindamycin was shown to suppress/eradicate *L. crispatus* and induce the selective accumulation of *L. iners* and *L. gasseri*.

Bacterial Vaginosis and Urinary Tract Infections

Many women experience a transient, often recurrent, loss of a lactobacilli-dominated vaginal microbiota and reduced vaginal acidity, which is associated with increased risk of urogenital infections as the reduction in lactobacilli makes for a more conducive vaginal environment for the proliferation of many anaerobic bacteria such as *Gardnerella vaginalis* (*G. vaginalis*) and *Atopobium vaginae* (*A. vaginae*).

BV and UTIs are common infections, afflicting hundreds of millions of women annually,[48,49] with BV the most common cause of vaginal symptoms among women. In the United States, the prevalence of BV (determined by a Nugent score of 7-10) was estimated to be 21.2 million (29.2%) among women aged 14 – 49 years, based on a nationally representative sample of women who participated in the National Health and Nutrition Examination Survey (NHANES) 2001 – 2004.[42] BV is a risk factor for acquisition of both bacterial (gonorrhea, chlamydia, and *Trichomonas vaginalis* infection) and viral (HIV, HSV, and HPV) sexually transmitted diseases as well as adverse obstetric outcomes (e.g., miscarriage, fetal distress syndrome, PROM, preterm birth).[3,6,50]

G. vaginalis and *A. vaginae* are commonly associated with BV[51,52] whereas the majority (>80%) of UTIs are caused by uropathogenic *E. coli* (UPEC) and often associated with AV.[53] These pathogenic bacteria colonize the vagina via the formation of biofilms, which results in increased tolerance to adverse conditions for better persistence in hostile environments (i.e., protection from the immune system and decreased susceptibility to antibiotics).[54,55]

Adherent biofilm comprised of mostly *G. vaginalis* and *A. vaginae* was observed to persist for three weeks following one-week treatment with orally administered metronidazole in women with BV.[52] In the UK, BV is frequently treated with topical clindamycin. The proportion of group B streptococci isolated from neonatal blood cultures that are resistant to clindamycin or erythromycin has risen substantially over recent years in the UK (Health Protection Report 2013, 7:46), most likely as a result of exposure to these antibiotics.

Lactobacillus Strains to Support Women's Urogenital Health

Bacterial migration from the colon to the vagina across the perineum occurs naturally, thus is a source of both potential pathogens as well as certain lactobacilli. Given that lactobacilli are generally recognized as the hallmark of a healthy vaginal microbiota, the rationale for probiotic use in support of women's urogenital tract health is strong.[56] Certain lactobacilli strains can safely colonize the vagina after oral as well as vaginal administration, displace and kill pathogens, and modulate host immune responses. Maintenance of a healthy vaginal microbiota could reduce the incidence of urogenital infections, the spread of sexually transmitted infections, and adverse pregnancy outcomes, thus decrease the need for conventional treatments.[57]

However, it is important to keep in mind that these inhibitory mechanisms and activities are generally strain specific; therefore, not all strains of a given lactobacillus species have the same probiotic potential. Furthermore, strains contained in a multi-strain combination need to be compatible (i.e., not antagonistic) and preferably synergistic for a targeted health condition beyond general gastrointestinal health (e.g., women's urogenital tract health), which must be demonstrated by clinical research. Although administration of vaginal suppositories is the most common way of delivering lactobacilli to the vagina, oral administration represents a more user-friendly alternative that may be more effective as a preventative strategy in the long run, given the recognition of the gastrointestinal tract as a reservoir for vaginal colonization by lactobacilli for the maintenance of a normal vaginal microbiota. It should be noted that any vaginally inserted capsule should not be enteric-coated, common for oral probiotics to protect the live bacteria from stomach acid, thus appropriate for orally administered probiotics to support women's urogenital tract health.

It is worth noting the current internationally endorsed definition of probiotics established by an expert panel commissioned in 2001 by the Food and Agriculture Organization (FAO) of the United Nations and supported by the World Health Organization (WHO), which states, "Live microorganisms that, when

administered in adequate amounts, confer a health benefit on the host." A health benefit to the host, humans in our case, must be realized and demonstrated to be superior to that of placebo/control (i.e., clinical research), but the majority of fermented foods and products labeled as or as containing probiotics on the market have not been appropriately tested and verified as such. How "probiotic" containing products are regulated, marketed, and sold often has nothing to do with the definition. Many consumers/patients appear to be influenced by the live cell count (quantity) and number of strains offered in products labeled as containing probiotics, naively believing the more of each the better. Companies indulge this naivety and even actively propagate this messaging to consumers, often masquerading as educational, and eluding the lack of clinical validation for these strains (when strains are even identified on the label). Yet, the definition of probiotics militates against excessively high counts (dosing) of strains lacking clinical validation as touted by many commercially available products in favor of efficacious strains and dosing, substantiated by clinical research.

Orally and vaginally administered probiotic lactobacilli strains have been investigated as both an adjuvant and alternative therapy for the treatment and prevention, including recurrence post-treatment, of BV and UTIs. For example, orally administered (twice daily) probiotic lactobacilli strains *L. rhamnosus* GR-1 (1 billion) and *L. reuteri* RC-14 (1 billion) for 30 days in conjunction with oral metronidazole (500 mg) treatment during the first week was shown to be significantly more effective at curing BV than metronidazole treatment alone in premenopausal women, with significantly higher abundance of vaginal lactobacilli at day 30 in women receiving oral probiotic supplementation.[58] Additionally, oral supplementation with probiotic lactobacilli strains was as effective as daily antibiotics for UTIs.[59] Used in conjunction with and following antibiotic treatment helps restore a healthy vaginal microbiota to increase cure rate and reduce relapse.[56,58]

"Kitchen sink" products marketed to support women's vaginal health often tout a laundry list of different bacterial species and claim as many as 100 billion per capsule, albeit generic, clinically unsubstantiated strains for this indication. These levels have no rationale in light of the fact that the successful clinical studies utilized dosing in the 1 - 10 billion live organisms per day range, the difference being clinically validated strains with probiotic attributes to serve this function. Clinically validated strains are expensive, thus a product containing 100 billion (live organisms guaranteed through the listed "best used before date" and not at time of manufacture) clinically validated strains per capsule would be prohibitively expensive and excessively dosed. Again, and most importantly, the specific probiotic strain(s) indicated to support women's urogenital tract health must be provided in sufficient quantity as validated by clinical research; otherwise, it does not constitute a true probiotic for this condition.

Not All Strains Are Equal

Again, it should be noted that not all lactobacilli strains, even those recognized more generally as a probiotic to support gastrointestinal health, are effective for supporting women's urogenital tract health. For example, daily oral administration of the widely recognized probiotic strain to support gastrointestinal health, *L. rhamnosus* GG, for 28 days failed to influence vaginal health despite the administration of 10 billion, whereas oral administration of only 1.6 billion of the combination of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 supported a healthy vaginal microbiota.[60] Furthermore, daily oral administration of a commercially available dietary probiotic containing *L. rhamnosus* GG (40 billion) for six months failed to demonstrate vaginal colonization by this specific *L. rhamnosus* strain or reduce the recurrence of UTIs.[61]

Vaginal Microbiota

The majority of probiotic products marketed for support of women's vaginal health, generally multi-strain combinations of lactobacilli with or without strains from additional genera such as *Bifidobacteria*, are not supported by clinical research for this indication. Additionally, the strain designation for each bacterium within the combination is often not disclosed (only genus and species). It is well recognized scientifically that probiotics are strain, dose, and condition specific. Strains of the same bacterial species can be different as exemplified by aforementioned examples comparing *L. rhamnosus* GR-1 vs. *L. rhamnosus* GG (unique strains of the same bacterial genus and species) to support women's urogenital tract health (condition), a functional distinction that was not overcome with administration of markedly greater abundance (dose) of *L. rhamnosus* GG.

Strain functionality and associated health claims beyond general support of gastrointestinal health in humans require substantiation of efficacy with clinical trials. Strain designation links unique bacterial strains to the scientific research supporting probiotic characteristics and efficacy for a specific condition in target host organisms (e.g., humans).

Guidelines established by an expert working group, convened jointly by the FAO of the United Nations and the WHO, state, "Proper identification to the level of strain of all probiotics in the product," and Dr. Mary Ellen Sanders of the International Scientific Association for Probiotics and Prebiotics, an internationally recognized consultant in the area of probiotic

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microbiology, has stated, "Manufacturers should designate the strains in their products so that consumers know what they're getting. It's pretty much a consensus among probiotic scientists that this is the responsible thing to do."

Four Unique Vaginal Probiotic Lactobacilli Strains

Domig et al.[62] demonstrated an extensive, multi-step scientific process to identify candidate probiotic strains, representing the predominant *Lactobacillus* species colonizing the vagina of healthy pregnant women (*L. crispatus, L. jensenii, L. gasseri, L. rhamnosus*), for oral administration to support women's urogenital tract health. From 68 isolates belonging to these species, which were derived from 99 isolates from the genus *Lactobacillus* out of a total of 127 isolates from healthy pregnant women in their late-first trimester, four final candidate strains were selected for targeted formulation based on a battery of criteria such as ability to grow under both aerobic and anaerobic conditions, acidification capacity, glycogen utilization, extracellular hydrogen peroxide production, stability under acidic conditions and resistance to bile salts (important for survival during gastrointestinal transit post-oral administration), anti-microbial activity against multiple strains of common vaginal pathogens (i.e., *Candida albicans*, *Candida krusei, Candida glabrata, E. coli*, and *G. vaginalis*), compatibility, safety (e.g., lack of virulence factors, antibiotic susceptibility/lack of antibiotic resistance), and encapsulated stability of the multi-strain formulation (forecasting shelf-life stability for use in commercial dietary supplements).

The strains of this probiotic formulation representing the predominant *Lactobacillus* species of the vaginal microbiota of healthy pregnant women have been designated *L. crispatus* LbV 88, *L. jensenii* LbV 116, *L. gasseri* LbV 150N, and *L. rhamnosus* LbV 96. These strains, as part of multi-strain probiotic formulation, were subsequently demonstrated in multiple clinical studies to increase vaginal lactobacilli abundance and acidification in support of urogenital tract health.

The Neovagina: A Challenging Microbial Environment

The neovaginal microbiota of male-to-female transsexual women is a diverse community of both aerobic and anaerobic species with very limited colonization by lactobacilli, more reflective of the abnormal vaginal microbiota characteristic of BV.[63] The neovaginal environment may not adequately support the growth of lactobacilli despite transsexual women having comparable estrogen levels to those of postmenopausal women receiving hormone replacement therapy,[63] with one study observing a neovaginal lactobacilli colonization rate of only 4%.[64]

In a prospective, randomized, placebo-controlled study, twice daily oral supplementation with the multi-strain probiotic formulation (2 X 2.5 billion live cells/dose) for only one week significantly enriched lactobacilli and resulted in a lower Nugent score in the neovagina of male-to-female transsexual women compared to placebo.[65] Neovaginal lactobacilli abundance was five to six times higher in the intervention group compared to the placebo group. In contrast to previous observations reported in the scientific literature, an unexpectedly high proportion (30%) of the participants in this study had a normal Nugent score of $\leq$ 3. When those participants with a baseline Nugent score $\leq$ 3 were excluded from the analysis or only those participants with BV (Nugent score > 7) were included, an improvement in the Nugent score was observed in the intervention group, but not in the placebo group.

Fortified vs. Conventional Yogurt as Adjuvant Therapy for Bacterial Vaginosis

In another randomized, double-blind, placebo-controlled clinical trial, oral supplementation with the selected probiotic strains and yogurt significantly improved cure rate and symptoms of BV compared to control.[66] Women with newly diagnosed BV (based on Amsel criteria, diagnostic criteria for BV of which 3 of 4 criteria must be met: pH > 4.5, positive whiff test, presence of discharge, and presence of clue cells in the wet smear) were administered metronidazole (2 x 500 mg/day) for one week and the multi-strain probiotic formulation twice daily in 125 g yogurt (intervention group; n = 17) or acidified yogurt (control group; n = 17), which naturally contained live fermentation starter cultures *Lactobacillus delbrueckii* subspecies bulgaricus and *Streptococcus thermophilus*.

After a four-week intervention period, 0/17 women had BV in the intervention group vs. 6/17 (35%) in the control group, a statistically significant and clinically relevant difference in cure rate. Amsel score was significantly decreased in the intervention group by a median value of 4 compared to a median value of only 2 in the control group. Odor and discharge (Amsel 2 and 3) was significantly decreased in the intervention group vs. control group, 2 vs. 1, respectively.

Immunosuppressed Pregnant Women and Obstetric Outcomes

The mother is the main source of microbes, both non-pathogenic and pathogenic, for newborn colonization. Dysbiotic vaginal microbiota characteristic of BV with marked reductions of lactobacilli increases risk of obstetric complications such as placental insufficiency, premature birth, fetal growth restriction, and postpartum endometritis,[6,50,67,68] which is particularly relevant for women with immunosuppression and herpes virus infection (HVI).

The selected probiotic strains were evaluated for efficacy in the complex therapeutic and preventative intervention for pregnant women with HVI.[69] Sixty pregnant women with HVI either received a patented food supplement to restore and support the vaginal microbiota twice daily for one week containing the selected probiotic strains and the prebiotic carbohydrate, fructooligosaccharides (intervention group; n = 30), or only prenatal care (comparator group; n = 30). Fifty healthy pregnant women without HVI were included as a control group. Intestinal lactobacilli and bifidobacteria were significantly increased in conjunction with significant decreases in pathogenic microbes (hemolytic *E. coli, Klebsiella pneumoniae, Staphylococcus aureus*, candida yeast species) in the intervention group vs. the comparison group, post-intervention levels which were similar to levels in healthy pregnant women of the control group. Prior to the intervention, 40% of women with HVI complained of symptoms associated with dysbiosis of the intestinal microbiota, namely bloating/abdominal discomfort, constipation, and mucus in the feces, but these complaints were reduced to only 12% of participants in the intervention group.

At the start of the study, vaginal lactobacilli were only detected in 13.3% and 16.7% of participants in the intervention and comparison groups, respectively, which was significantly increased in the intervention group to 46.7% after the one-week intervention, but not significantly different in the comparison group (20%). The percentage of women in the intervention group with a vaginal pH > 4.5, complaining of profuse vaginal discharge, swelling (hyperemia), and itching (pruritus), and with a positive amine test of vaginal discharge, were significantly decreased in the intervention group and no longer different than healthy pregnant women of the control group, whereas these parameters did not change in the comparison group.

The incidence of placental insufficiency and fetal distress were significantly reduced about two-fold in women of the intervention vs. comparison group. The percentage of aggravated pregnancy was significantly lower in women of the intervention group (33.3%) vs. the comparison group (53.3%). Furthermore, the percentage of women with other pregnancy complications (i.e., threatened miscarriage, threat of premature birth, pre-eclampsia, and pathology of amniotic fluid) was 25-50% fewer in the intervention vs. comparison group, which may be clinically relevant, but was not statistically significantly different in this study. This result was likely due to the small study population and variability and worth investigating in future, larger clinical trials.

Postmenopausal Women

Given the positive influence of estrogen on vaginal lactobacilli abundance, postmenopausal women experience a decrease in vaginal lactobacilli and increase in vaginal pH with increased incidence of UTIs due to increased colonization by enterobacteria. Clinical symptoms include vaginal dryness, burning, itching, dyspareunia, dysuria, urinary frequency, and recurrent UTIs.[70,71]

The genitourinary symptoms of menopause are particularly common in women with breast cancer due to chemotherapy and estrogen deprivation therapy. Vaginal estrogen therapy increases vaginal lactobacilli and decreases colonization by UPEC to reduce UTI recurrence,[72] but estrogen treatment for women with breast cancer is used with restraint due to frequent estrogen sensitivity of the tumor.[73] Thus, an appropriate probiotic intervention would be an alternative therapeutic option to enhance vaginal lactobacilli to discourage vaginal dysbiosis and recurrent UTIs.

Indeed, in a proof-of-principle pilot study,[74] twice daily oral supplementation with the multi-strain probiotic formulation (2 X 2.5 billion live cells/dose) for two weeks in postmenopausal women with breast cancer receiving chemotherapy, with vaginal atrophy and an intermediate vaginal microbiota (Nugent score 4 - 6) (n = 11/group), improved the Nugent score (-1.3) towards a normal microbiota (≤ 3), whereas there was a deterioration in the control group receiving placebo (+0.45). One week post-discontinuation, the Nugent score regressed in those women previously receiving the probiotic intervention (to only -0.57 from baseline) and further deteriorated in the control group (+2.5 from baseline), suggesting the protective effect of the probiotic intervention is not sustained with discontinuation in this at-risk group.

True Probiotics

The application of true probiotics to support women's vaginal health (i.e., clinically validated dosing of probiotic formulations such as *L. crispatus* LbV 88 + *L. jensenii* LbV 116 + *L. gasseri* LbV 150N + *L. rhamnosus* LbV 96) in clinical practice has gained increasing recognition as a therapy and for prophylactic prevention. However, in a society that focuses on disease and drug therapy more so than natural preventative measures, significant efforts will be needed to get such probiotics into mainstream practice. The failure of most medical education programs to teach future physicians about the human microbiota, its relationship to health, and appropriate applications of specific, validated probiotic strains and multi-strain formulations, ultimately diminishes care for patients. It is critical that healthcare practitioners acknowledge the human microbiota and consider its role in health maintenance. Clinical research, dissemination of research results, and education will be key, as confusion about what constitutes a true probiotic-based intervention and misinforming marketing campaigns are widespread.

References

1. Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. *Nature* 2012, 486:207-214.
2. Green KA, et al. Gynecologic health and disease in relation to the microbiome of the female reproductive tract. *Fertil Steril* 2015, 104:1351-1357.
3. Lewis FM, et al. Vaginal Microbiome and Its Relationship to Behavior, Sexual Health, and Sexually Transmitted Diseases. *Obstet Gynecol* 2017, 129:643-654.
4. Petrova MI, et al. Lactobacillus species as biomarkers and agents that can promote various aspects of vaginal health. *Front Physiol* 2015, 6:81.
5. Kovachev SM. Obstetric and gynecological diseases and complications resulting from vaginal dysbacteriosis. *Microb Ecol* 2014, 68:173-184.
6. Dingens AS, et al. Bacterial vaginosis and adverse outcomes among full-term infants: a cohort study. *BMC Pregnancy Childbirth* 2016, 16:278.
7. Wilson WA, et al. Regulation of glycogen metabolism in yeast and bacteria. *FEMS Microbiol Rev* 2010, 34:952-985.
8. O'Hanlon DE, et al. Vaginal pH and microbicidal lactic acid when lactobacilli dominate the microbiota. *PLoS One* 2013, 8:e80074.
9. Tachedjian G, et al. The role of lactic acid production by probiotic Lactobacillus species in vaginal health. *Res Microbiol* 2017.
10. Boskey ER, et al. Acid production by vaginal flora in vitro is consistent with the rate and extent of vaginal acidification. *Infect Immun* 1999, 67:5170-5175.
11. Boskey ER, et al. Origins of vaginal acidity: high D/L lactate ratio is consistent with bacteria being the primary source. *Hum Reprod* 2001, 16:1809-1813.
12. Witkin SS, et al. Influence of vaginal bacteria and D- and L-lactic acid isomers on vaginal extracellular matrix metalloproteinase inducer: implications for protection against upper genital tract infections. *MBio* 2013, 4.
13. Conti C, et al. Inhibition of herpes simplex virus type 2 by vaginal lactobacilli. *J Physiol Pharmacol* 2009, 60 Suppl 6:19-26.
14. Graver MA, Wade JJ. The role of acidification in the inhibition of Neisseria gonorrhoeae by vaginal lactobacilli during anaerobic growth. *Ann Clin Microbiol Antimicrob* 2011, 10:8.
15. Juarez Tomas MS, et al. Growth and lactic acid production by vaginal Lactobacillus acidophilus CRL 1259, and inhibition of uropathogenic Escherichia coli. *J Med Microbiol* 2003, 52:1117-1124.
16. Aldunate M, et al. Vaginal concentrations of lactic acid potently inactivate HIV. *J Antimicrob Chemother* 2013, 68:2015-2025.
17. Owen DH, Katz DF. A vaginal fluid simulant. *Contraception* 1999, 59:91-95.
18. Aldunate M, et al. Antimicrobial and immune modulatory effects of lactic acid and short chain fatty acids produced by vaginal microbiota associated with eubiosis and bacterial vaginosis. *Front Physiol* 2015, 6:164.
19. Mossop H, et al. Influence of lactic acid on endogenous and viral RNA-induced immune mediator production by vaginal epithelial cells. *Obstet Gynecol* 2011, 118:840-846.
20. Haas R, et al. Lactate Regulates Metabolic and Pro-inflammatory Circuits in Control of T Cell Migration and Effector Functions. *PLoS Biol* 2015, 13:e1002202.
21. Reid G, et al. Microbiota restoration: natural and supplemented recovery of human microbial communities. *Nat Rev Microbiol* 2011, 9:27-38.
22. Ravel J, et al. Vaginal microbiome of reproductive-age women. *Proc Natl Acad Sci U S A* 2011, 108 Suppl 1:4680-4687.
23. Gajer P, et al. Temporal dynamics of the human vaginal microbiota. *Sci Transl Med* 2012, 4:132ra152.
24. Zhou X, et al. Differences in the composition of vaginal microbial communities found in healthy Caucasian and black women. *ISME J* 2007, 1:121-133.
25. Petricevic L, et al. Characterisation of the vaginal Lactobacillus microbiota associated with preterm delivery. *Sci Rep* 2014, 4:5136.

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26. Lamont RF, et al. The vaginal microbiome: new information about genital tract flora using molecular based techniques. *BJOG* 2011, 118:533-549.
27. Martin HL, et al. Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. *J Infect Dis* 1999, 180:1863-1868.
28. Hawes SE, et al. Hydrogen peroxide-producing lactobacilli and acquisition of vaginal infections. *J Infect Dis* 1996, 174:1058-1063.
29. van de Wijgert JH, et al. The vaginal microbiota: what have we learned after a decade of molecular characterization? *PLoS One* 2014, 9:e105998.
30. Bradshaw CS, Brotman RM. Making inroads into improving treatment of bacterial vaginosis - striving for long-term cure. *BMC Infect Dis* 2015, 15:292.
31. Fettweis JM, et al. Differences in vaginal microbiome in African American women versus women of European ancestry. *Microbiology* 2014, 160:2272-2282.
32. Fredricks DN, et al. Molecular identification of bacteria associated with bacterial vaginosis. *N Engl J Med* 2005, 353:1899-1911.
33. Fox C, Eichelberger K. Maternal microbiome and pregnancy outcomes. *Fertil Steril* 2015, 104:1358-1363.
34. MacIntyre DA, et al. The vaginal microbiome during pregnancy and the postpartum period in a European population. *Sci Rep* 2015, 5:8988.
35. Romero R, et al. The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women. *Microbiome* 2014, 2:4.
36. Kiss H, et al. Vaginal Lactobacillus microbiota of healthy women in the late first trimester of pregnancy. *BJOG* 2007, 114:1402-1407.
37. Brotman RM, et al. Microbiome, sex hormones, and immune responses in the reproductive tract: challenges for vaccine development against sexually transmitted infections. *Vaccine* 2014, 32:1543-1552.
38. Mirmonsef P, et al. Free glycogen in vaginal fluids is associated with Lactobacillus colonization and low vaginal pH. *PLoS One* 2014, 9:e102467.
39. Farage M, Maibach H. Lifetime changes in the vulva and vagina. *Arch Gynecol Obstet* 2006, 273:195-202.
40. Nunn KL, Forney LJ. Unraveling the Dynamics of the Human Vaginal Microbiome. *Yale J Biol Med* 2016, 89:331-337.
41. Achilles SL, Hillier SL. The complexity of contraceptives: understanding their impact on genital immune cells and vaginal microbiota. *AIDS* 2013, 27 Suppl 1:S5-15.
42. Koumans EH, et al. The prevalence of bacterial vaginosis in the United States, 2001-2004; associations with symptoms, sexual behaviors, and reproductive health. *Sex Transm Dis* 2007, 34:864-869.
43. Riggs M, et al. Longitudinal association between hormonal contraceptives and bacterial vaginosis in women of reproductive age. *Sex Transm Dis* 2007, 34:954-959.
44. Vodstrcil LA, et al. Hormonal contraception is associated with a reduced risk of bacterial vaginosis: a systematic review and meta-analysis. *PLoS One* 2013, 8:e73055.
45. Mayer BT, et al. Rapid and Profound Shifts in the Vaginal Microbiota Following Antibiotic Treatment for Bacterial Vaginosis. *J Infect Dis* 2015, 212:793-802.
46. Schmitt C, et al. Bacterial vaginosis: treatment with clindamycin cream versus oral metronidazole. *Obstet Gynecol* 1992, 79:1020-1023.
47. Reid G, Bruce AW. Urogenital infections in women: can probiotics help? *Postgrad Med J* 2003, 79:428-432.
48. Allsworth JE, Peipert JF. Prevalence of bacterial vaginosis: 2001-2004 National Health and Nutrition Examination Survey data. *Obstet Gynecol* 2007, 109:114-120.
49. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. *J Infect Dis* 2001, 183 Suppl 1:S1-4.
50. Denney JM, Culhane JF. Bacterial vaginosis: a problematic infection from both a perinatal and neonatal perspective. *Semin Fetal Neonatal Med* 2009, 14:200-203.
51. Hummelen R, et al. Deep sequencing of the vaginal microbiota of women with HIV. *PLoS One* 2010, 5:e12078.
52. Swidsinski A, et al. An adherent Gardnerella vaginalis biofilm persists on the vaginal epithelium after standard therapy with oral metronidazole. *Am J Obstet Gynecol* 2008, 198:97 e91-96.
53. Donders GG, et al. Definition of a type of abnormal vaginal flora that is distinct from bacterial vaginosis: aerobic vaginitis. *BJOG* 2002, 109:34-43.
54. Danese PN, et al. Biofilm formation as a developmental process. *Methods Enzymol* 2001, 336:19-26.
55. Hardy L, et al. Bacterial biofilms in the vagina. *Res Microbiol* 2017.
56. MacPhee RA, et al. Probiotic strategies for the treatment and prevention of bacterial vaginosis. *Expert Opin Pharmacother* 2010, 11:2985-2995.
57. Spurbeck RR, Arvidson CG. Lactobacilli at the front line of defense against vaginally acquired infections. *Future Microbiol* 2011, 6:567-582.
58. Anukam K, et al. Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14: randomized, double-blind, placebo controlled trial. *Microbes Infect* 2006, 8:1450-1454.
59. Bruce AW, Reid G. Intravaginal instillation of lactobacilli for prevention of recurrent urinary tract infections. *Can J Microbiol* 1988, 34:339-343.
60. Reid G, et al. Probiotic Lactobacillus dose required to restore and maintain a normal vaginal flora. *FEMS Immunol Med Microbiol* 2001, 32:37-41.
61. Kontiokari T, et al. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. *BMJ* 2001, 322:1571.
62. Domig KJ, et al. Strategies for the evaluation and selection of potential vaginal probiotics from human sources: an exemplary study. *Benef Microbes* 2014, 5:263-272.
63. Weyers S, et al. Microflora of the penile skin-lined neovagina of transsexual women. *BMC Microbiol* 2009, 9:102.
64. Weyers S, et al. Cytology of the 'penile' neovagina in transsexual women. *Cytopathology* 2010, 21:111-115.
65. Kaufmann U, et al. Ability of an orally administered lactobacilli preparation to improve the quality of the neovaginal microflora in male to female transsexual women. *Eur J Obstet Gynecol Reprod Biol* 2014, 172:102-105.
66. Laue C, et al. Effect of a yoghurt drink containing Lactobacillus strains on bacterial vaginosis in women - a double-blind, randomised, controlled clinical pilot trial. *Benef Microbes* 2017:1-16.
67. Vedmedovska N, et al. Preventable maternal risk factors and association of genital infection with fetal growth restriction. *Gynecol Obstet Invest* 2010, 70:291-298.
68. Jacobsson B, et al. Bacterial vaginosis in early pregnancy may predispose for preterm birth and postpartum endometritis. *Acta Obstet Gynecol Scand* 2002, 81:1006-1010.
69. Anoshina TM. Role of microbiota correction in complex treatment of pregnant women with herpesvirus infection. *Perinatologiya Pediatriya* 2016, 4:22-25.
70. Portman DJ, Gass ML, Vulvovaginal Atrophy Terminology Consensus Conference P. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Maturitas* 2014, 79:349-354.
71. Pandit L, Ouslander JG. Postmenopausal vaginal atrophy and atrophic vaginitis. *Am J Med Sci* 1997, 314:228-231.
72. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med* 1993, 329:753-756.
73. Krychman ML, Katz A. Breast cancer and sexuality: multi-modal treatment options. *J Sex Med* 2012, 9:5-13; quiz 14-15.
74. Marschalek J, et al. Influence of orally administered probiotic Lactobacillus strains on vaginal microbiota in women with breast cancer during chemotherapy: A randomized placebo-controlled double-blind pilot study. *Breast Care* 2017, 12:335-339.

Anthony Thomas, PhD, earned his bachelor's degree in nutrition, food science, and dietetics from California State University Northridge, his doctorate in nutritional biology from the University of California at Davis, and conducted postdoctoral research at the University of California at Los Angeles Larry Hillblom Islet Research Center. His primary research interests (via both pre-clinical and clinical studies) have focused on the influence of dietary and lifestyle factors (i.e., physical activity, circadian disruption) on the pathogenesis of chronic cardiovascular/metabolic diseases including obesity, insulin resistance syndrome, and type 2 diabetes. He has authored/co-authored multiple peer-reviewed scientific manuscripts and has served as a referee with relevant expertise in the fields of nutrition, obesity, and diabetes for multiple scientific journals.

