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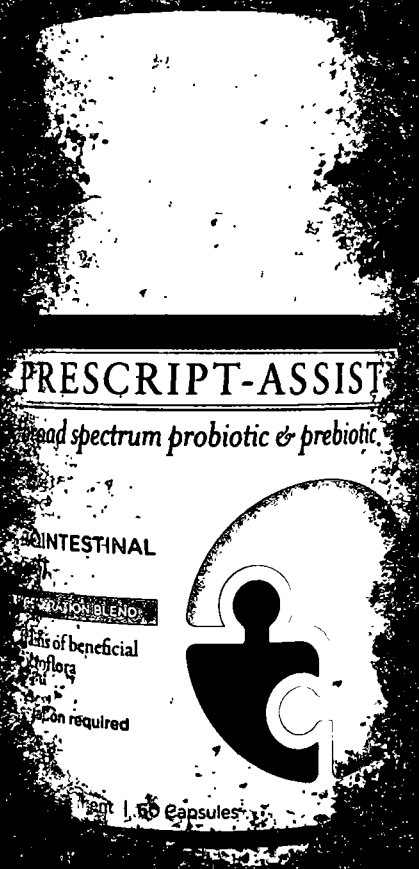

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The Next Big CAM Battle Is Here and It's Ugly

by Richard Jaffe, Esq.

CAM or integrative medicine doctors have had their problems with the state medical boards. And CAM organizations have had their run-ins with governmental agencies. However, the groups have always survived in large part because they have had a steady income from membership dues and from their annual conferences, where their members learn the latest and greatest from their thought leaders. But the CAM organizations' income stream is now in jeopardy and, thus, so is their existence, based on what looks to be well-planned, systematic effort to put CAM groups out of business and stop the dissemination information about CAM therapies. AND THAT MY FRIENDS IS A VERY BIG DEAL.

Here Is What's Going On

For months, at least two CAM groups have been under review/investigation by the primary private CME accrediting company, the ACCME (Accreditation Counsel for Continuing Medical Education). Recently, the ACCME has determined that a significant portion of the groups' prior year's CME courses does not meet various ACCME standards. ACCME is demanding that everyone involved in these courses be informed that "they were presented invalid information..." and that the groups "instruct them [everyone] to avoid making any clinical decisions for testing and/or treatment based on what was presented, and direct the registrants to accurate and valid sources of information for the problems or systems presented."

I should point out that this "incorrect" information came from some of the most accomplished, respected, and published thought leaders/teachers in the CAM community. These folks have been giving CME courses without incident for decades. Further, in terms of future CME courses at their conferences, ACCME has informed these groups—and this is the key to understand what this is all about—the following:

> ...recommendations involving clinical medicine must be based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients and all patient care recommendations must conform to evidence emanating from guidelines and data that meet generally accepted standards of experimental design, data collection, and analysis.

In short, ACCME is trying to require these groups to only teach mainstream medicine! This is crazy and a huge deal!

Furthermore, the effect on the members of these organizations who attended the conferences last year and who used these courses to satisfy their state CME requirements is unclear.

I am not familiar with ACCME's inner workings or guidelines, but it doesn't seem out of the question that ACCME could contact state boards about these groups' "noncompliance" and the retroactive withdrawal of CME credits. That could cause the state boards to retroactively hold the doctors non-CME compliant. I'm not saying that this will happen, but only that it's a possibility. But I am saying that if the idea is to delegitimize CAM and cause problems for its practitioners, notifying the state boards would certainly advance that goal.

continued on page 4 ➤

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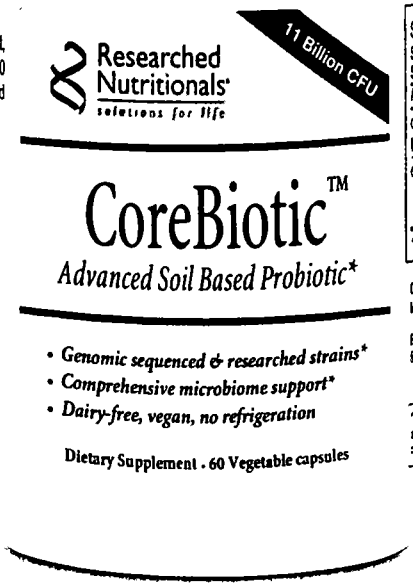

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Next Big CAM Battle

➤ *continued from page 1*

A Specialty Interest Group Also Gets the Same Treatment

Beyond these two professional groups, a disease-based group has recently been informed that its CME status for future conferences has been rescinded by its CME intermediary. The intermediary denies that it received any pressure or orders from ACCME.

In the last few months, three CAM groups, which have previously received ACCME course certification without any undue problems, have had their prior CME course approval rescinded and/or their future CME approval withdrawn or placed in serious doubt. Is this all a coincidence? Not a chance in hell.

My guess is that more of the same has or is going to happen to other CAM groups.

What to Do?

At this stage, these groups need information about what's behind this campaign to deny CME credit and delegitimize CAM teachings.

We need to get the word out to the CAM community. Why? Someone out there has to know something or know someone who knows something about how this came about, and who or what group is behind it. (My guess is that ACCME is the vehicle not the originator.)

I think there is a smoking gun out there, and if we find it, we can probably reverse ACCME's decision quickly, so my suggestion is that all the CAM groups and interested parties get the word out to search for the smoking gun.

But let's dig in to this and see if there is anything else that can be done. A logical place to start is to consider the following: What exactly is the ACCME and what does it do?

I don't have any special info on ACCME, but here is what it says about itself:

> CME ACCREDITATION OF, BY, AND FOR THE PROFESSION OF MEDICINE.
>
> The ACCME was founded in 1981 in order to create a national accreditation system. It is the successor to the Liaison Committee on Continuing Medical Education and the American Medical Association's Committee on Accreditation of Continuing Medical Education. The ACCME's purpose is to oversee a voluntary, self-regulatory process for the accreditation of institutions that provide continuing medical education (CME) and develop rigorous standards to ensure that CME activities across the country are independent, free from commercial bias, based on valid content, and effective in meeting physicians' learning and practice needs. The ACCME accreditation process is of, by, and for the profession of medicine.
>
> The ACCME's founding and current member organizations are the American Board of Medical Specialties, the American Hospital Association, the American Medical Association, the Association of American Medical Colleges, the Association for Hospital Medical Education, the Council of Medical Specialty Societies, and the Federation of State Medical Boards of the United States.
>
> Throughout its history, the ACCME has been dedicated to maintaining a relevant and responsive accreditation system that supports CME as a strategic asset to US health care quality and safety initiatives.

Very noble and reassuring, isn't it?

Basically, it's a bunch of health care trade associations, organizations in charge of medical education and specialization credentialing. (Ironically, the medical specialty societies are the

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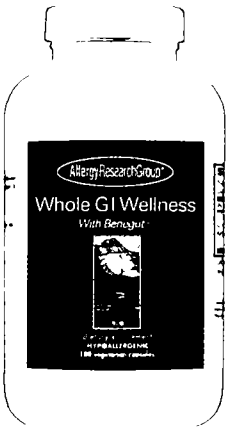

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Next Big CAM Battle

➤ *continued from page 4*

reason it's illegal for practitioners to advertise their CAM board certifications.) And last but not least is CAM's long-time adversary, the Federation of State Medical Boards. So maybe not so reassuring.

Did you know that the ACCME is accountable to the public? Yeah, just ask them and they will tell you so. Here is what it says about that:

> Accountability to the Public
>
> The ACCME is accountable to the public for setting and maintaining accreditation requirements that are designed to ensure that CME accredited within the ACCME system is based on valid content, is free from commercial influence or bias, and contributes to the quality and safety of health care. As the US health care system continues to evolve, the ACCME will respond by making changes to its requirements or processes that are necessary to assure that CME serves the best interests of the public.

I'm still not clear exactly how it is accountable to the public, and nothing in its web site gives any further elucidation. I do have a couple ideas of how it might actually be made accountable to the public.

Some Basic Facts

It's obviously a matter of individual state law what type of courses a state medical board will accept as acceptable CME. The ACCME might be the primary CME credentialer, but it is not the only one. For example, here is the Texas law regarding CME accreditation; it is Board Rule 166.2 and it requires the following:

> (1) At least 24 credits every 24 months are to be from formal courses that are:
>
> (A) designated for AMA/PRA Category 1 credit by a CME sponsor accredited by the Accreditation Council for Continuing Medical Education or a state medical society recognized by the Committee for Review and Recognition of the Accreditation Council for Continuing Medical Education;
>
> (B) approved for prescribed credit by the American Academy of Family Physicians;
>
> (C) designated for AOA Category 1-A credit required for osteopathic physicians by an accredited CME sponsor approved by the American Osteopathic Association;
>
> (D) approved by the Texas Medical Association based on standards established by the AMA for its Physician's Recognition Award; or
>
> (E) approved by the board for medical ethics and/or professional responsibility courses only.

Other states have similar types of CME rules. The bottom line is that ACCME is a very important source of state-approved CME accreditation, especially for everyone other than the major national and state medical trade groups. But there's another way of looking at it. Without a state accepting its accreditation, ACCME doesn't have much of a purpose or job.

What About CAM Laws?

Texas, California, and some other states recognize the rights of patients to receive CAM therapies. Texas, for example, provides the following:

> The purpose of this chapter [Texas Board Rule Chapter 200] is to recognize that physicians should be allowed a reasonable and responsible degree of latitude in the kinds of therapies they offer their patients. The Board also recognizes that patients have a right to seek complementary and alternative therapies." (Board Rule 200.1)

continued on page 8 ➤

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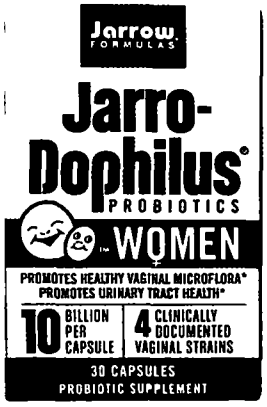

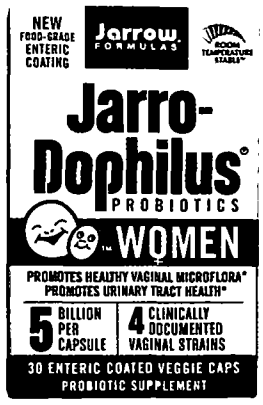

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Next Big CAM Battle

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What are CAM therapies in Texas?

> Complementary and Alternative Medicine–Those health care methods of diagnosis, treatment, or interventions that are not acknowledged to be conventional but that may be offered by some licensed physicians in addition to, or as an alternative to, conventional medicine, and that provide a reasonable potential for therapeutic gain in a patient's medical condition and that are not reasonably outweighed by the risk of such methods.

Convention medicine is defined as "Those health care methods of diagnosis, treatment, or interventions that are offered by most licensed physicians as generally accepted methods of routine practice, based upon medical training, experience and review of the peer reviewed scientific literature." (California has a similar definition of CAM at B&C code 2234.1)

So, Texas gives practitioners the right to provide non-conventional, not generally accepted therapies to patients; and patients have the right to receive these CAM or non-conventional therapies.

But even though Texas docs can provide CAM or non-standard therapies to Texas patients, ACCME now takes the position that Texas physicians can't obtain CME credit for learning about these Texas-sanctioned treatments. How can the ACCME be acting consistent with Texas law by its insistence that CAM medical groups can only teach "...recommendations involving clinical medicine...based on evidence that is accepted within the profession of medicine...." My view is that ACCME's position is inconsistent, if not in violation of the Texas CAM Rule (and the California CAM statute) and probably every other state that has a CAM law.

What to Do? Complain to ACCME? Won't hurt, but it won't help. It's doing what it's doing intentionally, and some external pressure has to be brought forth. Complain to the boards? Maybe, but it would take a lot of complaints.

In all the big CAM states like Texas and California, I know there are legislators who are pro-CAM. My suggestion would be to identify who they are (not hard in Texas). I think the boards in a few of these states need to hear from some legislators about how ACCME is undercutting board rules (in Texas) or the CAM statutes (like in California).

These legislators should copy ACCME on their concerns expressed to the boards. If one of them is on a legislative health committee, even better. Better still would be for a couple states to start an investigation on ACCME's motives. Maybe even an invitation to appear at a specially called hearing. Legislators can hold hearings for all kinds of reasons. So, can federal legislators. I think with all the politically connected CAM docs out there, multiplied by their politically connected patients, well I think there's a heap of trouble that could be stirred up for ACCME.

It doesn't have to happen in every state, or even many states, just a couple of the big ones. The story is going to get out, and questions are going to be raised. The widespread dissemination of ACCME's action might even turn-up that smoking gun I mentioned earlier. And once the nefarious motive and scope of the conspiracy publicly surfaces, I think ACCME will be forced to rescind its actions. So, we need to shine some light on these jokers.

This could all happen pretty quickly if there's a big enough outreach to the CAM community.

Something to think about anyway.

Rick Jaffe, Esq.
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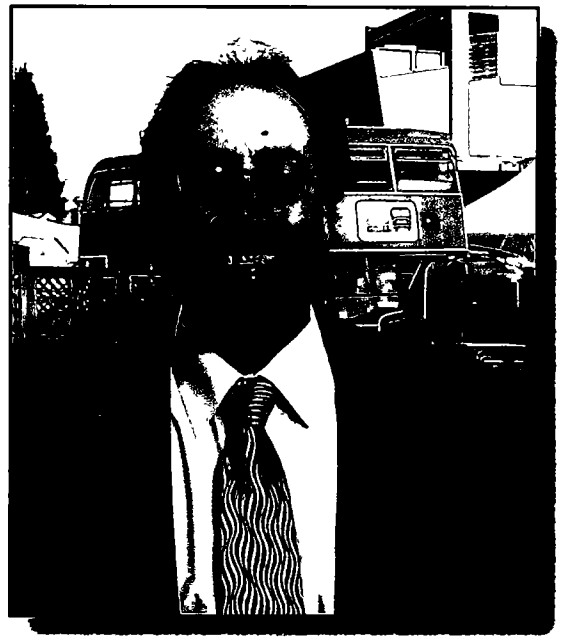

From the Publisher

New England Compounding Pharmacist Guilty of RICO

As most of you know, the New England Compounding Center (NECC) in Framingham, Massachusetts, distributed tainted injectable corticosteroids in 2012 that resulted in a huge number of fungal meningitis cases. The CDC reported that 751 individuals developed the rare meningitis and 64 of them died. The meningitis followed the injection of the steroid into the spinal cord to treat back pain and related disorders. How the corticosteroid became contaminated with fungus is not explained. However, the federal prosecution stated that NECC, a compounding pharmacy, manufactured the vials in an environment contaminated with fungus, bacteria, detritus, and "seeping oil." The defense attorney for NECC pharmacist, Barry Cadden, denied that the injectable manufacturing conditions were contaminated. Yet, if the compounding rooms were clean, how did fungal meningitis develop in so many patients across 20 states?

According to the news report in the March 23, 2017 *USA Today*, Cadden was cleared by a jury of second degree murder charges.[1] However, he was found guilty of RICO (Racketeer Influenced and Corrupt Organizations) violations that include mail and interstate commerce fraud. Cadden's business operation was supposed to be a compounding pharmacy. However, he made tens of millions of dollars manufacturing medical injectables and distributing them to a wide number of clinics. The guilty finding for RICO may result in 20 years in prison for Cadden when sentencing is made in June. Another 12 individuals involved with NECC have been charged and will face court trials.

As a result of this medical disaster, Congress acted to empower the FDA with new regulatory oversight of compounding pharmacies in 2014. The new regulations that are beginning to come on line have greatly limited the scope of compounding. Essentially, pharmacies involved in the production of injectable medicines are required to demonstrate pharmaceutical manufacturing standards. Such standards have effectively made older equipment and facilities obsolete. Injectable compounding pharmacies are required to elect whether they will meet the standards as a manufacturing facility

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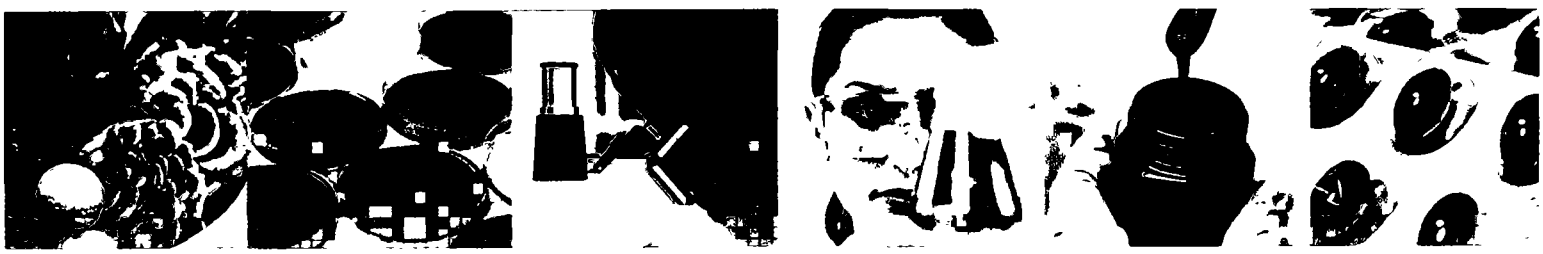

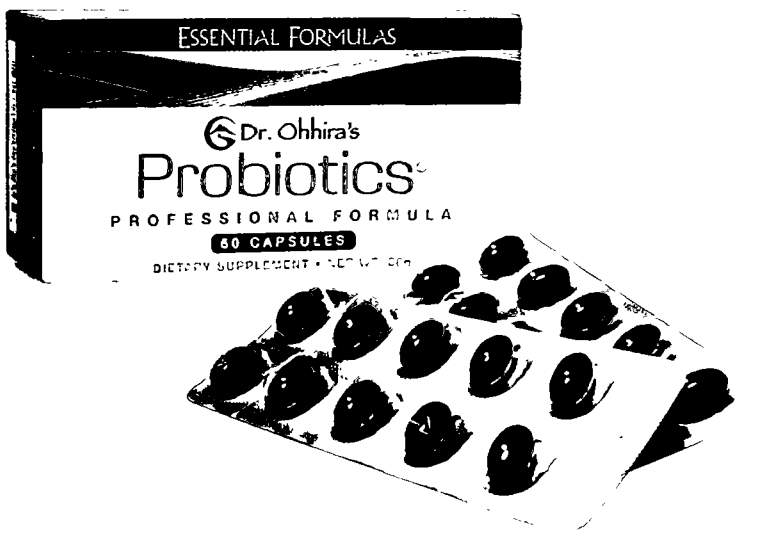

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From the Publisher

➤ *continued from page 10*

or follow a reduced standard as a local compounding pharmacy. Needless to say, many compounding pharmacies elected to quit compounding injectables due to their inability to upgrade their equipment and facilities. For those compounders who continue to produce injectables, the FDA is breathing down their necks to ensure that the draconian standards are met. One compounding facility in Texas, Downing Labs, recently announced that they have met the guidelines as an injectable manufacturing facility.

As far as Cadden is concerned, he did not apologize for his role in the manufacture of the contaminated corticosteroids resulting in many patient deaths and chronic illness. As a result of his disregard for safe manufacturing practices, compounders have needed to shut down their compounding facilities resulting in less access for patients and physicians. What Cadden did was a horror for the ill and dead patients as well as consumers who benefit from compounded medications. The jail time he will receive is well deserved.

A Mud Bath in Calistoga

While travelling to Calistoga, California, for the wedding of our friends' daughter and fiancé, we decided to pass the morning before nuptials at one of the local spas and have a mud bath. The last time we enjoyed such a treatment was at the Dead Sea. Memories change over the years, but I recalled the Israeli spa had a cabana atmosphere with a boardwalk leading from the heavily salted waters. The mud was applied to us from top to bottom and we were caked with it basking in the sun. After a time, we showered outdoors and then relaxed not departing before being sold mineral salts to do our own baths in the US. The mud bath and bathing in the Dead Sea were wonderful memories but, like other travel adventures, were slowly forgotten until we found ourselves in Calistoga. Now part of the wine tasting circuit in Napa Valley, Calistoga has always been a retreat for dwellers of San Francisco to escape the drudgeries of city life and enjoy the sulfur-containing mineral springs. Along with the mineral baths, spas like the Indian Springs Resort offer massage and mud baths. We couldn't pass up this opportunity to enjoy another treatment like we enjoyed in the Middle East.

Of course, I didn't really know what I was in for and took instructions from the spa staff with a certain degree of trepidation. After a preliminary shower, I was directed to a rather large rectangular "bath" of brownish-black, tarry, odoriferous viscous mud and told to step in and then lie supine. It wasn't quite like molasses, but it was thicker and stickier that I would have imagined. The mud was heated from the bottom as I discovered later when I plunged my hand downward. It was primarily squishy in consistency, but there were hard lumps and cubical stones scattered in the mud. The density of the mud prevented one from submerging, and the attendant needed to sweep mud over the body in layers to cover one entirely. In some ways, it was what I imagined quicksand might be if one stood in a barrel of the mud, although after descending a few feet one would not be able to sink any further, while quicksand reportedly sucks one down continuously until fully submerged (an urban myth?).

After a few minutes of becoming adjusted to the embracing mud and closing my eyes, I became aware of muscle tension lightening, stress reducing, and worrying dissipating. Where some joints had been painful, the inflammation was changing, becoming less. The relaxation was both as soothing as a massage but invigorating at the same time. I didn't quite fall asleep, but I was aware that the mud was healing myself physically, mentally, if not spiritually. It was supposed to last twelve minutes but I asked to stay in longer. Arising from the bath was a challenge, becoming so languorous after twenty minutes. Scraping much of the mud off oneself before stepping out of the tub, I was pointed to a shower that was alternatively warm and cool, perhaps not purposely. The mud did come off easily although with some effort. I then had a very warm bath and drank cool lemon/apple water. A steam bath was next, and I stayed only as long as I could tolerate. Finally, one lay on a comfortable cot with light music and pale light regaining stamina.

Altogether, I would rate the mud bath a first-rate experience definitely deserving repeating on a routine basis. I didn't see any downside. My wife, Deborah, thought her bath had been wonderful as well. We both found the spa experience was quite different in Calistoga than at the Dead Sea – but both were very therapeutic. Spa treatments have been considered especially therapeutic in other cultures, especially in Europe, the Middle East, and in the Orient. In the US, we appreciate the mineral bath and warm springs. But the mud bath is not so readily available. That is too bad as it has much to offer. Even less available is treatment with a specialized peat, peloids, as discussed by Sussanna Czeranko, ND in the Feb./March *Townsend Letter*.

Functional Gastroenterology

To many physicians and patients, gastroenterology only becomes important after age 60 when one is ordered to have a colonoscopy. The increasing incidence of colon cancer justifies such screening although the prognosis for aggressive tumors remains poor. Younger adults and children requiring gastroenterology care for ulcerative colitis and Crohn's disease are managed with immunosuppressive drugs with minimal dietary intervention. The recent advent of drugs capable of arresting Hepatitis C virus has overturned the only partially effective interferon treatment previously used for hepatitis, a boon for gastroenterologists, patients, and pharmaceutical companies. However, for many patients, digestive symptoms are largely managed with antacids, omeprazole, and psychiatric medications. Unfortunately, medicine largely ignores functional GI tract disorders simply labeling the lot as irritable bowel syndrome and gastric hyperacidity. The result is that while patients experience hypochlorhydria, pancreatic enzyme deficiency, or hiatal hernia syndrome their symptomatology does not get a workup in the primary care practice or with the specialist. Of course, a major reason there is no evaluation is that gastroenterology focuses on pathology—disorders with definable pathologic findings. Symptomatic disorders lacking pathology are given short shrift during the medical exam.

Steven Sandberg-Lewis ND, DHANP has devoted much of his professional naturopathic career to studying functional gastroenterology. His work examines the medical literature and includes functional medicine assessments that go largely unused in the conventional medical practice. Sandberg-Lewis embraces the tenets and traditions of naturopathic medicine employing diet modification, herbal medicine, homeopathy, and visceral manipulation to treat diverse functional disorders such as hiatal hernia syndrome and ileo-cecal valve syndrome. The combined focus of standard-of-care gastroenterology, functional medicine, and naturopathic traditional medicine is offered in Sandberg-Lewis's recently published second edition of *Functional Gastroenterology:*

continued on page 14 ➤

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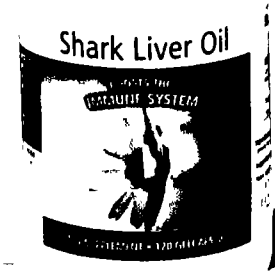

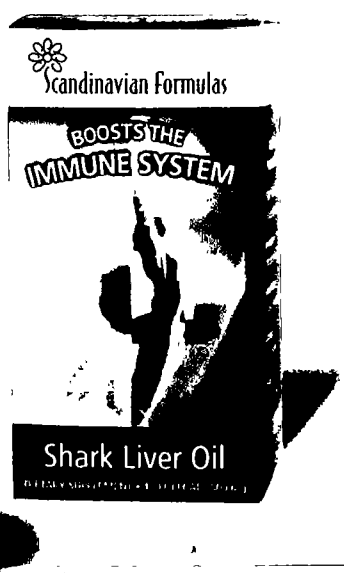

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From the Publisher

➤ *continued from page 12*

Assessing and Addressing the Causes of Functional Gastrointestinal Disorders. From comprehensive exam questionnaires, physical exam, and laboratory, Sandberg-Lewis provides the basis for primary and specialty physicians to diagnose and treat functional GI tract disorders.

What is the extent of symptomatology? In Chapter 1, he discusses heartburn, dysphagia, reflux, dyspepsia, nausea and vomiting, abdominal bloating, constipation, diarrhea, abdominal pain, incontinence, and defecation disorders. Sandberg-Lewis reminds us that gastrointestinal bleeding, weight loss, and severe diarrhea indicate that functional symptoms may represent more serious conditions. While irritable bowel syndrome (IBS) is generally recognized as a functional GI disorder, it is not unusual for most patients to have significant low-grade pathology, such as increased pro-inflammatory cytokine activity. For many individuals with IBS, abnormal intestinal pathogens are produced by dysbiosis. In fact, there is an overlap between the symptoms of small intestine bacteria overgrowth (SIBO) and IBS. Unfortunately, SIBO is another functional disorder that is largely ignored and thereby undiagnosed and untreated. Hence, IBS sufferers are given prescriptions for symptomatic support, such as Bentyl, but do not undergo laboratory examination and receive neither definitive dietary support nor appropriate prescription for SIBO. Sandberg-Lewis emphasizes that IBS may benefit from the use of botanical and homeopathic remedies, betaine hydrochloride, enzyme replacement, organ extracts, probiotics, visceral and spinal manipulation, breathing exercises, mindfulness, and counseling.

It is important to have a good conceptualization of the hormone system of the GI tract. Understanding how physiologic disorders, such as hypochlorhydria, can disrupt gastrointestinal hormones, provides an understanding of how functional disorders develop. The iatrogenic use of proton pump inhibitors further disrupts these interdependent GI hormones, potentially threatening the development of early neoplasia in the intestine as well as the stomach. Furthermore, when the intestinal microbiome is disrupted by hormonal abnormalities, hypochlorhydria, and pancreatic enzyme insufficiency, it is not surprising that SIBO worsens together with intestinal permeability. Sandberg-Lewis emphasizes that the judicious employment of appropriate diet, nutrition, botanical medicine, manipulation, and, if needed, medication not only can improve SIBO, hypochlorhydria and enzyme deficiency, but rebalance the GI hormonal system. Unlike conventional medicine that considers gastrointestinal pathology to be wholly unknown as to causation, this book identifies the functional disruption of the gastrointestinal tract's physiology as the key to development of inflammation and, potentially, cancer.

The diagnosis of SIBO through hydrogen/methane breath testing is perhaps the hallmark of functional gastroenterology diagnostics. A solution of lactulose that is non-absorbable is swallowed to test fermentation of intestinal bacteria. As the lactulose transits through the stomach and intestine within two hours, bacterial digestion is noted by the production of hydrogen and methane gas. Specimens are obtained every 20 minutes for three hours. While testing is generally performed at the office, patients may collect specimens at home for later testing. Elevated measurements of hydrogen and methane gas are diagnostic for overgrowth of intestinal bacteria. Medicine treats SIBO with antibiotics and elemental diet; naturopathy employs diet and herbal antimicrobials. Sandberg-Lewis credits Allison Siebecker, ND, MSOM, for developing the SIBO Specific Food Guide, a combination of the low FODMAP diet, Specific Carbohydrate diet, and Cedars-Sinai diet.