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Pathways to Healing

by Elaine Zablocki

Breathe OUT for Well-Being

We tend to take breathing for granted. After all, we've been doing it forever. Our breath goes in and out, in and out, and we don't think about it. We don't pay attention to it.

Betsy Thomason, BA, RRT, believes it's time to pay attention to the breath. She's one of those rare people who notices the process of breathing and the many ways it affects bodily functions. "Breathing affects every organ and cell in your body," she says. "Fast, shallow, inefficient breathing activates adrenalin and other counterproductive hormones, so you end up feeling revved up and tired at the same time, all the time."

Betsy Thomason, BA, RRT

Thomason's childhood desire to learn how to paddle a canoe, fulfilled as a young adult, led to her becoming a breathing expert. In 1981 she created an organization called Adventures for Women to share the wisdom of being outdoors. In the process, she learned how to get up mountains without huffing and puffing, using the BreatheOutDynamic system (BODs) developed by Olympic cycling coach Ian Jackson.

An elementary school teacher who took time off to have children, Thomason later trained as a respiratory therapist to increase her knowledge of breathing and the human body. "During my two years of training, I discovered that conventional respiratory therapy focuses on mechanical ventilation and medications. It's not about how to use your body efficiently and effectively in the breathing process."

After receiving her associate's degree in respiratory therapy, Thomason spent two years working in the ICU to give herself a thorough grounding in hospital-based respiratory therapy. "I recall a patient who was intubated, anxious, and fighting the ventilator. I really wanted to help her, so I tried a new idea. I asked her if she had a good imagination, and she indicated that she did. I asked her to imagine that she was blowing up a balloon. As she did that, the ventilator stopped racing. Her blood pressure normalized. Her oxygen saturation improved. This patient taught me the power of the imagination and the outbreath. With her imagined outbreath, she was in fact activating her parasympathetic nervous system, the system that relaxes you."

Thomason worked at an ALS clinic in Manhattan for 11 years, testing the lung function of people with neuromuscular weakness. She wanted to provide more than just testing, and she developed quick ways to help people learn to use their outbreath for relaxation. "I would ask a patient to hold up a finger and pretend to blow on a pinwheel, and keep it spinning comfortably. Their breathing would automatically slow and their belly would go in during each outbreath. Then it would relax and expand for each in breath. I'm a better respiratory therapist because I was first of all a breathing trainer, and I was creative in working with patients to achieve well-being."

Just Breathe Out – A How-to-Breathe Guidebook

In 2016 Thomason published *Just Breathe Out: Using Your Breath to Create a New, Healthier You*. She introduces her readers to the BreatheOutDynamic system, described as focused breathing with emphasis on the active, spine-stretching outbreath and passive, relaxed inbreath. "This cycle of outbreath and inbreath is the opposite of what is considered 'normal' breathing," she says. "Breathing is essential for life, but HOW you breathe affects your well-being. This outbreath focus promotes relaxation, increased energy, and management of stress and pain."

The ideas in the book are based on methods developed by Jackson, Thomason's personal experience with BODs, as well as her professional experiences as a wilderness guide and respiratory therapist. "Actually, being an elementary school teacher has helped me because breathing is very elementary,

very basic," she says. "When teaching outdoor skills, I wanted to teach beginners and start with basic subjects so people would have a good foundation for developing advanced skills. Now I'm teaching the most basic of all subjects – breathing."

This book provides the tools for developing a user-friendly body. It includes basic instructions to develop outbreath awareness, and then helps the reader choreograph their outbreath with movement, exercise, and activities of daily living. Thomason says, "Muscles are smart, but they are slow learners, so practice is essential." She recommends practicing three times a day. "Find a quiet place with no distractions – perhaps when you are waking up, or sitting in a straight back chair, or before a meal. With this quiet BODs practice you will become deeply acquainted with your body and experience the ebb and flow of your breath."

She uses a bellows as a mental image to encourage people to explore this new way of breathing. "If you push the air out of your body using your belly, creating a vacuum, the same amount of air comes bounding back automatically the instant your belly expands, creating suction. Try this long, active, spine-stretching outbreath followed by a brief, passive, relaxed inbreath."

Why Do Breath Patterns Matter?

Personally, when I start to pay attention to my breath, I realize most of the time I'm breathing with the top six inches of my chest. Most of the time I'm think, think, thinking, and not aware of my body or my breath. I asked Thomason whether this is normal.

She responded that unfortunately, in our 21st century culture, many people are used to fast, shallow breaths. "The normal breathing rate is said to be 12 to 20 breath per minute, but nowadays most people are breathing faster than that, and they're not even aware of it," she says. "We are all in a hurry. Our cars are fast, our schedules are packed, and we're all trying to move fast. The human body has never gone so fast before."

It's worth taking the time to slow down and focus on the outbreath, because this has long-term physical and mental benefits, Thomason says. "The outbreath energizes and relaxes everybody because the outbreath activates the parasympathetic nervous system, which relaxes you. The inbreath activates the sympathetic nervous system, which revs you up."

Mike Ramsay, MD, chairman of the Department of Anesthesiology and Pain Management at Baylor University Medical Center, wrote the foreword to *Just Breathe Out*. When he tried the BODs program, he was surprised to experience the profound effect. "I started by spending 30 minutes first thing in the morning working at the active process of breathing out.... While working through the BODs process, I started to use muscles that I have only been conscious of in the gym.... My spine awakens and gets involved," he writes. "Now, weeks into my BODs program, I realize that I am a little more lithesome – I can bend a little easier – and a spring has come back into my step.... In this book, Betsy Thomason takes us to another level of physical and mental performance that improves both physical and cognitive functions."

But can the BreatheOutDynamic system really help people who have such individual needs and abilities? "The body is very smart," Thomason observes. "One of the key messages of the book is that the body is smart but we're not paying attention to it. When we pay attention to it by focusing on the active outbreath, the body responds with relaxation, energy, and healing." Her book offers a road map for listening to, working with, and supporting our body, mind, and spirit, – the key to well-being.

Resources

OutBreath Institute: www.outbreathinstitute.com

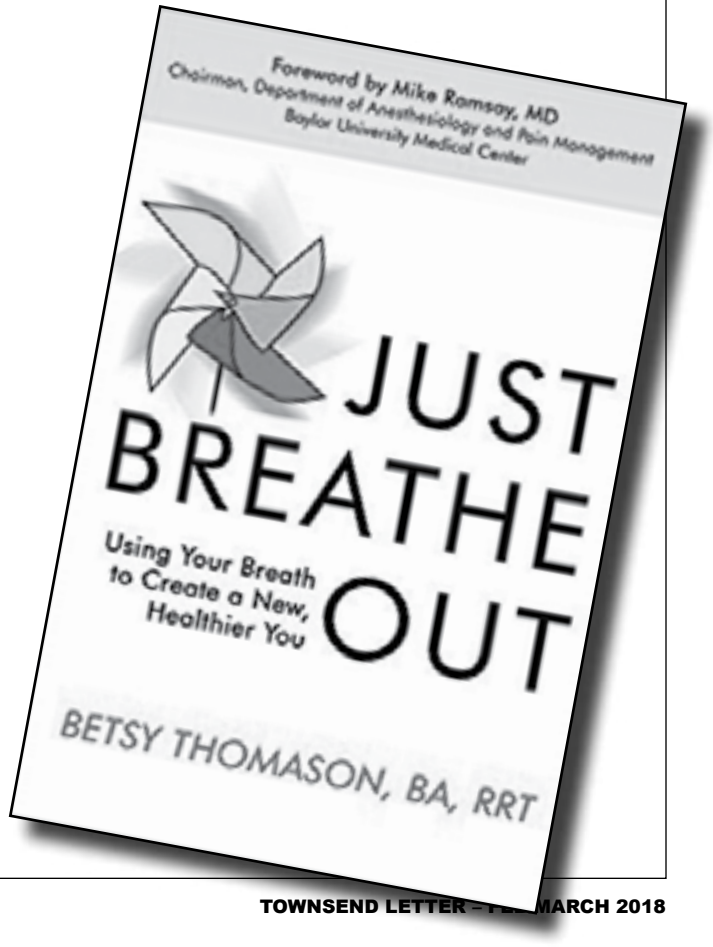
The book, *Just Breathe Out – Using Your Breath to Create a New, Healthier You*, is available in print, e-book, and iTunes Audible formats at www.justbreatheout.com.

For a one-hour Thomason interview with Ronald Hoffman, MD, go to:

http://drhoffman.com/podcast/the-science-of-breath-part-1/
http://drhoffman.com/podcast/the-science-of-breath-part-2/

Adventures for Women, a non-profit organization, is one of the few "women only" outdoor clubs in the US. http://www.adventuresforwomen.org/

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



Shorts

briefed by Jule Klotter
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Vitamin C and Pregnancy

What is a safe amount of vitamin C during pregnancy? In her keynote speech for 2017 LiveAware Expo (San Francisco, California), Suzanne Humphries, MD, discussed the medical literature that she was able to track down regarding supplemental vitamin C use during pregnancy. She had received multiple questions from women via email about safe dosage, rebound scurvy, and concerns that too much C might cause spontaneous abortion.

Guinea pig studies indicate that a newborn whose mother was on high-dose vitamin C supplementation during pregnancy can experience a rebound effect if supplementation is discontinued after birth. Like humans, guinea pigs do not produce vitamin C in their bodies. Pups whose mothers were given the human equivalent of 1500 mg/day throughout pregnancy developed scurvy after birth four days sooner than pups from mothers without supplementation (Norkus 1975, PMID 1060409). Pups whose mothers received supplementation during pregnancy metabolize ascorbic acid at a faster rate than those who do not (Norkus 1981, PMID 7218035), which explains why the pups from supplemented mothers developed signs of scurvy sooner. This evidence of "rebound scurvy," is one reason that people who take high doses of ascorbic acid for extended periods are advised to reduce the dose gradually rather than stopping abruptly.

The sole report about spontaneous abortion apparently originated with a Russian study that Humphries was in the process of acquiring at the time of her talk. That being said, Humphries referred to the 2015 Cochrane review on vitamin C use in pregnancy that reported "no convincing evidence" of harms (Rumbold 2015, PMID 26415762). Also, Rumbold et al found good evidence from eight high-quality studies that supplementation (1000 mg/day, according to Clemetson) produced 36% relative reduction in placenta abruption.

In addition to the Cochrane review, Frederick R. Klenner wrote about his use of high-dose vitamin C in 300 women (J Applied Nutrition, Winter 1971;23(3&4)). The women took about 4,000 mg/day (divided doses) in the first trimester, 6,000 mg/day in the second trimester, and 8,000-10,000 mg/day (with about 20% taking 15,000 mg) in the third trimester. Eighty percent of the women also received booster injections of 10,000 mg upon arriving at the hospital. No miscarriages occurred. In this study, Klenner said, "Observations made on over 300 consecutive obstetrical cases using supplemental ascorbic acid, by mouth, convinced me that failure to use this agent in sufficient amounts in pregnancy borders on malpractice." Humphries notes that Klenner undoubtedly made sure that the mothers continued to take vitamin C after delivery, avoiding any rebound effects for mother and breastfeeding infant.

Vitamin C is vital for the growth and repair of all tissue, as well as being an antioxidant and an anti-viral. The amniotic fluid contains three times the amount of C found in the mother's blood. The placenta after birth and cord blood have twice the maternal blood level. The stress of labor and vaginal delivery uses up a lot of this antioxidant. Babies often display jaundice due to high bilirubin levels after birth. Bilirubin, produced in the body, is also a strong antioxidant that neutralizes free radicals. Supplementation with vitamin C during pregnancy with 500 mg/day reduces the incidence of neonatal jaundice (Garbelli 1957, PMID 13420320).

Dr. Humphries advises women to "start slow and low" in order to learn their own tolerance for vitamin C supplementation. Women with type 1 diabetes or who smoke, use alcohol, and/or eat a lot of carbohydrates have a need for more vitamin C. Sugars – even from carbohydrates like sweet potatoes – compete with vitamin C's entry into cells. She encourages people to include high-vitamin-C food sources (i.e. red peppers, kiwi fruit, and parsley) in a diet of organic, low-processed foods. Humphries, board-certified in nephrology and internal medicine, recommends that people hydrate/drink water before taking vitamin C supplements to protect the kidneys. In other lectures, she reports finding little evidence that ascorbic acid or sodium ascorbate cause kidney stones but advises hydration to be on the safe side. Finally, she says to taper the dosage down, rather than stopping abruptly, to avoid rebound effects.

Humphries S. Vitamin C and Pregnancy – Experience and the Medical Literature. http://liveaware.com/videos/.

The Placenta

Although the placenta has been long recognized as a conduit for nutrition from mother to fetus, its role as a neuroendocrine organ and regulator of the fetus' environment and development is new territory. That conduit linking the mother's blood supply to the fetus' does not become active until about 10 weeks gestation, but placental cells have a major role in pregnancy success from the very beginning. With current molecular and imaging technologies, researchers are investigating placental changes in structure and function that occur throughout pregnancy. They are also looking at environmental factors that affect the placental epigenome, fetal development, and infant health. "Epigenetic studies are starting to show links between the placental epigenome and a number of infant health markers," says journalist Lindsey Konkel. "Variations in DNA methylation patterns in certain gene regions have been associated with infant birth weight, gestational age at birth, and neurobehavioral measure."

In early pregnancy, when major organs are beginning to develop, the placental cells secrete proteins and hormones such as human chorionic gondotropin (hCG). This hormone, which has several functions, tells the mother's ovaries to produce steroid hormones needed to maintain the pregnancy. hCG also stimulates testosterone production, which is needed for gender differentiation in the male fetus. Environmental exposures present in the mother's blood can affect the placenta's hormone signals. For example, Jennifer Adibi, a molecular biologist at the University of Pittsburgh, found that cultured placental cells exposed to phthalates (found in plastics) produced less hCG than non-exposed cells. Phthalates are commonly found in the blood of Americans.

The placentas for male and female fetuses appear to respond to environment stresses differently. In her laboratory research with mice, environmental scientist Cheryl Rosenfeld found that change in the mother's diet produced different placental DNA methylation and gene expression patterns according to gender. These placental changes were associated with gender-dependent responses to eating a high-fat diet after birth. The placental epigenome also responded to maternal stress according to gender; male offspring showed "maladaptive inflammatory and behavioral responses to stress as adults."

At this time, researchers are using embryonic stem cells converted into placental cells to identify environmental factors that affect early pregnancy. Human placentas delivered at term are also being studied. Researchers have not yet identified ways to follow the organ's changes in function and structure that occur throughout pregnancy. No animal models make a good surrogate for the human placenta. David Weinberg, a translational scientist at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, says, "'To really understand placental function and development, we need to be able to monitor it all across pregnancy.'" Weinberg heads the institute's Human Placenta Project (HPP), initiated in 2014. He and his colleagues are looking for non-invasive, real-time methods for assessing placental development, function, and response to environmental factors.

Konkel L. Lasting Impact of an Ephemeral Organ. *Environmental Health Perspectives.* July 2016;124(7):A124-A129.

Fetal and Postnatal Metal Dysregulation

A recent twin study, conducted by Manish Arora and colleagues, found an association between prenatal and early postnatal exposure to neurotoxic metals, essential mineral deficiencies, and autism spectrum disorder (ASD). The researchers recruited 32 ASD-discordant twin pairs (one twin diagnosed with ASD and the other without ASD) enrolled in Sweden's Roots of Autism and ADHD Twin Study in Sweden (RATSS) from whom naturally shed deciduous teeth could be obtained; 17 were monozygotic pairs (MZ) and 15 were dizygotic (DZ) pairs. The authors used tooth-matrix biomarkers to assess uptake of ten elements from the second trimester to early childhood: barium, chromium, copper, lithium, magnesium, manganese, lead, tin, strontium, and zinc. Unlike earlier studies that used whole ground teeth (and found no correlation between ASD and metals), their technique uses a laser to slice the tooth from top to bottom to obtain time-series data samples for mass spectrometry analysis.

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The researchers found different levels for six of the ten elements in twins with ASD compared to non-ASD twins. Manganese, zinc, and lead were the most significant. Manganese levels were lower and lead levels were higher (particularly after birth) in twins with ASD, compared to unaffected twins. The manganese difference was statistically significant for two periods: between 10 weeks prenatally and birth, and from week 5 to week 20 after birth. "The greatest difference was observed at postnatal week 15 when cases had 2.5 times lower manganese than their co-twins (Holm-Bonferroni 95% CI 1.1-4.5 times lower). Differences of a similar magnitude were also observed 7 weeks before birth." The zinc pattern was more complex, say the authors. Zinc levels declined around birth in non-ASD twins and earlier, during the prenatal period, for the twins with ASD. Zinc levels then markedly increased postnatally in the ASD twins, "surpassing the levels in their non-ASD co-twins." In addition, twins with ASD had higher tin and strontium levels and lower chromium levels.

The researchers correlated the tooth-matrix biomarkers with autism severity scores about a decade later, using Social Responsiveness Scale Second Edition (SRS-2) and Autism Diagnostic Observation Schedule Second Edition (ADOS-2). Lead was positively associated with scores from these assessments. Manganese concentrations were inversely associated with autistic traits with the strongest association at 15 weeks of age for SRS-2 and at 12 weeks for ADOS-2. None of the other tested elements showed a statistically significant association with the autistic trait measures

"Our findings along with other recent studies bolster the premise of joint interaction of environmental exposures with genetic variations in the etiology of ASD," say Arora et al. "Notably, many of the genes associated with ASD are also linked with elemental homeostasis, and it is intriguing that genes implicated in ASD converge to specific neuronal co-expression networks especially during the same critical early developmental periods we have observed in this study." They note that fetal zinc deficiency causes epigenetic alterations in gene coding for the metal transporter, metallothionein-2. The authors would like to see if larger non-twin studies support their findings. (It would also be interesting to measure for other elements, such as mercury and aluminum.)

As an aside...I was surprised by the significant association between manganese deficiency and ASD severity reported in this study. It brought to mind a recent review by pathologist James E. Beecham and MIT computer scientist Stephanie Seneff that suggests a correlation between the widespread use of glyphosate herbicides and increased incidence of ASD. Glyphosate chelates manganese ions. The manganese blood levels of cows given glyphosate-exposed feed were extremely low in a recent study. Beecham and Seneff explain that manganese deficiency interferes with the function of manganese-dependent enzymes, leading to a reduction in maternal serum levels of thyroid-stimulating hormone (TSH) – affecting mother and fetus.

Arora M et al. Fetal and postnatal metal dysregulation in autism. *Nature Communications.* June 1, 2017.
Beecham JE, Seneff S. Is there a link between autism and glyphosate-formulated herbicides? *J Autism.* 2016;3(1).

Inhalation for Vaginismus and Pelvic Floor Pain

Erik Peper, PhD, and Tal Cohen say that relaxation of the pelvic floor muscles during inhalation is a key step for addressing involuntary perineal and paravaginal muscle contraction (vaginismus) that interferes with sexual intercourse and can cause pain (dyspareunia). Vaginismus is usually treated by sequential dilation of the vaginal opening with progressively larger cones, psychotherapy, and medication for anxiety and pain. The authors say, "The dilation is effective if the pelvic floor muscles are relaxed; however, the patient may not be aware whether the muscles are relaxed or contracted." In their article, they discuss the biological processes that contribute to vaginismus and dyspareunia.

Before engaging in sequential dilation exercises, the woman needs to learn how to use diaphragmatic breathing, relaxing the neck and shoulder muscles during exhalation and the pelvic floor muscles during inhalation. Biofeedback monitoring of the breathing pattern and lower abdominal muscle activity is helpful when learning to breathe effectively. "The pelvic floor descends and relaxes, especially when sitting up when you can even feel the anus slightly going down and widening," the authors explain. "This occurs during effortless abdominal breathing when one feels safe...." Fostering a sense of safety is important because fear or anticipation of pain causes the abdominal and pelvic floor muscles to contract in an attempt to protect the body's core.

Once the woman can sense pelvic floor relaxation, she is ready to begin dilation practice, with a lubricant, by inserting a very small-diameter dilator and progressing to a larger diameter. The authors advise pushing the dilator only during the midphase of inhalation. If pain arises, they say to relax the shoulders and simply breath until the pain subsides, then push very little on the next inhalation: "Go much slower and with more tenderness." Trying to stretch a muscle too quickly causes an automatic contraction response; this automatic stretch reflex is the body's method for preventing muscle damage from over-stretching.

"Be patient," Peper and Cohen write. "Explain to your partner that your body and mind need time to adjust to new feelings. However, don't stop having sex – you can have great sex without penetration. Practice both alone and with your partner; together find the best angle and rate. Use different lubricants to check out what is best for you." For more information, they recommend Dr. Lonnie Barbach's books *For Each Other: Sharing Sexual Intimacy* and *For Yourself: The fulfillment of Female Sexuality.*

Peper E, Cohen T. Inhale to Breathe Away Pelvic Floor Pain and Enjoy Intercourse. *Biofeedback.* Spring 2017;45(1):21-24.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Vitamin E for Menopause-Related Vaginal Atrophy

Fifty-two postmenopausal Iranian women (aged 40-65 years) with symptoms of vaginal atrophy were randomly assigned to receive 100 IU of vitamin E as a vaginal suppository or 0.5 g of conjugated estrogen cream intravaginally for 12 weeks. The treatment was given every night for the first two weeks, then twice a week for 10 weeks. The effect of treatment was assessed by the vaginal maturation value (VMV), which was defined as (0.5 x the percentage of intermediate cells) plus the percentage of superficial cells. The mean VMV in the vitamin E group at baseline and after four, eight, and 12 weeks of treatment was 43.8, 69.1, 77.9, and 80.6, respectively. The corresponding values in the estrogen group were 42.9, 87.0, 92.7, and 91.6, respectively. VMV improved significantly in both groups compared with baseline ($p < 0.001$).

Comment: The results of this study suggest that intravaginal administration of vitamin E suppositories can improve vaginal atrophy in postmenopausal women. Further studies are recommended to determine whether these results can be replicated in countries other than Iran. If the results can be confirmed, vitamin E may be considered for first-line treatment of menopause-related vaginal atrophy. Although vitamin E was somewhat less effective than intravaginal estrogen, it carries a much lower risk of adverse effects.

Parnan Emamverdikhan A, et al. A survey of the therapeutic effects of Vitamin E suppositories on vaginal atrophy in postmenopausal women. *Iran J Nurs Midwifery Res*. 2016;21:475-481.

Dried Plums for Osteoporosis

Serum samples were collected from five healthy women before and one and two hours after they ingested 100 g of dried plums (also called prunes). Compared with serum collected before ingestion, serum collected after ingestion of dried plums increased the activity of mouse osteoblasts *in vitro*. An earlier study in animals suggested that the effect of dried plums on osteoblastic activity is due at least in part to polyphenols.

Comment: In previous research, a diet containing 5% dried plums by weight prevented bone loss in ovariectomized rats. Daily ingestion of dried plums for six months also slowed the rate of bone loss in postmenopausal women with osteopenia. A dosage of 50 g per day (equivalent to 5-6 dried plums per day) was as effective as 100 g per day.[1] The results of the present study suggest that the mechanism of action of dried plums involves stimulation of osteoblastic activity, an effect that would increase new bone formation. As noted, this effect may be due in part to certain polyphenols present in dried plums. The beneficial effect of dried plum may also result in part from its high content of nutrients that play a role in bone health, such as vitamin K, magnesium, and boron.

Delgado Cuenca P, et al. Dried plum ingestion increases the osteoblastogenic capacity of human serum. *J Med Food*. 2017;20:653-658.

***Helicobacter pylori* Infection as a Cause of Iron Deficiency**

Eighty adults with unexplained iron-deficiency anemia and *Helicobacter pylori* infection received pantoprazole, bismuth subcitrate, tetracycline, and metronidazole for 14 days in an attempt to eradicate the *H. pylori*. The mean serum ferritin level increased from 15.6 µg/L at baseline to 36.8 µg/L at one month after eradication therapy ($p < 0.001$). The mean transferrin saturation level also increased significantly. The improvement in ferritin and transferrin saturation levels was restricted to those patients in whom eradication therapy was successful. The mean hemoglobin level increased significantly in patients in whom eradication therapy was successful, and

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increased non-significantly and to a lesser extent in patients in whom eradication therapy was not successful.

Comment: Gastric hydrochloric acid enhances the absorption of non-heme iron, and iron absorption is frequently impaired in people with hypochlorhydria. *H. pylori* can suppress gastric acid secretion, an effect that is reversible by eradication of the organism. In this study, eradication of *H. pylori* resulted in an improvement in iron status in patients with unexplained iron-deficiency anemia. *H. pylori* infection should be included in the differential diagnosis of unexplained iron deficiency.

Sapmaz F, et al. The impact of Helicobacter pylori eradication on serum hepcidin-25 level and iron parameters in patients with iron deficiency anemia. *Wien Klin Wochenschr*. 2016;128:335-340.

Probiotic Prevents Gestational Diabetes

Four hundred twenty-three pregnant women in New Zealand, 85% of whom had a history of atopic disease (asthma, eczema, or hay fever), were randomly assigned to receive, in double-blind fashion, *Lactobacillus rhamnosus* HN001 (6×10^9 colony-forming units per day) or placebo, beginning at 14-16 weeks of gestation and continuing until delivery. The incidence of gestational diabetes (diagnosed at 24-30 weeks) was significantly lower by 68% (2.1% vs. 6.5%; $p = 0.03$) according to the New Zealand definition of gestational diabetes, and was nonsignificantly lower by 41% (8.2% vs. 13.8%; $p = 0.08$) according to the International Association of Diabetes and Pregnancy Study Groups definition of gestational diabetes, in the probiotic group than in the control group. Using the latter definition, compared with placebo the probiotic significantly decreased the incidence of gestational diabetes in women aged 35 or older (69% reduction; $p < 0.01$) and in women with a history of gestational diabetes ($p = 0.004$), but had no significant effect in women without these characteristics.

Comment: This study demonstrated that a particular probiotic strain prevented the development of gestational diabetes in pregnant women. The beneficial effect was restricted to women who were over age 35 or who had a history of gestational diabetes. The mechanism of action is not known.

Wickens KL, et al. Early pregnancy probiotic supplementation with Lactobacillus rhamnosus HN001 may reduce the prevalence of gestational diabetes mellitus: a randomised controlled trial. *Br J Nutr*. 2017;117:804-813.

Different Strains of Wheat Have Different Effects on Health

Non-obese diabetic mice (an animal model for type 1 diabetes) were fed various genetic strains of wheat flour at a level of 20% of the diet for 10 weeks. At the end of the study, all animals fed modern wheat flour had developed type 1 diabetes, whereas none of the mice fed strains of *T. aestivum, T. turgidum* spp. *dicoccoides*, or *T. turgidum* spp. *dicoccum* grown locally in Israel had developed type 1 diabetes.

Comment: Hybridization techniques have been used in the United States since the 1950s to produce new strains of wheat in order to increase crop yield. Celiac disease-triggering gluten proteins are expressed at higher levels in modern wheat, whereas non-triggering proteins are expressed less. At least 14 new gluten proteins have been identified in hybrid strains that were not present in either parent.[2] It is possible that some of these new proteins have a high degree of allergenicity. The increased incidence of celiac disease and non-celiac gluten sensitivity observed in recent years might be due in part to the genetic modification of wheat.

Animal studies and circumstantial evidence in humans suggest that dietary gluten may also contribute to the pathogenesis of type 1 diabetes. The results of the present study suggest that certain strains of wheat are more diabetogenic than other strains. Of note, I have seen several patients with non-celiac gluten sensitivity who can tolerate wheat when traveling to various other countries but not when they are in the United States.

Gorelick J, et al. The impact of diet wheat source on the onset of type 1 diabetes mellitus - lessons learned from the non-obese diabetic (NOD) mouse model. *Nutrients*. 2017;9:E482.

Magnesium Prevents Kidney Injury in Critically Ill Patients

One hundred forty-three critically ill patients in an intensive care unit (ICU) who had hypomagnesemia were randomly assigned to receive, in double-blind fashion, a daily infusion of 24 mmol of magnesium (type not specified) for three days and repeated whenever hypomagnesemia recurred during the ICU stay, or the same volume of saline (placebo). The incidence of acute kidney injury was significantly lower in the magnesium group than in the control group (23% vs. 39%; p value not stated). The proportion of patients who developed hypermagnesemia was significantly higher in the magnesium group than in the placebo group (34.2% vs. 5.7%; $p < 0.0001$).

Comment: The results of this study suggest that intravenous administration of magnesium can prevent acute kidney injury in critically ill patients with hypomagnesemia. Hypomagnesemia is common in critically ill patients, occurring in 20% of cases in one study. Hypermagnesemia is also relatively common in critically ill patients, so serum magnesium levels should be measured before considering intravenous magnesium therapy. Serum magnesium levels should be monitored closely during treatment, so as to reduce the risk of causing iatrogenic hypermagnesemia.

Barbosa EB, et al. Effects of magnesium supplementation on the incidence of acute kidney injury in critically ill patients presenting with hypomagnesemia. *Intensive Care Med*. 2016;42:1084-1085.

Sodium Alginate for Gastroesophageal Reflux Disease

One hundred thirty-six patients with gastroesophageal reflux disease (GERD) who remained symptomatic on a proton pump inhibitor (PPI) continued their PPI and were randomly assigned to receive, in double-blind fashion, 10 ml of a sodium alginate suspension (Gaviscon Advance) four times per day (30 minutes after meals and at bedtime) or placebo for seven days. Symptoms were assessed using the Heartburn Reflux Dyspepsia Questionnaire (HRDQ). The mean improvement in the HRDQ reflux score was significantly greater in the active-treatment group than in the placebo group (53% vs. 33%; $p = 0.01$). The mean improvement in the HRDQ heartburn score was also significantly greater in the active-treatment group

than in the placebo group (55% vs. 33%; p < 0.01). The mean number of nights with symptoms decreased from 3.9 to 2.2 in the active-treatment group and from 3.6 to 3.0 in the placebo group (p < 0.01 for the difference in the change between groups).