Functional Gastroenterology is updated and includes up-to-date citations including many from 2016. Sandberg-Lewis also includes the manipulation work of past naturopathic physicians; his use of visceral manipulation for hiatal hernia syndrome and ileo-cecal valve syndrome would be a welcome addition to the conventional gastroenterologist office. I was also pleased that he explained his use of focalized muscle testing as a means to assess functional disorders; too often muscle testing has been dismissed by individuals who do not understand its methodology. This is a welcome text for the newcomer to understand functional gastroenterology as well as a reference text for physicians needing to substantiate their diagnostics and treatments.

For a sample of Sandberg-Lewis's writing read his article in this issue of the *Townsend Letter*.

Low-Dose Immunotherapy

There are few therapies that come along that deserve immediate practitioner study but low-dose immunotherapy may fit the bill. This treatment combines the principles of allergy desensitization together with patient individualized therapy. In this issue, Ty Vincent, MD reviews his work with enzyme-potentiated desensitization (EPD), low-dose allergy therapy (LDA), and low-dose immunotherapy (LDI). Shrader and McEwen treated about 11,000 patients from 1993-2001 with EPD; more than 75% of patients had excellent response for their allergies. Vincent's early work with LDA, starting in 2008, demonstrated immediate and dramatic response not only to allergic-based disorders but also to many autoimmune conditions. Vincent has modified LDA into an oral sublingual therapy rather than injection treatment he calls LDI. The treatment permits practitioners to treat patients at home rather than the office and offers the best of EPD and LDA as well as "autologous" treatment derived from the patient's own body fluids or stool.

Vincent is convinced that much of what we label as autoimmune disease need not be treated with immunosuppressant medication. Chronic Lyme disease need not be treated with antibiotics or antimicrobials. Instead, these conditions are easily and dramatically treatable using LDI-derived (or LDA-derived) low dose antigens in a base of low dose beta-glucuronidase. Vincent's explanation is that the LDI antigen(s) switch off the misbehaving T-regulator cells that are attacking body tissues, leading to chronic illness. Vincent's experience has shown that LDI is effective in the treatment of 60 different conditions including inflammatory bowel disease, systemic lupus, and multiple sclerosis. His work has been remarkably effective in treating Lyme disease patients, albeit, the treatment does require patience as these patients respond very differently and require individualized treatment strategies. Perhaps the most surprising use of LDI is treating the autism patient.

Vincent wants to teach practitioners this treatment approach so that the treatment becomes widely available. He has set up LDI training and clinical services and invites all practitioners to become proficient.

Jonathan Collin, MD
Publisher

1. MacDonald G, Bacon J. Pharmacist cleared of murder in steroid case *USA Today*. March 23, 2017

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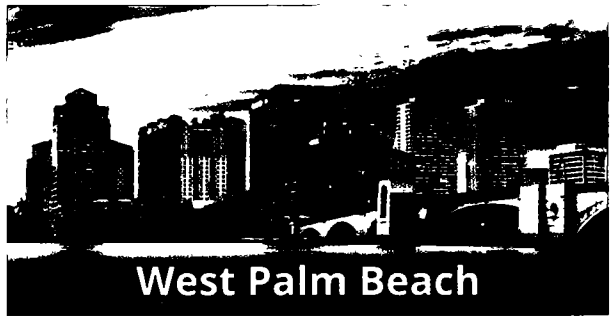

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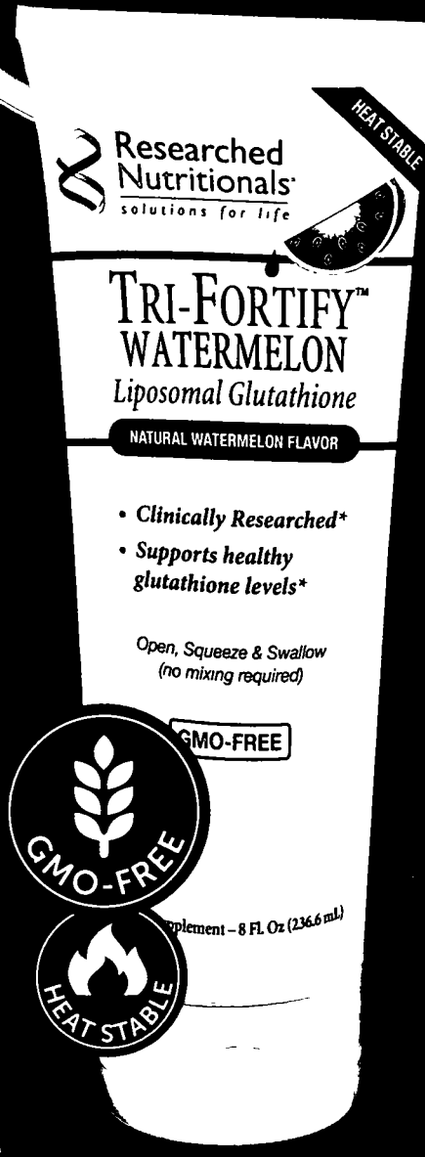

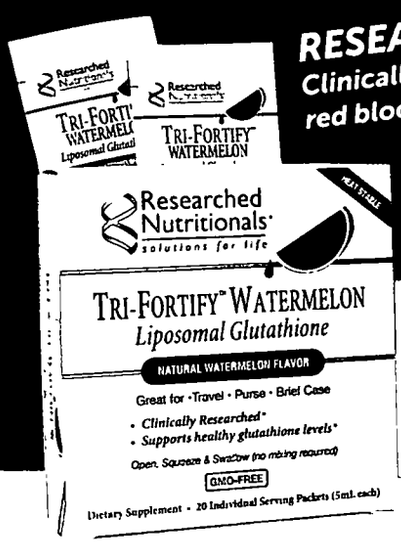

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ON THE COVER: Ty R Vincent, Low-Dose Immunotherapy for GI and Autoimmune Disorders (26); Glutathione, Anti-Aging, and ME-3 (53), Specific Carbohydrate Diet for Inflammatory Bowel (46), Healing Leaky Gut Syndrome with Colostrum (33); 5-Alpha-Reductase in Women's Health (60)

The 5th International Workshop on Biobran

The 5th International Workshop on Biobran is organized by DHD Europe on the 9th, 10th, and 11th of June 2017, in the city of Krakow, Poland. Biobran is an immunomodulator, an anticancer agent that is well known in many countries. It is made from bran rice modified on shitake culture with the property to activate immune cells, particularly natural killer cells. Over the past 20 years, Biobran has attracted the interest of many researchers and was initially tested widely by Dr. M. Ghoneum, PhD, of Charles Drew University, Los Angeles. Today, considerable new research has shown the anticancer properties of Biobran,

A panel of top researchers and doctors will participate in this workshop, all with clinical experience using Biobran.

- Prof. R. Haudgretinger, MD, professor of hematology and oncology and head of University Children's Hospital, Department of Pediatrics (Germany).
- Dr. Joseph Brenner, MD, oncologist, founder and director of the New Hope Medical Center for Integrative Cancer Treatment (Israel). Dr. Brenner is a pioneer in integrative cancer and is a specialist in hyperthermia. He will present his lecture based on using hyperthermia and Biobran in treating cancer.
- Prof. T. Hajto, MD, is a researcher in immunology and in cancer disease, helping patients to enhance the synergistic effects of conventional treatment (Hungary).
- Professor G. Hegyi, MD, PhD, chief medical officer of Yamamoto Institute and president of Hungarian Biophysical Association for Doctors.
- Prof. Basant K. Puri, Faculty of Medicine, Dept. of Medicine, Imperial College London (England).
- Prof. Serge Jurasunas, ND is a researcher, author, and doctor of naturopathic medicine with 20 years of experience using Biobran with cancer patients. He works with immunology and apoptotic genes to increase apoptosis during chemotherapy treatment. He will present some interesting clinical cases.

This workshop is an occasion to become acquainted with one of the most powerful immunomodulator and anticancer agents available while becoming informed about the last research done with Biobran. Some cancer protocols will include Biobran with other active compounds like curcumin or fish peptides. A full day is dedicated to the presentation of scientific lectures while another day is for Biobran distributors in Europe. Also, one day is organized to visit Krakow, one of the most beautiful cities in Europe.

Everyone is welcome to join and learn more about how to treat cancer.

Contact:
DHD Europe (Bratislava, Slovakia)
Monika Ebertova
Email. monika@dhdeurope.com
Tel. 421 254630314
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The 8th Annual Integrative Medicine for Mental Health Conference

Don't miss the 8th Annual Integrative Medicine for Mental Health Conference (IMMH), September 28 – October 1, 2017, in Orange County, California! This conference will give practitioners a whole-body approach to successfully diagnose and treat underlying issues contributing to the manifestations of neurological, social, and behavioral disorders. Research has revealed that many disorders such as depression, bipolar disorder, anxiety, OCD, eating disorders, and autism spectrum disorders often have biomedical causes that contribute to symptoms, from nutritional deficiencies to chronic infections. Patients have better outcomes when these causes are addressed and treated through a combination of specialized testing and nutritional therapies, even in combination with traditional approaches.

This year's conference will have more new speakers and new topics than ever before! Our featured keynote speakers are Daniel Amen, MD, James Greenblatt, MD, and Dale Bredesen, MD. New topics for this year include integrative treatments for head injuries, chronic pain and depression, PANDAS, mold and mycotoxin exposure, and more! CMEs and CEs are available.

The conference venue is the Hyatt Regency Orange County in Garden Grove, California, just three miles from Anaheim's Disneyland Resort and just 13 miles from John Wayne Airport (SNA). Visit the venue section of the conference web site for hotel room block information.

Go to www.IMMH2017.com for all conference details, including the full list of speakers and presentations. Register by July 31 and save $100!

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Can Field Control Therapy (FCT®) Save Homeopathy?
Part I
by Savely Yurkovsky, MD

In the April issue of this periodical, Dana Ullman expressed a legitimate concern over the recent FTC ruling on homeopathy. Among the two required disclaimers for the manufacturers of over-the-counter homeopathic products, one carries a particular threat to the survival of homeopathy, especially if examined in light of other recent ominous events. It requires labeling homeopathy based on outdated and unfounded scientific information that deems it as unacceptable to "most modern medical experts." This seems to be the exact replica of the recent conclusion of the Russian Academy of Science that directs people to abandon homeopathy and seek 'real' or conventional medicine. Just as recently, no less than the House of Common Science and Technology Committee of Great Britain has called for removing homeopathy from coverage by its National Healthcare Service (NHS). Furthermore, the 'experts' have expressed realistic hope that once NHS drops homeopathy, this "death blow will be followed by other countries," too.

In blogs run by 'modern medical experts' and throughout the internet, homeopathy is defined as pseudoscience using over-diluted water-placebos. Even though the ultimate science of all, physics, and physicists including even Nobel laureates such as the world-renowned professor Brian Josephson deem the conclusion of 'medical experts' on 'over-diluted placebos' as "primitive criticism" reflecting "ignorance in science," our tragic medical reality is that neither medical scientists, doctors, nor politicians read or even want to know this opinion. Will the people of the United States soon become the victims of being deprived of this wondrous medicine and its inexpensive remedies in such a 'scientific' political climate, once homeopathy falls in Great Britain or Russia?

This threat is very real for two main reasons. One is that conventional medical care and its blindfolded wasteful research have caused such a profound economic bleeding that the British may have no choice but to dump homeopathy out of their socialized coverage, even if believing that homeopathy is useful. But, the great majority of politicians will shun the truth that allopaths have taken the British Treasury to the cleaners, leaving no shillings for other beneficial medical services. Instead, like most politicians everywhere, they'll conveniently use an opinion of 'experts' and sell this decision as being 'for the sake and protection of the people' – in this case, protection

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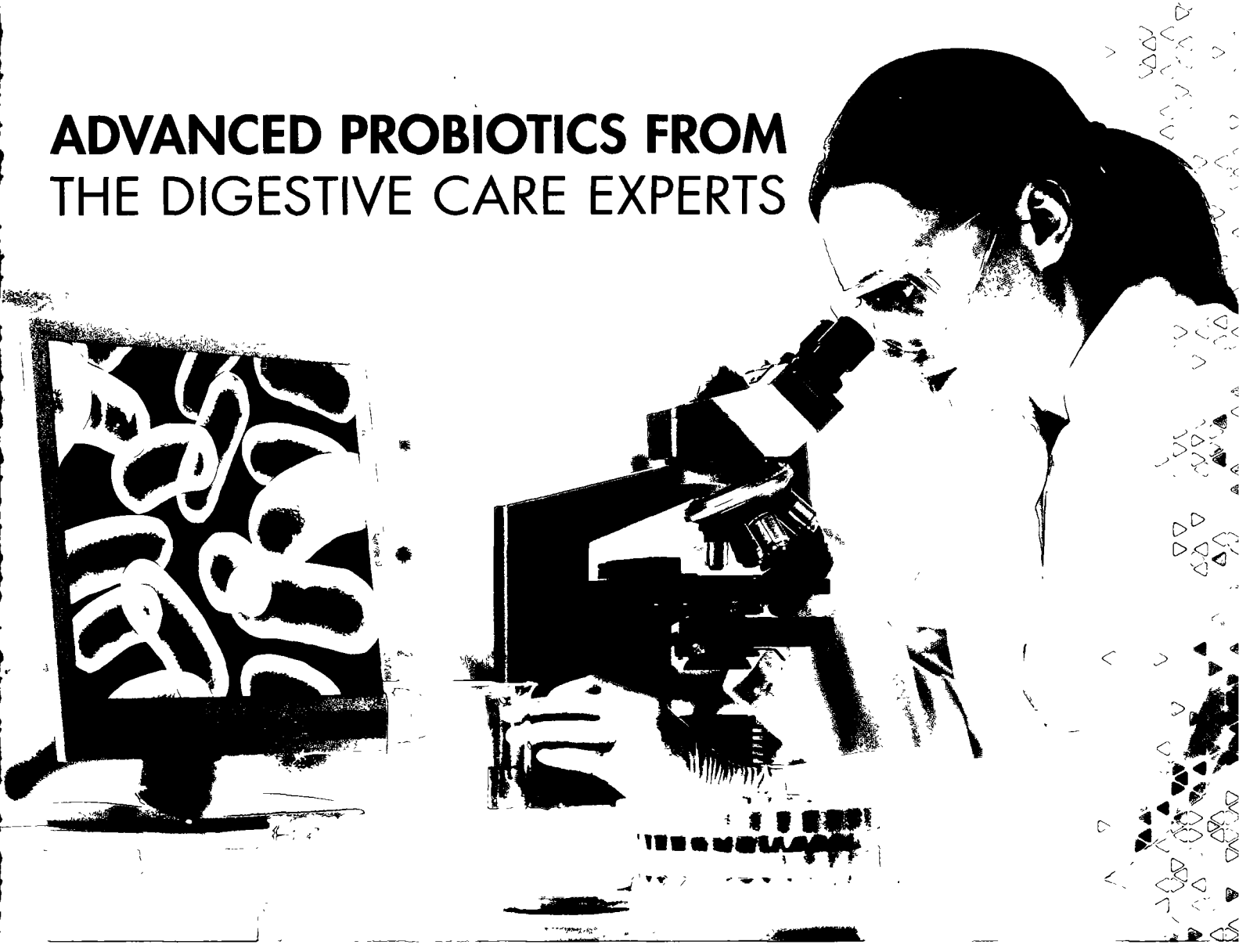

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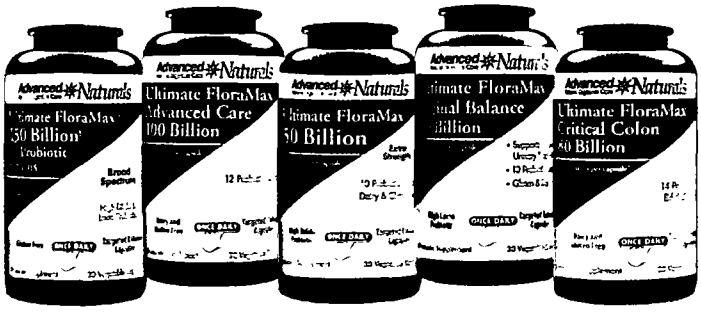

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Can FCT® Save Homeopathy?

➤ *continued from page 20*

from 'bad homeopathic medicine'. And while the same economic bleeding will preclude the United States insurance sector to even think of covering homeopathy, our medical 'Founding Fathers' – pharmaceutical industry and allopathic medicine – will gladly ban it. It will certainly help them address the thorn in their side – high consumer spending on alternative medicine and its products – in order to divert money to real 'medicine' with its services and drugs.

However, homeopathy is under threat for another reason, a reason that traditional or classical homeopaths and their professional organizations have chosen to ignore, to their detriment, but which is being legitimately used by their enemies as evidence that homeopathy is a worthless placebo. It is a virtual absence of large clinical trials demonstrating homeopathy's impressive clinical results or well-documented reversals of chronic diseases! This important problem, which I brought forward many years ago through my FCT teachings, and how to overcome this major Achilles' heel of homeopathy have been confirmed recently by distinguished conventional medical academicians and other scientists who support homeopathy as a legitimate medicine.[1]

By homeopathy, I refer to classical homeopathy, as founded by Samuel Hahnemann, MD, in the 18th century, not its many haphazard and dangerous varieties such as homotoxicology, complex homeopathy, Helmkulst and others used to treat chronic diseases, which were born out of desperation, following prevailing failures of classical homeopathy. It is these failures, and certain technical statistical difficulties in conducting homeopathic trials that have led the Office of Alternative and Complementary Medicine under our NIH to exclude homeopathy from its research and funding program! Speaking of signs of the end...I discovered this shocking surprise accidentally, two years ago, when I sought their support in treating a deadly Ebola infection, using FCT® homeopathic approach. The only way to reverse these signs of homeopathy's demise is not by complaining to executioners about injustice, but by delivering a heavy blow to them by fulfilling actual scientific requirements. These requirements, as correctly stated by the aforementioned authors, involve a production of impressive clinical results along with evidence of significant cost savings in comparison to allopathic medicine.

Why Has Homeopathy Failed to Produce These Trials?

What went wrong with homeopathy is no different from what went wrong with medicine, conventional and alternative/integrative, where practitioners have been taught to unlock chronic diseases through seemingly impressive but misfit keys because of unknowingly misplaced notches. What makes all of these

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Can FCT® Save Homeopathy?

➤ *continued from page 22*

approaches impressive and logical, on the surface, is that they all seem to be addressing some real pathological findings, or factors in disease – whether laboratory, energetic, structural, toxic, infectious, nutritional, or any other. Homeopathy has chosen to address disturbed energy balance, like Chinese medicine and other energetic approaches, but by just using certain disease symptoms. It, then, as any specialty, offers a seemingly logical treatment, saying "Aha, these things are obviously bad and that is why our treatment is obviously good, because it is meant to fix'em."

However, such a spirited perspective has largely failed because it usually misplaces the key notches in relation to the lock. What the lock will yield to is, first, the notch that can determine and match its very nature and, second, the specialty that is able to successfully address it. The aforementioned authors have expressed this, concerning homeopathy, in more general and well-known terms as a delicate interplay found in all science, between theory that underlies practiced approach and the data or actual results it produces. This implies that, certainly, when the results do not fulfill the expectations of the theory, it must be either dropped or adjusted.

Since, unlike many other medical approaches, homeopathy carries an enormous potential in medicine when properly applied (and that is why it is an important part of FCT) and because it is grossly misunderstood, even by the alternative community, it deserves a further detailed examination.

In the next issue, we will examine how homeopathic theory can be best adjusted to treat the profoundly poisoned modern populations in our sick world today.

1. Walach H, et al Research on Homeopathy: State of the Art *The Journal of Alternative and Complementary Medicine* 2005; 11 (5): 813-829

Savely Yurkovsky, MD, a pediatrician, internist and cardiologist, has evolved a novel medical model that interfaces important knowledge from biology, medicine, toxicology and physics. Its primary focus is on the most important aspect of chronic diseases – its causes – along with the most effective diagnostic and therapeutic means to address these. This has transformed the often imprecise medical interventions into a far more effective, exact and predictable science. He has founded a teaching organization, SYY Integrated Health Systems, Ltd., which provides training in this medical system under the concept of FCT®, Field Control Therapy. This concept as medicine of the future was suggested by Professor Emeritus, of Materials Science at Stanford University, William A Tiller, PhD. Dr. Yurkovsky has presented FCT® at many professional symposia in both the US and Europe, including the annual Bio-terrorism 2005 conference: "Unified Science & Technology for Reducing Biological Threats & Countering Terrorism" with affiliation to the Homeland Security Office, and Harvard Medical School, among others. Dr. Yurkovsky was nominated for the prestigious Bravewell Leadership Award for "significant contributions to the field of medicine" and "compelling vision for the future of medicine," in 2005. He has authored numerous articles and the book, *The Power of Digital Medicine* that was endorsed by prominent scientists from MIT, Columbia and Stanford Universities and contributed a chapter on homeopathy to the textbook of *Integrative Gastroenterology*, edited by the Chief of Integrative Gastroenterology at Johns Hopkins University medical school, Gerard Mullin, MD. Dr. Yurkovsky maintains a private practice in Chappaqua, New York. ◆

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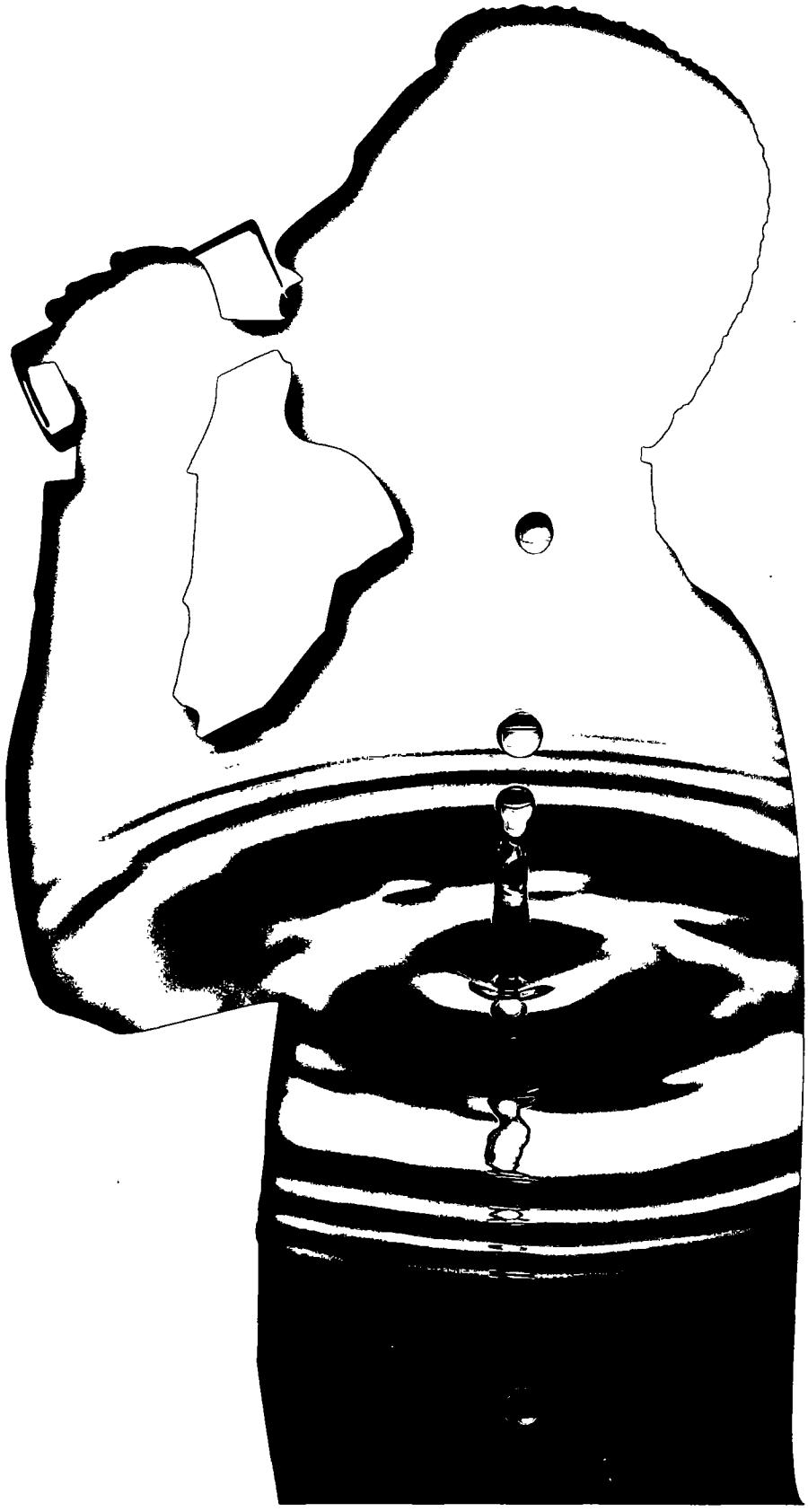
The editors of the *Townsend Letter* recommend that all patients (and physicians) review further reports provided in the article's references and investigate the practitioner's techniques before undertaking an alternative diagnosis, examination, or treatment. Please discuss such treatments and examinations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



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Low-Dose Immunotherapy (LDI)

by Ty Vincent, MD

Based on an interview with NJ Faass, MSW, MPH

Low-dose immunotherapy is an expanded application of LDA (low-dose allergy therapy), treatment made available to practitioners in the US by W. A. Shrader, MD, for the resolution of allergies and select autoimmune disorders. An earlier version of that technique, EPD (enzyme-potentiated desensitization), has been used in the field of integrative medicine since it was developed in the 1960s by Leonard McEwen, MD, an allergist in the UK. These techniques have been applied very successfully in the treatment of more than 60 indications, primarily allergy, asthma, and chemical sensitivities; autoimmune disorders including rheumatoid arthritis, systemic lupus, and ankylosing spondylitis; and other select immune-mediated conditions.

The efficacy of EPD was confirmed in a study conducted from 1993 to 2001 by Drs. Shrader and McEwen involving approximately 10,500 patients and more than 100 participating physicians. The study, which documented 68,428 treatment regimens (comprised of over 175,000 EPD injections), found that 76% of patients reported excellent, very good, or good health outcomes. Only 2% reported adverse effects, with 14% indicating a fair response and 8% indicating no change. LDA is virtually the only option currently available to prevent the occurrence of life-threatening reactions or death as a result of acute food allergy.

When I took the LDA training in 2008, I was amazed by the effectiveness of this approach. Within a year or two, I began to realize that the applications for this technique were much broader than the initial conditions for which it was indicated. Since that time, my contribution to this form of immunotherapy has been to apply the same technique to a much greater range of other immune-mediated conditions, including a number of disorders that had previously been thought to be "infections." In the process, I discovered changes in the technique that have made the treatment easier to use and in some cases yield faster results. In my practice and teaching, I now use sublingual antigens, rather than subcutaneous injections, and have found the oral dosing to be equally effective. Our research has also shown that "fresh" antigens are not essential, so LDI dosages can be sent directly to the patient through the mail to self-administer in their own home, rather than requiring repeated office visits to the physician for subcutaneous injections, significantly reducing the cost of therapy. Over the past nine years, I have expanded the application of this approach to the treatment of an additional 40 indications, including numerous difficult-to-treat autoimmune disorders.

An Epidemic of Immunological Illness

Autoimmune disease and allergies have increased dramatically over the last thirty years. Autism, for example, is an immunological illness in the vast majority of cases. In total, the incidence of immune-mediated illness has reached epidemic proportions.

Although the focus in healthcare tends to be on cancer and heart disease (still the leading killers), autoimmune disease and severe allergic disorders can cause decades of suffering in those who are afflicted. This has resulted in an incredible burden of chronic illness that persists for millions and millions of people. These diseases typically do not kill patients, but their quality of life is terrible. Given the debilitating nature of conditions such as rheumatoid arthritis, multiple sclerosis, and Crohn's disease, other categories of disease pale by comparison in terms of disability and compromised quality of life.

People with conditions such as Lyme disease are often not properly diagnosed for many years, if ever. They are given a diagnosis of fibromyalgia or chronic fatigue syndrome and are marginalized by our healthcare system and our psychiatric system. Practitioners and family members assume that these patients have a psychosomatic disorder, but in reality, they have some type of chronic inflammatory response that their immune system is propagating against them. They will suffer for decades if no one is able to correct that.