Comment: Sodium alginate is a compound derived from seaweed. It interacts with gastric acid within a few minutes and forms a viscous gel that floats on top of the gastric contents like a raft and physically inhibits the reflux of gastric contents into the esophagus. In previous clinical trials, sodium alginate was at least as effective as an antacid or a proton pump inhibitor in patients with symptomatic GERD. The results of the present study indicate that, in GERD patients who do not respond adequately to a PPI, the addition of sodium alginate can decrease symptoms.

Reimer C, et al. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. *Aliment Pharmacol Ther*. 2016;43:899-909.

5-Methyltetrahydrofolate for Schizophrenia

Fifty-five outpatients (mean age, 45.5 years) with chronic schizophrenia (mean duration of illness, 20.4 years) were randomly assigned to receive, in double-blind fashion, 15 mg per day of 5-methyltetrahydrofolate (5-MTHF; also called L-methylfolate) or placebo for 12 weeks. Compared with placebo, 5-MTHF significantly improved the mean Positive and Negative Syndrome Scale (PANSS) total score (mean improvement, 9.5% vs. 1%; p = 0.03), as well as the PANSS Negative (p = 0.02) and General Psychopathology (p = 0.004) subscales. Significant between-group differences persisted when anticonvulsant use was included as a covariate (anticonvulsants can cause folate deficiency).

Comment: In this study, supplementation with 15 mg per day of 5-MTHF produced modest improvement in patients with chronic schizophrenia. Considering the refractory nature of this chronic condition, even a modest improvement is noteworthy. Additional research is needed to determine what patient characteristics might predict a positive response to 5-MTHF.

Roffman JL, et al. Biochemical, physiological and clinical effects of L-methylfolate in schizophrenia: a randomized controlled trial. *Mol Psychiatry*. 2017 Mar 14 [Epub ahead of print].

References

1. Hooshmand S, et al. The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: a randomized, controlled trial. *Osteoporos Int*. 2016.;27:2271-2279.
2. de Lorgeril M, Salen P. Gluten and wheat intolerance today: are modern wheat strains involved? *Int J Food Sci Nutr*. 2014;65:577-581.

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On the cover

Female Infertility – Endocrine Disruptors Stealing Our Future

by Bonnie Nedrow, ND

Recent History

In 1991, a group of scientists were brought together for a Wingspread conference to discuss whether xenobiotics, non-biological chemicals found in people and animals, disrupt the endocrine system. These experts reached consensus that environmental chemicals could biologically interfere with hormones, leading to the codification of the concept of endocrine disruption. Fast-forward to 2017 and we find a large body of research demonstrating how endocrine-disruptive chemicals (EDCs) damage human health in a myriad of ways. From developmental disorders to neurological disorders, from infertility to metabolic diseases, we are discovering that our dependence on everyday chemicals comes with an overwhelming cost to our health, and potentially to our future.

A growing concern is the impact of EDCs on the reproductive success of women in the childbearing years. Every year an increased number of women pursue assisted reproductive technology (ART). Since 2003, there has been a 65% increase in the use of IVF for women who are unable to get pregnant.[1] These women are experiencing estrous cyclicity abnormalities, increased time-to-pregnancy, increased miscarriage rate, and premature ovarian failure.[2] Medicine has rapidly advanced in the field of ART, helping many infertile people conceive a child, but why are so many seeking help? Are EDCs at fault?

A complete infertility assessment and treatment strategy would take multiple factors into consideration. However, I will limit this review to endocrine disruptors and female fertility, leaving out the other half of the fertility equation; the ever-declining sperm count. By doing so, I will also skip the important contribution of xenobiotic oxidation on infertility for both sexes. Other crucial fertility concerns are the epigenetic inheritable impacts of EDCs on the reproductive health of the next generation, the role of age on fertility, chronic stress contribution and the impact of infections and chronic disease. In truth, the "why" of infertility appears to be all of these factors.

Mechanisms of EDCs

EDCs can mimic or block hormones, interfere with receptor binding, alter steroidogenesis, and change the metabolism of hormones. The function of all reproductive hormones can be altered including estrogens, androgens, progesterone, gonadotrophin releasing hormone (GnRH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid hormones. Almost every chemical grouping has been implicated in fertility-related endocrine disruption including polycyclic aromatic hydrocarbons, pesticides, heavy metals, phthalates, polybrominated diphenyl ethers, bisphenol-A and BPA alternatives, dioxins, nonylphenols, polychlorinated biphenyls, perfluorinated compounds, triclosan, and parabens. Of concern to the general populace, many of these chemicals are frequently encountered in non-occupational exposure settings.

BPA is one of the world's highest production volume chemicals; ubiquitous in most people's daily lives, it has been recognized as a significant player in reproductive health concerns. BPA is thought to decrease fertility in part by acting as an agonistic to alpha and beta estrogen receptors.[3] Because BPA has a weak estrogenic effect at the receptor site, it can mute overall estrogen expression by blocking endogenous estrogens.

Some of the best studies on EDCs and infertility come from ART participants. Unlike live sperm that can easily and inexpensively be studied outside the body, assessment of the ovum is expensive and often invasive. Because families suffering from infertility are willing to invest in this costly testing, we now have a body of research on the etiology of EDC-driven female infertility. Ovarian reserve and ovarian response tests, currently available and well defined, are FSH, LH, inhibin-B, the ovarian antral follicle count (AFC), and anti-Müllerian hormone (AMH). A 2015 study of 209 women undergoing infertility treatments demonstrated a significant trend (p-trend 0.001) of higher BPA associated with lower AFC. BPA affects oocyte maturation by altering the granulosa cells' effectiveness at assisting follicular growth, steroidogenesis, and oocyte nourishment in the intra-ovarian and intra-follicular environment. In this study, the highest documented BPA urinary level in the 4th quartile showed a 17% decrease in AFC. Interestingly, there was a 22% decrease in AFC at the third quartile, which is a lower amount of BPA.[4]

One of the challenges of EDCs is that their dose response curve can be U-shaped instead of linear; very low doses of a toxicant show endocrine disruption while very high doses show toxicity, via mechanisms such as oxidation. It is important to note that the BPA-free plastics contain chemicals such as BPS and BPF, which have the same mechanism of action on the endocrine system as BPA and are equally linked to infertility.

Polycystic ovarian syndrome (PCOS), one of the most common endocrine disorders of women in the reproductive years, affects 6-21% of women, depending on diagnostic criteria, and is the primary cause of anovulatory infertility. There is an association of PCOS, elevated androgens, and elevated BPA; but causality has not been defined. Two hypotheses have surfaced to explain this observation; elevated androgens impair excretion of BPA or that BPA displaces testosterone from sex hormone binding globulin (SHBG), thereby increasing free testosterone. The relationship between androgens and BPA may indeed be bi-directional, both a cause and a consequence of deregulated androgens and PCOS.[5]

Discovering the Root of the Problem

I have focused on BPA, a well-studied ubiquitous endocrine disruptor, but what about the other 2,999 chemicals that your infertility patient has likely been exposed to? To further complicate the picture, we know that people are not exposed to chemicals one-by-one, but rather to a constantly fluctuating chemical soup. Where does a clinician start to unravel and treat the cause?

Step one is a thorough environmental health questionnaire with an in-depth look at daily chemical exposures via food, water, air, and topical routes. A complete exposure assessment and education of personal care products, cleaning products, furnishing, building materials, storage of chemicals, car, and workplace can significantly reduce daily contact with EDCs. To assess endogenous sources of xenobiotics, a comprehensive time-line correlating potential chemical exposures in the past to the temporal onset of new symptoms, can help you determine if testing could be fruitful.

While we are still not able to test all 3,000 high-volume environmentally relevant compounds, a growing list of diagnostic tests is available. There are several labs that offer serum, whole blood, and urine tests on phthalates, BPA, parabens, chlorinated and phosphorylated pesticides, PCBs, dioxins, solvents, toxic metals, and glyphosate. When choosing a test, consider the half-life of the compound. For example, the rapid half-life of phthalates and BPA, and even the slightly longer half-life of organophosphate pesticides, indicates that levels reflect current exposure. The prime treatment for chemicals that are quickly metabolized is avoidance. In this case, treat first with assessment and exposure reduction and then test to demonstrate the effectiveness of the avoidance strategy.

For persistent EDCs such as lead, mercury, cadmium, dioxins, PBDE flame-retardants, PCBs, and organochloride pesticides, testing assesses current exposure plus body burden. While it is beyond the scope of this review, it is imperative to use the right test for the compound you are looking for. For example, a urine test is ideal to screen for cadmium overload, whereas whole blood is a more appropriate sample for initial lead testing. In the case of persistent compounds, while avoidance is crucial, it is often not sufficient with significant chemical body burden.

Functional tests indicating inflammation, oxidation, and liver metabolism are alternatives to testing for specific chemicals. These tests are more affordable and therefore more practical for monitoring therapy. My favorite functional test is a hepatic panel including AST, ALT, GGT, and bilirubin. GGT, a known marker of excessive alcohol consumption, has also been proposed as a sensitive biomarker for xenobiotic exposures and body burden.[6,7] Moderate elevation of GGT, within its normal range, has been linked to various chemicals including lead, cadmium, organochlorine pesticides, dioxin, and PCBs. Other inexpensive and informative biomarkers of potential body burden and inflammatory or suppressive effects are hs-CPR and CBC assessing for cytopenia.[8,9]

Lab	Optimal Value
AST and ALT	16-24 UL
GGT	8-12 UL
Hs-CRP	<1.0 mg/L
Bilirubin	<1 mg/dL
Platelets	200-250 thousand/uL
WBC and RBC	4.5-5.5 thousand/uL

Detoxification of Body Burden of Xenobiotics (Depuration)

A first step in any depuration protocol is avoidance. Reducing daily chemical exposure and eliminating processed foods and alcohol is imperative. Sugar, in ➤

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particular, should be avoided due to its contribution to inflammation and its displacement of nutrient-dense food. A general cleanup of the home environment is also crucial, particularly the bedroom where healing and detoxification occur during sleep.

Opening the channels of elimination is the next step; mobilization of endogenous xenobiotics without adequate elimination can cause harm. Specific treatment for dehydration/sub-hydration, constipation, anhidrosis (poor or lack of sweating) and shallow breathing is critical. Of all the depuration therapies, sauna is undoubtedly the most extensively studied and validated.[10,11] Other physical modalities that have empirically shown benefit are colon hydrotherapy, dry skin brushing, castor oil packs, acupuncture, yoga, and lymphatic massage to name a few.

The third foundational step for any depuration protocol is an adequate protein diet, high in phytonutrient-rich foods and fiber, and low in pesticides and other contaminants. Avoiding animal products, particularly animal fat and mercury-toxic fish, decreases exposure to bioaccumulated compounds. A hypoallergenic diet will help your patient avoid inflammation from food sensitivities

Once a general depuration plan is in place, you can add specific therapeutics for identified and/or suspected contaminants. The two main chemical forms of endogenous xenobiotics are metals and fat-soluble chemicals. Due to the risks associated with chelation of toxic metals, testing must always be done prior to treatment and, optimally, post-treatment. In addition, an informed consent with a strong recommendation for birth control during treatment of embryo toxic metals is good preventive policy for your practice. Metal testing is most accurate with an unprovoked test using the appropriate sample, comparing the results to the CDC's NHANES data,[12] and following with chelation provocation specific to the metal when treatment is indicated.

Elimination of fat-soluble compounds starts with mobilization. Exercise and weight loss are both effective tools. For the overweight or obese infertility patients, weight loss is an effective and important component of treatment. A loss of as little as 5-10% body mass can restore ovulation in anovulatory women.[13] However, weight-loss without depuration of mobilized chemicals is a disservice to the health of your patient and their future child. Weight stabilization or weight gain is shown to reduce circulating persistent organic fat-soluble pollutants, which can expose baby in utero as well as the breast-feeding infant. Effective depuration of fat-soluble compounds includes the use of sauna, fiber[14] and other binders, lipase-inhibitors,[15] and nutrients and herbs supporting phase one and phase two liver enzymes.

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.

The Importance of Preconception Care

I am a champion of preconception care for all pregnancies due to the overwhelming exposure fertile people have to xenobiotics that are associated with long-term health outcomes for children. When infertility is a concern, application of the Precautionary Principle notches up considerably. If we suspect EDCs to be a component of infertility, then we should also be cognizant that these same compounds limiting fertility can also cause harm to gametes, embryos, fetuses, babies, and breast-feeding toddlers. Given the magnitude of chemical exposure in our modern world, I would argue that EDCs have at least some impact on all infertility, even when they are not the roots of the cause. Infertility is a sign that the body is not at optimal health. Helping infertile people to get pregnant at any cost is a core value of ART. Helping people, even those who ultimately choose ART, to become healthier before attempting conception is an investment to the next generation.

References

1. www.rmanj.com/infertility-in-america-2015-survey-report/
2. Rattan S, et al. Exposure to endocrine disruptors during adulthood: consequences for female fertility. *Journal of Endocrinology*. 2017 Jun;233(3):R109-R129
3. La Rocca C, et al. Exposure to Endocrine Disrupters and Nuclear Receptor Gene Expression in Infertile and Fertile Women from Different Italian Areas. *Int J Environ Res Public Health*. 2014;11:10146-10164
4. Zhou W, et al. Bisphenol A and Ovarian Reserve among Infertile Women with Polycystic Ovarian Syndrome. *Int J Environ Res Public Health.* 2016 Dec 27;14.
5. Caserta D, et.al. Bisphenol A and the female reproductive tract: an overview of recent laboratory evidence and epidemiological studies *Reprod Biol Endocrinol*. 2014 May 9;12:37.
6. Lee DH, Jacobs DR Jr. Serum gamma-glutamyltransferase: new insights about an old enzyme. *J Epidemiol Community Health*. 2009 Nov;63(11):884-6
7. Serdar B, et al. Potential effects of polychlorinated biphenyls (PCBs) and selected organochlorine pesticides (OCPs) on immune cells and blood biochemistry measures: a cross-sectional assessment of the NHANES 2003-2004 data. *Environ Health*. 2014 Dec 16;13:114.
8. Sirivarasai J, et.al. Association between inflammatory marker, environmental lead exposure, and glutathione S-transferase gene. *Biomed Res Int.* 2013;2013:474963.
9. Chatterjee S, et al. An animal model of chronic aplastic bone marrow failure following pesticide exposure in mice. *Int J Stem Cells.* 2010 May;3(1):54-62.
10. Crinnion WJ. Sauna as a Valuable Clinical Tool for Cardiovascular, Autoimmune, Toxicant- induced and other Chronic Health Problems. *Alt Med Review*. 2011.
11. Genuis SJ, et al. Blood, Urine, and Sweat (BUS) Study: Monitoring and Elimination of Bioaccumulated Toxic Elements. *Arch Environ Contam Toxicol*. 2011 Aug;61(2):344-57.
12. https://www.cdc.gov/nchs/nhanes/index.htm
13. Duval K, et al. The Obesity-Fertility Protocol: a randomized controlled trial assessing clinical outcomes and costs of a transferable interdisciplinary lifestyle intervention, before and during pregnancy, in obese infertile women. *BMC Obes*. 2015 Dec 1;2:47
14. Kohda N, et al. Effect of chitosan intake on fecal excretion of dioxins and polychlorinated biphenyls in healthy men. *Biosci Biotechnol Biochem*. 2012;76(6):1195-200.
15. Jandacek RJ, et al. Effects of yo-yo diet, caloric restriction, and olestra on tissue distribution of hexachlorobenzene. *Am J Physiol Gastrointest Liver Physiol.* 2005 Feb;288(2):G292-9.

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Supporting Healthy Estrogen Metabolism During Bioidentical Hormone Replacement Therapy

by Chris D. Meletis, ND, and Kimberly Wilkes

As we grow older, an important component of any health-related regimen is the balancing of hormones to compensate for declining levels of estrogen and testosterone. Bioidentical hormone replacement therapy (BHRT) is a common and effective way to achieve this goal. However, one common mistake is to use BHRT without taking the correct dietary supplements to offset the poor metabolism of hormones. Gut health and any imbalances in the gut microbiota – the population of bacteria, fungi, and other microorganisms that inhabit the intestines – also need to be addressed to ensure the body is able to properly use estrogen and testosterone.

In this article, we will discuss the reasons why an imbalanced gut microbiota leads to dysfunctional hormone metabolism during menopause, as well as which dietary supplements are helpful in ensuring the body processes estrogen in a safe and efficient way. Finally, we will discuss why mitochondrial support is an often-neglected but critical component of bioidentical hormone replacement therapy.

The Gut as A Source Of Steroid Hormones

When considering the origin of estrogen production, the ovaries and adrenals normally come to mind. Surprisingly, however, it is now known the intestine can generate and metabolize sex hormones.[1] Bioactive steroids have been identified in both the rodent and human gut.[1] The cells lining the intestines (known as epithelial cells) are a cellular source of steroid production.[1] In addition, intestinal epithelial cells are able to metabolize estrogen.[1]

17β-estradiol, a powerful estrogen made primarily by the ovaries of females and the testes of males, influences the development and function of the reproductive system. 17β-estradiol also is produced in tissues not related to reproduction where it governs a number of actions, including inflammatory responses. Lymph nodes located in a membrane that attaches the intestine to the abdominal wall and lymphatic tissue in the small intestine produce 17β-estradiol.[2] In mice, these intestinal lymphatic areas contained 17β-estradiol levels significantly greater than those in blood, and there was more 17β-estradiol in lymph-related organs compared with the ovaries and testes.[2]

The estrogen estradiol also protects the lining of the intestines known as the epithelial barrier from damage.[3] It keeps the gut walls strong and stops "leaky gut," what scientists call intestinal permeability, where bacteria and food allergens slip through a weak intestinal lining and out into the blood stream, where they can wreak havoc in the body.[3]

Further evidence of a link between estrogen and the gut comes in the form of studies that show there is a relationship between estrogen and inflammatory bowel syndrome (IBS).[4] Estrogen helps regulate the development of IBS in part through its ability to interact with the hormone serotonin,[4] a large amount of which is produced in the gut and helps regulate intestinal function. Estrogen also reduces the effect of psychological stress on the brain and the gut.[4] Some studies have found that, while in postmenopausal women, there is a significant *decrease* in incidence of IBS,[5] symptom severity may *increase* following menopause.[6]

Estrogen and Your Gut Bacteria

The beneficial microbes in a woman's gut are affected by age and her declining estrogen levels.[7] But the relationship between the gut microbiota and estrogens is a two-way street because the gut microbiota also help regulate levels of estrogens.[7]

The parent estrogens estrone and estradiol are metabolized in several ways including the 2-, 4-, and 16-hydroxylation pathways. Each of these estrogen metabolites differs in how easily they are used by the body and the strength of the metabolite. And each of these estrogen metabolites has different effects on the body. In many cell culture and animal studies, a higher level of 2-hydroxylated estrogen metabolites is associated with a lower risk of postmenopausal breast cancer. The gut microbiota may play an important role in assuring that estrogen is metabolized through the safer 2-hydroxylated pathway. One group of researchers found that in 60 postmenopausal women, greater diversity of the microbiota was associated with higher ratios of 2- and 4-hydroxylated metabolites to parent

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estrogens such as estrone and estradiol, suggesting that gut microbes are associated with estrogen metabolism and optimal counts of beneficial bacteria may reduce postmenopausal breast cancer risk.[7]

Researchers also have shown that the use of conventional estrogen replacement therapy is able to boost levels of beneficial vaginal bacteria.[8] In one study of 40 postmenopausal women receiving hormone replacement therapy (HRT) and 20 who were not on HRT, the probiotic species lactobacilli were present in the vagina of 95% or more of the participants in both groups.[8] However, in the HRT group, *Lactobacillus* was more often the dominant and only beneficial species present. In addition, in the HRT group, there were significantly fewer harmful bacteria. Plus, an infection known as bacterial vaginosis occurred less often in the HRT group compared with the women not receiving HRT.

Adding to the evidence that there is a connection between steroid hormones and the gut is the fact that the probiotic organism *Lactobacillus reuteri* when given to mice in their drinking water, improved markers of gonadal aging.[9] The study authors believe this was due to the anti-inflammatory actions of the probiotic. Even though this study was done in male mice, it provides an interesting perspective that could be applied in clinical practice to females.

The Microbiota's Far-Reaching Role in Postmenopausal Health

Declining estrogen levels during menopause makes women more vulnerable to increased bone loss and fracture risk.[10,11] The microbiota are involved in protecting against age-related bone loss. In mouse models of menopause, supplementation with the probiotic *L. reuteri* stopped bone loss and reduced bone breakdown related to estrogen deficiency.[12]

The way the gut microbiota accomplishes its bone-protecting effects is in part through raising levels of insulin-like growth factor 1 (IGF-1), which plays a role in bone health.[13] Clinically, IGF-1 also serves as a marker of biological aging and growth hormone levels.[14,15] The lower your IGF-1, the lower your growth hormone levels and the faster you age and suffer from effects like cognitive decline.[15]

Phytoestrogen Supplements and Gut Bacteria

Menopausal women commonly use phytoestrogen supplements to ease symptoms such as hot flashes. Phytoestrogens such as soy have a similar chemical structure to human estrogens, produce estrogenic activities, and cause effects similar to estrogen. Intestinal bacteria metabolize phytoestrogens into compounds that are more bioavailable and have more estrogenic/anti-estrogenic and antioxidant activity than the parent phytoestrogens themselves.[16,17] These compounds also have anti-inflammatory effects, stop the multiplication of cells, which is linked to cancer, and trigger the death of unhealthy cells.[17,18]

Some individuals have the ability, through the actions of the intestinal microbiota, to convert phytoestrogens into these more bioavailable metabolites, which may make them less vulnerable to hormone-dependent diseases.[19-21] The intestinal microbiota's transformation of phytoestrogens into their bioavailable metabolites is critical to the reduction of menopausal symptoms and certain chronic diseases, such as cancer, cardiovascular disease, and osteoporosis.[19-21]

One group of researchers suggested, "the clinical effectiveness of soy protein in cardiovascular, bone, and menopausal health may be a function of the ability to biotransform soy isoflavones to the more potent estrogenic isoflavone, equol" and that this transformation was dependent on intestinal bacteria.[22] The researchers pointed out that past studies did not distinguish between participants who were "equol-producers" and "nonequol producers," which could explain why studies on the health benefits of soy have yielded conflicting results.

The Importance of Blocking a Harmful Enzyme

The body processes hormones as well as drugs and environmental toxins using a sugar called glucuronic acid. In the liver, this sugar attaches itself to drugs, hormones, and toxins meant to be excreted from the body through the bile duct to the GI tract. In doing so, glucuronic acid neutralizes the potentially harmful substance. However, an enzyme called beta-glucuronidase searches for this sugar because it needs to use it as a source of carbon. Once beta-glucuronidase separates the glucuronic acid from the hormone, toxin, or drug, metabolites of these substances are not always completely eliminated from the body.[23] They can be reactivated and highly toxic to GI tissues.[23] That's why it is essential that beta-glucuronidase levels be balanced in people on BHRT, so that estrogen does not become reabsorbed.

A small number of the thousands of intestinal microbiota organisms – about 50 species, including *E. coli* – can release beta-glucuronidase.[24] On the other hand, a number of probiotic organisms can inhibit the production of beta-glucuronidase. A study of the fecal water of 15 people who were a variety of ages (children, adults, and elderly) found that when the water was incubated with a carcinogen, the toxicity and the beta-glucuronidase activity of the water was increased.[25] However, the probiotic organism *Lactobacillus paracasei* reduced beta-glucuronidase by 76% in the fecal water of the children and by 82% in the elderly.

Another study investigated the effects of a multispecies probiotic supplement consisting of *Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* Lc705, *Propionibacterium freudenreichii* ssp. *shermanii* JS, and *Bifidobacterium breve* on intestinal microbiota and beta-glucuronidase in patients with irritable bowel syndrome (IBS).[26] In this placebo-controlled, double-blind trial, 55 IBS patients received either the multispecies probiotic or a placebo daily for six months. At the study's conclusion, researchers observed a decline in beta-glucuronidase activity in 67% of the subjects given the probiotic

compared with only 38% of participants given the placebo.

In an animal study, rodents that were exposed to one of three conditions – a chemical that causes colon cancer, atherosclerosis triggered by a high-fat diet, or an imbalance of the gut microbiota caused by antibiotic administration – were supplemented daily with *Lactobacillus plantarum* alone or combined with antibiotics.[27] In the rats exposed to the cancer-causing chemical, the probiotic lowered beta-glucuronidase activity. In the atherosclerosis group and the imbalanced gut microbiota rodents, combining the probiotic with an antibiotic also reduced beta-glucuronidase activity.

Calcium D-Glucarate

Calcium-D-glucarate is the calcium salt of D-glucaric acid, which humans synthesize naturally in small amounts. Many fruits and vegetables, especially oranges, apples, grapefruit, and cruciferous vegetables, are also a source of glucaric acid. Oral supplementation of calcium D-glucarate blocks the beta-glucuronidase enzyme for five hours.[28]

Calcium-D-glucarate's ability to suppress beta-glucuronidase helps hormones such as estrogen to be excreted before they are reabsorbed. Large oral doses of calcium-D-glucarate fed to rats resulted in a 23% drop in serum estrogen levels.[28] In rats exposed to a chemical carcinogen that causes breast cancer in the animals, calcium D-glucarate blocked tumor development by over 70%.[29]

Scientists have also studied calcium-D-glucarate in breast, lung, colon, and liver cancers in rodent models, and the beneficial results occurred due to a variety of mechanisms including inhibiting beta-glucuronidase activity.[28,30,31]

Because calcium D-glucarate blocks beta-glucuronidase and therefore improves the excretion of estrogen from the body, Dr. Meletis uses it in his clinical practice in patients on estrogen replacement therapy as a precaution against estrogen re-absorption and the resulting harmful effects.

Funneling Estrogen Through the Safest Pathway

As we mentioned earlier, there are several ways in which estrogens are metabolized in the body, including the 2-, 4-, and 16-hydroxylation pathways. A type of estrogen produced in the body known as 17beta-estradiol can be converted into 16alpha-hydroxyestrone (16alphaOHE$_1$) or 2-hydroxyestrone (2OHE$_1$). Compared with 2OHE$_1$, which can act as an anti-estrogen, 16alphaOHE$_1$ is extremely estrogenic; and in cell culture studies, it caused estrogen-sensitive breast cancer cells to multiply.[32] Consequently, researchers have hypothesized that changing the way 17beta-estradiol is metabolized from the 16alphaOHE$_1$ pathway toward the 2OHE$_1$ pathway could lower the risk of estrogen-sensitive cancers, including breast cancer.[33,34]

However, the scientific community is debating the extent to which the urinary 2OHE$_1$:16OHE$_1$ ratios can protect against breast cancer risk, based on conflicting results among studies. A trial of 272 women with breast cancer and 291 controls concluded that the ratio of 2-OHE1 to 16alpha-OHE1 did not predict breast cancer risk.[35] In another study of 66 breast

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cancer patients and 76 control patients, the mean level of urinary 2-OHE1, which is thought to be protective against breast cancer, was actually *higher* in the women with breast cancer compared with controls.[36]

Evidence to the contrary includes one study of 65 women with breast cancer, in which the ratio of $2OHE_1$ to $16OHE_1$ significantly predicted whether the women would develop breast cancer or not.[37] In another study of 42 postmenopausal breast cancer patients and 64 women who visited the hospital for a routine mammogram, $16OHE_1$ was a strong risk factor for breast cancer as was a higher level of $16OHE_1$ compared with $2OHE_1$.[38] Another group of researchers studied 10 normal women and 33 breast cancer patients. The scientists found that there was greater 16 alpha-hydroxylation in the women with breast cancer.[39]

A recent trial offered one explanation as to why not all studies show that higher levels of 2-hydroxylation are associated with breast cancer risk. In this trial, researchers measured levels of the estrogens estradiol, estrone, and 13 metabolites in 1,298 postmenopausal women with breast cancer and 1,524 matched controls.[40] There was a strong link between total estrogen levels and an increased risk of breast cancer. When the researchers normalized estrogen levels in the women, they observed that both a relative increase in levels of 2-hydroxylation and an increase in the ratio of 2-hydroxylation to 16-hydroxylation resulted in a lower risk of breast cancer. The greatest risk of breast cancer occurred in women who had the highest estrogen levels accompanied by lower levels of 2-hydroxylation or a lower ratio of 2-hydroxylation to 16-hydroxylation. Past studies finding that the $2OHE_1$:$16OHE_1$ ratio is not associated with breast cancer risk did not determine how total estrogen levels impacted the risk associated with the $2OHE_1$:$16OHE_1$ ratio.

It is also interesting to note that mutations in the catechol-*O*-methyltransferase (COMT) gene can lead to the body processing estrogen metabolites differently compared to women who don't have this mutation. If a person has a defect in the COMT gene, it can lead to altered levels of $2OHE_1$ and $16OHE_1$.[41] Tests are available to detect COMT genetic mutations.

Nutrients That Encourage the Safe Metabolism of Estrogen

Cruciferous vegetables such as broccoli, cauliflower, kale, and Brussels sprouts contain the phytochemical indole-3-carbinol (I3C). In the body, I3C is broken down to 3,3-diindolylmethane – DIM, for short. Studies in animals and humans have shown that

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supplementation with I3C or DIM or eating a lot of cruciferous vegetables can change the way the body metabolizes estrogen from the possibly harmful 16-hydroxylation pathway to the safer 2-hydroxylation pathway.[34]

Increased urinary $2OHE_1$ levels or urinary $2OHE_1$:16αOHE$_1$ ratios have occurred in a number of controlled clinical trials using oral supplementation with 300-400 mg/day of I3C in women. In one of those studies, 400 mg/day of I3C daily for three months resulted in a significant mean increase in the $2OHE_1$:16alphaOHE$_1$ ratio in all but three of 20 women.[42] In another study of both men and women, I3C significantly increased 2-hydroxylation and lowered levels of nearly all other estrogen metabolites, including estradiol, estrone, estriol, and 16alpha-hydroxyestrone.[43] In a trial of 60 women who had an increased risk of breast cancer, 300 mg/day of I3C improved the urinary estrogen metabolite ratio of $2OHE_1$ to 16alphaOHE$_1$.[44]

DIM works similarly to I3C. Supplementation with 108 mg/day of DIM in postmenopausal women with a history of early stage breast cancer increased urinary $2OHE_1$ levels.[45] In women with thyroid proliferative disease, 300 mg of DIM per day led to an increase in the ratio of 2-hydroxyestrone to 16alpha-hydroxyestrone.[46] In a randomized, controlled clinical trial, 2 mg/kg/day of DIM was shown to cause a high rate of improvement in cervical dysplasia,[47] a precancerous condition where cells grow abnormally on the outside of the cervix or in the opening between the uterus and the vagina.