Breakthroughs in Treatment

All these conditions can be treated with a high rate of success using LDA and LDI. Both therapies involve a form of immunotherapy enhanced by a minute dose of the enzyme beta glucuronidase (10^{-13}), paired with miniscule doses of various allergens (10^{-6} to 10^{-17}) to stimulate the production of T-suppressor cells (T regulator or T reg cells). The therapy is thought to actively "switch off" helper cells erroneously misidentifying commensals as allergens. Clinically, LDA encompasses the antigens produced for food, environmental, and chemical allergens, and I still use those myself. I have also developed additional antigen formulations that are available to practitioners for the treatment of a range of diagnoses. Additionally, I have developed an approach to this therapy using "autologous" antigen samples derived from the patients themselves, to treat conditions that do not respond to any of the standardized mixtures.

In my experience, LDI can be roughly 90% successful when properly applied. If the patient remains engaged and is a good communicator, we have an excellent chance of dramatically recovering their health with no drugs, no side effects, and no toxicity. They typically will not need most of the other diverse therapies they have been doing to maintain some semblance of wellness. LDI has the potential to replace all of that treatment with a single, very safe therapeutic technique.

Autologous Therapy for Ulcerative Colitis

One of the major discoveries with this technique has been the use of autologous LDI for people with autoimmune-type phenomena who are reacting to microorganisms within their body's ecosystem. The beauty of the autologous LDI concept is that you do not have to identify the organism that is causing the reactivity. This is especially helpful for complex conditions such as inflammatory bowel disease, irritable bowel syndrome, SIBO, and in some cases, inflammatory arthritis.

When I began expanding the applications of LDI, I treated a patient with ulcerative colitis who was having more than a dozen bloody bowel movements a day and a great deal of abdominal pain – despite medical therapies, prescription drugs, and numerous alternative therapies from a clinic that specialized in this condition. In his case, we used a sample of his own stool, I diluted it out to a 6c dilution (one part per trillion), sterilized it through a millipore filter, and gave it to him as an antigen. This completely eliminated his symptoms. After the first dose, his symptoms stopped 100% within just a few days.

We gave him a few more doses on the two-month cycle, and he was asymptomatic for a year. That was a dramatic discovery for me. In his case, I did not have to identify the target antigen. I just had to have a good suspicion as to the source of that antigen and how to manipulate it using this technique.

Since then, I have found success using that concept with samples from the mouth and throat, the urinary tract, and the skin. In the case of a patient with chronic eye inflammation, I simply had him collect a sample of fluid from his eye, using a piece of wet gauze, and desensitized him with that fluid. I discovered this aspect of the technique more than six years ago and have worked with over one hundred patients, using autologous LDI as a broad concept technique. At this point, I am in a position to train other providers in the use of this approach, based on years of experience with a broad range of patients. We are now fine-tuning the technique to deliver these concepts to practitioners, so they will not have to go through the same process of discovery that I went through over the years.

New Paradigms in Lyme Disease Treatment

Lyme disease is a good example of the expanded applications of LDI. Lyme patients are among the most complex people I treat. One person might have a great deal of prominent joint pain and peripheral nerve symptoms such as numbness and tingling in their feet. The next person may have headaches, brain fog, and night sweats. So, the condition is very protean, and it requires a great deal of time to carefully document the symptoms of each individual. The patient must observe their own specific symptoms with every dose of LDI and report back as to whether the symptoms improved, got worse, or stayed the same. This is a constant process of working through the different doses of antigen until you get a significant response, and then you must work with that, within the guidelines and time schedule inherent in this technique.

Many of the Lyme patients that I have helped in the last few years came to us after years of antibiotic therapies and various integrative modalities of treatment. At this point, many have spent their whole life savings, typically a hundred thousand dollars or more, trying to get well. Some have been overseas, traveling to as many as ten different countries in their efforts to heal. For many of those people, nothing ever really made a difference. In most cases, we have been able to put their symptoms into remission with very good success.

Perspectives on the Infectious Model of Lyme Disease

Having worked with LDI for several years, I have effectively treated more than one hundred patients with Lyme disease, located all over the world. In my experience, borrelia and the "coinfections" tend to trigger immune-mediated inflammatory disorders rather than true infections. A growing body of research also indicates that these organisms are common commensals. In the patients I am seeing, the Lyme disease process is much more like an allergy than an infection.

Consider acne as a comparable example. Although acne is treated as an infection, this is not actually an infectious process because everyone carries that same bacteria, *Propionibacterium acnes*. The defining difference between having acne or not does not rest on whether the bacteria are present – it rests upon whether or not one has an adverse immune response to those bacteria. The same scenario appears to be true with Lyme disease. If you test people with dark field microscopy, DNA-probe technology, or sensitive blood culture techniques, you will find that most completely healthy, asymptomatic people are walking around with multiple species of borrelia, bartonella, babesia, ehrlichia, and anaplasma. All these species of Lyme and the co-infections are present in totally healthy individuals.

I began to see things in this way as I became aware of the Lyme problem in my population of patients in Alaska, which is interesting, since Lyme disease is thought not to exist in Alaska. I was seeing people who had chronic inflammatory problems with no clear cause. I would treat them with antibiotics and some would get better, some would get worse, and some here and there would go into remission – typical response patterns. Then I tried treating with homeopathic remedies, and I got a certain amount of positive response once again, but still no significant progress for most patients. Based on the response to these therapies and the way the disease seemed to behave, it occurred to me that it was more like an allergy or an autoimmune disorder than an infection.

To test my theory, in the summer of 2014, I developed a mixture of bacteria that included eight species of borrelia, seven species of bartonella, and a single species of babesia. I began giving that mixture as an LDI solution, starting at the "6C" dilution, to all the patients I suspected might have Lyme disease. The first 40 cases nearly all responded to this quite significantly. Approximately half initially got worse and I had to make the dilution weaker, but many of them had complete

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Low-Dose Immunotherapy

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resolution of their symptoms once their ideal dose was found. The results were quite dramatic, and the experience solidified for me the theory that Lyme disease is an immune activation syndrome. It clearly involves an immunological intolerance or an autoimmune reaction, as a few others have theorized before me.

Among these Lyme patients, I saw people who had been on antibiotics for years. In some cases, the antibiotics would control their symptoms for a while; but when the drug was stopped, some would immediately relapse. That is not how infection works. Even the worst true infections, such as endocarditis and osteomyelitis, tend to resolve completely with just six weeks of intravenous antibiotic therapy. Lyme patients will be given multiple antibiotics for many years on end with poor success and often serious negative effects. What I discovered by using LDI with Lyme disease patients confirmed my suspicion that the real issue is the immune response. Now that we have this tool, it is no longer necessary to treat Lyme with antibiotics after the initial month of antibiotics following a bug bite or onset of symptoms.

Over the past few years, I have modified my broad-spectrum Lyme mixture to include 74 total species in a formulation with borrelia, bartonella, babesia, and ehrlichia/coxiella. I have refined the therapeutic technique even more in order to segregate out antigens category by category, to isolate the most relevant of these four genera. Each set of antigens is isolated within its own genus, so I can identify which symptoms are corresponding to which category of antigen. That way I can give patients the different genera at different concentrations based on their symptom response patterns. It is very common for these complex patients to need a different dosage/dilution for one genus versus another. It has been educational and very encouraging to find that people with these constellations of horrible chronic symptoms can, in many cases, become completely asymptomatic without resorting to antibiotics or antimicrobial therapies. LDI therapy simply reestablishes immunological harmony and tolerance to organisms that have probably always lived within our bodies. It is possible that these bacterial organisms are a gift from our mothers at birth, if not beforehand.

Underlying Triggers in MS and RA

Most autoimmune conditions appear to have diverse triggers; but in some disorders, specific triggers are more prevalent. With multiple sclerosis, about 90% of the MS patients I see actually seem to have a more advanced neurological version of "Lyme disease." I say that because for most of these people, we can

Infection, Commensals, and Tolerance

The concept of *infection* requires a particular interaction between an organism and the host. By definition, when a true infection is present, the organism has been found in a location within the body where it does not belong. The mere presence of the organism within that tissue site causes a predictable and reproducible immune-inflammatory reaction that is necessary to protect the host and eradicate the invasive organism. Common examples of routine infections include bladder infections with *E. coli* or pneumonia with *Streptococcus pneumoniae*. Both the *E. coli* and *S. pneumoniae* organisms are common in human beings; they live within the bowels and nasal/sinus passages respectively. They only become "infections" if they enter a body compartment where they do not belong (the bladder or the lungs in these scenarios). The other essential feature of a true infection is that it can be *cured* by a relatively short course of antimicrobial therapy.

Certain organisms are truly foreign and seem to have a more intense inherent virulence or immune reactivity when encountered by the human immune system. They do not reside normally anywhere in the body and are always attacked when they are encountered there. Examples include the Ebola virus, salmonella, and typhoid organisms. However, even those rules are not absolute because many organisms thought to be obligate pathogens have a certain asymptomatic carriage rate. Humans have been forced to co-evolve with microbes since there were first humans; and our tolerance for these organisms improves over time with persistent colonization or exposure. In part, that is related to the fact that highly "susceptible" or highly "reactive" (the difference is very blurry) individuals will all die off fairly quickly after the introduction of a new pathogen, leaving only more "tolerant" individuals behind. Examples of such microbial culling include the cholera pandemics of the past, measles, tuberculosis, influenza, and others. Different strains of influenza have certainly demonstrated highly variable rates of immune reactivity. This was evidenced by the pandemic of 1918 that killed millions of people and, also, by the way in which a typical strain of the virus killed a significant percentage of the Alaskan native people upon introduction to that immunologically naive population. It is not clear why certain pathogens are more immunogenic than others, just as it is not clear why certain foods such as peanuts and shellfish are more inherently allergenic than others. Why are those foods frequently lethal allergens, rather than rice or olives, for example, which are more common in the human diet?

The difference between "infection" and an immune-based chronic disorder targeting a specific microorganism is a critical paradigm shift. Consider the example of *Streptococcus pyogenes*, the bacterium that causes strep throat. *S. pyogenes* is commonly a true pathogen and an "infectious" bacterial species, meaning that it tends to cause a predictable inflammatory response in the vast majority of humans upon inoculation. Probably 90% of people will develop a fever, terrible sore throat, swollen tonsils, fatigue, and other symptoms within a few days of colonization. However, up to 10% of people will have none of those symptoms and will simply "carry" the organism with no reactivity. That is an example of variable individual "tolerance" for this particular microbe, and it means those tolerant carriers will spread the infection to others unknowingly. Another manifestation of differential tolerance for this organism is evidenced by the fact that strep is known to trigger at least four very different types of "autoimmune" reactions, including rheumatic fever, post-streptococcal glomerulonephritis (technically an immune-complex disease, but bear with me), guttate psoriasis, and PANDAS. These conditions affect very different systems in the body through a distant or systemic immune response that is somewhat unique to the

get their symptoms to go into complete remission using the LDI Lyme antigen mixture.

Early on, I had patients who had been diagnosed with multiple sclerosis; but because they had other Lyme-ish symptoms, I tried giving them the Lyme LDI mix, and all of their MS symptoms resolved. Some of the MS patients using the LDI antigens for years have had repeated MRI brain scans, and most of their brain lesions have gone away. There is a small population that does not seem to respond, so there must be more than one antigen causing these symptoms. With rheumatoid arthritis, 90% respond to the *Proteus* antigen; and for the rest, the trigger is something else. I have found success for most of those patients using an autologous oral LDI antigen.

Despite the extensive number of possible triggers, we hope to gain success by applying the concept of cross-reactivity. Within each formulation for borrelia, babesia or bartonella, I have more than 20 individual species. If a patient is reacting to a related species that is not in the mix, there is a good chance immunologically that it will cross-react with species that are present in the antigen formulation. Typically, we get some degree of beneficial response in any case. That has been demonstrated through decades of clinical experience using the LDA food and environmental mixtures, with additional antigens to elicit more cross-reactivity.

Reprogramming Immune Tolerance

In conventional medicine, the strategy for treating autoimmune disease is to *disable* the immune system using drugs. That is often effective in alleviating symptoms, but this is a double-edged sword. Yes, their autoimmune symptoms may be better, but now they risk having a life-threatening complication because their immune system is not functioning. There is drastically increased risk of fatal infection or cancer when using immunosuppressant drugs, similar to having AIDS; and some of these drugs even cause new autoimmune problems.

With LDI, we reprogram the immune response to promote immune tolerance. This concept is central to LDI. We are re-establishing immunological acceptance or tolerance of the antigen that is triggering the symptoms. The "antigen" can be a food, natural environmental antigen (e.g. mold, pollen, animal), chemical substance, bacterium, virus, fungi or protozoan. In recent years, I have also found that hormones, minerals, and essential nutrients may also act as antigens. The key, once we have identified the right antigen, is to find that magical dilution – the point at which the immune system stops attacking. Those are the keys to success with this approach.

In some cases, I do not possess a standardized sample of the right microbe for a given patient. In that instance, I can often treat them by taking an autologous sample from their own body. For my group of patients with rheumatoid arthritis who do not respond to the *Proteus* antigen, I found that treating with microbes from the oral cavity works very well. For many

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individual, based on genetic susceptibility and the degree to which the immune system is dysfunctional.

Generally speaking, the human immune system has become increasingly dysfunctional due to accumulated environmental toxins within our species over time, and the resulting epigenetic changes that have ensued. Allergies and autoimmune diseases have skyrocketed in recent decades, and I believe this is a response to the environmental pollution we have inflicted upon ourselves and future generations. The result in terms of immune function is that the immune system has developed increasing difficulty in distinguishing "friend" from "enemy" and has begun to attack harmless substances such as foods, plant pollens, and commensal microbes with increasing regularity. The vast majority of autoimmune diseases can be shown to be initiated by an immune attack on some type of internal microorganism, part of our normal flora, which then cross-reacts with the host tissue in some manner due to a lack of appropriate discrimination. Another relevant term is "molecular mimicry" (things look more similar the worse your vision becomes). The fundamental problem is a loss of immune tolerance, which underlies all allergic and autoimmune response, and most chronic inflammatory conditions.

When someone with the high-risk HLA genotype for a disease becomes colonized with the relevant triggering microbe, and then some form of stressor agitates the immune system, an autoimmune disease can ensue. Most patients with rheumatoid arthritis, for example, are actually reacting to bacteria within the genus *Proteus,* cross-reacting with their joint tissues due to their HLA type. Every autoimmune disease seems to have those same components: molecular mimicry between a host tissue and microorganism, with the inflammatory response set off by some sort of immune-stimulating event. That event can be something like a true infection, a vaccine, physical trauma, intense psychological stress, or a drastic hormonal change (childbirth, for example, is an extremely common "catalytic event").

In my experience, chronic "Lyme disease" fits this model extremely well. Borrelia organisms and other bacteria thought to be "co-infections" appear to actually be commensal flora, not true pathogens. I say this because sensitive detection techniques such as blood cultures or PCR testing will demonstrate the presence of these organisms within the vast majority of completely healthy adults. That means they are *not* true pathogens, and the disease associated with them is *not* an "infection" in the true sense of the word. Consequently, we have to presume the virulence of the organisms themselves is not the issue, and the disease process rests entirely upon the host immune response. I believe this is why LDI has been so effective in treating chronic conditions due to borrelia, bartonella, babesia, candida, mycoplasma, and numerous other microbes. This is also the reason that taking antibiotics for years still fails to solve the problem for the great majority of those who are afflicted. The "infection model" of Lyme disease does not correlate with the growing evidence, and the "immune response" model at this point seems more relevant.

The keys to success with LDI for autoimmune and chronic inflammatory conditions are to properly identify the triggering organisms or agents and to find the ideal neutralizing dose for that antigen. If you can determine those two things, you can make 90% or more of these people well to a significant degree. At this point, I have hundreds of Lyme disease patients all around the world; many have responded dramatically to this therapy and no longer need any kind of antimicrobial treatment whatsoever. For me, that has been very eye-opening.

people with inflammatory bowel disease, using a sample of their own stool can be miraculous. Samples are diluted and sterilized through a millipore filter before use as autologous LDI. I have successfully treated patients with samples from the mouth, sinuses, bowel, vagina, skin, and conjunctiva.

Mediating Intricate Ecology in GI Disorders

The complexity of GI disorders is usually greater than that of conditions such as rheumatoid arthritis or multiple sclerosis. Crohn's disease, ulcerative colitis, and undifferentiated IBD are typically multifactorial. I have treated dozens of people with these disorders and usually they are not reacting to a single trigger. These are among the more challenging cases I treat, but LDI has a very high success rate nonetheless. Common antigens include the following:

- ***Foods.*** I use the LDA food antigens.
- ***Yeast.*** I have a mixture of yeast species including candida, bakers', and brewers' yeasts.
- ***Mycobacteria.*** In the case of Crohn's disease and ulcerative colitis, there is a documented association involving *Mycobacterium avium paratuberculosis.* I have a mix that includes that antigen and two additional species of mycobacteria in a formulation that is often effective in IBD cases.
- ***Parasites.*** I have a parasite mixture (all protozoans), which has been dramatically effective in some inflammatory bowel cases.

Autologous Stool: Another approach is to use autologous LDI. When we try the above antigen mixtures and still do not get complete resolution of symptoms, I have patients collect a stool sample and process that into an LDI antigen. The theory is that whatever is inflaming their gut is residing within their gut, so all I need is a sample of it and the right dilution and I can resolve their symptoms. Autologous LDI has been instrumental in resolving inflammatory bowel problems for a number of patients I have treated over the years.

Multiple Issues in Autism

Autism is another good example of a multifactorial immune-mediated condition. For many of these young patients, the condition is primarily caused by some type of immunological inflammatory process. The target organ for their inflammation is primarily the brain, and that can manifest in a wide range of symptoms including learning disabilities, communication problems, stimming behaviors, and other neurological manifestations. Working with colleagues who have larger autism patient populations, we have found that many LDI antigens may work for them. Antigens that are commonly relevant in the autism population include the following:

- Borrelia, bartonella, babesia, mycoplasma;
- Herpes simplex, streptococcus, clostridia;
- Yeast and foods;
- MMR and DTaP vaccines;
- Chemical and environmental allergens.

With many chronic conditions, one difficulty lies in the fact that symptoms caused by different antigens can look very similar. This is very common in autism. To determine which antigens to use, the provider must ask a great many questions. Some of these patients have digestive problems. Some have symptoms such as rashes, fevers, or swollen lymph nodes, as well as psychological symptoms like OCD tendencies. To determine which antigens are going to fit, it is essential to develop a comprehensive list of specific symptoms. A great deal of clinical experience goes into making good decisions early on, and not every clinician has the patience and diligence to master this technique. An experienced practitioner can figure out difficult cases eventually if they are thorough and get communication from the family or the patient. Through experience, one gets better and better over time, able to get to the right answer quicker. I equate using LDI to playing a piano. When you first sit in front of a piano, you are more likely to make "noise" than music. With practice and experience, you will be able to make music for your patients using LDI.

Modified Allergy Protocol

Allergies have skyrocketed in the last few years, reflected in the number of children in the public school system who need to have an Epi-Pen and emergency measures in place. More and more people now have life-threatening allergies not only to peanuts and shellfish, but also to common foods such as corn, strawberries, or coconut. The low-dose antigen (LDA) mixes have been extremely successful in eliminating those allergy problems for people. I have modified the LDA protocol to a certain degree and gotten even better results in people with the most severe cases, finding that some people need to take the antigens in even more diluted form in order to achieve a good response. Those highly sensitive patients cannot tolerate the standard LDA concentrations without a severe flare of symptoms. I have also used certain foods in isolation such as corn, wheat, egg, or milk with people who have severe reactions to that particular substance. Again, one of the keys to success is achieving the right dilution.

Conclusion

Ultimately, one of my goals is that this therapy (and the underlying concepts) become standard of care for people with autoimmune disorders. This approach is safe, efficacious, inexpensive, and user-friendly. LDI can now be administered in the home using sublingual low-dose antigen formulations, and treatment is often successful for disabling conditions for which there are currently no other effective form of therapy. Although I can only treat a thousand people in my own practice, if I can train a thousand other physicians to do this, then we can treat a million people. There is strength in numbers, and great power in knowledge.

Ty R. Vincent, MD

Dr. Ty Vincent grew up in Alaska, graduated from the University of Alaska, magna cum laude, and earned his medical degree at the University of Washington. A family practice physician in Alaska for more than a decade, Ty has been a board member of the American Academy of Environmental Medicine and the

American College for the Advancement of Medicine. With diplomate status from the American Board of Family Medicine, he has also completed additional training and fellowships in environmental medicine, medical acupuncture, and Chinese herbal medicine. Recognized as an expert and innovator in the field of low-dose antigen therapy, he has received awards from the American Academy of Family Practice, the Society of Teachers of Family Medicine, and the American Academy of Environmental Medicine. Dr. Vincent now provides training for professionals and co-management of patient care through his company, Global Immunotherapy, LLC, based in Kona, Hawaii.

Resources

LDI Training and Clinical Services

Global Immunotherapy offers distance provider training and patient care. Patients receive consultations with Dr. Vincent by phone or Skype in the comfort of their own home. Provider membership enables practitioners to receive the LDI Training Manual and to order LDI antigens, as well as customized autologous samples. Membership facilitates direct contact with Dr. Vincent, answers questions about LDI, supports case review, and gives practitioners the opportunity to converse with other professionals who are using LDI treatment. Global Immunotherapy also provides LDI antigens for healthcare professionals, to be diluted and used for the treatment of their own patient populations. We have had very good success treating all manner of allergies, autoimmune diseases, and chronic inflammatory disorders. Dr. Vincent also provides consultations and patient co-management in conjunction with local primary care physicians on medical needs beyond the parameters of LDI.

Low-Dose Immunotherapy

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Web-based Information

We now have a series of short video clips on YouTube and linked to our Facebook page and website. Most of the videos are brief, conceptual discussions of 5 minutes or less on different aspects of LDI therapy. We are finding that this is a very effective tool for helping patients work with their provider on LDI treatment, and at this point the videos have received more than 10,000 views.
Website: globalimmunotherapy.com
Book: *Thinking Outside the Pill Box* (available through Amazon, Barnes and Noble, Google Books, etc.)

LDA Providers

Dr. W. A. Shrader maintains a website listing physicians he has trained who administer LDA, alphabetical by state in the US, Canada, the UK, and elsewhere, available at www.drshrader.com/lda_physicians.htm.

Editorial: Nancy Faass, MSW, MPH

Ms. Faass is a writer and editor in San Francisco who has participated on more than 50 books to date. Director of the Health Writers' Group for the past 20 years, she works collaboratively with clients to develop books, articles, Web content, white papers, manuals, and blogs, and can be reached by emailing info@HealthWritersGroup.com or calling 415-922-623 ◆

The One Healthy Doctor Challenge

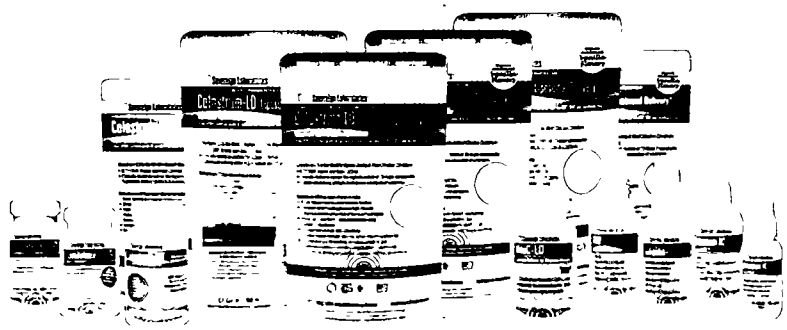
Are you healthy? We are offering a $1,000.00 reward to any medical professional who can pass a simple blood test, proving that they do not have Leaky Gut Syndrome (LGS). Having LGS is the primary means of identifying those who will incur one or more major chronic diseases (if not already underway) that can shorten lifespan and decrease quality of life. The goal of the One Healthy Doctor Challenge is to educate medical professionals about the vital necessity of bovine colostrum as the one true gut healing substance. Colostrum is critical for absolutely everyone – physicians and patients alike.

The One Healthy Doctor Challenge is being offered to all those who have an active medical practice and regularly interact with patients. The test is for food sensitivities and is offered by Life Extension (Food Safe Allergy #LCM73001) and is available at www.LifeExtension.com. This test will show any food sensitivities to 95 foods in the panel. Why? By identifying the presence of undigested food particles crossing into the bloodstream, it confirms gut permeability.

We are so confident that currently espoused LGS treatments, such as elimination diets, L-glutamine, and probiotics, do not work that we're offering this reward to encourage self-examination and bring to all those who participate a vital and critically needed remedy. Not only for the professional to heal thyself, but to encourage an understanding that reversing this process and healing the gut is the only path to chronic disease prevention. This includes Inflammatory disease conditions, autoimmune diseases of all types, diabetes 1 and 2, prediabetes, heart disease, asthma, cancer, and a majority of infectious disease. Plus, LGS is a leading contributor to a majority of mental health conditions including: depression, Alzheimer's, ALS, Parkinson's, bi-polar, schizophrenia, ADHD, autism, dementia etc. Unless the gut is healed and the flow of toxins into the body ceases, the immune system cannot function properly to prevent disease.

Additional One Healthy Doctor Challenge details and required consent form are available on www.ColostrumTherapy.com

*Not Eligible: The challenge is not open to anyone currently using Colostrum-LD™ from Sovereign Laboratories.



Colostrum-LD is clinically proven to heal and prevent Leaky Gut Syndrome

The Total Leaky Gut Solution

Colostrum-LD™ heals gut lining inflammation, decreases permeability, increases the surface area of the small intestine for improved absorption of critical nutrition, and stimulates cellular repair and regeneration. Simultaneously, concentrated proline-rich polypeptides in IRM™ inhibit the initiation of inappropriate inflammatory cascades associated with allergy and autoimmune responses, halt the progression of tissue destruction, and decrease pain.

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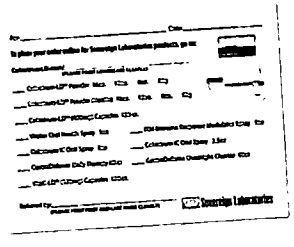
- Decrease pain
- Eliminate gut-based infections
- Help the immune system fight pathogens
- Stimulate production of anti-aging hormones
- Increase lean muscle mass & strength
- Boost metabolism and fat burning
- Balance blood sugar
- Increase bone mass & density
- Accelerate recovery from injuries, wounds, & burns
- Eliminate skin infections & accelerate healing
- Regenerate youthful & healthy skin
- Enhance mental focus & concentration
- Improve mood by increasing seratonin and dopamine



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Best Practices vs. Band-Aids for Healing Leaky Gut Syndrome

Douglas A. Wyatt, Director

Sovereign Health Initiative Foundation

The growing problem of leaky gut syndrome, or gastro-intestinal permeability, has triggered a health crisis in Western civilizations, the likes of which we may be wholly unprepared to deal with. The chronic and systemic inflammation resulting from a leaky gut is now believed to be responsible for nearly every type of allergy, autoimmune condition, and chronic disease. Many physicians now agree that nearly everyone will die of an autoimmune condition. Moreover, there will be untold physical and mental pain, disability, and suffering along the way, which crescendos with shorter lifespans. Unfulfilled human potential doesn't have to be our fate, but we need to take action early and consistently to heal the gut. Physicians also must understand that the current treatments for healing the gut are mere "band-aids" that do little more than provide moderate symptom relief.

Before delving into the current treatments for healing the gut, I want to address the issue of laboratory testing for leaky gut and a common misconception about food allergies. Many physicians perform food sensitivity testing to identify which foods the patient is allergic to and subsequently instruct patients to avoid the foods that resulted in a positive test. Food sensitivity testing is an indicator of intestinal permeability, but food allergies themselves are a definitive, no-cost indicator of leaky gut syndrome. Here's why: Food allergies result when undigested food particles crossover through a permeable gut lining into the bloodstream wherein the immune system recognizes them as foreign and initiates a process of eliminating them. This immune response, or allergic reaction, involves the creation of antibodies against the foreign substance, and these antibodies show up on the allergy panel. Don't get me wrong. Food sensitivity testing is the best way to test for leaky gut syndrome, and it may put patients at ease to know what exactly they're allergic to; but it's really only a confirmation of what we already know.

Elimination Diets

If laboratory testing identifies a particular food or chemical sensitivity, physicians often prescribe elimination diets. This dietary restriction can be quite severe in the case of multiple food allergies. In the case of gluten sensitivity/allergy, avoiding gluten-containing foods can require a significant effort on the patient's part. Merely by avoidance, such food particles and/or chemicals do not crossover into the bloodstream. Patients may feel better, but the underlying problem remains; their gut lining is still permeable. The specific food will continue to cause an allergic reaction if consumed, and foods previously eaten without causing an allergic reaction can, in fact, become problematic in the future. Elimination diets are nothing more than a band-aid treatment. They do nothing to address the root problem of food allergies – leaky gut syndrome – and they do not heal the gut.