Supporting Mitochondria During Hormone Therapy

All hormones originate in the mitochondria, where the conversion of cholesterol to pregnenolone – the precursor to all steroid hormones – occurs.[48,49] Additionally, the electron transport chain of mitochondria plays a role in testosterone production and altering this pathway increases production of testosterone.[50]

More evidence that hormones are involved in mitochondrial function is that receptors for estrogens, androgens, and thyroid hormones are located in the mitochondria of many cell types.[51,52] Scientists have found estrogen receptors in mitochondria of rat uterine and ovarian cells, breast cancer cells, cultured human lens epithelial cells, and rat hippocampus and neuronal cells. Moreover, estrogen receptors were found in mitochondria of heart cells, liver cancer cells, osteosarcoma cells, human sperm cells, and in human ligament cells of the gums.[51] Estrogens and male hormones play a role in shielding the mitochondria from damage.[53] Plus, estrogen controls many aspects of mitochondrial function as well as the generation of new mitochondria.[54,55]

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Because of the relationship between estrogen and mitochondrial health, Dr. Meletis often includes a mitochondrial-supporting supplement in the regimen of patients on hormone replacement therapy. Coenzyme Q10 (CoQ10), alpha-lipoic acid, acetyl-L-carnitine, and quercetin can all be used to support mitochondrial function.

CoQ10 is one of the best-known mitochondria-supporting nutrients. Human studies have shown that giving CoQ10 to patients before cardiac surgery raises levels of this nutrient in the mitochondria of the heart and makes the mitochondria more efficient.[56] It also protects the mitochondria from the stress that occurs when blood vessels are deprived of oxygen during surgery and then reoxygenated.[56] In people with mitochondrial diseases known as mitochondrial cytopathies, taking 150 mg of CoQ10/day for six months improved brain health and enhanced mitochondrial function in the skeletal muscle of the CoQ10 group compared with controls.[57]

In animal models of aging, alpha-lipoic acid and/or acetyl-L-carnitine block the generation of harmful oxidants and improve mitochondrial function.[58] In humans with coronary artery disease, alpha-lipoic acid and acetyl-L-carnitine lowered blood pressure and improved vascular function, probably in part through enhancing mitochondrial function.[59]

Quercetin has also emerged as a mitochondrial rejuvenating nutrient. In untrained men, 1,000 mg/day of quercetin led to a small but significant improvement in 12-minute treadmill time trial performance and a modest improvement in mitochondrial function and genes related to the creation of new mitochondria.[60] Quercetin improved mitochondrial function and/or stimulated the production of new mitochondria in models of traumatic brain injury,[61] the muscle atrophy that occurs after disuse,[62] and aluminum-caused free radical damage.[63]

Conclusion

When implementing a bioidentical hormone replacement therapy regimen, it is essential to support the safe metabolism of estrogen. The gut is an important source of steroid hormones such as estrogen, and probiotic organisms play a role in how the gut metabolizes estrogens. A balanced gut microbiota also increases the effectiveness of phytoestrogen supplements such as soy. I3C and DIM are important supplements that ensure that estrogen is escorted out of the body through the safest possible pathway. Calcium-D-glucarate also assists with estrogen metabolism as it blocks an enzyme known as beta-glucuronidase, which interferes with the body's ability to safely process estrogen and potentially harmful substances such as drugs and toxins. Additionally, mitochondrial support also is recommended during hormone replacement therapy, as all hormones originate in the mitochondria, which possess steroid hormone receptors.

References

1. Bouguen G, et al. Intestinal steroidogenesis. *Steroids*. 2015 Nov;103:64-71.
2. Oakley OR, et al. Estradiol Synthesis in Gut-Associated Lymphoid Tissue: Leukocyte Regulation by a Sexually Monomorphic System. *Endocrinology*. 2016 Dec;157(12):4579-87.
3. Diebel ME, et al. Estrogen modulates intestinal mucus physiochemical properties and protects against oxidant injury. *J Trauma Acute Care Surg*. 2015 Jan;78(1):94-9.
4. Mulak A, et al. Sex hormones in the modulation of irritable bowel syndrome. *World J Gastroenterol*. 2014 Mar 14;20(10):2433-48.
5. Triadafilopoulos G, et al. Bowel dysfunction in post—menopausal women. *Women Health.* 1998;27(4):55-66.
6. Olafsdottir LB, et al. Natural history of irritable bowel syndrome in women and dysmenorrhea: a 10-year follow-up study. *Gastroenterol Res Pract*. 2012;2012:534204.
7. Fuhrman BJ, et al. Associations of the fecal microbiome with urinary estrogens and estrogen metabolites in postmenopausal women. *J Clin Endocrinol Metab*. 2014 Dec;99(12):4632-40.
8. Heinemann C, Reid G. Vaginal microbial diversity among postmenopausal women with and without hormone replacement therapy. *Can J Microbiol*. 2005 Sep;51(9):777-81.
9. Poutahidis T, et al. Probiotic microbes sustain youthful serum testosterone levels and testicular size in aging mice. *PLoS One*. 2014 Jan 2;9(1):e84877.
10. McNamara LM. Perspective on post-menopausal osteoporosis: establishing an interdisciplinary understanding of the sequence of events from the molecular level to whole bone fractures. *J R Soc Interface*. 2010 Mar 6;7(44):353-72.
11. Riggs BL, et al. Sex steroids and the construction and conservation of the adult skeleton. *Endocr Rev*. 2002 Jun;23(3):279-302.
12. Britton RA, et al. Probiotic L. reuteri treatment prevents bone loss in a menopausal ovariectomized mouse model. *J Cell Physiol*. 2014 Nov;229(11):1822-30.
13. Yan J, et al. Gut microbiota induce IGF-1 and promote bone formation and growth. *Proc Natl Acad Sci U S A.* 2016 Nov 22;113(47):E7554-63.
14. Arnarson A, et al. Insulin-Like Growth Factor-1 and Resistance Exercise in Community Dwelling Old Adults. *J Nutr Health Aging*. 2015 Oct;19(8):856-60.
15. Okereke O, et al. Plasma IGF-I levels and cognitive performance in older women. Neurobiol Aging. 2007 Jan;28(1):135-42.
16. Gaya P, et al. Phytoestrogen Metabolism by Adult Human Gut Microbiota. *Molecules*. 2016 Aug 9;21(8). pii: E1034.
17. Landete JM, et al. Bioactivation of Phytoestrogens: Intestinal Bacteria and Health. *Crit Rev Food Sci Nutr*. 2016 Aug 17;56(11):1826-43.
18. Seeram NP, et al. Pomegranate ellagitannin-derived metabolites inhibit prostate cancer growth and localize to the mouse prostate gland. *J Agric Food Chem*. 2007 Sep 19;55(19):7732-7.
19. Chan YH, et al. Dietary intake of phytoestrogen is associated with increased circulating endothelial progenitor cells in patients with cardiovascular disease. *Eur J Cardiovasc Prev Rehabil*. 2011 Jun;18(3):360-8.
20. Yohwan Y, et al. Isoflavones from phytoestrogens and colorectal cancer risk: A nested case-control study within the Korean Multicenter Cancer Cohort. [abstract 4823]. In: Proceedings of the 104th Annual Meeting of the American Association for Cancer Research; 2013 Apr 6-10; Washington, DC. Philadelphia (PA): AACR; *Cancer Res*. 2013;73(8 Suppl).
21. Poluzzi E, et al. Phytoestrogens in postmenopause: the state of the art from a chemical, pharmacological and regulatory perspective. *Curr Med Chem*. 2014;21(4):417-36.
22. Setchell KD, et al. The clinical importance of the metabolite equol-a clue to the effectiveness of soy and its isoflavones**.** *J Nutr*. 2002 Dec;132(12):3577-84.
23. Wallace BD, et al. Structure and Inhibition of Microbiome β-Glucuronidases Essential to the Alleviation of Cancer Drug Toxicity. *Chem Biol*. 2015 Sep 17;22(9):1238-49.
24. Pellock SJ, Redinbo MR. Glucuronides in the Gut: Sugar-Driven Symbioses Between Microbe and Host. *J Biol Chem*. 2017 Apr 7. pii: jbc.R116.767434.
25. Nowak A, Śliżewska K. β-Glucuronidase and β-glucosidase activity and human fecal water genotoxicity in the presence of probiotic lactobacilli and the heterocyclic aromatic amine IQ in vitro. *Environ Toxicol Pharmacol*. 2014 Jan;37(1):66-73.
26. Kajander K, et al. Effects of multispecies probiotic supplementation on intestinal

microbiota in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2007 Aug 1;26(3):463-73.
27. Hijová E, et al. Ability of Lactobacillus plantarum LS/07 to modify intestinal enzymes activity in chronic diseases prevention. *Acta Biochim Pol*. 2017;64(1):113-116.
28. No authors listed. Calcium-D-glucarate. Altern Med Rev. 2002 Aug;7(4):336-9.
29. Walaszek Z, et al. Dietary glucarate as anti-promoter of 7,12-dimethylbenz[a] anthracene-induced mammary tumorigenesis. *Carcinogenesis*. 1986 Sep;7(9):1463-6.
30. Hanausek M, et al. Detoxifying cancer causing agents to prevent cancer. *Integr Cancer Ther.* 2003 Jun;2(2):139-44.
31. Zoltaszek R, et al. Dietary D-glucarate effects on the biomarkers of inflammation during early post-initiation stages of benzo[a]pyrene-induced lung tumorigenesis in A/J mice. *Oncol Lett*. 2011 Jan;2(1):145-54.
32. Telang NT, et al. Induction by estrogen metabolite 16 alpha-hydroxyestrone of genotoxic damage and aberrant proliferation in mouse mammary epithelial cells. *J Natl Cancer Inst*. 1992 Apr 15;84(8):634-8.
33. Bradlow HL, et al. 2-hydroxyestrone: the 'good' estrogen. *J Endocrinol*. 1996 Sep;150 Suppl:S259-65.
34. Higdon JV, et al. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. *Pharmacol Res*. 2007 Mar;55(3):224-36.
35. Cauley JA, et al. Estrogen metabolites and the risk of breast cancer in older women. *Epidemiology*. 2003 Nov;14(6):740-4.
36. Ursin G, et al. Urinary 2-hydroxyestrone/16alpha-hydroxyestrone ratio and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst*. 1999 Jun 16;91(12):1067-72.
37. Ho GH, et al. Urinary 2/16 alpha-hydroxyestrone ratio: correlation with serum insulin-like growth factor binding protein-3 and a potential biomarker of breast cancer risk. *Ann Acad Med Singapore*. 1998 Mar;27(2):294-9.
38. Kabat GC, et al. Urinary estrogen metabolites and breast cancer: a case-control study. *Cancer Epidemiol Biomarkers Prev*. 1997 Jul;6(7):505-9.
39. Schneider J, et al. Abnormal oxidative metabolism of estradiol in women with breast cancer. *Proc Natl Acad Sci U S A*. 1982 May;79(9):3047-51.
40. Sampson JN, et al. Association of Estrogen Metabolism with Breast Cancer Risk in Different Cohorts of Postmenopausal Women. *Cancer Res*. 2017 Feb 15;77(4):918-25.
41. Tworoger SS, et al. Association of CYP17, CYP19, CYP1B1, and COMT polymorphisms with serum and urinary sex hormone concentrations in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2004 Jan;13(1):94-101.
42. Bradlow HL, et al. Long-term responses of women to indole-3-carbinol or a high fiber diet. *Cancer Epidemiol Biomarkers Prev*. 1994 Oct-Nov;3(7):591-5.
43. Michnovicz JJ, et al. Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans. *J Natl Cancer Inst*. 1997 May 21;89(10):718-23.
44. Wong GY, et al. Dose-ranging study of indole-3-carbinol for breast cancer prevention. *J Cell Biochem Suppl*. 1997;28-29:111-6.
45. Dalessandri KM, et al. Pilot study: effect of 3,3'-diindolylmethane supplements on urinary hormone metabolites in postmenopausal women with a history of early-stage breast cancer. *Nutr Cancer*. 2004;50(2):161-7.
46. Rajoria S, et al. 3,3'-diindolylmethane modulates estrogen metabolism in patients with thyroid proliferative disease: a pilot study. *Thyroid*. 2011 Mar;21(3):299-304.
47. Del Priore G, et al. Oral diindolylmethane (DIM): pilot evaluation of a nonsurgical treatment for cervical dysplasia. *Gynecol Oncol*. 2010 Mar;116(3):464-7.
48. Ramalho-Santos J, Amaral S. Mitochondria and mammalian reproduction. *Mol Cell Endocrinol*. 2013 Oct 15;379(1-2):74-84.
49. Strushkevich N, et al. Structural basis for pregnenolone biosynthesis by the mitochondrial monooxygenase system. *Proc Natl Acad Sci U S A*. 2011 Jun 21;108(25):10139-43.
50. Le B, et al. New targets for increasing endogenous testosterone production: clinical implications and review of the literature. *Andrology*. 2014 Jul;2(4):484-90.
51. Psarra AM, Sekeris CE. Steroid and thyroid hormone receptors in mitochondria. *IUBMB Life*. 2008 Apr;60(4):210-23.
52. Wickramasekera NT, Das GM. Tumor suppressor p53 and estrogen receptors in nuclear-mitochondrial communication. *Mitochondrion*. 2014 May;16:26-37.
53. Vasconsuelo A, et al. Role of 17β-estradiol and testosterone in apoptosis. *Steroids*. 2011 Nov;76(12):1223-31.
54. Gigli I, Bussmann LE. Exercise and ovarian steroid hormones: their effects on mitochondrial respiration. *Life Sci*. 2001 Feb 16;68(13):1505-14.
55. Klinge CM. Estrogenic control of mitochondrial function and biogenesis. *J Cell Biochem*. 2008 Dec 15;105(6):1342-51.
56. Rosenfeldt F, et al. Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and in vitro contractility of myocardial tissue. *J Thorac Cardiovasc Surg*. 2005 Jan;129(1):25-32.
57. Barbiroli B, et al. Coenzyme Q10 improves mitochondrial respiration in patients with mitochondrial cytopathies. An in vivo study on brain and skeletal muscle by phosphorous magnetic resonance spectroscopy. *Cell Mol Biol* (*Noisy-le-grand*). 1997 Jul;43(5):741-9.
58. Hagen TM, et al. Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. *Proc Natl Acad Sci U S A.* 2002 Feb 19;99(4):1870-5.
59. McMackin CJ, et al. Effect of combined treatment with alpha-Lipoic acid and acetyl-L-carnitine on vascular function and blood pressure in patients with coronary artery disease. *J Clin Hypertens* (*Greenwich*). 2007 Apr;9(4):249-55.
60. Nieman DC, et al. Quercetin's influence on exercise performance and muscle mitochondrial biogenesis. *Med Sci Sports Exerc*. 2010 Feb;42(2):338-45.
61. Li X, et al. Protective Effects of Quercetin on Mitochondrial Biogenesis in Experimental Traumatic Brain Injury via the Nrf2 Signaling Pathway. *PLoS One*. 2016 Oct 25;11(10):e0164237.
62. Mukai R, et al. Preventive effect of dietary quercetin on disuse muscle atrophy by targeting mitochondria in denervated mice. *J Nutr Biochem*. 2016 May;31:67-76.
63. Sharma DR, et al. Quercetin protects against aluminium induced oxidative stress and promotes mitochondrial biogenesis via activation of the PGC-1α signaling pathway. *Neurotoxicology*. 2015 Dec;51:116-37.

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PCOS Variants in the Management of Infertility: Low-Androgen, Lean-Type and Post-Contraceptive Amenorrhea

by Corina Dunlap, ND, MS

Unusual polycystic ovarian syndrome (PCOS) presentations make recognition and management challenging. This article will walk through two variants, one highlighted in the literature and the other through clinical practice. The first variant is newly discussed in the literature: a low-androgen, lean, PCOS-type. The second is often misunderstood as being a post-pill syndrome, but rather is a PCOS-induced amenorrhea discovered post-contraceptive discontinuation. Details of both are discussed herein. Since PCOS is the most common endocrine disorder of reproductive-aged women worldwide and one of the top contributors to ovarian factor infertility,[1] this article serves as a tool to increase natural pregnancy and live birth rates through better recognition and treatment of these variants.

The Society for Reproductive Endocrinology and Infertility (SREI) states that 5-10% of women worldwide have PCOS.[2] Women are at especially high risk if they have a history of oligoovulatory infertility; obesity and/or insulin resistance; diabetes type 1, 2, or gestational; premature adrenarche (stage of puberty when the adrenal cortex begins to secrete androgens, typically signified by pubic and axillary hair growth); any first-degree relatives with PCOS; or use of antiepileptic drugs.

As we know, the PCOS diagnosis is typically made by Rotterdam criteria, when an individual has two of the three characteristics:

- Chronic anovulation,
- Hyperandrogenism (clinical or biological), and/or
- Polycystic ovarian morphology (PCOM).[3]

This criterion is endorsed by the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and the Androgen Excess and PCOS Society (AES).

There is an exception to the Rotterdam criteria, as recently discussed in the literature. A study published in the *Journal of Steroid Biochemistry & Molecular Biology* identified a previously unknown *lean*, PCOS-like phenotype characterized by the following:

- High anti-Müllerian hormone ≥ 75th quartile for respective age,
- Atypically low-testosterone (<19.0 ng/dL),
- Low DHEAS,
- Low cortisol, and
- Predisposition toward autoimmunity; with likely an adrenal autoimmune etiology.[4]

Based on findings, this subgroup appears more phenotypically PCOS-normal at a younger age, then later shifts from hyperandrogenic (non-obese) to still high AMH, but low-testosterone (non-obese) with advancing age.

Anti-Müllerian hormone (AMH) is a substance produced and released by the granulosa cells of small ovarian follicles and is a biomarker used to measure ovarian reserve.[5] AMH can decrease with age, history of chemotherapy and radiation, obesity, and oophorectomy. AMH can increase when there is a higher than average number of small ovarian follicles, such as is the case for some women with PCOS. Adding AMH to a fertility panel is not only an effective way to evaluate ovarian reserve, but can add clues about the presence of polycystic ovarian morphology (PCOM) in the absence of ultrasound, especially if AMH is ≥ 75th quartile for the patient's respective age.

Total testosterone (T) is typically measured in women suspected to have PCOS, especially with clinical evidence of hyperandrogenism (hirsutism, acne, and/or male-pattern hair loss).[6] Measured by liquid chromatography-tandem mass spectroscopy (LC-MS/MS), upper end of normal range is 45 to 60 ng/dL. In women, testosterone can be produced both by adrenals and ovaries; and thus, low-T (<19.0 ng/dL) cannot definitively be due to the dysfunction of either unless there is a concomitant abnormal biomarker to differentiate between the two.[4] In this study, the women with high-AMH and low-T also consistently had low dehydroepiandrosterone sulfate (DHEAS) and low cortisol, suggesting an adrenal cause. The authors further propose that there is a potential autoimmune link. When immune and inflammatory markers were examined, anti-TPO antibodies were significantly correlated. Although non-significant, the inflammatory markers, C-reactive

protein (CRP, mg/L) and interleukin-6 (IL-6, ng/mL), were twice as high in the identified PCOS-variant subgroup.

In the same study, all participants with high-AMH and low-T were given DHEA, 25 mg tid for at least 6-8 weeks, until their total T levels reached 30 ng/dL.[4] They concomitantly were given CoQ10, 333 mg tid, until positive pregnancy test. It was found that. once T levels normalized, they had significantly higher oocyte count, embryo quality, and live birth rates. Those with T levels greater than >30 ng/dL, comparatively, did not have as favorable outcomes.

This study offers a unique treatment approach for someone who presents with the above outlined characteristics who may otherwise 1) go undiagnosed, or 2) not receive support in the way of natural medicine and/or be forced into assisted reproductive technologies (ART) prematurely.

Another PCOS variant worthy of discussion is highlighted in the case of post-contraceptive amenorrhea. This clinical presentation is discussed within the context of this article because of the importance of timely recognition and treatment, and high likelihood for being easily misdiagnosed.

Amenorrhea, or the absence of menses, and anovulation, the absence of ovulation, are not always synonymous. As one of the Rotterdam diagnostic criteria for PCOS, chronic anovulation can present in multiple ways.[7] Commonly, chronic anovulation presents when the cycle length is >35 days long, beyond the two-to-three-year period post menarche. However, chronic anovulation can also occur when cycles are of normal length (25-32 days). In fact, hyperandrogenic women with normal length cycles are anovulatory 10-15% of the time. On the other end of the spectrum, women with amenorrhea are also commonly anovulatory. If women have experienced three-months or more of amenorrhea after menarche, they are given the diagnosis of secondary amenorrhea. PCOS is one of many possible underlying etiologies of secondary amenorrhea.

The literature states that amenorrhea occurs at the same frequency post-pill discontinuation as it does spontaneously[8]; however, women are often very stressed when their menses do not immediately resume post discontinuation. This is especially apparent in women who are actively trying to conceive.

It is important to follow a thorough evaluation and workup of secondary amenorrhea if a woman hasn't had menses for ≥ 3 months after initial menarche, regardless of prior pill use. Serum hCG is necessary to rule out any pregnancy at onset, followed by thyroid stimulating hormone (TSH), prolactin (PRL), follicle stimulating hormone (FSH), and estradiol (E2).[9] FSH and E2 may be tested at any time in those with amenorrhea since no information is available about days of the cycle. If TSH, PRL, FSH, and E2 are normal and there is evidence of hyperandrogenism, then PCOS is most likely the cause of amenorrhea. As evidenced by the first PCOS variant discussed in this article, even if hyperandrogenism is *not* present, you might still consider PCOS a potential cause.[4] This would be especially true if you concomitantly find high-AMH (≥ 75th quartile for respective age), atypically low-testosterone (<19.0 ng/dL), low DHEAS, and low cortisol.

Once you identify someone as having PCOS as the underlying cause of their amenorrhea, you can further identify if they fall into the insulin-resistant and/or obese category. This will help determine what treatment(s) may be effective to restore menses and ovulation. There are many lifestyle, diet, and natural medicine treatments to consider, depending upon PCOS subtype. In my recently published article in *Townsend Letter*, "Evidence Based Botanicals for the Treatment of PCOS & Fertility" (January 2018; p.93-94), recent literature on botanicals used for PCOS is reviewed. In the case of insulin-resistance and obesity, diet and exercise targeting weight loss is a first line approach.[10] Metformin may be used to restore cycles in women with insulin-resistant PCOS; however, many women prefer a natural medicine approach prior to trying to conceive. A commonly preferred natural medicine insulin-sensitizing agent for women with PCOS and infertility is myo-inositol. The studied dosage of 4 g/day, along with lifestyle recommendations, can be very helpful for restoration of menses and ovulation.[11] It is important not to forget to counsel women that restoration of ovulation can occur prior to resuming menstruation. Women may conceive while treating their PCOS-induced amenorrhea and not accurately identify their pregnancy symptoms.

References

1. March WA, et al. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Human Reproduction*. 2009;544-551.
2. American Society for Reproductive Medicine (ASRM). Polycystic Ovary Syndrome (PCOS). http://www.reproductivefacts.org/topics/topics-index/polycystic-ovary-syndrome-pcos/. Accessed December 2017.
3. Rotterdam, E. S. H. R. E., and ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human Reproduction (Oxford, England)*. 2004;19(1):41.
4. Gleicher N, et al. New PCOS-like phenotype in older infertile women of likely autoimmune adrenal etiology with high AMH but low androgens. *Journal of Steroid Biochemistry and Molecular Biology.* 2017;167:144-152.
5. Seifer DB, Baker VL, Leader B. Age-specific serum anti-Müllerian hormone values for 17,120 women presenting to fertility centers within the United States. *Fertility and Sterility.* 2011;95(2):747-750.
6. UpToDate. Diagnosis of polycystic ovary syndrome in adults. https://www-uptodate-com.nunm.idm.oclc.org/contents/diagnosis-of-polycystic-ovary-syndrome-in-adults?search=PCOS&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3#H3727155361. Accessed December 2017.
7. Ecochard R, et al. Chronological aspects of ultrasonic, hormonal, and other indirect indices of ovulation. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2001;108.8:822-829.
8. Jacobs, HS, et al. Post-"pill" amenorrhoea--cause or coincidence? *Br Med J.* 1977;2(6092):940-942.
9. UpToDate. Evaluation and management of secondary amenorrhea. https://www-uptodate-com.nunm.idm.oclc.org/contents/evaluation-and-management-of-secondary-amenorrhea?search=secondary%20amenorrhea&source=search_result&selectedTitle=1~58&usage_type=default&display_rank=1. Accessed December 2017.
10. Legro, RS, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism.* 2013;98(12):4565-4592.
11. Gerli S, et al . Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo controlled trial. *Eur Rev Med Pharmacol Sci*. 2003;7(6):151–159.

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Cortisol Deficiency: Frequent, Life-Impairing, and How to Give Patients Their Lives Back by Correcting It, Part 2

by Thierry Hertoghe, MD

Part 1 that discusses the signs and symptoms of cortisol deficiency appears in the January 2018 issue and is also available online.

To Treat or Not to Treat Cortisol Deficiency?

People with cortisol deficiency who do not get treatment continue suffering from the psychic and physical consequences of cortisol deficiency at every moment of their lives. In the long term, the absence of treatment permits the cortisol deficiency to aggravate and produce chronic inflammatory diseases such as rheumatoid arthritis and psychological disorders, from irritability to the extreme form of paranoid psychosis. Because of the adverse consequences of not treating cortisol deficiency, forgoing treatment is not really an option.

Natural Treatments to Improve Cortisol Levels

The first natural treatment to get a higher cortisol level is to increase light.[154] After moving from a dark room into full daylight, an individual's cortisol level increases by 50% or more within minutes. Thus, the golden rule is to expose oneself to more light: switching all the lights on in the office and at home and going outdoors at least once a day in full daylight for a minimum of half an hour. This quickly increases not only cortisol levels but also the number of cortisol receptors.

Second, it is of great importance to breathe cleaner air and eat organic foods to avoid airborne and foodborne pollutants, as toxins usually aggress the zona fasciculata of the adrenal glands that produces cortisol or block the target cells' glucocorticoid receptors, inhibiting part of the action of cortisol.

One of these irritant pollutants is formaldehyde,[155] which pollutes many homes and offices. It is part of many types of glue that fix floor coverings to the ground and bind compressed wood together in home and office furniture. It is often part of plastic carpets and toys and slowly outgasses from these objects into the indoor atmosphere over the years, being inhaled through breathing. What to do about it? Apart from getting rid of these formaldehyde-containing materials inside homes, simply open the windows in rooms where such materials are and let outdoor air enter. Regularly ventilating rooms with outdoor air drastically reduces the formaldehyde concentration in the indoor air and, thus, the risk of adrenal gland damage.

Third, increasing the consumption of protein-rich foods,[156-157] such as meat, poultry, and fish, and fat-rich foods,[158-161] such as eggs, yolk, butter (preferably clarified butter), liver, and other organ meats, elevates the cortisol production and level by providing the ingredients for production of cortisol. Augmenting protein is not always easy with patients with cortisol deficiency, as they tend to accumulate nitrogen in the blood by consuming these nitrogen-rich foods. Indeed, once they consume meat and other protein-rich foods, the high level of nitrogen in their blood (azotemia) gives them nausea and disgust for meat. Fat intake also poses problems, as fats seem hard to digest by these patients, frequently causing indigestion. The solution consists of correcting the cortisol deficiency with a cortisol supplement and encouraging the patients to increase the intake of the protein- and fat-rich foods they tolerate.

People with cortisol deficiency should also avoid "bad" carbs, carbohydrate-rich foods that reduce the production of cortisol, like sweets, sugars,[162] unsprouted bread, muesli, porridge, and rice. These foods can reduce the secretion of cortisol by 20–40%, enough to create problems. If ever they give in to the temptation of a chocolate bar or soft drinks, let them do it after a healthy meal, which dilutes the sugar into a bigger volume, reducing sugar's hyperglycemic effect that blocks cortisol production (peak levels of glucose inhibit cortisol release).

Fourth, some rare nutritional supplements can help the adrenal glands function better, although modestly. Vitamin C is one of them.[163-164] With 500 mg to 2 g of vitamin C a day, the action of cortisol may get a boost. L-acetyl-carnitine, the activated form of L-carnitine, is another nutrient whose intake has been shown to significantly increase serum cortisol levels in humans.[165] A dose of 2 g/day may be efficient.

Fifth, several herbal extracts may weakly mimic cortisol activity by increasing its bioavailability and stimulating cortisol receptors, providing limited relief to adrenal-deficient patients. Plants also produce hormones that may have beneficial effects in humans. Extracts of licorice root may, for example, lessen complaints in patients with cortisol deficiency.[166-167] In my experience, licorice root extract has about 10-25% of the beneficial action of an adequate cortisol or hydrocortisone treatment.

Sixth, as the storage of cortisol in the adrenal glands is small in patients with adrenal deficiency, these patients should avoid exposing themselves to any unnecessary stressors, which deplete the adrenals of their cortisol stores. Selecting jobs and leisure activities that do not put excessive strain on the adrenal glands may be a wise decision for people who do not get or want to take a cortisol treatment. Spiritual meditation has been reported to be helpful in improving cortisol levels. Regular meditators respond to stressful conditions with a greater production of cortisol than non-meditators, while the cortisol level is lower in resting states, minimizing spillage.[168]

Table 1 summarizes the main interventions you can do yourself with the help of a nutritionist to improve your cortisol secretion.