Nutritional Treatments Aimed at Altering Gut Bacteria Balance

Several nutritional methods are currently being employed to alter the bacterial composition of the gut microbiome in an effort to prevent dysbiosis. These either increase beneficial bacteria or destroy pathogenic bacteria, so as to favor health over illness. The most commonly recommended treatments include probiotics, fermented foods, fiber, and essential oils. The first three are intended to increase the beneficial bacteria and crowd out the pathogenic bacteria, whereas the fourth is intended to destroy pathogenic bacteria without negatively impacting the beneficial bacteria.[1] Research on the combined use of probiotics and essentials oils has been suggested for its potential synergistic effects; the probiotics retard the growth of antibiotic-resistant enteric pathogens and the essential oils kill them.[2]

Research in animal models and cell culture systems has shown that specific lactobacilli strains can exert a counteractive effect on increased intestinal permeability initiated by infections, chemicals, or stress.[3] A 2016 review article by Di Cerbo et al. on the therapeutic uses of lactobacilli found that long-term supplementation had a qualitative and quantitative effect on the human gut microbiome with encouraging results for treating pathology.[4] However, the researchers noted that the benefits of lactobacilli supplementation could be tempered by

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the risk of sepsis and bacteremia. Not only is specific dose of the probiotic of concern, but also the specific strain. To date, the research in humans is generally lacking and often inconclusive. Nonetheless, the probiotics industry has capitalized on the consumers' perceptions that taking "good" bacteria must be good for the gut.

In my view, some practitioners have interpreted the research to mean that probiotic therapies designed to attenuate gut dysbiosis will, in themselves, lead to the healing of intestinal permeability. This is not the case, and I argue that probiotic supplementation should not be prescribed until the gut lining is healed and fully intact. Just as undigested food particles or toxins can cross a leaky gut so can probiotics, thereby leading to an immune reaction against the probiotic strain(s). Antibodies against the probiotic strain will attack every time it crosses into the bloodstream. Essentially, probiotic supplementation is worthless and even unhealthy if the gut remains leaky. Therefore, the first step in healing the gut is to heal intestinal permeability.

Antioxidant, Amino Acid, and Mineral Supplementation to Heal Intestinal Permeability

Glutathione, sometimes called the "ultimate antioxidant," prevents damage caused by reactive oxygen species, including free radicals, lipid peroxides, and heavy metals. Glutathione plays a significant role in the life of a cell, replication and death.[5] Some have suggested that because lower levels of liver glutathione are common in patients with leaky gut syndrome, supplementation will increase the immune system's effectiveness, fight inflammation, and neutralize toxins, and by extension, heal intestinal permeability. While glutathione is important, it is quite a leap to suggest that a single antioxidant (or even a combination of antioxidants) can attenuate a leaky gut. Many antioxidants are spent on food digestion in the stomach, so it's questionable how much free-radical neutralizing power remains for the small intestines. Additionally, oral glutathione does not appear to be effective in increasing glutathione levels in the body, although some foods may be able to help the body create its own.

Glutamine is an essential amino acid made by the human body that plays a role in maintaining the integrity of the gut lining, among several other biological functions.[6] Because of its role in preventing intestinal permeability, supplementation with widely-available L-glutamine has been espoused as a natural treatment for leaky gut syndrome. Glutamine supplementation is not without risks. Patients with kidney disease, liver disease, or Reye syndrome are advised not to take glutamine supplements; psychiatric patients and those with a history of seizures are urged to use caution, as these conditions may be worsened by glutamine.[7] Organic bone broth, which is presently quite popular, is heralded as having a high glutamine content. It is increasing recommended for patients with leaky gut syndrome and as a key component of the gut and psychology (GAPS) diet. The risk of bone broth is that bones are known to sequester lead which leaches into the broth during the cooking process. A study of three different organic chicken broths revealed that the broths contained substantially higher concentrations of lead than the water used to make the broth.[8]

Zinc carnosine (ZnC), also known as polaprezinc, is an approved drug utilized in Japan as a treatment for gastric ulcers. Its ulcer-healing action is thought to be a combination of free-radical scavenging, anti-oxidation and accelerated wound healing.[9] Similar healing action has been observed in the gut, and more supplement manufacturers are now including ZnC in their GI products. Research in vitro showed that ZnC stimulates cell migration and proliferation and, in mice and rats, decreased gastric and small intestine damage.[10] The same study showed that the increase in gut permeability caused by NSAIDs could be attenuated with ZnC in humans.

Although potentially beneficial for helping to heal the gut, glutathione, glutamine, and zinc carnosine are not the miracle supplements people have hoped for. Leaky gut syndrome is a multi-faceted condition which simply cannot be fixed by a single antioxidant, a single amino acid, a single mineral, a single strain of probiotic, or a single extract of an herb. That is not to say that patients won't experience some symptom relief, but true healing can only be achieved with the one substance designed by Mother Nature and provided by every mammalian mother to her newborn – colostrum.

Colostrum is produced by all mammalian mothers for the two-fold purpose of passing immunity to the newborn and closing the newborn's leaky gut. The gut is leaky by design, for it allows immunoglobulins to pass easily into the bloodstream whereby they prime the immune system. Colostrum is expressed for about 72 hours following the infant's birth, and the epithelial growth factors in colostrum seal up the leaky gut after the first three days of life. Preventing intestinal permeability at this point is important so that as colostrum is gradually replaced with milk, the milk proteins will not enter the bloodstream. A mother's colostrum contains a plethora of immune and growth factors that assist in the healthy development and growth of the infant, including beneficial bacteria which seed the gastrointestinal tract. An infant who is breastfeed immediately after birth and for at least two years receives the best possible start in life due to the health-preserving effects of immune and growth factors.

Bovine Colostrum Supplementation to Heal Intestinal Permeability and Rebalance Gut Bacteria

Beyond infancy, during childhood, or in adulthood, the holes in the gut can re-open and cause intestinal permeability. Essentially, without a consistent supply of immune and growth factors, everyone will develop leaky gut syndrome and in time, the allergies, autoimmune conditions, and chronic disease that follow. Leaky gut

syndrome occurs for a variety of reasons, including gut infections, ingestion of glyphosate and other herbicide or pesticide-contaminated foods, GMOs, oral antibiotics, antibiotics in foods, over-the-counter and prescription pain medications, corticosteroids, refined carbohydrates and simple sugars, alcohol, sodas, caffeine, and other gut irritants. Many of these are a consequence of our modern lifestyle and, thus, unavoidable to some degree.

However, all is not lost, and our understanding of how a mother's colostrum heals her newborn's leaky gut gives us the power to heal the gut in adults as well as children who may not have had the extraordinary benefits of breastfeeding. Bovine colostrum is the ideal supplement to heal the gut for a variety of reasons. First, it contains about forty times more immune and growth factors than human colostrum. This is because baby calves, like most mammals outside of humans, are expected to hit the ground running shortly after birth. This is particularly true for mammals in the wild; for example, the newborn gazelle will become the lion's prey if it is unable to run with the herd rather soon after birth. Unlike humans who receive some immunity in utero, these mammals receive all of their immunity from their mothers' colostrum. Second, the growth and immune factors in bovine colostrum are nearly bioidentical to those in human colostrum. Third, bovine colostrum contains the antibodies to all the pathogens that a dairy cow has been exposed to during her lifetime plus those she received from her own mother. When the colostrum of thousands of cows is combined to make supplements, the immune-protecting potential for humans is tremendous. Fourth, bovine colostrum is plentiful, particularly that which comes from herds that give birth year-round. Female cows produce about eighteen liters, of which approximately four liters are necessary for calves. Lastly, and fortunately for consumers, bovine colostrum can easily be made into shelf-stable supplements that are low-cost compared to the cost of having a major chronic disease.

In terms of scientific research, colostrum as a whole or its individual components have proved their usefulness in mammalian gut health. Studies in both animals and humans have demonstrated colostrum's ability to reduce intestinal permeability caused by NSAID-induced damage or by heavy exercise.[11-16] The growth factors, including insulin-like growth factor and epithelial growth factor help stimulate cell proliferation in the gut lining. Anti-pathogenic activity has also been demonstrated in the literature, most prominently with HIV/AIDS-associated diarrhea[17-22] and influenza.[23-25]

Moreover, colostrum contains glutathione and its precursors; glutamic acid, which converts ammonia in the brain to glutamine; a wide array of antibodies, immunoglobulins, ➤

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lactoferrin, lactoperoxidase, proline-rich polypeptides, cytokines and other immune factors to destroy pathogens; and beneficial bacteria strains, such as *Lactobacillus acidophilus*, *Lactobacillus bifidus*, and *Bifidobacterium* spp., to help recolonize the gut once the pathogenic bacteria is eliminated.

For the above reasons, it's clear to see how bovine colostrum has a role in attenuating intestinal permeability, rebalancing gut bacteria, and assisting the immune system's ability to fight infection. Consistent colostrum supplementation may actually help some alternative therapies work better, but colostrum should always be the foremost treatment for healing the gut. A recent study examined the combined supplementation of bovine colostrum and zinc carnosine in truncating gut permeability due to heavy exercise.[26] The combined effect was greater than either treatment alone, and researchers concluded that this could prove valuable for preventing heat stroke in athletes and military personnel.

With respect to probiotics, I recommend that a leaky gut be healed before any probiotic supplements are introduced. This entails four to six weeks of a therapeutic dose of liposomal delivery colostrum. Once the gut lining is healed, continued colostrum use will help any probiotic strains to colonize while keeping any pathogenic bacteria in check.

I'm such a staunch advocate of bovine colostrum as a best practice for healing the gut, that the Sovereign Health Initiative Foundation has issued a health challenge to any doctor with an active medical practice to prove that he/she is free of intestinal permeability. The proof we're seeking is a negative food sensitivities test, but we're quite certain that this will be difficult to find. Our goal in issuing the challenge is for doctors to understand how pervasive leaky gut syndrome is and to realize just how critical bovine colostrum is for healing the gut, not only for themselves but for their patients as well. For more information, see the Colostrum-LD™ ad in this issue, or view complete rules at ColostrumTherapy.com.

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Douglas Wyatt, JD, is the founder of Sovereign Laboratories LLC, a Sedona-based company dedicated to developing natural products that provide the public with the best solutions for optimal health. He is honored to be listed as the leading expert in colostrum and is credited with reintroducing bovine colostrum into human use. Additionally, he serves as the director of the Sovereign Health Initiative, a 501(c)(3) nonprofit organization dedicated to recognition of personal health sovereignty and the belief that one's commitment is essential to achieving optimal health and well-being. Douglas is a leader in the research and a proponent of colostrum's unique and powerful healing components that show incredible promise for turning the tide on the prevention and treatment of the world's increasing chronic disease epidemic. As a publisher, author, writer, scientist, and public speaker, Douglas has appeared nationwide on television and radio shows and at health conventions worldwide. He is dedicated to the prevention of chronic disease through natural nutritional intervention and has worked with the World Health Organization and other internationally recognized research organizations on clinical trials on HIV/AIDS other infectious disease, autoimmune disease, and bowel health issues.

Ask Dr. J

by Jim Cross, ND, LAc
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Environmental Health Symposium: The Elephant in The Waiting Room – Neuroinflammation

This is an overview of the second annual Environmental Health Symposium, a collaboration of the Annual Updates in Environmental Medicine and the Seeds of Doubt Conferences held in San Diego, California, on March 3-5, 2017. Their goal was to choose the topic of neuroinflammation, study it thoroughly, and then seek out the best speakers on the topic so that attendees could fully learn the causes, presentations, and treatment of this pervasive problem. They also wanted the attendee to leave there feeling that they were fully capable of recognizing this condition in their patient population and would be able to help those individuals in their clinics on Monday.

I do not have enough space to cover every presenter, and I will be synopsizing the various presentations I feel spoke to me most powerfully. Hopefully, I don't offend any of the speakers I don't include or any attendees who can't believe I didn't write about their favorite lecture.

Walter Crinnion, ND, and Lyn Patrick, ND, are the driving forces behind this wonderful constellation of stellar presenters and topics apropos of the present neuroinflammatory epidemic that exists in the United States. Unfortunately, truth is no match for belief, and we are facing an administration whose Environmental Protection Agency head thinks there are no problems with astronomical levels of CO2 in the atmosphere and thousands of chemicals in our food, water, and air. Shades of James Watt!

Walter started out the pre-conference on Thursday with a wonderful statement: It is never a question of if someone is burdened with toxicants. It is a question of whether their toxicant burden is a causative factor in their illness or an obstacle to their cure. I am going to add a slight addendum to his prescient statement: or is it both a causative factor and an obstacle? I think in many of our current patients this is the case. Now, if we could only convince most of our patients of this statement (more importantly our politicians), maybe we could also begin the arduous task of ridding our environment of noxious chemicals and heavy metals!

Walter presented again on Thursday and gave three really useful resources:

1. A website that showed an air pollution map of the world: http://aqicn.org/map/world/.
2. A website that listed fracking sites around the United States: http://earthjustice.org/features/campaigns/fracking-across-the-united-states.
3. Finally, he gave us an all-inclusive questionnaire for determining an environmental patient's biotransformation ability, their current exposure history, their residential and job history, and their heavy metal exposures. What a wonderful armamentarium of information that left you feeling locked and loaded in terms of determining what the causative and aggravating factors are for each patient.

On Friday, the official first day of the conference, Walter's talk focused on what I think is a very useful metaphor, "the elephant in the room." You know, the one sitting in the corner, invisible, while everyone's brain is being bombarded by environmental pollutants. Here is his list of documented neuroinflammatory agents:

- Urban air pollution (esp. diesel exhaust),
- Organophosphate pesticides,
- Chlorinated pesticides (dieldrin),
- Mercury and Lead,
- Solvents (alcohol is the classic one),
- Formaldehyde,
- Bisphenol A (no articles yet on phthalates), and
- Rotenone and paraquat.

All are pro-oxidants, all deplete GSH, and all suppress antioxidant enzymes. Tough to avoid this rogue's gallery of corporate greed. Fortunately, we integrative medicine practitioners have the means with which to help the few among the many who arrive at our door with the various modern maladies plaguing our society.

The next speaker to really catch my eye was Aristo Vodjani, PhD in microbiology and clinical immunology. I have heard Dr. Vodjani speak at several conferences and am always amazed at what test or tidbit he comes up with next. I don't think he believes in the status quo. He also admitted to being chemically sensitive, which might be a driving force in his continued push to expand his immunological knowledge.