Table 1. Interventions to Improve Cortisol Secretion

- Increase light: daylight, intense indoor light, sunny holiday resorts
- Increase fat-rich foods (butter, egg yolk, liver, etc.)
- Take vitamin C supplements: 0.5 to 2 g/day
- Avoid indoor pollutants: stay away from plastic furniture or floor coverings, wood preservatives; keep windows open
- Reduce unhealthy carbohydrate-rich foods (sugar, sweets, chocolate, unsprouted bread, muesli, porridge, rice, pasta, soft drinks, alcohol)
- Herbal extract of licorice root: 450 to 1800 mg/day
- Increase protein-rich foods (fish, poultry, meat)
- Increase fruit intake (contains vitamin C, which may increase adrenal function)
- Avoid unnecessary stressful conditions (which deplete cortisol stores); regularly relax or meditate

Glucocorticoid Treatment of Cortisol Deficiency

Glucocorticoid is the common name given to the whole family of natural or synthetically produced cortisol-like molecules, which share the property of increasing the blood sugar levels. "Gluco" means "glucose" (sugar), and "corticoid" signifies that it "comes from the cortex," the outer part of the adrenal glands that produces this type of hormone. The human body makes two major bioidentical glucocorticoids: cortisol and cortisone. Bioidentical means that these hormones have the same molecular structure as the body's own corresponding compounds. Corticosterone, which in rodents is more potent than cortisol, is another natural hormone that is found in humans.

Cortisol, also called hydrocortisone when it is used in therapy, is the body's most potent glucocorticoid hormone. Cortisone is the precursor glucocorticoid made by the adrenals. It has 80% of cortisol's action. Supplementation with cortisone is therefore always at a slightly higher dosage than with cortisol or hydrocortisone to get the same effects: To do the same job, 25 mg per day of cortisone is needed where the body requires 20 mg of hydrocortisone.

However, the name cortisone is misleadingly used nowadays to name synthetic derivatives of cortisol, such as prednisone and methylprednisolone. These compounds are not identical to the body's own cortisol and cortisone. They may have different effects and indications. They are also used at lower dosages, as they have more potent effects.

Bioidentical glucocorticoids have better psychological effects and improve the blood pressure better than synthetic derivatives. The use of bioidentical cortisol and cortisone is indicated to treat most cases of cortisol deficiency, particularly when the predominant complaints are psychological. Bioidentical glucocorticoids better improve the mind, mood, energy, stress resistance, and other personality features compared to non-bioidentical glucocorticoids[169-172] because they are entirely adapted to the human body, particularly its glucocorticoid receptors.

Hydrocortisone is also a better choice to treat arterial hypotension because it retains salt and water more than synthetic derivatives.

Safety of Bioidentical Hormones

Because cortisol and cortisone are completely adapted to the human body, they are also safer. The risk of side effects such as skin atrophy is lower with these bioidentical glucocorticoids than with synthetic derivatives.[173] Long-term behavioral outcome and neuromotor development are also better in children who neonatally have received hydrocortisone rather than synthetic dexamethasone to avoid bronchial dysplasia.[172] Whenever side effects, usually overdose symptoms, occur with these natural compounds, they persist for a shorter time (6-24 hours) because of a quicker breakdown and inactivation by the body than when caused by synthetic derivatives (a few days). For this reason, at comparable doses, cortisol and cortisone reduce the endogenous cortisol production of the adrenal glands considerably less than synthetic derivatives. The risk of adrenal gland suppression is also less with bioidentical glucocorticoids.[51,174-175]

Table 2 (adapted from Chrousos et al., 2011)[51] shows that synthetic derivatives of cortisol at equivalent doses suppress the adrenal glands more. The greater their glucocorticoid (and thus anti-inflammatory) potency, the more they suppress the endogenous cortisol secretion.

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Table 2. Comparison of Synthetic Cortisol Derivatives

Glucocorticoids	Equivalent dose	Glucocorticoid potency	Hypothalamo-pituitary-adrenal axis suppression	Biologic half-life
Cortisol	20 mg	1.0	**1x**	8-12 h
Prednisone	5 mg	4.0	**4x**	18-36 h
Triamcinolone	4 mg	5.0	**4x**	18-36 h
Methylprednisolone	4 mg	5.0	**4x**	18-36 h
Dexamethasone	0.375 mg	30	**8.5x**	36-54 h

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The safety of all these glucocorticoids is greatly increased with the use of lower doses of glucocorticoids, such as 30 mg/day or less of hydrocortisone and 5 mg/day or less of prednisolone.[28]

Non-bioidentical glucocorticoids reduce inflammation better but may suppress the adrenal glands more. Non-bioidentical glucocorticoids, such as prednisone, prednisolone, methylprednisolone, and dexamethasone, are more indicated than bioidentical cortisol whenever inflammation prevails. Indeed, these compounds reduce inflammation more efficiently and persistently due to their (much) longer duration of action, usually 24 hours or more after intake (see table above).[51,56,176-178] A good strategy is to prescribe them for a limited time (2–6 months is the time necessary to reduce the inflammation) and then switch to bioidentical cortisol once the inflammation is gone.

As previously mentioned, there are two bioidentical hormones available at pharmacies: cortisol (usually delivered under its synonym, hydrocortisone) and cortisone (the precursor to cortisol, with 20% less potency). In most cases, for patients with no tendency toward high blood pressure, being overweight, or swelling of the feet, hydrocortisone is the preferred treatment.[179] The science behind bioidentical cortisol treatment is strong. Pubmed, the main Internet medical databank, presents 270 placebo-controlled studies in adults (almost all double-blind; 256 with systemic therapies,[180-433] 14 with topical therapies[434-447]).

Daily Cortisol Production

How much cortisol do humans produce? Researchers have found that the cortisol production rate in sedentary adults assessed in an in-hospital resting unit is on average more in men (22.5 mg per 24 hours) than in women (9.2 mg per 24 hours)[448] due to the bigger body surface area and adrenal glands of men. The average body surface area is 1.9 m² in men and 1.6 m² in women.[449] Other investigators have found lower cortisol levels in men, an average of 9.1-10.9 mg/m² of the body,[450-451] which equals about 17.3- 20.7 mg/day of cortisol for men with average body surface area.

However, these productions are valid only for sedentary resting conditions in laboratory units. In real life, the multiple mental and physical activities and higher stress conditions require and stimulate the adrenal glands to produce more cortisol. An average day in "real life" conditions requires at least 30–50% more cortisol production so that the real daily average cortisol production is probably 30 mg/day in men and 20 mg/day in women.

In people with heavy physical activity, daily cortisol production may even triple. Urinary cortisol excretion in female long-distance runners, for example, is threefold higher than that in sedentary persons.[452]

How much cortisol do cortisol-deficient patients need? My personal experience is that doses of less than 15 mg/day in female and less than 20 mg/day in male cortisol-deficient adults, respectively, do not work well. At too-low doses, patients feel – after an initial modest and short improvement in cortisol activity two-to-four hours after intake – a noticeable drop in energy, due to a fall in cortisol activity. Low doses of 5–10 mg/day of cortisol are just not sufficient to keep the baseline cortisol levels high enough for a satisfying quality of life.

How much cortisol is absorbed after intestinal intake? Does this mean that we need a maximum of 20 to 30 mg per day cortisol intake to correct a near total deficiency? No, because, on average, less than half – only 43% – of oral hydrocortisone (cortisol) is absorbed.[453] This means that a patient who does not have any cortisol production, needs to take a dose equivalent to double the normal endogenous cortisol production – 40 to 60 mg per day of oral hydrocortisone – to compensate for the absence of endogenous cortisol production.

In fact, cortisol absorption in the intestines might even be lower because the 43% of hydrocortisone absorption was measured in optimal conditions in which hydrocortisone was perfused with water in the intestinal lumen. The more water is added, the more hydrocortisone is absorbed. Thus, water intake may improve hydrocortisone absorption.

Food ingestion before hydrocortisone intake, on the other hand, delays hydrocortisone absorption.[454]

Divided doses of hydrocortisone usually, but not always, work better. For most patients, hydrocortisone should be taken in divided doses, at least twice a day,[455-456] for example, a higher dose in the morning after waking and the remaining dose during lunch. I recommend taking doses 5-20 minutes before breakfast and lunch, but some people experience stomach irritation because of the acetate that is bound to the hydrocortisone; it is pharmaceutically delivered as hydrocortisone acetate, which is an acid, and not as hydrocortisone alone. To avoid acidity, the hydrocortisone can be taken after meals or, if problems persist, prescribe the hydrocortisone pills with a protective (enteric coated) layer for the stomach.

Some people need to divide the doses further into three to four smaller portions taken at regular intervals throughout the day.[454,456-458] In these cases, they can take a supplementary dose of 5 mg of hydrocortisone at 4 p.m. and before bedtime. The 5 mg of hydrocortisone at bedtime is too small to keep the patient awake at night, but it does provide better energy upon waking the next morning.

What if a patient forgets the second dose of hydrocortisone or cortisone at lunch? He or she should take it later (4 p.m., for example), but not too late (after evening meal). Patients who tend to forget to take the second dose can try taking the full daily dose after

Table 3. Glucocorticoid Hypertensive Potencies

Glucocorticoids	Equivalent dose	Mineralocorticoid (water-retaining and hypertensive) potency
Cortisol	20 mg	1.0
Prednisone	5 mg	0.3
Methylprednisolone	4 mg	0

waking. Some people do fine and stay energized until bedtime; others do not and need two or even three bioidentical hydrocortisone or cortisone doses to feel well throughout the day.

Treatment with Synthetic Glucocorticoid Derivatives

In inflammatory diseases, such as the flu and rheumatoid arthritis, the synthetic cortisol derivative prednisone and its active metabolite, prednisolone, provide more efficient relief and the ability to avoid permanent adverse consequences, such as joint deformations, thanks to their prolonged duration of action.[51,459-460]

In overweight people and individuals with a tendency to foot edema and arterial hypertension, permanent use of methylprednisolone is generally a better option because, at equivalent doses, it retains less water and weight and increases blood pressure less than other glucocorticoids, particularly much less than the bioidentical hydrocortisone. When I prescribe it, I start with a period of two to six months and may continue administering it if the patient remains prone to the aforementioned disorders.

Table 3 (adapted from Chrousos et al., 2011)[51] shows the absence at physiological dose of the water-retaining and blood pressure-increasing effect of methylprednisolone compared to cortisol and prednisone.

Dexamethasone is a potent synthetic derivative of cortisol. A dose of 0.25 mg of dexamethasone equals the activity of 20 mg of hydrocortisone. Because of its longer 48-hour duration of action, dexamethasone may considerably reduce adrenal hormone secretion, including the production of androgens (male hormones). Dexamethasone's capacity to drastically reduce adrenal androgens is useful in reducing excessive body hair growth in women resulting from an excessive production of adrenal androgens. A once-daily morning intake of dexamethasone is usually sufficient to considerably suppress adrenal androgen production for more than 24 hours. I do not find its intake every two days efficient, as patients do not usually feel well on the second day, perhaps due to recurrence of adrenal deficiency.

To reduce skin rashes or to avoid keloid (voluminous scar) formation, a cream of 1-3% hydrocortisone may prove efficient. A concentration of 3% equals 30 mg of hydrocortisone per gram of cream. If this does not suffice, a lotion with a synthetic glucocorticoid derivative may help, but only if the area of skin application is small (several square centimeters), otherwise too much of the more potent synthetic derivative will penetrate through the skin into the body and cause side effects.

In emergencies, injections with high doses (50 to 250 mg) of cortisol or synthetic derivatives may be helpful, but this should be limited to exceptional cases as overdoses produce side effects. Table 4 summarizes the various cortisol treatments.

Dealing with Inflammation, Infections, Allergies, or Stresses

In nature, vigorous adrenal glands react to stress by increasing their secretion of cortisol and other adrenal hormones. People with adrenal deficiency have lost a great part of their ability to produce additional amounts of cortisol in cases of extra need. Their inability to increase their secretion of cortisol explains why they suffer from stress much more than people with healthy adrenal glands. Their excessive stress sensitivity can progress into a real hate of any kind of stress.

The solution for these patients is to mimic nature by taking additional cortisol in conditions where more cortisol is needed. Taking a dose of 5 mg of hydrocortisone, 1.25 mg of prednisolone or prednisone, or 1 mg of methylprednisolone every 30 minutes until mild or moderately important infections or stressful feelings disappear may do the job.[91,461] In cases of severe inflammation or infection, this small dosage may have to be doubled. In most cases, stressful feelings and infections disappear within two hours. Continuously increasing every 30 minutes for more than three hours is not recommended. The total amount of cortisol that may be needed the day of an infection or heavy stress may be the double or triple of the regular daily dose without any side effects other than the disappearance of inflammation or stress.

Transiently increasing cortisol is really efficient when the increase is applied **in the minutes that the patient feels the first signs of infection or stress**. The longer patients wait to increase their doses, the less efficient this method becomes. When I start to get a sore throat, or feel my body aching because of the flu, even if it is in the middle of the night, I take an extra dose of hydrocortisone or, even better, switch to 1 to 2.5 mg prednisolone or prednisone every 30 minutes. These synthetic glucocorticoids are more efficient in alleviating flu symptoms thanks to their greater anti-inflammatory effects and prolonged 24-hour action. In general, ➤

Table 4. Typical Glucocorticoid Treatment Schedules

Products	**Average daily dose** (usual dose range)		**Typical schedule**			
	Men	Women	Morning	Lunch	16h	Before bedtime
Hydrocortisone	30 mg (20-40 mg)	20 mg (15-30 mg)	10-20 mg	10 mg	(5 mg)	(5 mg)
Cortisone	37.5 mg (25-50 mg)	25 mg (20-37.5 mg)	12.5-25mg	12.5 mg	(6.25 mg)	(6.25 mg)
Prednisone, prednisolone	5 mg (2.5 -7.5 mg)	5 mg (2-6.75 mg)	5 mg	///////	///////	///////
Methylprednisolone	4 mg (2-6 mg)	4 mg (2-6 mg)	4 mg	///////	///////	///////
Dexamethasone	To ¯ body hair growth in women; not for daily	0.35 mg (0.15-0.5 mg)	0.25 mg	///////	///////	///////

Note: In most cases, the dose between parentheses is not administered, but there are exceptions in which intake is necessary for patients to benefit from continuous cortisol.

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one, two, or three additional intakes every 30 minutes are necessary to alleviate flu symptoms or a sore throat.

When patients wait too long after the start of an infection – two days for example – to increase their cortisol treatment, they often do better by limiting the increase in cortisol intake to an average of 50% more than their usual daily dose and must often continue this higher dose for three to ten days to rid themselves of the persisting infection, inflammation, or allergy. Such a prolonged intake of a higher dose of cortisol is generally unnecessary when the patient intervenes quickly and increases the dose in the minutes after noticing the first signs of an infection or allergy symptoms.

In stressful conditions, such as speaking at a meeting or participating in a radio or TV show, people with adrenal deficiency greatly benefit from taking 5–10 mg, 30 minutes to two hours before speaking. They experience more punch and perform better.

Can people not on glucocorticoid treatment occasionally take cortisol? Each time a person has a flu or another type of viral infection or has to face a stressful event, occasional intake of cortisol (preferable with an equal amount of protective DHEA) may stimulate the immune system without harm so that the infection is overcome in a matter of hours if the patient reacts quickly. A dose of 5-10 mg of hydrocortisone before a stressful event or 20-30 mg in one intake at the occasion of an infection may be sufficient to alleviate acute viral infections.

Side Effects and Risks of Cortisol Treatment

Three types of side effects of cortisol treatment can occur:

- **Overdose effects** due to excessive cortisol levels.
- **Imbalance effects** due to an absence or deficiency in anabolic hormones, whose roles are to block any unwanted catabolic effects from cortisol.
- **Adrenal gland suppression** is when secretion of hormones by adrenal glands is partially or totally blocked by treatment through negative feedback to the pituitary gland's secretion of ACTH.

Total suppression of the hormone secretions of the adrenal glands usually occurs only with very high glucocorticoid doses that are considerably higher than those proposed in Table 4. Total adrenal suppression may endanger life in cases in which cortisol secretion stops suddenly, as life is not sustainable without cortisol.

In general, at 20 to 30 mg per day of hydrocortisone, adrenal suppression is only partial (20–35%) and transient. After stopping these physiological doses, patients recover their initial cortisol secretion within two to six weeks. However, when very high doses are given for four to six months, as with some patients with severe rheumatoid disorders, the decrease in adrenal secretion of cortisol may persist for eight months before returning to the initial state.

Neglecting to correct other hormone deficits and a high-carb diet may increase the need for higher cortisol doses. In my experience, patients whose rheumatism does not sufficiently respond to physiological doses of cortisol, in fact, have other hormone deficiencies (testosterone, estrogen, thyroid, DHEA, etc.) that contribute to their rheumatoid disorder. Their diets (sweets, artificial sweeteners, grains) trigger inflammation and block cortisol action. These patients need to correct their diets and other hormone deficits, not to take pharmacological glucocorticoid doses.

How to Stop a Treatment

Patients on long-term high glucocorticoid doses should never abruptly stop their treatments. Rather, they should slowly decrease the dose over a period of two to four months, lowering their dose by 5 mg/day of cortisol or 1-1.25 mg/day of synthetic glucocorticoid every 10-14 days. If this slow and gradual decrease in cortisol supplementation does not gradually revive adrenal glands, regular stimulation of adrenal production with intramuscular injections of 1–2 mg of long-acting ACTH twice a week may restore cortisol production in two to four months.

Table 5 presents an overview of the most frequent complaints and physical signs of glucocorticoid treatment excess.

Additional Use of DHEA and Other Anabolic Hormones

Adrenal glands simultaneously secrete cortisol and protective hormones, such as DHEA and aldosterone. In young adults, secretion of both cortisol and its protective hormone DHEA by the adrenal glands are similar – approximately 20 mg per day for women and 30 mg per day for men. Whenever increased amounts of cortisol are secreted, healthy adrenal glands also release proportionately more DHEA and other adrenal hormones.

In many medical offices, cortisol or one of its derivatives are generally prescribed alone without protective anabolic hormones. This imbalanced treatment produces a number of side effects – mostly tissue atrophy – as shown in Table 5. To avoid these undesirable catabolic effects, DHEA and other anabolic hormones such as testosterone, female hormones, and possibly even growth hormone should

Table 5. Glucocorticoid Excess

Overdose	Imbalance	Adrenal suppression
Symptoms • Euphoria • Agitation • Sleep disorder • Heart-pounding	**Physical signs** • Swollen, balloon-shaped face • Buffalo neck (fat mass at the back and base of the neck) • Weight gain • Upper-body obesity	**Physical signs** due to DHEA and other anabolic hormone deficiencies • Ulcers • Skin thinning, muscle loss • Bruising • Osteoporosis	**Symptoms and physical signs** of increased cortisol deficiency **after interruption of cortisol treatment** • Lack of energy • Loss of consciousness • Low blood pressure • Immune suppression

be systematically administered (if the patient is deficient in these hormones), whenever hydrocortisone or one of its derivatives is prescribed.

Intolerance to Cortisol

A minority of cortisol-deficient patients, usually those with the weakest adrenals, does not tolerate oral intake of cortisol. They may experience unbearable stomach acidity that can be overcome by enrobing the cortisol in a protective coat (a supplementary layer at the outside of the pill). Enteric coating protects the stomach against the pills' acidity by dissolving in the small intestine rather than in the stomach.

Patients may also feel weird, overwhelmed by a general malaise that spreads over the body with feelings of fainting and great weakness, when taking oral hydrocortisone or one of its synthetic derivatives. These patients find that cortisol therapy aggravates their cortisol deficiency symptoms. The usual cause is aldosterone deficiency induced or aggravated by glucocorticoid-induced reduction of pituitary secretion of ACTH, the hormone that stimulates secretion of all major hormones of the adrenal cortex. Aldosterone is another hormone secreted by the adrenal cortex. It keeps the blood pressure up. Treatment of aldosterone deficiency and its associated feeling of empty-headedness consists of adding fludrocortisone, the synthetic derivative of aldosterone.

A tiny minority of cortisol-deficient patients may still not tolerate or do well with cortisol, despite their desperate need for it. These cortisol-intolerant patients often experience all types of allergic or intolerance reactions to whatever medication they take. Their cortisol levels in blood and urine are usually dramatically low. Physicians may get headaches from trying to find strategies that could solve the problem.

Two alternate routes of administration may provide relief. Subcutaneous injections of cortisol at 30 to 50 mg a day may help, as may the application of 4–6 g/day of a liposomal gel with 5% cortisol applied to the buttocks, back, and belly in a very thin layer to avoid skin atrophy. A liposomal gel offers the best penetration of the body. If the applied layer is thin and if the patient rubs it ten times over a large surface, it should penetrate quickly, leaving the skin intact. I tried these two forms, and they provided the same efficacy as my daily 30 mg/day of hydrocortisone intake.

How to Make Cortisol Treatment Safe

First of all, **avoid excess**. Doses of 15–30 mg per day of hydrocortisone in women and 20–35 mg per day in men are usually physiologically safe[28-31] but may need to be reduced for smaller individuals. High cortisol doses should only be administered for a limited time in exceptional crises – to rescue a patient or an organ, for example – but always with concomitant anabolic hormone treatment.

The best method is to inform patients of cortisol excess signs and recommend they reduce the dose by 25 to 50% if there are ever signs of cortisol excess, such as a swollen face, weight gain, high blood pressure, or excessive agitation.

Second, **administer simultaneously protective anabolic hormones**. DHEA is the number one anabolic hormone that neutralizes excessive catabolic effects of cortisol associated with cortisol treatment.[35-39]

Young adult adrenals secrete DHEA and other anabolic hormones concomitantly with cortisol. Because DHEA is anabolic and builds up tissue, its presence blocks the excessive catabolic effects of cortisol. Cortisol is predominantly catabolic because it hastens catabolism to eliminate excessive tissue and unblocks energy by breaking glycogen down into glucose.

Both catabolism and anabolism are essential for health, but they must be appropriately balanced. To do so, both cortisol and anabolic hormones, such as DHEA, should be given in equivalent doses. Physicians should therefore mimic nature and provide DHEA with cortisol to avoid tissue wasting.

With aging, the production of DHEA declines considerably more than that of cortisol, resulting in an imbalance that favors catabolism above anabolism, which explains the progressive acceleration of aging in individuals past the age of 45. ➤

Cortisol Deficiency

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The third way to make cortisol treatment safe is to **avoid consuming "bad" carbohydrates**. In my experience, intake of sweet foods and cereals (that were not sprouted (such as traditional bread, pasta, muesli, porridge, etc.), tend to block the major beneficial effects of glucocorticoid treatment and to increase the occurrence and intensity of undesirable side effects, especially swelling and weight gain. Thus, patients should avoid bad carbs in their die**t** at least five days a week. A protein-rich diet (180 g/day or more of meat, fish, and poultry) is also protective against excess glucocorticoid catabolism.

Follow-Up

Follow-ups are mainly based on clinical assessments. More than for other hormone therapies, follow-ups of cortisol treatments should be done clinically for the most part, assessing for the presence of complaints and signs and avoiding any overdose signs.

Please note that saliva, serum, and 24-hour urine laboratory tests usually provide inconsistent results for follow-ups of bioidentical hydrocortisone and cortisone treatments. They are unstable and unreliable.

If hydrocortisone treatment is taken 30 minutes to three hours before blood and saliva tests, abnormally high free (and total) cortisol levels can be found in the serum due to peak levels of cortisol after absorption.

If hydrocortisone treatment at physiological doses is taken much later – seven to 24 hours after blood and saliva tests – cortisol levels usually drop back to their initial levels (from before treatment) or even to a supplementary 20-30% lower concentration (usually not more) because of transient and partial inhibition of the adrenal cortisol secretion.

In blood and saliva, cortisol levels are not stable during treatment. Not only is there a cortisol circadian rhythm, which makes cortisol levels fluctuate, with two to three times higher cortisol levels in the early morning than in late afternoon, but orally ingested cortisol does not bind strongly to cortisol-binding globulin (CBG), so the cortisol, which penetrates into the blood or saliva, quickly leaves for the target cells, decreasing cortisol levels.

The 24-hour urine test is not good for follow-ups either because it can show abnormally high levels of cortisol due to peak cortisol absorption with increased losses in urine, as well as unusually high excretion rates of cortisol metabolites (17-hydroxysteroids), even if cortisol treatment is adequate or insufficient. After intestinal absorption, the cortisol passes into the liver. Much of the cortisol is then broken down in the liver into inactive metabolites, which pass into the blood and then the urine, not reflecting real cortisol metabolic activity. The 24-hour urine is a must to control the reduction in adrenal androgens when dexamethasone is given to reduce body hair growth.

For non-bioidentical glucocorticoids, laboratory tests are even more inadequate for follow-up. None of the traditional laboratory tests can measure these synthetic glucocorticoids because of their different molecular structures. They might have some value to check the grade of adrenal suppression they may cause. Finding undetectable or nearly undetectable endogenous cortisol levels and very low metabolite levels in urine tests indicates that endogenous cortisol secretion by adrenal glands might be excessively suppressed by treatment, possibly by overdose.

Conclusion

Adrenal deficiency, particularly cortisol deficiency, is one of the most underestimated and misdiagnosed hormone deficiencies.

Untreated cortisol deficiency severely affects a patient's quality of life and brings a long road of unnecessary suffering. The hormone cortisol makes most stress bearable and considerably reduces suffering. Patients who remain in cortisol deficiency suffer excessively and continue to do so throughout their lives – the more severe the deficiency, the more suffering there is.

Many physicians and laypeople are reluctant to prescribe or take supplements of cortisol or one of its derivatives because of the unacceptable side effects of pharmacological doses of cortisol. These fears should not prevent physicians from treating cortisol-deficient patients with small, well-adjusted physiological doses of cortisol that are balanced with a protective DHEA supplement.

To correct a cortisol deficiency, the first things to do are to improve the environment, the lifestyle, and the diet. Let patients expose themselves to daylight and intense indoor light more. Recommend that they avoid pollutants – most pollutants are indoors. Regularly meditating or relaxing may also help increase cortisol levels when supplementary amounts are necessary. Avoiding unnecessary stress preserves cortisol stores from spillage. In addition, increasing the intake of protein- and fat-rich foods and avoiding sweets and cereals may also noticeably improve cortisol levels. In a minority of cases, these interventions may suffice.

In all other cases where cortisol treatment must be installed, these interventions optimize treatment results.

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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.

http://www.hertoghe.eu

There are 461 references. Please see the digital version of the article on our website in the January and Feb/ March 2018 issues for the complete reference list.

HYPERCOAGULATION

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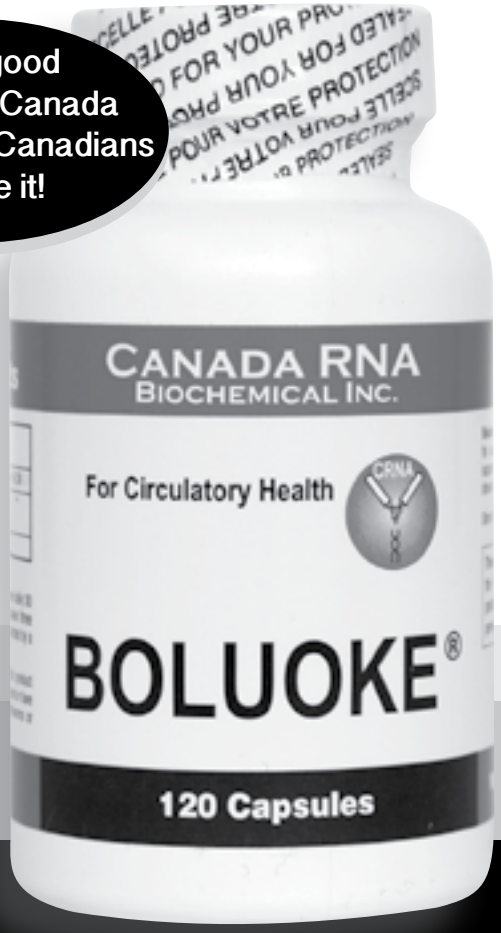

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A Dietitian's Experience Working in a Psychiatric Children's Hospital

by Kim Koepp Hovey, MS, RD, LD

The number of psychiatric children's hospitals in the US is growing. (www.ushosptial.info), I am the clinical dietitian of a psychiatric children's hospital in Georgia. The hospital treats 80 children and is always full with a waiting list for admission. Approximately 86% admissions are males, 92 % are African American and 65% are re-admissions. Medicare/Medicaid pays for 100% of admissions.

Diagnosis and Treatment

The hospital provides psychiatric and mental health treatment for children and adolescents between the ages of 9 and 17 where they treat mood, behavior, and anxiety disorders. Some of the children have committed a crime and are too young to be jailed. At times, the hospital seeks placement in a group or foster home following therapy.

Most are diagnosed with "conduct disorder," their parents being unable to manage them.

Other children have disorders manifested from family neglect and abuse. Other diagnoses might include anxiety, ADHD, mental retardation, chronic fatigue, substance abuse, and self-mutilation. Medical diagnoses include diabetes, hypertension, and hyperlipidemia (high cholesterol and/or triglycerides). Most children present with multiple diagnoses.

My job responsibility at this facility is to complete an initial assessment on each patient, addressing special diet orders written by the physician. If available, I evaluate blood levels for vitamin deficiency. I am expected to recommend low-fat diet protocols for hyperlipidemia and monitor weight trend during the hospitalization. I feel that the true reason a dietitian is employed at most facilities is to meet state guidelines for reimbursement rather than for implementing nutritional therapy.

If a diet instruction is performed, it must be requested/ordered by the physician. One diet instruction has been requested in my three years working at this facility, despite the fact that most of the children eat horribly and many are morbidly obese. The single instruction requested a low-fat, low-cholesterol diet to "lower cholesterol." The patient was 13 years old and taking a statin drug.

Most physicians feel diet changes are not important, especially if the patient returns to the home environment where the family is not eating or unable to afford proper foods. The hospital's treatment plan is based upon and relies upon pharmaceutical intervention. Changing dietary habits are not a part of the treatment plan.

A patient's diagnosis and treatment might look like this (from an actual 16-year-old, African American male patient):

- Diagnosis: bipolar, ADHD, mild mental retardation (low IQ), oppositional/defiant behavior, depression (two past suicide attempts), hypertension, hyperlipidemia, morbid obesity (Ht: 64 inches, Wt: 242 lb., BMI:41).
- Treatment: Lipitor (high cholesterol), clonidine (blood pressure, ADHD), lithium (bipolar, depression), Seroquel (bipolar). metformin (to control the increased appetite caused by Seroquel), social services (social worker).

A diet instruction was not requested. The diet history is poor, consisting of mostly refined foods and sugars. The patient does not drink milk and gets little sunshine. No blood nutritional levels were drawn. No vitamin/mineral therapy is in place.

A Holistic Approach

The patient discussed above is taking Seroquel, a frequently prescribed psychotropic medication. A side effect of this medication is increased appetite and weight gain. The patient was later prescribed metformin to suppress the increased appetite caused by the Seroquel. This medication, usually used to control blood glucose in diabetics, is often prescribed to control appetite in adolescents.[1,2]

Metformin is the diabetes drug I often think of when I think of nutrient depletion. Metformin is thought to decrease the absorption of vitamin B12 by lowering intrinsic factor, or possibly through other mechanisms.[3,4] Reduced serum levels occur in up to 30% of those individuals who take metformin chronically. Those who have a higher risk of developing the deficiency include this group, whose diet is poor and vitamin B12 intake is most likely inadequate.[2] At B12 levels only slightly lower than normal for a very short period of time,

a range of symptoms such as poor memory, fatigue, and depression may be experienced.[5]

A holistic approach would treat the "source" of the disorder, which might include nutritional deficiency. Evaluate B12 blood levels, especially since the child presents with two of the symptoms caused by B12 deficiency. If B12 is low, analyze B12 intake, ability to absorb B12 and suggest vitamin supplementation if he is unable to meet his increased B12 requirements by food.

Vitamin D levels should also be evaluated, given the fact that this patient does not drink milk, spends most of his days indoors, and has a diagnosis which many studies link to low vitamin D levels.[6,7] In my three years working at this hospital, I have never seen a vitamin D or B12 level tested or nutritional supplementation initiated.

A healthy diet program of whole, unrefined foods that work within the family budget should be initiated. The family should be involved in this new nutritional plan.

This approach should not devalue the benefit accomplished by pharmaceutical intervention, which is often necessary. Pharmaceutical therapy to suppress symptoms in combination with healing modalities such as nutritional therapy would be the ideal approach.

The Reality

The prospect of treating psychiatric conditions nutritionally with or without pharmaceutical intervention is promising and researched, but rarely implemented. I feel nutritional therapy is not part of the treatment plan nor is it sought because the physician conducts the treatment plan and he is not aware of and/or does not understand this mechanism.

Unless a physician has studied outside what the pharmaceutical industry presents, he only understands how to treat a disease process pharmaceutically. A physician's education and continuing education (classes, seminars, workshops, books, articles, studies) are conducted and presented via a pharmaceutical partner or investment partner who is involved and financially motivated within the industry.

Other physicians feel a therapy must be firmly grounded in fact before utilized, something only afforded by the pharmaceutical industry because studies are expensive to conduct.

My biggest frustration is watching a physician's reluctance to give up "control" of the patient, never asking another practitioner's advice about a treatment he does not understand, even if the treatment has no ill side effects.

Good News

I observe more pharmacists, nutritionists, and researchers conducting evidence-based studies on the dangers/side effects of pharmaceutical therapy. Natural Medicines Comprehensive Database (www.naturaldatabase.therapeuticresearch.com) is a good reference, providing a list of medications that cause nutritional depletion with corresponding studies. It discusses the medications' side effects as well as other herbal or homeopathic remedies that may be used alternatively. It lists evidence-based studies linked to the use of herbal and homeopathic remedies and encourages researchers to study and submit material.

I find it encouraging that this is a reference suggested by the Academy of Nutrition and Dietetics (American Dietetic Association) practice group Dietitians in Functional and Integrative Medicine.

Food

On my first day at this hospital, the administrator requested that I change the menu plan. After seeing the menu, I assumed the request was because the menu contained many refined foods and sugars. I later found it was because the patients were complaining about the food. This is what the menu plan looks like. It follows the guidelines of the Academy of Nutrition and Dietetics (American Dietetic Association):

Breakfast:
Eggs
Sausage/Bacon
Toast/Biscuit/Muffin/Sweet Roll/Pop Tart/Pancakes
Cold Cereal /Oatmeal
Lowfat or Skim Milk
Fruit Juice

Lunch/Dinner:
Chicken Nuggets
Pizza
Hot Dogs/Hamburger
Fried/Baked Chicken
Tacos
Salad or Vegetable
French Fries/Potatoes
Roll/Bread
Cake/Cookies/Lowfat Ice Cream/Sherbert
Canned/Fresh Fruit
Lowfat or Skim Milk
Fruit Punch/Lemon Lime Soda

Snacks:
Pre-packaged crackers, cookies or chips
Fruit juice/Fruit Punch/Lemon Lime Soda/Lowfat or Skim milk

*Products are frozen, pre-packaged or canned. Salad or fruit may be fresh.

I had big plans for changing this menu, hoping to meld Weston A. Price Foundation principles into the guidelines of the Academy of Nutrition and Dietetics and teach the patients about dietary changes with classes.

The administrator asked me to first interview the patients to find out what they did not like about the food (the real reason he consulted me). Among their requests for improvement were ranch dressing with everything (the low-fat type because it is sweeter), Froot Loops and Cocoa Puff cereals, chocolate milk, chicken wings with BBQ sauce dip, ketchup at every meal, Coke or Pepsi, sugar substitute in the pink package, icing on the cake, coffee, and Red Bull. When asked what they felt they should eat to be healthier, the answers were cereal, oatmeal, Ensure, energy bars, Gatorade/sports drinks, and low-fat and non-fat foods

One hundred percent of the children obtained their nutrition education from television commercials.

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I approached the administrator with a proposal to provide healthier meals and snacks, consisting of less sugar and refined foods, and to start weekly nutrition classes. I let him know the cost of the meals would increase, as well as the cost for me to conduct the classes. I also informed him that this is not what the patients had "requested." My proposal was immediately vetoed, followed by an explanation that they must contain costs.

A few months later I was asked to conduct nutrition classes in order to meet state funding requirements. I found the instruction difficult, as I was telling them to avoid the very foods that were served.

Conclusion

Treatment success looks only at results. Outward appearance is not the inward reality. These children are not healing at this hospital. The treatment is merely combating/masking symptoms with pharmaceutical intervention: "Illness maintenance based on system suppression …." To heal these children, physicians must rely on a practitioner with training outside of the pharmaceutical model in the treatment plan.

We must end the monopoly the pharmaceutical and refined food industry hold on nutrition and health care. Until we do this, we will only become sicker while the current health care industry of pharmaceutical therapy and invasive procedures explodes.

References

1. G Paoliso, Effect of metformin on food intake in obese subjects. *European Journal of Clinical Investigation*. June 1998;28 (6):441-446.
2. MB Davidson. An overview of metformin in the treatment of type II diabetes mellitus. *American Journal of Medicine*. January 1997;102 (1):101-110
3. Callagan TS, Megaloblastic anemia due to Vitamin B12 malabsorption associated with long term metformin treatment. *Br Med J*. 1980;280:1214-16.
4. Gilliagan MA, Metformin and B12 deficiency. *Arch Internal Medicine*. 2002;162:484-5
5. Dietary Supplement Fact Sheet – B12. Office of Dietary Supplements, National Institute of Health. 28 September 2011.
6. Heyes JD. Your depression may be due to vitamin D deficiency. March 26, 2013. www.naturalnews.com.
7. Cannell J. Newsletter: Major Depression and Vitamin D. March 20, 2003. www.vitamindcouncil.org.

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Kim Koepp Hovey is a consultant dietitian who originally obtained her training from the world of allopathic medicine and the American Dietetic Association. After becoming ill with diabetes, obesity, severe chronic fatigue syndrome, and relying on pharmaceuticals, she looked for methods of healing outside of what mainstream medicine offered.

For 10 years, she studied nutrition among naturopaths, chiropractors, acupuncturists and other nutritionists, resolving her health problems with dietary changes that included saturated fats and whole food supplements. She has since helped others do the same via a private nutrition practice.

Kim hopes to see our health care system (Medicare/Medicaid) reimburse this type of nutrition therapy so that nursing homes, hospitals and rehabilitation facilities can use it, finally affording patients a real healing process.

Dangers in Household Products

by Alfred J. Plechner, DVM

It is becoming more and more apparent every day that many household products are causing major diseases in humans with possible consequences for animals also. Many household items such as cleaning products, air fresheners, bath products, toothpaste and mouthwashes contain different toxic chemicals, including parabens (e.g., methylparaben, propylparaben, and butylparaben).

What is a paraben? A paraben is a class of chemicals used by the cosmetic and pharmaceutical industries as a preservative to stop bacterial and fungal growth in their products. It may be important for manufacturers to sustain non-bacterial and non-fungal products for your protection and theirs, but are they exposing you to far greater dangers that they do not mention? What are the hidden, health dangers for you, your family, and your pets?

A recent article, appearing in *The Daily Health* journal from the United Kingdom, states that the *Journal of Toxicology* recently published a study in which researchers tested the malignant mammary tissue of 160 human patients and found that 99% of the tissues contained at least one type of paraben. Parabens are known as estrogen mimickers and, as we know, elevated estrogen may be the cause of many different types of cancers and many other catastrophic diseases.

My clinical studies in animals have shown that all of the cancer patients that I have been involved with over the years, whether humans or animals, all had elevated total estrogen, which not only measures ovarian estrogen but also adrenal estrogen in both males and females. My clinical studies have further indicated that an elevated total estrogen will suppress the B lymphocytes production of antibodies (immunoglobulins).

Chemical estrogen mimickers, like parabens, will not be included in the tests for total estrogen because of their chemical structure; yet, they still function as damaging estrogens. A possible indicator of a patient's exposure to an estrogen mimicker may be determined by performing a simple blood test; test results indicate a normal, total estrogen with suppressed antibodies (immunoglobulins). For more information on this simple blood test, please go to www.drplechner.com.

In addition to parabens, commonly used household products contain other toxic chemicals. According to *The Daily Health*, be aware of products used for bathing that contain sodium lauryl sulfate and cocamide DEA. Be aware of chemicals contained in deodorants like DMDM hydantoin, imidazolidinyl urea, and limonene.

Makeup, like eye shadow, may contain propylene glycol, bronopol, and formaldehyde. Mascaras may contain nanoparticles, and perfumes may contain isopropyl alcohol, phthalates, and fragrances.

Prescription medications may contain chemicals, preservatives, colorings, and stabilizers. Toothpaste, mouthwash, and breath fresheners may all contain fluoride, which is a dangerous neurotoxin even though it is routinely added to our municipal water supply.

Many cleaning products contain trichosanthes, which can be inhaled and may be very damaging even when you are wearing rubber gloves. Air fresheners contain limonene and linalool.

What about eating a simple breakfast? Coffee and tea may contain fluorides and pesticides. Some artificial sweeteners contain synthetic roach poison while other artificial sweeteners process into formaldehyde. Bacon and other processed meat products may contain parabens and sodium nitrites. Jams and jellies often contain high levels of corn fructose.

You need to be concerned about manufactured fruit juices because they can contain artificial colorings, additives, and high amounts of fructose from corn syrup. A further concern of mine is that the fructose may be refined from corn from genetically modified seeds.

The truth of the matter is that the manufacturers believe that the small number of parabens and harmful chemicals contained in their products will cause no health problems. In reality, this may not be true. After prolonged use and in combination with other products that contain parabens, there may be definite health concerns.

It seems that we are damned if we do and damned if we don't when using all these household products for our pleasure and convenience. Are we subtlety killing ourselves, our family, and our pets?

I hope this article will make you aware of some of the subtle parabens that reside in your household and in your environment that just might be an important health deterrent for you, your family, and your pets. ◆

Dr. Alfred J. Plechner, DVM, has practiced veterinary medicine for 50 years and performed clinical research on the causes of allergies, autoimmunity, and cancer in animals and humans. He discovered an endocrine immune mechanism that contributes to these disorders using a simple endocrine immune blood test on 90,000 animals and 2,000 humans. Dr. Plechner has published more than 30 clinical papers and six books. In addition to his work as a practicing veterinarian and researcher, Dr. Plechner was a pioneer in the development of non-meat and healthy pet foods for dogs and cats, creating Nature's Recipe formulas over 40 years ago. He also had a wildlife preserve, Stone Wood Meadows, in the Santa Monica Mountains for 35 years and was licensed by the California Department of Fish and Game and the Federal Wildlife Service. For more information about his life and work, please go to www.drplechner.com.

Letters to the Editor

Adrenal Fatigue Article

A hearty thank you to Holly Lucille, ND, RN, for a much needed expansion of our therapeutic considerations about the HPA axis. (Cover story, November, 2017)

What concerns me is that her article's catchy title and detailed text may mislead novice readers away from the very real possibility that many people DO have primary adrenal insufficiency.

For instance, consider the many millions with Hashimoto's thyroiditis and/or other autoimmune illness. Their often observed HPA axis dysfunction is likely due to some degree of concomitant autoimmune attack of the adrenal gland parenchyma. In these cases, the HPA axis issue might mainly be autoimmune adrenalitis. And, that condition is simply a mild version of what causes 70% of true Addison's disease.

Many of my patients with mild adrenalitis seem to need actual low-dose cortisol replacement, in addition to the many fine therapeutic suggestions outlined in the article.

Richard L. Shames, MD, author of *Thyroid Power*
San Rafael, California

Dr. Lucille's Response

I agree one hundred percent with Dr. Shames's comments in regard to my article. My intent on the "catchy title" was to dissuade the use of the "catchy" and almost "slang" term "fatigue" when speaking about matters such as primary adrenal insufficiency and HPA axis dysregulation/dysfunction and as I mentioned, be more consistent with the literature.

Also, I am certainly in favor of low-dose cortisol therapy in clinical situations as Dr. Shames described. The conversation regarding autoimmunity is vast and needs to continue to be considered in so many of our patients presenting these days, so not only do we seek to treat the HPA or HPAT axis but also the autoimmune issue.

Holly Lucille, ND, RN

Metal Toxicity

I enjoyed David Quig's article on implants. However, he left out some that we see with severe metals reactions. Even the small amounts are seen. We just saw an animal radiologist whose symptoms were provoked by molybdenum. In addition, we have seen the multiple implant syndrome where patients may have two or three implants like ankle, legs, teeth, and jaw. It appears to be accumulative and removal of one or two may solve the problem.

Dr. Quig also needs to emphasize the hypersensitivity caused by implants. Synthetic breast implants, hernia mesh, and aortic valves are some of the synthetics as well as polyethylene, polyvinyl, and polyurethane, that can sensitize. We have had to neutralize intradermally or remove, if possible.

The poly(s) for hernias are not the worst because these tissues grow into the mesh holes. The synthetics can combine with the metals and cause cumulative problems with immune deregulation of T-cells, complements and gamma globulin 1,2,3,4. They have to be replaced.

We have treated over 1,000 patients with the implant syndrome over the past 35 years.

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When the News is Bad

review by Katherine Duff

Life After Diagnosis: Expert Advice on Living Well with Serious Illness for Patients and Caregivers, by Steven Z. Pantilat, MD
Da Capo Press, 44 Farnsworth Street, 3rd Floor, Boston, Massachusetts 02210; ©2017; $16.99; 352 pp.

There is life and then there is death. In between there are the good and bad times and eventually, the bad news. A diagnosis of a serious or terminal illness is the bad news that changes everything. Patients and their loved ones may be left reeling with the news at the same time they are faced with a multitude of decisions. This is new territory for anyone, so the path out of confusion to making plans and treatment decisions may feel like a solitary one but it is not. It is an experience shared by many and synthesized in the wonderful book, *Life After the Diagnosis*, by Steven Z. Pantilat, MD.

Dr. Pantilat is a pioneer and authority in the field of palliative medicine. He has treated thousands of patients, conducted research, and teaches about palliative care. Like hospice care was decades ago, palliative care is an emerging field of medicine now. The goal of palliative medicine is to give patients the best quality of life possible, which includes relief from the stress, depression, pain, and an understanding of what they are going through. It is this understanding that Dr. Pantilat brings to the book.

The news is terrible without a doubt. Patients may be so overwhelmed they cannot absorb any more information. Dr. Pantilat offers the advice to make another appointment for the additional information and be prepared with written questions, and another person or audio recorder. Most of all, he reminds us to not judge ourselves for how we react to such bad news.

Some may respond with denial, which while it may alarm loved ones, can be a coping mechanism to carry on, but only for the short term. Blame and shame for causing one's own illness are other natural reactions but not helpful for proceeding. The author suggests it is best to let it go. This is a time for grief, and the five stages of grief developed by Elizabeth-Kubler Ross may be experienced in a non-linear fashion.

Isolation is one of the stages of grief that the author wants people to avoid. Telling others and allowing support from friends and family is imperative for quality of life. Again, Dr. Pantilat is realistic as he warns that not all responses would be as we would wish. Some friends will disappear or be insensitive, and some will regale the patient with their own medical stories. Simply, that should be expected but not prevent anyone from seeking help.

Making decisions about treatment takes some work, and there are guides to help the patient do that. The first order is to identify the overall goal. Living as long as possible seems a reasonable goal; but if that involves pain and worse disability, the goal may change to a life that enables the person to spend more time with loved ones. The author takes the reader through many considerations when setting a goal. The plan for reaching that goal is what assists the patient in making decisions about treatment.

"Serious illness changes everything. It casts us into new and mysterious territory, somewhere we never wanted to go and know little or nothing about."

There may be several options for treatment. The doctor is there to answer questions and help but it is ultimately up to the patient. The book offers several methods for evaluating the treatment plan starting with the Best Case/Worst Case approach developed by colleagues of Dr. Pantilat. This method asks the questions: What is the best and the worst outcome for a particular treatment? What is the best and worst outcome for no treatment? And finally, what is the likely outcome?

Another way to analyze a treatment is by the categories of those that can be stopped and those that cannot. He gives the example of kidney dialysis as one that can be stopped but surgeries and implants cannot. They are permanent. One must also be realistic about the hidden effects of treatments. Can the patient withstand the effects of chemotherapy and radiation? Will a treatment leave the person unable to enjoy the time they have left? This book brings light to these questions and more.

The author knows that the patient is grounded in hope, which can result in some miscommunications with the doctor. The language used by physicians can be interpreted by those unfamiliar with it as positive signs when it is not. The author gives the examples of words that cause problems, such as response or response rate. This may sound like hopeful news to the patient but further investigation of what exactly research has shown is necessary to get the accurate picture. A question commonly used by doctors is, "Would you like us to do everything possible"? This question invites a reaction, which is always yes, but without the patient's understanding of what that means. Dr. Pantilat implores doctors to not ask that question at all.

The book addresses the many practical aspects of this time of life. Whether one is preparing for a doctor appointment, trying to manage symptoms, or attempting to figure out how to hire caregivers, there is advice. The author takes us through the requirements for hospice care and even the pros and cons of aid in dying which is legal in a few states.

Dr. Pantilat has done a great service with this book. He has exposed the process of living life while facing a terminal illness

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and introduced us to the field of palliative care and our need for it. Currently, it is a misunderstood specialty that is usually associated with dying. It is really about living a better life. As part of a medical team, the palliative specialist recognizes patients as the experts in their own lives and can help them meet their goals, whether it be staying at home and out of the hospital or living with as little pain as possible. The palliative specialist should be called upon at the time of diagnosis of conditions that are listed in the book.

This is not a book of "to do lists" but rather a deep and sensitive understanding of the humans experiencing serious or terminal illness and the choices they face. This would include the treating physician as well. Everyone is placed in an awful position, but all can benefit from open and well understood communication. The doctor focused on disease treatment would surely welcome the expertise of the palliative care specialist.

Death is a fact of life, but most of us are left to navigate that precious time before death for ourselves or loved ones as if we are the first to do so. Unless we must, most of us would rather not think about it. I kept putting off reading this book until the "right time"; but now having read it, I feel comforted and more prepared. Nothing will make the bad news go away, but this book can help people find their way when that kind of help is needed most. Better yet, read it now, and be prepared.

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A Passion for Science

review by Jacob Schor, ND

Lab Girl by Hope Jahren
Vintage/Penguin Random House, https://www.penguinrandomhouse.com.
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I've taken a time out from reading all the big textbooks that I intend to review and have picked up the book *Lab Girl* with the intent of finally finishing it. My friend Dan Rubin had Amazon send this book to me last year, and I thoroughly enjoyed reading the first two-thirds. I put it down to save for later; I didn't want to use it up as it was such pleasure to read Jahren's book that I wanted to make it last longer.

The book is a memoir by a geochemist/geobiologist named Hope Jahren, who when she wrote the book had a research lab at the University of Hawaii. Since publication she has moved to Norway and is now at the University of Oslo. I learn this from her occasional op-ed pieces in the *New York Times* where she has written extensively about the problem of sexual harassment in the sciences. Given how much sexual harassment is in the news today, reading her pieces from a few years back, the term "prescience" can't help but come to mind. Well, isn't that what scientists are supposed to do in a way, predict and see things before the rest of us can?

There are so many reasons to love this book. First it is the writing; her use of words to paint pictures is a pleasure to experience; she is an artist of the first order. Second, the picture she captures through these words is beautiful; she brings one to an overlook, a perspective, a view of how we should see or understand plant life that, not to sound cliché, slowly reveals a shifting paradigm to the reader…how we should view life itself. The experience is illuminating.

But third, and in a way perhaps the most important aspect of this book, she shares the process of research and discovery, the expansion of knowledge, and the world of the scientist with a passion that is contagious. Not even finished with the book, now months after putting the book down, I am still convinced that doing what Hope Jahren does for a living in her research laboratory is the most noble occupation that any human being might engage in. Granted that caring for the ill, being Mother Theresa or someone of that sort, may rank a close second. Yet, really, what should a human being, a society, a culture, or a world strive toward beyond expanding our understanding of life, the world and our universe?

A book that instigates such thoughts is a rare thing. Such thoughts of late have taken on new meaning in this past year. Advocating for science and scientific discovery has become a partisan issue. The White House has recently cancelled their annual reception for the year's Nobel Laureates. The tax proposal recently passed by the House would begin taxing my daughter who is in graduate school in a manner that will make completion of her program financially impossible. She currently receives free tuition at Denver University in exchange for her work as a researcher and, hopefully, if all goes well, as an instructor in future years. The current plan will tax her as if that tuition were a salary.

Now, of course she won't be forced to drop out of school. In our view of the world, education takes high priority and we will find the money to keep her studying no matter what it takes. It's just how we see things.

Thus, even though Hope Jahren's book is beautifully written and educational, reading it has also become a political act, one that supports gaining knowledge of and expanding our understanding of the world. It is in a quiet and poetic sort of way a hymn to science that gives praise to the beauty and complexity of our world. Read the book for pleasure. Read Jahren's book because these days believing in science has become a political act.

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Curmudgeon's Corner

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What Is Health Food?

A recent paper authored by Valerio Sanguigni and colleagues from the University of Rome Tor Vegata has me wondering what we mean when we use the term "health food."

Sanguigni and friends set up a single-blind crossover study in which they fed a group of fourteen volunteers good-sized bowls filled with a quarter pound of either homemade chocolate ice cream or a frozen chocolate dessert made following their own recipe. In addition to solid measures of cocoa powder, their experimental dessert was made with hazelnuts and a solid portion of green tea extract. The goal was to provide a substantial dose of polyphenol antioxidants under the cover of what looked like junk food. The ground hazelnuts substituted for the fat normally provided by cream. Thus, technically the experimental confection wasn't really ice cream but more like a distant cousin of frozen Nutella, or as this study was done in Italy, gelato. A few hours after their ice cream feasts, the volunteers were tested for measures of oxidative stress and vascular function. In addition, they were subjected to a treadmill stress test.

It was no surprise that the participants that ate the experimental high antioxidant ice cream had significantly higher blood levels of polyphenols and significantly lower measures of oxidative stress. Available antioxidant capacity and NO (nitric oxide) availability both improved significantly. Measures of endothelium-mediated artery dilation also improved significantly. Exercise performance also significantly improved.[1]

The antioxidant "ice cream" was made from a combination of milk solids, ground hazelnuts, and cocoa with added green tea extract. Both ice creams were relatively low fat (about 9%) but the experimental nut-cream mix was lower in saturated fat (1.4% vs. 6%). The control ice cream consisted of 100 grams of unsweetened milk chocolate ice cream. The experimental ice cream contained 1817 mg/L polyphenols while the control product contained less than 100 mg. The organoleptic characteristics of the two products were similar; that fancy word simply means they tasted pretty much the same.

At this point, we have a rudimentary enough understanding of the health benefits of some number of chemical constituents present in foods that we can start formulating foods that, while similar to traditional versions of foods, will have positive effects on health. This study of a 'heart healthy chocolate ice cream' is a good example. This may be the first study to show that with a little intelligent tinkering ice cream might be modified to improve vascular function and physical performance simply by increasing polyphenols to reduce oxidative stress. In other words, ice cream can be made that is good for you while still tasting good. Technically we should probably call this stuff a frozen confection rather than ice cream as it did not in fact contain cream. If we were to call it chocolate gelato, its appeal goes up a notch.

We all know that diets high in fruits and vegetables are protective against heart disease, cancer, and diabetes. These benefits are now thought to result from the higher polyphenol content provided by these foods and that these polyphenols stimulate powerful antioxidant action in the body. There is an inverse association between high dietary polyphenol intake and cardiovascular disease (CVD) with high polyphenol diets reducing CVD mortality by about 65%. [2,3]

This is why following a Mediterranean diet pattern is so good for your heart. Yet, figuring out what people should eat and getting them to do so are two very different challenges. People are impressively reluctant to make lasting changes in the foods they eat. The natural inclination of most humans is to choose calorically dense, highly processed, low polyphenol foods, what we commonly call junk food. Our assumption is that this inclination toward junk food results from evolutionary pressure to identify easy to digest sources of ready calories. It should be no surprise when a four-year-old displays addiction-like behavior toward sugar-sweetened products. What we are looking at are the end results of millions of years of evolution.

Efforts to educate the public to make healthy food choices have met with very limited success. Look at the PREDIMED trial if you need evidence. Years of regular counseling by trained dieticians hardly shifted the diet of study participants, all of who should have been highly motivated to change. A recent report on members of the PREDIMED cohort suggest an inverse association between dietary polyphenol intake and adiposity. In other words, eating this Italian chocolate gelato might help people lose weight and not just prevent heart disease. [4]

There is more than one way to skin the cat, so to speak, or given that this is the *Townsend Letter*, more than one way to peel an eggplant. Thus, attention is shifting to whether food formulations may be modified to make healthier versions of unhealthy foods, doctor them up so to say, or enrich or better said, fortify them. We've a long history of food enrichment in

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the US, which in general means adding back in the vitamins that were lost in processing. Though the first fortified food, iodized salt, was an exception to this rule. Iodine was added to salt starting in 1924 as a way to reduce goiter incidence. Salt provides a reasonable vehicle to add iodine to as most people consume similar amounts of salt daily. Vitamin D was added to milk in 1933. Recall that it wasn't until the 1930s and 1940s that a number of specific deficiency disease syndromes were first identified and not until 1940 that the Food and Nutrition Board recommended the addition of thiamin, niacin, riboflavin and iron to flour.[5] Currently iron, folic acid, and perhaps calcium are also added.

Sanguigni's mimicry of chocolate ice cream using healthy ingredients seems to be in a class of its own. Rather than replacing nutrients lost in processing, or using ice cream as a simple carrier, Sanguigni has capitalized on the fact that chocolate is a solid source of polyphenols to begin with and simply added to them.

This healthy version of chocolate ice cream was created by reducing saturated fats, replacing milk fat with ground hazelnuts, and increasing the polyphenols through addition of cocoa solids and green tea extracts.

Moderate chocolate consumption is associated with reduced CVD in men and women who report eating chocolate several times a week. This protective benefit disappears at high consumption levels, that is, when chocolate is eaten daily. In fact, daily chocolate consumption actually increases risk of CVD.[6,7] The caffeine, theobromine, and fat in chocolate are generally held to blame for this biphasic response though it is unclear what specifically is responsible.[8]

In past years the high fat content of ice cream was perhaps falsely blamed for its inflammatory effect in consumers. A 2010 study that gave low-fat ice cream to obese subjects and tracked markers of inflammation and metabolic syndrome suggests that this belief was in error; there was no benefit to low fat substitution.[9] A 2012 trial also failed to show that full fat dairy foods increased biomarkers related to inflammation or atherogenesis.[10]

A 2013 meta-analysis that compared whole-fat vs. low-fat dairy food consumption noted that high fat was associated with some weight gain but had only minor effects on other cardio-metabolic risk factors[11] making it appear that the historic focus on low-fat dairy products was less useful than we hoped. According to a separate 2013 study, fermented full-fat dairy products were no worse than low-fat dairy and in some ways a better choice.[12] Thus one must wonder whether Sanguigni's substitution of nut fats for dairy fat in this current chocolate ice cream study was even necessary to improve CVD markers. Perhaps simply using fermented whole milk products might have been adequate. Admittedly the combination of chocolate and hazelnut does sound delicious tasting.

The problem with ice cream may not be that it is calorically dense but that it is polyphenol light. If polyphenol levels are brought up so that they balance the calories, foods that we traditionally think of as unhealthy may no longer be detrimental.[13]

Other strategies are being tested to turn ice cream into health food. One idea that is growing is the addition of probiotics, in particular bacteria that have been enriched with magnesium.[14] Another angle is to add prebiotic or synbiotic fiber to the ice cream along with probiotics.[15]

While there seem to be multiple ways to turn junk food into health food, product development and retail availability appear to be lagging behind. We would wish those in food product development might translate these ideas into consumer products with a bit more speed and enthusiasm.

Obviously current government regulations that insist on specific defined ingredients and specific ratios of those ingredients in specific foods may be seen as a hindrance to new product development. Ice cream is very tightly defined to the degree that label ingredient lists are optional. It would be unlikely for the chocolate hazelnut concoction used in this study to ever make it to a freezer case in the US in a package labeled ice cream. After all it has no cream in it.

We have known for years that chocolate polyphenols are responsible for chocolate's CVD benefit, yet we have yet to see any of the 'healthy' chocolates actually label their packages with polyphenol content. Is this a result of government labeling rules or company intransigence? Until the labels specify, consumers will find it challenging to discern which products have the most benefit. While we may not know the ideal daily polyphenol intake, it would still be nice to know how much is in our various foods and be able to compare products available for purchase.

While it is unlikely that there is a universally agreed on definition for 'health food', most members of the public will probably assume that any definition must include the fact they are less fun to eat than the more refined and processed stuff on the shelf; they take more effort to chew, they are less satisfying, and so on. Perhaps it's time to broaden our minds. The very first restaurant was established in 1765 by Monsieur A. Boulanger in Paris and served "restoratives," meat broth soups advertised to restore health to the upper society, depleted by wanton lifestyles, products that were probably not far removed from the bone soups popular today and promoted for similar ends. Have we reached a time today where health-focused gelato stores may come into fashion?

References

1. Sanguigni V, et al. Natural antioxidant ice cream acutely reduces oxidative stress and improves vascular function and physical performance in healthy individuals. *Nutrition*. 2017 Jan;33:225-233.
2. Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. *Am J Clin Nutr*. 2005;81(suppl):317S–25S.
3. Hooper L, et al. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2008;88:38–50.
4. Guo X, et al. Polyphenol Levels Are Inversely Correlated with Body Weight and Obesity in an Elderly Population after 5 Years of Follow Up (The Randomised PREDIMED Study). *Nutrients*. 2017 May 3;9(5). pii: E452.
5. Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification. Institute of Medicine (US) Committee on Use of Dietary Reference Intakes in Nutrition Labeling. Washington (DC): National Academies Press (US); 2003. https://www.ncbi.nlm.nih.gov/books/NBK208880/
6. Steinhaus DA, et al. Chocolate intake and incidence of heart failure: Findings from the Cohort of Swedish Men. *Am Heart J*. January 2017;183:18–23.
7. Mostofsky E, et al. Chocolate intake and incidence of heart failure: a population-based prospective study of middle-aged and elderly women. *Circ Heart Fail*. 2010 Sep 1;3(5):612-6.
8. Mumford GK, et al. Discriminative stimulus and subjective effects of theobromine and caffeine in humans. *Psychopharmacology* (Berl) 1994;115:1–8.
9. van Meijl LE1, Mensink RP. Effects of low-fat dairy consumption on markers of low-grade systemic inflammation and endothelial function in overweight and obese subjects: an intervention study. *Br J Nutr*. 2010 Nov;104(10):1523-7.
10. Nestel PJ, et al. Circulating inflammatory and atherogenic biomarkers are not increased following single meals of dairy foods. *Eur J Clin Nutr*. 2012 Jan;66(1):25-31.
11. Benatar JR, Sidhu K, Stewart RA. Effects of high and low fat dairy food on cardio-metabolic risk factors: a meta-analysis of randomized studies. *PLoS One*. 2013 Oct 11;8(10):e76480.
12. Nestel PJ, et al. Effects of low-fat or full-fat fermented and non-fermented dairy foods on selected cardiovascular biomarkers in overweight adults. *Br J Nutr*. 2013 Dec;110(12):2242-9.
13. Khor A, et al. Postprandial oxidative stress is increased after a phytonutrient-poor food but not after a kilojoule-matched phytonutrient-rich food. *Nutr Res*. 2014 May;34(5):391-400.
14. Góral M, et al. Magnesium enriched lactic acid bacteria as a carrier for probiotic ice cream production. *Food Chem*. 2018 Jan 15;239:1151-1159.
15. Di Criscio T, et al. Production of functional probiotic, prebiotic, and synbiotic ice creams. *J Dairy Sci*. 2010 Oct;93(10):4555-64. doi: 10.3168/jds.2010-3355.

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Monthly Miracles

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Voltage-Gated Calcium Channels, EMF and Chronic Disease

A Powerful Mechanism of Cellular Disruption

Research has found that calcium channel blocking drugs could mitigate the non-thermal damaging effects of electromagnetic fields (EMFs). Numerous articles indicate that voltage-gated calcium channels (VGCCs) in our cell membranes are powerfully affected by EMF radiation and allow a massive increase of calcium to flood into our cells, about one million ions per second per channel. This increased calcium greatly boosts nitric oxide (NO), which in physiological levels has beneficial health effects; but excessive NO forms peroxynitrite and superoxide, which are potent oxidant stressors. NO is broken down by superoxide dismutase (SOD) to form hydrogen peroxide and hydroxyl free radicals. Dr. Martin Pall explains that the result is extreme harm, as increased oxidative stress and nitrosative stress are involved in nearly all chronic disease. Dr. Pall, *professor emeritus* of biochemistry and basic medical sciences, Washington State University, feels the current EMF safety standards are off by a factor of about seven million.[1]

Dr. Pall and other scientists have shown that low-level microwave EMF exposure can result in VGCC activation and elevated intracellular calcium.[1-3] Unlike normal VGCC activation that occurs for milliseconds, EMF causes the VGCCs to open for longer periods, allowing more calcium to enter the cells. In a recent study,[3] calcium channel blockers, which block voltage-gated calcium channels, also blocked the increased influx of calcium caused by EMFs.

Dr. Pall, in his papers,[1,2] shows that the increase in intracellular calcium can result in numerous problems:

- Oxidative stress, leading to DNA breaks that can cause possible cancer cell formation;
- DNA breaks of gamete precursor cells, resulting in a decrease in fertility and adverse effects on sperm count, morphology, and function;
- Activation of matrix metalloproteases, leading to degraded tight cell/cell junctures and breakdown in the blood-brain barrier;
- Activation of kinases, leading to apoptosis (cell death); and,
- Depressed melatonin levels leading to sleep disruption.

Dr. M. Pall has four articles on PubMed that give more of his research findings under VGCCs and EMF.

Neuropsychiatric Effects of EMF Exposure

The highest density of VGCCs are in the central nervous system (CNS), reports Pall; and studies dating back to the 1950s and 1960s show that the CNS is the organ that is most sensitive to EMFs. Some of the studies show major changes in the structure of neurons, including cell death and synaptic dysfunction. As the VGCCs are stimulated in the brain, they release neurotransmitters and neuroendocrine hormones. The consequences of EMF exposure to the brain may include anxiety, depression, autism, and Alzheimer's.[4] Pall shows that the increase in intracellular calcium can result in numerous problems.[2] Epidemiological studies also trace fatigue, insomnia, memory and concentration difficulties. VGCCs are present in nearly every biological system in the human body, for example, in the immune, endocrine, nervous,

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and circulatory systems. EMFs can thus result in increases of allergies and inflammation, and affect hormone regulation, brain function, and heart rhythms.

Heart Effects

The heart is very sensitive to EMFs, particularly the pacemaker cells which have the highest density of VGCCs. Cardiac arrhythmias such as atrial fibrillation/atrial flutter, premature atrial contractions (PACs), premature ventricular contractions (PVCs), tachycardia and bradycardia may be related to EMF exposure.[5,6] Anecdotally, I had a 67-year-old female with chronic atrial fibrillation that I treated for some years with nutrients, herb tinctures from Germany, homeopathic remedies, and standard medication with periods of moderate success. After reading the VGCC information, I realized that she wore a digital wrist device that monitored her arrhythmias and sleep disturbances. I suggested that she discontinue the device, and her atrial fib improved greatly.

EMFs and Cancer

Carcinogenesis is a powerful consequence of mitochondrial damage, a lá Warburg and Seyfried. Dr. Thomas Levy, MD, JD, in his book *Death by Calcium* presents formidable data relating excess calcium to cancer, heart disease, and arteriosclerosis. I have had two entrepreneurs with brain cancer, one on the right side of his brain and he always used his cell phone on the right ear and the other with brain cancer on the left side and always held his phone on the left.

Limiting one's exposure to EMFs including cell phone towers, cordless phones, Wi-Fi routers, Bluetooth headsets, wireless mice, keyboards, smart thermostats, baby monitors, smart meters, and microwaves in the kitchen among others is important to work toward.

Protecting Against EMFs

Pall revealed magnesium deficiency will aggravate the effects of VGCCs and that most of us should supplement it. I am particularly fond of magnesium glycinate.

Nrf2, (nuclear factor erythroid-2-related factor) upregulates SOD, catalase, and other beneficial intracellular antioxidants and lowers inflammation, improves mitochondrial function, stimulates mitochondrial biogenesis, and helps detoxify the body from xenobiotics, carbon-containing toxins, and toxic metals. It improves and activates the transcription of over 500 genes in the human genome, most of which have cytoprotective functions, including three genes that encode enzymes required for the synthesis of reduced glutathione, one of our body's most important antioxidants.

Nrf2 can be activated many ways by consuming sulforaphane from cruciferous vegetables, foods high in phenolic antioxidants, omega-3 fats, DHA and EPA, carotenoids (especially lycopene), sulfur compounds from allium vegetables, isothiocyanates from cabbage, and terpenoid-rich foods.

Understanding VGCCs as the principle causative agent in EMF damage to our cells and that it is even more important than ionizing radiation will encourage us to avoid this energy and do more to shield ourselves and neutralize its damaging effects.

Some Implications for Research

The BioInitiatives Report[7] as well as Dr. Pall[2] recommend new, biologically based, safety standards that include lowering EMF exposures by 100 to 1000-fold. Dr. Pall proposes using three types of biological response tests to assess safety: measurement of nitrous oxide levels in cell culture sensitive to EMFs; biological tests such as cardiac, hormone, and neurological changes in animals in response to EMF; and whole animal studies looking at nitrous oxide levels in blood.

Pall has also reviewed numerous research papers demonstrating the similarities of animal response to VGCCs and plant responses. Plants exposed to EMF had localized effects and distant effects in shielded parts of the plants.[8] *Arabidopsis thaliana* (thale cress) is a popular model organism in plant biology and genetics carrying the aequorin gene, a gene producing the calcium-dependent bioluminescent protein aequorin to measure increased Ca^{2+} in response to low level 50 Hz sinusoidal EMF exposure. This bioluminescence response in a plant should make testing of EMF-blocking strategies more practical in the future.[9]

References

1. Pall ML. Electromagnetic fields act via activation of voltage-gated calcium channels to produce beneficial or adverse effects. *J Cell Mol Med*. 2013;17:958-965.
2. Pall M. Microwave Electromagnetic Fields Act by Activating Voltage-Gated Calcium Channels: Why the Current International Safety Standards Do Not Predict Biological Hazard. *Recent Res Devel Mol Cell Biol*. 7 (2014): 0-00 ISBN: 978-81-308-0000-0, in press; apps.fcc.gov/ecfs/document/view?id=7521102473
3. Pilla AA. Electromagnetic Fields Instantaneously modulate Nitric Oxide Signaling in Challenged Biological Systems. *Biochem Biophys Res Commun*. 2012;426: 330-3.
4. BioInitiative 2012: A Rationale for Biologically-based Exposure Standards for Low-Intensity Electromagnetic Radiation: Conclusions. www.bioinitiative.org/conclusions/
5. Striessnig J, et al. L-type Ca^{2+} channels in heart and brain. *Wiley Interdiscip Rev Membr Transp Signal*. 2014 Mar, 3(2):15-38.
6. Mesirca P, et al. Functional role of voltage gated Ca^{2+} channels in heart automaticity. *Front Physiol.* 2015;6:19.
7. Hardell L, Sage C, Biological Effects from Electromagnetic Field Exposure and Public Exposure Standards. *Biomed Pharmacother*. 2008;62:104-109.
8. Pall M. Electromagnetic Fields Act Similarly in Plants as in Animals: Probable Activation of Calcium Channels via Their Voltage Sensor. *Current Chemical Biology*. April 2016;10(1):74-82.
9. Pazur A, Rassadina V. Transient effect of weak electromagnetic fields on calcium ion concentration in *Arbidopsis thaliana. BMC Plant Biol*. 2009;9:47.

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Cool Beans

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Introduction to Chronic Kidney Disease

Dysfunction of the world's kidneys has taken epidemic proportions, some say pandemic. Millions in America and so many more worldwide have some level of kidney disorder (aka chronic kidney disease: CKD).

It is time to awaken awareness about incipient (aka early) and moderate CKD (stage 3 and early stage 4) and shine a light on its relationship with the acute kidney injury (AKI) risk lurking in the noxious environment. The hidden epidemic lies in wait, in the shadows of early disease, and all we see is the tip of the iceberg. Integrative lifestyle medicine has many solutions to enhance basic guidelines that aim to slow down the progress of CKD – avoiding toxins and supporting metabolic balancing, possibly regressing/reversing injured (non-sclerosed) nephrons.

We can explore some simple "aha's" as ways to look at kidney care, as a wake-up call for the "Kidney WholeLifeRx." and then explore some basic "yes's" that can gently guide a motivated CKD patient along a holistic, integrative, naturopathic, functional SlowDown path.

Some Aha's

- First: There is a major drop off of incident cases of CKD from Stage 3 to stage 4.
- Second: Acute kidney injury causes CKD, and CKD is a major risk factor for more severe AKI.
- Third: Normal aging causes decreased renal function - which increases risk for AKI.
- Fourth: All causes of CKD are associated with inflammation and oxidative stress.

The KDOQI (Kidney Disease Outcomes Quality Initiative of 2002) created a staging system for kidney disease to help clinicians more easily navigate the unique needs of renal dysfunction at varying CKD stages, independent of cause. At each stage, there are very unique characteristics, personality, presentation, prognosis, and needs. Like the glomerular filtration rate (GFR), staging is a conceptualized way of categorizing needs.[1]

The CDC National Chronic Kidney Disease Fact Sheet 2017 notes that 30 million people or 15% of US adults are estimated to have CKD. But only 48% of those with severely advanced dysfunction (not on dialysis) are aware of having CKD. And an alarming 96% people with kidney damage or mildly reduced kidney function are not even aware of having CKD.[2]

Take a look at an example of CKD incidence statistics:

CKD Stage 1 - GFR >90	5,900,000 patients;
CKD Stage 2 - GFR 60-895	300,000;
CKD Stage 3 - GFR 30-59	7,600,000;
CKD Stage 4 - GFR 15-29	400,000;
CKD Stage 5 - GFR <15	300,000.[2]

The First Aha!

The most notable aha! is the statistical drop-off from stage 3 to stage 4. The epidemic train stops at stage 3 for millions of people. It is often said that stage 3 is "asymptomatic." A thorough functional history provides a kaleidoscope of portals into the complex and comorbid needs of those with dysfunctional kidneys. The majority in stage 3 who do not "proceed" to stage 4 will perish from comorbidities – 50% of those from cardiovascular disease (exacerbated and accelerated by CKD).[1]

The allopathic recommendations include ACE inhibitors, diabetes and hypertension pharma, and statins, with a modicum of lip service made to lifestyle interventions.[1] The guidelines specify that nephrologists will manage more advanced patients, and primary care will address those less advanced. In short, this is not happening.

Primary care practitioners have been neither enlisted nor engaged or educated. Unfortunately, although the guidelines suggest that primary care manage CKD patient care until eGFR reaches <30 and because most primary care providers remain unaware of the extensive ramifications of this complex ailment, this still is not widespread or standard of care. In fact, as noted, the majority of people are frankly unaware.

Interestingly, what is missing in this CKD conversation is clinical passion for the personalized lifestyle approach, a concept coined by Jeff Bland. Historically, lifestyle therapy (so-called "conservative" treatment) was taken seriously by nephrology. When dialysis became available, the new novel option for nephrologists led to a veritable abandonment

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of clinical lifestyle interventions – and to a great extent has remained so. The multi-billion-dollar dialysis industry provides much research funding, the focus being heavily weighted on end-stage insights and care.[1]

Individualizing early lifestyle awareness and care for patients with CKD and comorbidities is one way to side step the reality that we can no longer afford to dialyze and transplant all who need it - in America or worldwide. With the limited cadre of nephrologists, an integrative interspecialty and interdisciplinary share-care is critically needed. Reviewing the statistics noted above, it's obvious that the time has come to use collective holistic smarts and step up to the Incipient CKD epidemic.[2,3]

The Second Aha!

AKI leads to CKD. Acute kidney injury was called acute tubular necrosis (ATN) in the past. CKD, in turn, is a major risk factor for developing more severe consequences of AKI. Studies have shown a high incidence of CKD developing post-AKI, sometimes immediately, often delayed.[4]

A primary preventive care focus becomes a strong portal for anticipatory guidance: toxin avoidance and awareness of consequences. Offenders like soda, dietary indiscretion, dietary toxins, cigarettes, and sedentary living are easy starting places. Sleep, hydration, household toxins, and infectious exposures are basic primary care issues. Most often, people are unaware of the diagnosis, prognosis, or the risk from environmental exposures.[5]

Genomics and nutrigenomics are rich resources. Multiple gene loci have been identified with increased susceptibility to the development of CKD, with single nucleotide polymorphisms (SNP) testing to guide. Further kidney care comes with deeper explorations of the metabolic, mitochondrial, microbiome, etc. aspects.

The Third Aha!

"Normal aging causes decreased renal function and increased risk for AKI." This attitude is fraught with controversy: some (not all) in the nephrology community feel that diminishing eGFR comes with the normal aging territory (elders >65). Stage 3a, GFR 45-60 is often considered "normal" - and why medicalize it? True, without a preventive lifestyle, nutrition approach, there may in fact be little to offer a >65-year-old with diminishing kidney function.[6]

With increasing age, there is variably diminishing renal function between individuals. In *The Kidney*, Maartin Taal writes, "CKD increases in prevalence with age and heralds a poor outcome."[7] Older kidneys adapt less well and recover more slowly after acute ischemic injury, infections, exposure to toxins, or immunological processes, or in the presence of other organ dysfunction.[8] Astute holistic cardiovascular risk management can mitigate exaggerated responses and decompensation, even without frank uremia. After age 65, the risk of end stage renal disease (ESRD) only exceeds the risk of death from other causes when the eGFR falls below 15.[7]

The Fourth Aha!

All causes of CKD are associated with inflammation and oxidative stress. An initial goal for every CKD patient is identifying sources of inflammation and calming the flames of inflammation. Beginning with the plagues of our times – diet, living quarters sanitation and detoxicology, dental – it is possible to make CKD the fulcrum of a WholeLifeRx plan that can decrease the inflammation-associated comorbidities for each person.[9]

The Integrative Holistic Yes's

Much of the current nephrology literature expresses a clear intent for lifestyle change, with the admonition that time and further research will elucidate what may be effective in slowing down CKD progression. Scouring this literature, it is in fact possible to elaborate a list of actionable interventions that are not harmful, might be helpful for CKD, and are clearly useful as primary prevention or secondary prevention of a CKD-associated comorbidity like CVD, diabetes, or autoimmune disease.

The earlier the interventions start, the more kidney function there is to protect and preserve. The best chance of achieving maximal renoprotection is therefore when the therapy is established as early as possible, preferably in stage 1 or 2. A comprehensive approach to renoprotection is an achievable goal for all patients with CKD, to delay the need for dialysis in many and substantially reduce the number progressing to ESRD.[7]

Epigenetics and CKD

Speaking recently at the Functional Forum in September 2017, Jeff Bland said: "With the environmentally toxic milieu, including the food supply, epigenetic alterations respond to the rapidly changing environment, and this calls out the canaries. Alarmed genes are going into defensive battle against a hostile environment." Lifestyle changes that are personalized, according to Bland, become the golden ring to improving the health of the world, one person at a time. Each person with CKD presents a unique clinical collage, and astute interventions are likely to invite and achieve the optimal health many desire.[10]

Bland made a point about the patient who presents as "chronically unwell" before disease diagnosis is made: this cameo fits incipient CKD. Without embracing lifestyle amendments (and influenced by toxins and sedentary ways), alarmed genes may lead the way to an unfortunate legacy of illness. Methylation, which modifies epigenetics, needs to be evaluated early enough in CKD to slowly retrieve self-preserving health habits.

Yes! to Kidney Diet

At the heart of the CKD path to health is diet attunement. We know it takes years for diet, exercise, and lifestyle modification to be effective: the conclusion is to start early in the course

of the illness, with the awareness that slowed progression and even regression of damaged (not dead) nephrons can be achieved. It should be emphasized that without proper dietary education, the prognosis for patients with CKD is bleak.[7]

Basic labs are a fine place to start; knowing the eGFR, the creatinine, the potassium, sodium, phosphorus, calcium, CO2, albumin, glucose offers a strong entry. From these basics, many macronutrient adjustments can be made. Readiness assessment is wise, and discernment is useful: some patients need a "tip-toe" approach and others need a "swift kick."

Unfortunately, typical allopathic renal dietary advice lacks strong support to avoid packaged foods, eat less (but grass fed) meat, make organic non-GMO choices, with homemade alkaline and fermented foods, elimination of sugar, bad oils etc. For some this list is a tall order, and insightful integrative TLC will be needed. This list is skewed in favor of a strongly motivated natural-medicine-loving patient population. CKD does not usually have immediate or obvious consequences for most people. The professional voice emphasizing lifestyle Rx with the same passion as a pharma Rx will in time assist patient commitment to change.

YES! To NephroDetoxicology

Many toxins are produced internally from protein metabolism, and extensive toxic exposures occur externally. Functional medicine awareness offers a leg-up advantage in supporting patients to diminish production of and exposure to these uremics. Substances like ADMA and homocysteine are familiar in other contexts and represent a unique presence in CKD.[11]

The kidneys are targets for many types of chemicals – drugs, agricultural agents, industrial chemicals, and environmental pollutants. They function to eliminate xenobiotics and metabolites, which can accumulate if renal function diminishes. These chemicals can rise to toxic levels as the renal transport systems and urinary concentrating mechanisms lag. This accelerates AKI and CKD.[11]

NephroDetoxicology and microbiome awareness includes assessment of past and present toxic exposures. Taking a mental tour of the patient's house, garage, workplace, etc. for toxicants that might injure nephrons can elucidate some easy-to-remedy threats.

Conclusion: Turning Up the Dial

Becoming attuned and attentive to the profound nature of the kidney - the mystique, the metaphor, its poetry for the patient, and its significance in our times of toxic accumulation and inflammatory disease – opens doors to world health and healing. When we tend to maladjusted kidneys with awe, we inspire the (possibly frightened) patient who is scrambling to integrate the reality of evolving symptoms and complexities. It is possible to re-pace this epidemic by listening to the patient's stories and fixing the root causes of the blocks in the physical, mental, emotional, and spiritual needs of incipient CKD patients.

References

1. Kimmel PL, Rosenberg ME (editors) *Chronic Renal Disease.* 2015.
2. Centers for Disease Control and Prevention. *National Chronic Kidney Disease Fact Sheet, 2017.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2017.
3. Coresh J, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third national health and nutrition examination survey. *American J Kidney Diseases.* 2003;41(1):1-12.
4. Berger K, Moeller M. Mechanisms of Epithelial Repair and Regeneration after Acute Kidney Injury. *Seminars in Neph*. July 2014; 3(4): 394-403.
5. Kataria A, et al. The effects of environmental chemicals on renal function. *Nat Rev Nephrol*. 2015 Oct; 11(10): 610–625.
6. *Wang XH, et al.* The Aging Kidney- Increased Susceptibility to Nephrotoxicity. *Int J Mol Sci.* 2014; 15(9), 15358-76.
7. *Brenner & Rector's The Kidney,* 10th Edition. 2015
8. Rankin G. editor. Renal Toxicology – Epidemiology and Mechanisms. *Intnl J Molec Sci Special Issue.* 2014;15(11).
9. Cataldi L. The Kidney Through the Ages: Proceeding of the 8th International Workshop of Neonatal Nephrology, April 6-8'1998, Rome Italy Il Pediatra XX
10. Minich DM, Bland JS. Review Article: Personalized Lifestyle Medicine: Relevance for Nutrition and Lifestyle Recommendations. *The Scientific World Journal.* 2013.
11. Mishima E, et al. Evaluation of the impact of gut microbiota on uremic solute accumulation by a CE-TOFMS–based metabolomics approach. *Kidney International.* Sept 2017, 92(3);634-645.

Additional Resources

ADA Revises Diabetes Standards of Care. Medscape Educational Clinical Briefs. September 2017.

Bible Hub: http://biblehub.com/topical/k/kidneys.htm

Choi MJ. CKD for Primary Care Practitioners: Can We Cut to the Chase Without Too Many Shortcuts? *Am J Kidney Dis*. 2016; 67(6): 826-829.

Cupisti A, et al. Nutritional Support in the tertiary care of patients affected by chronic renal insufficiency: report of a step wise personalized pragmatic approach. *BMC Neph*. 2016; 17:124.

Greger M. Treating Chronic Kidney Disease with Food. Nutritionfacts.org. March 21, 2016.

Nash D, et al. Improving Care for Patient with or at Risk for CKD Using EMR Interventions: A Pragmatic Cluster – Randomized Trial Protocol. *Can J Kidney Health Dis.* 2017; 4:

Palmerson C. Detox and Your Health: 7 Channels of Elimination. November 16, 2004. online.

Vaziri ND, et al. Effect of Uremia on Structure and Function of Immune System. *Journal of Renal Nutrition*. Jan 2012; 22(1): 149-156.

Wouters OJ, et al. Early chronic kidney disease: diagnosis, management, and models of care

Nat Rev Nephrol. 2015Aug;11(8):491-502.

Dr. Rose has practiced eclectic holistic family medicine for many years, with a focus on individualized patterns of healing.

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Serge Jurasunas Honored for 50-Year Professional Career

In September 2017, Pan American University of Sciences and Natural Medicine School of Medicine conferred upon Serge Jurasunas, ND, MD(Hom), professor of naturopathic oncology, the degree of Doctor of Medicine (*Honorius Causa*) in recognition of his work in the field of alternative medicine, along with his unique contributions to medical science having developed live blood analysis, oxidative dried blood testing, and innovations in the science of iridology. The diploma of Doctor of Medicine (*Honorius Causa*) was awarded by the President of Pan American University, the honorable Prof. Charles McWilliam.

Dr. Jurasunas has traveled to more than 40 countries to both organize, participate, and teach at numerous conferences. He has authored numerous scientific articles, over 150 papers and seven books, and is a frequent contributor to the *Townsend Letter* magazine. Recently, he created a bridge between the field of integrative oncology and natural medicine and contributed to the development of a new paradigm in patient treatment in the field of integrative oncology and nutrition. His research in the clinical application of molecular markers came about as a result of having treated cancer patients for over four decades, developing new protocols.

Serge Jurasunas had been previously honored several times during his 50-year career. He received the degree of Doctor of Indigenous Medicine from the Minister of Indigenous Medicine in Sri Lanka where he spent time teaching and working in the Hospital of Colombo. In November 1996, he was appointed a Professor at Capital University of Integrative Medicine in Washington, DC, in recognition of all his work and teaching, his research and clinical practice in the field of cancer, and for his contributions to the development of medical microscopy and iridology.

To celebrate the 50th anniversary of his practice and research, an additional special honor was recently given him for his contribution to the development of integrative medicine and oncology and his practice with patients in his Lisbon clinic. During the 18th Annual Iridology and Integrative Health Care Congress 2017, held in Orlando, Florida, Serge Jurasunas was honored with the Life Achievement Award conferred on him by Dr. David Pesek, ND, PhD, President of the International College of Iridology, during a special ceremony. Dr. Pesek also presented Professor Jurasunas with Honorary Lifetime Membership to the International College of Iridology.

Professor Serge Jurasunas was honored for his major contributions in the field of cancer treatment and research, especially for devoting his life to the fight against cancer and for his time and energy serving patients. Serge Jurasunas' clinical experience lasted over a 50-year span, during which he treated cancer patients with all types and grades. He also devoted considerable time and energy to educating them in ways to better accept and fight this disease. It was not an easy task.

These honors bestowed upon him celebrate his entire life, which has been dedicated not only to treating disease, teaching, and conducting research but also to spreading the philosophy and principles of natural medicine throughout the world. ◆

Calendar

Please submit an announcement of your event 90 days in advance.
Event publication must be limited to 25 words or less. Multiple event listings require paid advertising.
Contact calendar@townsendletter.com for details.

FEBRUARY 1-3: INSTITUTE FOR FUNCTIONAL MEDICINE – CARDIOMETABOLIC APM in Atlanta, Georgia. CONTACT: 800-228-0622; https://www.ifm.org/

FEBRUARY 3-7: 2nd INTERNATIONAL CANCER CONGRESS in Toulouse, France. CONTACT: http://www.toulouse-onco-week.org/

FEBRUARY 4-6: INSTITUTE FOR FUNCTIONAL MEDICINE – IMMUNE APM in Atlanta, Georgia. CONTACT: 800-228-0622; https://www.ifm.org/

FEBRUARY 8-11: 15th ANNUAL NATURAL SUPPLEMENTS CONFERENCE in San Diego, California. CONTACT: https://www.scripps.org/event_schedules/1057-naturalsupplements

FEBRUARY 8-13: A4M & MMI present BIO-IDENTICAL HORMONE REPLACEMENT SYMPOSIUM in Charleston, South Carolina. CONTACT: https://www.a4m.com

FEBRUARY 9-11: LABRIX ADVANCED WORKSHOP in Las Vegas, Nevada. Adrenal/HPA axis hormone and neurotransmitter testing and treatment protocols. CONTACT: https://www.labrix.com/law

FEBRUARY 10-11: THE GREAT PLAINS LABORATORY presents GPL ACADEMY PRACTITIONER WORKSHOPS – Organic Acids Testing and Environmental Toxin Testing in Austin, Texas. Includes organic acids testing, toxic chemical testing, and mycotoxin testing. CMEs available. CONTACT: www.GPLWorkshops.com

FEBRUARY 10-11: 2018 FOOD AS MEDICINE SYMPOSIUM @ National University of Natural Medicine in Portland, Oregon. CONTACT: http://career-alumni.nunm.edu/continuing-education/

FEBRUARY 16-18: 7th ANNUAL OncANP NATUROPATHIC ONCOLOGY CONFERENCE in Tempe, Arizona. CONTACT: https://oncanp.org/

FEBRUARY 22-25: BRIMHALL HOMECOMING: The 6 Steps to Wellness in Phoenix, Arizona. CONTACT: Jason Matuszewski, 866-338-4883; http://www.brimhall.com

FEBRUARY 23-25: HOMEOPATHY FOR MUSCULOSKELETAL HEALING with Asa Hershoff, DC, ND, presented by Florida Homeopathic Society, in Orlando, Florida. ACHENA CEUs. CONTACT: https://www.floridahomeopathicsociety.org/

FEBRUARY 24-25: THE GREAT PLAINS LABORATORY presents GPL ACADEMY PRACTITIONER WORKSHOPS – Organic Acids Testing and Environmental Toxin Testing in Los Angeles, California. Includes organic acids testing, toxic chemical testing, and mycotoxin testing. CMEs available. CONTACT: www.GPLWorkshops.com

FEBRUARY 28-MARCH 1: INTRODUCTION TO PARACELSUS BIOLOGICAL MEDICINE near St. Gallen, Switzerland. CONTACT: https://www.paracelsus.com/

MARCH 2-3: CLINICAL MITOCHONDRIAL AND ENVIRONMENTAL MEDICINE in Heidelberg, Germany. Specialist lectures in English. Also, first of 4 weekends for German curriculum. CONTACT: info@mito-medizin.de; http://www.mito-medizin.de/

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Two-Time Winner of 2017 Best of Supplements Award!

Essential Formulas is excited to announce that Reg'Activ Detox & Liver Health is a second-time winner of 2017 *Better Nutrition* magazine's Best of Supplements Award. This formula contains the revolutionary probiotic strain *Lactobacillus fermentum* ME-3, able to produce the "master" antioxidant glutathione and support liver health and function on a cellular level.

Better Nutrition magazine recently selected the revolutionary Reg´Activ® Detox & Liver Health™ formula as a 2017 'Best of Supplements' Award Winner in the Detox and Cleansing category for the second year in a row.

To select the winning products, the editors of *Better Nutrition* magazine conducted retailer surveys and tallied up votes from readers and staffers. The Better Nutrition Supplement Advisory Board, consisting of naturopathic physicians, health writers, and nutrition educators, considered the nominated supplements quality of ingredients, reputation, and the science behind the products. The winners were featured in the November 2017 issue of *Better Nutrition* magazine.

Reg´Activ® Detox & Liver Health™, launched in 2014, is a superior glutathione supplement because it contains a patented and unique delivery system — a living probiotic strain, *Lactobacillus fermentum* ME-3, that produces glutathione within the body. ME-3 works through three pathways: synthesizing glutathione itself, promoting cellular uptake of glutathione, and regenerating "spent" glutathione back into its active state.*

Glutathione is the most important antioxidant manufactured in the human body, so pivotal to our health that it is considered "The Master Antioxidant." Glutathione's most significant function is that of detoxification, so maintaining the body's supply is critical for good health.

An increasing number of studies link glutathione depletion with an increase in oxidative stress and a greater incidence of health conditions related to cellular aging. However, until recently, glutathione was not effective when taken orally because it breaks down during digestion and is not absorbed.

"Since glutathione's antioxidant activity is crucial for every cell in the body, the discovery of ME-3, a strain that can synthesize glutathione and boost levels in humans represents an extraordinary breakthrough in health and medicine," said Essential Formulas Director of Scientific Research Dr. Ross Pelton, RPH, CCN.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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Calendar

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MARCH 10-11: MARIJUANA SYNDROME – HOW TO BALANCE AND OPTIMIZED THE EFFECTS OF CANNABIS WITH TCM in Vancouver, British Columbia. CTCMA, CNPBC, CAB, and NCCAOM approved. CONTACT: Sonia Tan, info@redtreewellness.ca; http://events.r20.constantcontact.com/register/event?oeidk=a07ee8eabj94c019753&llr=rwr9vymab&showPage=true

MARCH 19-23: INSTITUTE FOR FUNCTIONAL MEDICINE – APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE in San Diego, California. Also, **OCTOBER 1-5** in Washington, DC; **OCTOBER 4-8** in London, United Kingdom. CONTACT: 800-228-0622; https://www.ifm.org/

MARCH 21-22: THE 2nd PROBIOTICS CONGRESS: EUROPE in Rotterdam, The Netherlands. CONTACT: http://www.global-engage.com/event/probiotics-europe/

MARCH 21-22: THE 5th MICROBIOME R&D AND BUSINESS COLLABORATION FORUM: EUROPE in Rotterdam, The Netherlands. CONTACT: http://www.global-engage.com/event/microbiota/

MARCH 23-24: INTERNATIONAL ACADEMY OF ORAL MEDICINE & TOXICOLOGY (IAOMT) SPRING MEETING in Denver, Colorado. CONTACT: http://iaomt.org

MARCH 24-29: SAUDADE WELLNESS PROGRAM FOR PRACTITIONERS in Sao Jorge, Brazil. CONTACT: http://www.drtrindade.com/saudadetotalwellnessretreat/

MARCH 30-APRIL 1: INJECTION THERAPIES with Dr. Marc Harris – Permanent Pain Relief and So Much More in Orlando, Florida. CONTACT: Jason Matuszewski, 866-338-4883; http://www.brimhall.com

APRIL 5-7: THE FORUM FOR INTEGRATIVE MEDICINE – Treating the Untreatable: Unraveling Complex Chronic Illness in Chicago, Illinois. CONTACT: https://forumforintegrativemedicine.org/

APRIL 6-8: SOUTHWEST CONFERENCE ON BOTANICAL MEDICINE in Tempe, Arizona. Pre-conference on addiction. Botanicals for surgery, mood disorders, cognitive function, and lymph health. CE credits available. CONTACT: 541-482-3016; http://www.botanicalmedicine.org.

APRIL 6-8: ENVIRONMENTAL HEALTH SYMPOSIUM 2018 in Scottsdale, Arizona. Effective methods and interventions for reducing toxic load and body burden. CONTACT: 855-347-4477; http://www.EHS2018.com

APRIL 6-8: 13th ANNUAL JOINT AMERICAN HOMEOPATHIC CONFERENCE – Homeopathy: An Affordable Healthcare Solution in Phoenix, Arizona. CONTACT: http://www.homeopathycenter.org/

APRIL 12-14: A4M ANNUAL SPRING CONFERENCE in Hollywood, Florida. CONTACT: https://www.a4m.com/

APRIL 13-15: THE GREAT PLAINS LABORATORY presents GPL MASTER PRACTITIONER WORKSHOP in Chicago, Illinois. In-depth information about the Organic Acids Test, GPL-TOX (Toxic Non-Metal Chemical Profile), Glyphosate Test, GPL MycoTOX Profile, and more. CONTACT: www.GPLWorkshops.com.

APRIL 14-15: CALIFORNIA NATUROPATHIC DOCTORS ASSOCIATION with PsychANP present INTEGRATIVE PSYCHIATRY AND NEURO-IMMUNOLOGY in Torrance, California. CONTACT: http://www.calnd.org/

APRIL 18-22: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE SPRING CONFERENCE – "What Works" in Cincinnati, Ohio. CONTACT: http://icimed.com/

APRIL 19-21: 3rd CONGRESO SENMO (La Sociedad Española de Nutrición y Medicina Ortomolecular) in Barcelona, Spain. CONTACT: http://senmo.org/index.php/congresos/iii-congreso-menu/ponentes-iii-congreso-senmo

APRIL 20-21: INTEGRATIVE MEDICINE FOR THE TREATMENT OF TICK-BORNE DISEASES in Baltimore, Maryland. CONTACT: delmarvalyme@yahoo.com; http://integrativelyme.com

APRIL 26-29: 24th CLINICAL APPLICATIONS FOR AGE MANAGEMENT MEDICINE in Orlando, Florida. CONTACT: https://www.agemed.org

APRIL 27-28: 62nd NORTHWEST NATUROPATHIC PHYSICIANS CONVENTION – Golden Nuggets from the Golden Nugget in Las Vegas, Nevada. CONTACT: https://nwnpc.com/

APRIL 27-29: 47th ANNUAL INTERNATIONAL ORTHOMOLECULAR MEDICINE TODAY CONFERENCE in Tokyo, Japan. CONTACT: https://www.isom.ca/omt/

APRIL 29: CONNECTICUT NATUROPATHIC PHYSICIANS ASSOCIATION 10TH ANNUAL CONFERENCE in Cromwell, Connecticut. CONTACT: http://www.events.syncopatemeetings.com/cnpa/

MAY 4-5: FCT TRAINING SEMINAR – Its Major Breakthrough in Bio-Resonance Testing and Combining the Best in Medicine with Savely Yurkovsky, MD, in Chappaqua, New York. CONTACT: 914-861-9161; www.yurkovsky.com

MAY 4-6: KLINGHARDT ACADEMY LYME & LIGHT MASTERMINDS in Morristown, New Jersey. Energetic Detox-Brain Solutions. Also, **SEPTEMBER 14-23** in Kenmore, Washington with Neural Therapy-Autonomic Response. CONTACT: 908-899-1650; info@klinghardtacademy.com; http://www.kinghardtacademy.com

MAY 9-13: THE AMERICAN PROLOTHERAPY & REGENERATIVE MEDICINE CONFERENCE in Plano, Texas. CME credits available. CONTACT: http://prolotherapycollege.org/

MAY 10-12: BIOREGULATORY MEDICINE INSTITUTE CONFERENCE in Louisville, Kentucky. CONTACT: https://www.brmi.online/events

MAY 18-20: 5th ANNUAL TRADITIONAL ROOTS HERBAL CONFERENCE @ National University of Natural Medicine in Portland, Oregon. CONTACT: http://traditionalroots.org/tradrootscon2018/

MAY 19-20: THE GREAT PLAINS LABORATORY, INC. presents GPL ACADEMY PRACTITIONER WORKSHOPS in Charlotte, North Carolina. This workshop will review organic acids testing, toxic chemical testing, and mycotoxin testing. CONTACT: http://www.GPLWorkshops.com

MAY 31- JUNE 2: INSTITUTE FOR FUNCTIONAL MEDICINE ANNUAL INTERNATIONAL CONFERENCE – Solving the Puzzle of Autoimmunity: The Interplay of Gut, Genes, and Environment in Hollywood, Florida. CONTACT: 800-228-0622; https://www.ifm.org/

JUNE 1-4: MEDICINES FROM THE EARTH HERB SYMPOSIUM in Black Mountain, North Carolina. CE credits available. CONTACT: 541-482-3016; http://www.botanicalmedicine.org

JUNE 14-16: HOMEOPATHY RESEARCH INSTITUTE CONFERENCE in London, United Kingdom. CONTACT: https://www.hri-research.org/

JUNE 20-23: SOCIETY OF PROGRESSIVE MEDICAL EDUCATION (SOPMed) INTEGRATIVE THERAPY TRAINING AND ANNUAL CONVENTION in Colorado Springs, Colorado. Includes pre-conference events. CONTACT: 517-242-5813; https://sopmed.org/

JULY 6-8: 5th INTERNATIONAL CONGRESS ON NATUROPATHIC MEDICINE – Promoting Excellence in Natural Medicine in London, United Kingdom. CONTACT: + 44 (0)1745 828 400 Email: secretariat@icnmnaturopathy.eu; http://icnmnaturopathy.eu/en/

JULY 12-14: INSTITUTE FOR FUNCTIONAL MEDICINE – HORMONE APM in Portland, Oregon. CONTACT: 800-228-0622; https://www.ifm.org/

JULY 12-14: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS ANNUAL CONVENTION AND EXPOSITION in San Diego, California. CONTACT: http://www.naturopathic.org/aanp2018

JULY 15-17: INSTITUTE FOR FUNCTIONAL MEDICINE – ENERGY APM in Portland, Oregon. CONTACT: 800-228-0622; https://www.ifm.org/

AUGUST 4-5: THE GREAT PLAINS LABORATORY, INC. presents GPL ACADEMY PRACTITIONER WORKSHOPS in Denver, Colorado. This workshop will review organic acids testing, toxic chemical testing, and mycotoxin testing. CONTACT: http://www.GPLWorkshops.com

SEPTEMBER 6-9: 9th INTEGRATIVE MEDICINE FOR MENTAL HEALTH CONFERENCE (IMMH) in Dallas, Texas. Evidence-based diagnostic and treatment options to reduce symptoms of autism, ADHD, depression, anxiety, Alzheimer's, and more. CONTACT: http://www.IMMH2018.com

SEPTEMBER 14-15: CLINICAL MITOCHONDRIAL AND ENVIRONMENTAL MEDICINE in Heidelberg, Germany. Specialist lectures in English. CONTACT: info@mito-medizin.de; http://www.mito-medizin.de/

OCTOBER 18-22: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE – An Orthomolecular Approach to Cancer in Minneapolis, Minnesota. CONTACT: http://icimed.com/

OCTOBER 19-20: DERMVEDA INTEGRATIVE SKIN CARE SYMPOSIUM in Sacramento, California. CONTACT: http://2018.integrativeskinsymposium.com/

OCTOBER 25-27: INSTITUTE FOR FUNCTIONAL MEDICINE – GASTROINTESTINAL APM in Nashville, Tennessee. CONTACT: 800-228-0622; https://www.ifm.org/

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Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

These Are a Few of My Favorite Things – Research Highlights from Recent Times

Throughout 2017, I have reported monthly in this column on research important to women's health. I have selected several studies I have written and spoken about in 2017, that have influenced my clinical practice in gynecological and primary care for women. In case you missed this information from me or others, I hope these selections benefit you and your patients.

Another Reason to Avoid Douching

Douching is quite common among US women, especially African American women, despite previous research demonstrating negative health outcomes such as pelvic inflammatory disease and ectopic pregnancy. In the current prospective cohort study, researchers investigated whether douching or genital use of talcum powder was predictive of an increased risk for ovarian cancer. This was done in about 50,000 women who had a sister with breast cancer.

After an average follow-up of seven years, 154 women were diagnosed with ovarian cancer. Women who had reported douching at the baseline of the study had a significantly higher risk for ovarian cancer, with a hazard ratio of 1.8. The use of talc was not associated with the development of ovarian cancer.

Commentary: Vaginal douching disturbs the normal vaginal flora and may impair the local immune system defense mechanisms. In addition, environmental toxins such as phthalates are higher in women who douche. Any reason that a woman may think she needs to douche can be solved in other ways. If for infections, then there are vaginal and/or oral treatments, both conventional and natural; if for hygiene reasons, there are other methods including vaginal suppositories, enhanced personal washing, and perhaps getting more comfortable with what could be normal odors. A strong fishy odor is likely related to a vaginal infection and can be tested and treated appropriately. Women should be encouraged not to douche. If they resist this advice, then I would advise tap water.

Gonzalez N, et al. Douching, talk use, and risk of ovarian cancer. *Epidemiology*. 2016 June 20.

***Tribulus terrestris* for Low Libido in Postmenopausal Women**

This clinical study evaluated the effects of treating postmenopausal women with hypoactive sexual desire disorder (HSDD) using *Tribulus terrestris*. All women received testing including mammography, vaginal ultrasounds, and serum levels of prolactin, thyroid stimulating hormone, total testosterone, and sex hormone binding globulin before enrollment. Study participants were randomized to two groups with the treatment group receiving three pills of 250 mg of *Tribulus terristris* for 120 days and the control group receiving placebo for 120 days.

The Female Sexual Function Index (FSFI) and the Sexual Quotient Female Version (QS-F) questionnaires were used to assess female sexual function. A total of 36 healthy postmenopausal women with low libido were selected to participate in this study in Brazil with 20 in the study group and 16 in the placebo group, with three drop outs in each group. All women were between one and ten years postmenopausal and were between 43 and 65 years old. Women were excluded if they had interpersonal relationship problems or had partners with sexual problems.

The total mean score and scores of each of the six FSFI questionnaire domains before and after treatment did not show any significant difference between the two groups. Women receiving the *T. terrestris* scored significant improvements in all six domains as did the placebo, with the exception of lubrication which did not improve in the placebo group.

After 120 days of treatment with *T. terrestris*, the QS-F indicated significant improvement in the domains of desire, arousal/lubrication, pain and anorgasmia with the placebo group showing no improvements in any of these domains.

The initial testosterone levels in both groups did not vary before and after the treatment, although there was a significant increase in the levels of free and bioavailable testosterone in the *T. terrestris* group with no increase in the placebo group.

Commentary: To my knowledge, this is the first study suggesting a treatment effect of *T. terrestris* for HSDD in ➤

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postmenopausal women. While there was improvement yet no difference between treatment group and placebo for the FSFI domains except lubrication, which did improve more in the treatment group, that is in fact important in comfort during vaginal penetration. If sex is anticipated to be comfortable and pain free, then the desire to have sex tends to improve. The other scale, the QS-F questionnaire is a tool designed to assess sexual function in Brazilian women specifically. It could be interpreted that this questionnaire is more representative of results in Brazilian women, which might explain the difference in results between the questionnaires.

Dias de Souza K, et al. Efficacy of Tribulus terrestris for the treatment of hypoactive sexual desired disorder in postmenopausal women: a randomized, double-blinded, placebo-controlled trial. *Menopause*. 2017; 23;(11): 1252-1256

Saffron Similar to Fluoxetine in the Treatment of Postpartum Depression

Women with mild to moderate postpartum were enrolled in this study in Tehran, Iran, the site of many botanical studies in the last few years. Women were ages 18-45 and were 4-12 weeks post-childbirth. To be included in the study they had to have a score of 10 or more and 18 or less on the 17-item Hamilton Depression Rating Scale (HDRS). A total of 68 women entered the study, and received either 15 mg of saffron (1.65-1.75 mg crocin/capsule) twice daily or 20 mg of fluoxetine, a common selective serotonin reuptake inhibitor (SSRI), for six weeks. Other therapies such as psychotropic drugs or behavior therapy were not permitted during the study. Symptoms of postpartum depression were assessed with the HDRS at baseline and then at the end of weeks 1, 3, and 6. If a patient had a partial response, it was defined as having a 25-50% reduction in her HDRS score. A responder was defined as having a score of 50% or more reduction in the HDRS score. For those with total remission, they had to achieve a score of 7 or less.

At the end of the six weeks, 18.8% of the saffron group and 21.9% of the fluoxetine group were in remission, which is not statistically significant. Of the responders, the saffron group was 40.6% and 50% in the fluoxetine group, which again is not statistically significant. In total, all patients had at least a partial response. Two women from each group discontinued due to progressing from moderate to severe depression. There were more frequent headaches, dry mouth, daytime drowsiness, constipation, and sweating in the fluoxetine group.

Commentary: Postpartum depression is experienced by an estimate 10-15% of postpartum women. The standard of conventional medicine care included fluoxetine as a first-line therapy; however, remission rates are low and adverse effects are problematic. In other research, saffron flowers, have improved depression and premenstrual symptoms. Since this study was a randomized, double-blind, controlled study comparing saffron with fluoxetine in the treatment of mild to moderate postpartum depression, and no placebo group, it is not clear what the absolute antidepressant effects of these therapies would be. Saffron is considered to be safe postpartum and with lactation.

A longer and larger study, with a placebo group added, would be important to confirm the full value of saffron in mild to moderate postpartum depression

Kashani L, et al. Comparison of saffron versus fluoxetine in treatment of mild to moderate postpartum depression: a double-blind, randomized clinical trial. *Pharmacopsychiatry*. March 2017;50(2):64-68.

Vitamin E Suppositories for Genitourinary Atrophy in Menopause

One of the most common experiences of menopause are the changes that occur on the external genital tissue and intravaginal tissue that can then also affect urinary function. This is called genitourinary atrophy, and most recently coined, genitourinary syndrome of menopause. Symptoms can include one or more of the following: vulvovaginal discomfort, itching, burning, tingling, dryness, thinning of tissue, pain, pain with vaginal penetration related to dryness and/or tightness of vaginal opening, post coital bleeding, vaginal discharge, bladder leakage, urinary incontinence. These symptoms can affect comfort and quality of life with up to 40% of menopausal women being affected in their sex life, 17% their confidence, 13% their partner relationship, and 7% their social life.

There are many options to address these genitourinary atrophic changes and symptoms; the most studied and effective is vulvovaginal estrogen, which can be used with complete safety and effectiveness. Nonetheless, some women seek other options including over-the-counter lubricants, over-the-counter moisturizers, and herbal/nutrient agents. One such item that has been subject to a small amount of research are vitamin E suppositories.

The study I refer to here investigated vitamin E 100 IU suppositories, which were compared to vaginal estrogen cream in 52 menopausal women with symptoms of vulvovaginal atrophy and a vaginal pH above 5.0. Laboratory studies included the assessment of the vaginal maturation value (VMV), and Menopause-Specific-Quality of Life (MENQOL) questionnaire. Participants in the study were given 12 weeks of either vitamin E vaginal suppository or conjugated estrogen vaginal cream (0.625 mg; 0.5 gm is equivalent to 1.8 gm of the cream in the applicator). They were instructed to insert the item nightly for the first two weeks and then twice per week for the next 10 weeks.

Results showed that quality of life scores were not significantly different in the two groups after 4, 8, and 12 weeks of treatment.

Commentary: While this sounds positive, that the vitamin E suppository worked basically as well as the vaginal estrogen product, there were no specifics comparing burning, dryness, pain, itching, urinary incontinence, but rather physical symptoms were lumped together as one of the overall four categories of quality of life assessment: vasomotor symptoms (hot flashes/night sweats), psychosocial, physical and sexual. From my understanding of the tables, the physical symptoms did score about 20 points better in the vaginal estrogen group than the vitamin E group.

What do I think? I think vaginal estrogen is completely safe with this kind of regimen: nightly for two weeks then twice weekly maintenance. Even for breast cancer survivors, vaginal estrogen in the form of tablets or a ring or a suppository is not associated with a meaningful or lingering elevation in blood levels of estrogen, whereas cream raises blood levels more and is usually avoided in breast cancer patients. For women with a history of uterine or ovarian cancer, the published research would support the use of vaginal estrogen tablets/suppositories and a local dosing of a vaginal estrogen ring (eg., ESTRING), as safe.

Other natural products for vulvovaginal atrophy with a small amount of published research includes a fennel cream, a hyaluronic acid/E/A suppository, and a *Pueraria mirifica* vaginal gel.

Emamverdikhan A, et al. Comparing two treatment methods of vitamin E suppository and conjugated estrogen vaginal cream on the quality of life in menopausal women with vaginal atrophy. *JMRH*. 2014;2(4):253-261.

Lactobacillus rhamnosus Use in Pregnancy Can Significantly Reduce Postpartum Depression-Anxiety

According to the Centers for Disease Control, postpartum depression in the US is between 11%-20%. Postpartum depression is a disorder that affects the mother's ability to care for and bond with her new infant, as well as her functioning in day-to-day life. It can also produce long-lasting consequences in children's cognitive, social-emotional, and physical health outcomes. The depression does not come alone though; it is associated with insomnia, fatigue, agitation, appetite problems, low self-esteem, and anxiety. The anxiety often co-exists with the depression in postpartum states. If breastfeeding is occurring, it is even more important to explore prevention strategies as many women will not take pharmaceuticals while breastfeeding; they may have adverse effects on the breastfed infant. It can take several weeks for the therapeutic effect of pharmaceutical antidepressants to occur.

The current study is a two-center, randomized, double-blind, placebo-controlled trial testing the effect of *Lactobacillus rhamnosus* HN001 on atopic disorders including eczema, but also on pregnancy outcomes and postpartum symptoms of depression and anxiety. Pregnant women were randomized to receive either placebo of 1 billion colony forming units *Lactobacillus rhamnosus* HN001 daily, over a period of six months if breastfeeding. Mothers in the probiotic group reported significantly lower depression and anxiety scores than the placebo group

Commentary: There is a growing body of literature linking the gut microbiota to brain chemistry and thus mood and behavior. The list of pathways involved in a bi-directional microbiome-gut-brain axis are multiple; and many health problems, including mental-emotional disorders, are associated with altered gastrointestinal function and alterations in gut microbial make-up. The findings of the current study are consistent with two previous clinical studies of the effects of probiotics on mood. One was a randomized clinical trial in a population of 40 individuals with major depressive disorder treated with *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* or placebo, which found a significant reduction in symptoms of depression in the probiotic group. Another study in 39 individuals with chronic fatigue and anxiety were randomized to *Lactobacillus casei* or placebo and found a reduction in anxiety, but not in depression. Not all studies have demonstrated a significant therapeutic effect of probiotics on mood; but larger studies are being done to better understand this gut flora-brain connection and it will be interesting to watch this unfold and to better understand the possibilities for both prevention and treatment. In time, we will also better understand what might be the most effective choice of probiotics species and strains, duration, and dose.

Slykerman R, et al. Effect of *Lactobacillus rhamnosus* HN001 in pregnancy on postpartum symptoms of depression and anxiety: a randomised double-blind placebo-controlled trial. *EBioMedicine*. 2017. https://doi.org/10,1016/j.ebiom.2017.09.013

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FDA Approves Intravenous Vitamin C

In a 2016 editorial in the *Townsend Letter*, I pointed out that excessive and unnecessary regulations by the US Food and Drug Administration (FDA) had resulted in massive increases in the cost of injectable nutrients. At that time, a 25-g vial of sterile injectable vitamin C cost about $120, as compared with only $5 in the 1990s. Problems with the availability and affordability of injectable vitamin C began in the late 1990s, when Steris Laboratories, Inc., the only US company that was manufacturing injectable vitamin C, failed FDA inspections and was forced to stop producing the product. Compounding pharmacies took up the slack, but the FDA has put stumbling blocks in their way. Currently, there are restrictions on shipping injectable vitamin C out of state if the compounding pharmacy does not hold a license in the state to which the product is to be delivered. Other proposed FDA regulations, which have been published but not yet implemented, threaten further to restrict the interstate shipment of compounded medications.

In addition, in 2010 the FDA made the questionable ruling that injectable vitamin C is a new drug. Vitamin C is certainly not new; it has been administered intravenously for more than 70 years. Whether it is a drug should be more a philosophical than a legal question. However, the FDA considers any injectable substance to be a drug if it is intended for the prevention or treatment of a disease (scurvy in the case of vitamin C). The production and sale of injectable vitamin C had previously been allowed under the "Grandfather Clause," which seemed appropriate considering its long history of safe use. When its status was changed to "unapproved new drug," any company wishing to manufacture and sell injectable vitamin C had to go through the expensive and time-consuming new-drug-application process. That ruling did not apply to compounding pharmacies, but, as mentioned, compounding pharmacies have been subjected to various restrictions. Inexplicably, the prohibition against manufacturing injectable vitamin C was waived for Mylan, which took advantage of its monopoly by raising the price to obscenely high levels, just as it did with EpiPen.

Those of us who have seen the dramatic benefits obtainable with intravenous vitamin C have been dismayed and angered by its high cost and its intermittent lack of availability. Many practitioners have used intravenous vitamin C successfully as an antimicrobial agent. I saw a middle-aged woman with a three-week history of viral pneumonia who became permanently asymptomatic halfway into a three-hour infusion of 50 g of vitamin C. Another patient I saw with chronic hepatitis C was apparently cured by 20 weekly infusions of 50 g of vitamin C. A third patient was a 20-year-old male with infectious mononucleosis. He was given 50 g of vitamin C intravenously every other day for a total of three treatments, and was advised to take oral vitamin C to bowel tolerance. His severe fatigue improved dramatically within 48 hours of starting treatment, and he recovered without experiencing a recurrence of symptoms. In addition, as I discussed in the October 2017 issue of the *Townsend Letter*, intravenous vitamin C has been reported to decrease the mortality rate by 79% in patients with septic shock.[1] Vitamin C is also a component of the Myers cocktail, which has been of great benefit for many patients with chronic fatigue, fibromyalgia, asthma attacks, acute migraines, seasonal allergic rhinitis, and other conditions.

Recognizing the importance of injectable vitamin C and its uncertain future, the McGuff Company (a California-based manufacturer of sterile injectable drugs) began in 2006 the long process of seeking FDA approval. In October 2017, after 11 years of jumping through many regulatory hoops and investing substantial amounts of money, McGuff was notified that injectable vitamin C has been approved as a new drug and that they will be allowed to manufacture and sell it. At the time of this writing, the final price has not been determined, but I have been advised that it will be much lower than Mylan's price. We owe a debt of gratitude to the McGuff Company for their perseverance in an arduous process which (based on the FDA's long history of bias against nutrients) was never guaranteed to have a positive outcome. This company has done us a great service by securing the availability and affordability of such an important treatment. In addition, FDA approval of injectable vitamin C has opened the door for human clinical trials, which have the potential to expand the clinical uses of vitamin C. McGuff is currently providing support for nine such clinical trials.

The FDA, which I have criticized on numerous occasions during the past thirty years, should also be commended for its decision regarding vitamin C. While a case can be made that the agency should never have declared injectable vitamin C a new drug in the first place, it is encouraging that the FDA has chosen to get out of the way of medical progress.

Alan R. Gaby, MD

1 Marik PE, ert al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. 2017;151:1229-1238.

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