His talk revolved around autoimmune destruction of the tight junction proteins in the gastrointestinal epithelial layer. This destruction leads to leaky gut and then destruction of the blood brain barrier from leaked compounds of the GI tract traveling upwards and compromising the blood brain barrier, basically leaky brain. This is the initiating process for neuroinflammation. He has a wonderful slide demonstrating this process and then a research

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report showing that brain-reactive autoantibodies are nearly ubiquitous in human serum and linked to various brain pathologies. Cyrex Labs now has an antibody test specifically for this: Blood Brain Barrier Permeability. For my money, correcting leaky gut and the subsequent leaky brain that accompanies it are the basis of any treatment I use for chronic diseases.

The next interesting presenter for me was Kenneth Proefrock, ND. I could list his accomplishments, which are prolific, but I loved this little statement at the end of his written introduction: "In his spare time, when such a thing really exists, he is in the desert with his kids, honing his skills in primitive archery, gardening, home brewing, wildcrafting, reading and writing poetry, and studying obscure and old texts on spiritual matters, healing, and philosophy." Fortunately, he also gave a slam-bam talk on botanical agents, about which he appears to have a very eclectic knowledge.

What I found fascinating was his description of endocannabinoids as central nervous system regulators of many processes, including neuroinflammation. One slide showed the various brain areas that have CB-1 receptors. Another slide demonstrated the multiple areas around the body where CB-2 receptors occur in association with immune tissues. Finally, he showed a slide that demonstrated blending various cannabis strains often works the best. It appears that the various endocannabinoids will give us fantastic results in our treatment of neuroinflammation and brain trauma.

The next premier batter up was Michael Irwin, MD. Dr. Irwin is one of the world's foremost experts on the psychoneuroimmunological pathways by which psychosocial and behavioral factors influence health and disease. Much of his talk centered on sleep and the negative bodily effects less sleep has on the body.

He connected sleep, fatigue, and depression quite effectively. He also showed that decreased sleep is a gateway to neuroinflammation by activating cellular inflammatory signaling through adrenergic activation of nuclear factor kappa beta, which then leads to activation of pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha). If you're a biochemical geek like me, real juicy science!

He also showed that cancer survivors, especially breast cancer, have 50% increased incidence of insomnia, which would dampen their immune systems and possibly lead to a reoccurrence of their cancers or other downwind diseases of stress like cardiovascular disease, autoimmune diseases, or major neurological diseases. Finally, he said there is a huge variability in the effects of stress on each individual, and we need to be able to more precisely evaluate the specific effects of stress for each individual.

Next came Felice Gersh, MD. Dr. Gersh is one of only a small number of fellowship-trained integrative gynecologists in the nation. Wow, does she understand the female reproductive system, and did I ever discover female reproductive tibbits! She felt that estrogen is one of the major conductors of our endocrine system and that our world of increasingly larger numbers and amounts of endocrine disruptors are negatively impacting the positive effects of estrogen on our bodies. She also had a wonderful slide that demonstrated the multiple areas of the body, outside of the reproductive tract, with estrogen receptors and thus affected by estrogen.

A few quick hitters from Dr. Gersh:

- Estrogen is neuroprotective and crosses the blood brain barrier/BBB.
- Estriol only activates the beta estrogen receptors and downregulates the alpha estrogen receptors. Why not give the body bioidentical estradiol and let it decide which form it needs?
- Astrocytes produce estradiol, which inhibits microglia and decreases neuroinflammation.
- We need to start bioidentical hormone replacement therapy/BHRT earlier because estrogen receptors will then start to degenerate as the woman ages, which means older women who have not started BHRT may need larger doses initially because of receptor resistance.
- Too little estradiol may elicit no effect whereas too much could lead to cognitive dysfunction. You need to ascertain the sweet spot.
- Use variable dosing during a month's prescription of hormones to attempt to mimic a "normal menstrual cycle."

My recommendation: If you wish to practice integrative gynecology, study with this woman or entice her to start giving regular seminars!

We now find ourselves with Walter Crinnion again on the topic of the microbiome and neuroinflammation. Here again, an awesome amount of useful, clinical information. I will focus, though, on one line that he reframed from Kevin Costner's epic movie about baseball and life, *Field of Dreams*: If you feed them, they will come! I think it is possibly the simplest, most useful line I could ever use with patients.

My college basketball coach taught me that you could only get one point across in a time-out in the middle of a game. I think a similar attitude exists with our patients. We can't fill their heads with endless studies and information that either they don't care about or don't understand, but we can use one liners to get our points across that they will never forget and at the same time make Johnny Carson nod his head in approval!

Probiotic bacteria require food to thrive and survive. That food is cellulose, commonly called fiber. Where do we find it? Vegetables, fruits, nuts, beans, seeds, whole grain. I think we have our concept of superfoods mixed up. Locally grown, whole foods in their natural state are our real superfoods for numerous reasons but, here, they nurture and nourish the bacterial flora that will positively impact our health in multiple ways. Thanks, Walter, for giving me a line that I'll use with my patients until my dying day and hopefully into my next life!

Next up, Walter and Lyn brought in a heavy hitter from Greece, Artemis P. Simopoulos, MD. Her topic was "Intervention for Neuroinflammation: The Greek Mediterranean Diet." Dr. Simopoulos throws the whole idea of a "Mediterranean Diet" for a bit of a loop. First off, she had a wonderful picture of the 20 or so countries that actually line the Mediterranean Sea. Her point was that there are similarities between the diets of these various cultures but also significant differences that probably preclude one from scientifically pontificating on the value of the Mediterranean diet.

Being Greek, she focused on the extremely positive choices that Greeks, in particular, seem to be making dietarily, specifically on the Greek island of Crete. One was the omega-3:omega-6 ratio in the diet of various countries. Greece has the ratio closest to Paleolithic times (0.79), 1.00 – 2.00. Japan's ratio is 4.0 and, currently, the USA's is 16.74. She then had multiple slides touting the health effects of omega-3 fats to back up her superior Greek ratio.

One slide showed typical foods eaten by Cretans every day in the 1960s. They included omega-3 rich foods such as snails, fish,

herring, Greek eggs, Greek cheeses, and purslane. Purslane is a very interesting plant. Its omega-3 content is 8.5 mg/gram of plant material, which contains various omega-3 fats. The closest competitor to this amount is spinach at 1.6 mg/gram and mustard at 1.101 mg/gram. When I told my wife this, she said we have a purslane growing wild on our property. I think we're going to start including it in our spring salads! I also think we need to vacation in Crete for a month every Spring to consume their purslane!

Saturday was closed out by Joe Pizzorno, ND. His topic was "Toxins Have Become the Primary Drivers Of Disease." Dr. Pizzorno had just released his new book, *The Toxin Solution: How Hidden Poisons in the Air, Water, Food, and Products We Use Are Destroying Our Health – And What We Can Do to Fix It*. I highly recommend the book as I came away from the read with an immense amount of new information on what we're exposed to and how we can help ourselves and our patients avoid and deal with the environmental loading of our bodies with material that isn't very helpful to our various systems.

Dr. Pizzorno basically laid out, scientifically and in great graphic detail, the link between various chronic diseases, especially diabetes, and multiple environmental pollutants. He had a wonderful quote, "toxicity has become the new normal," on the side of a slide. He then proceeded to show on the rest of the slide the toxin, in what environmental chemical it is located, its use, its threshold for disease association, its percent of US use above the threshold, and disease associations for various common pollutants like BPA and arsenic. Extremely powerful information!

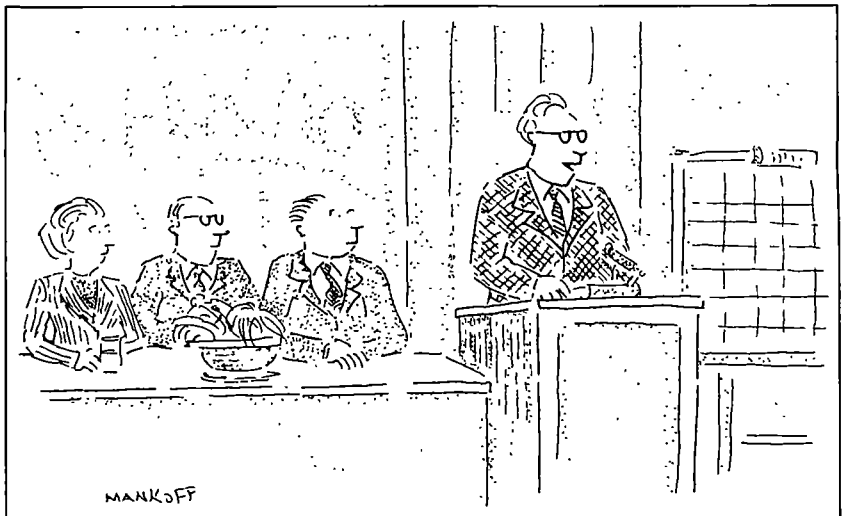
Next Dr. Pizzorno makes the powerful point that there is a huge detoxification variability in our clients because of their rather large genetic variability in their liver's ability to effectively eliminate these various pollutants in their Phase I and Phase II detoxification system. He also had a wonderful slide with various toxins' half lives in our blood and tissues. Finally, a slide contained the CDC's list of worst toxins. More importantly for us, he followed that slide up with a slide of the worst toxins clinically. This is real heady material, meticulously researched, and presented in an easy to understand and clinically useful format. Thanks, Joe!

The last person I will review is Tim Guilford, MD. Dr. Guilford's study of the role that glutathione plays in the basic mechanism of many diseases led him to perform some excellent research on glutathione and its role in the treatment of various chronic diseases. Many speakers touched on the role of glutathione in the effective elimination of the various pollutants, but Dr. Guilford appears to have raised the bar to an extremely high level in his research on how to clinically incorporate glutathione into your treatment protocol.

One of his slides was extremely interesting and talked about glutamate cysteine ligase/GCL. GCL catalyzes the rate-limiting step in the formation of the cellular antioxidant glutathione (GSH). The GCL holoenzyme consists of two separately coded proteins, a catalytic subunit (GCLC) and a modifier subunit (GCLM). Both GCLC and GLCM are controlled transcriptionally by a variety of cellular stimuli, including oxidative stress. Where it became very interesting was when Dr. Guilford stated that some autistics are missing the GLCM modifier, which would most definitely decrease their ability to make glutathione. He later stated that GCLC was blocked by mycotoxins, which would also decrease a person's ability to make glutathione when exposed to mycotoxins. This little bit of biochemical knowledge potentially sheds light on potential remedies for autism and persons beset with mycotoxins. This is potentially very useful information. Hopefully in the future, we'll find out how to positively intervene in GCLC and GCLM production, so we can foster positive glutathione production.

Finally, allow me a clinically observational aside. I really liked Dr. Guilford's information and sources. I found him leaving the seminar after the talk and approached him to ask a question. He had mentioned during the talk that he had been on a bit of a healing quest. He answered my question, but clinically he didn't look very well. Dr. Guilford, you're a tremendous asset to the profession. Hopefully, you successfully deal with whatever health issue is plaguing you!

So, to conclude, wonderful information but I think the real issue here is a slightly different elephant in the room. That elephant is corporate greed and corporate malfeasance. We, the integrative medical community, are the yin to the corporate yang. Without us, the public hears only one message of corporate innocence in the destruction of our environment and that corporate profits supersede environmental health. I feel it is our responsibility to not only treat our patients integratively but also to educate them about what is happening environmentally to our world and what they can do to help stop and reverse the negative corporate impact. Many people want to remain quiet and not rock the boat, but this strategy unfortunately allows corporate mentality unprecedented opportunities for profit without consideration of the unimagined environmental horrors that will result from their ill-considered economic adventures, as this political cartoon by Bob Mankoff so clearly illustrates.



"And so, while the end-of-the-world scenario will be rife with unimaginable horrors, we believe that the pre-end period will be filled with unprecedented opportunities for profit."

(Personal permission by the author of the political cartoon, Bob Mankoff)

Let me end, then, with a quote from one of the original truth tellers about our environmental destruction of the environment, Rachel Carson: "The human race is challenged more than ever to demonstrate our mastery, not over nature, but of ourselves!"

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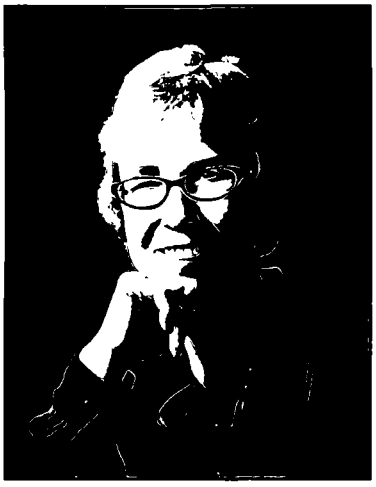

Shorts

briefed by Jule Klotter
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Autonomic Nervous System Imbalance and Diabetes

Back in 2005, a group of Swedish researchers reported a link between autonomic nervous system imbalance and insulin resistance. Insulin resistance precedes type 2 diabetes (T2D). The study, led by Stina Lindmark, investigated associations between visceral adipose tissue (VAT), the cortisol axis, the autonomic nervous system, and insulin resistance in humans. Thirty volunteers matched for age, sex, and body mass index (BMI) took part. Fifteen had first-degree relatives with type 2 diabetes, and 15 had no family history of diabetes.

Autonomic nervous system activity was assessed using heart rate variability. The researchers measured heart rate variability while the volunteers engaged in controlled breathing (12 breaths/min for 1 minute), rested in a tilted, 70-degree head-up position (4 minutes), and engaged in a cold pressor test (CPT) during which a lower arm was immersed in ice-cold water (2 minutes): "Controlled breathing stimulates parasympathetic nerve activity, whereas tilting and CPT stimulate sympathetic nerve activity." Additional tests included oral glucose tolerance test, low-dose tetracosactin stimulation test, corticotropin releasing hormone stimulation test, oral dexamethasone suppression test, and diurnal salivary and urinary cortisol testing as well as anthropometric measures. In addition, the researchers used the euglycemic hyperinsulinemic clamp technique to measure insulin resistance. Volunteers with diabetes in their family histories exhibited less insulin sensitivity than the healthy controls, but the difference was not statistically significant (9.2 ± 1 vs. 10.3 ± 0.7 mg/kg per minute).

Lindmark et al reported a significant association between visceral fat, high sympathetic/parasympathetic ratio, and insulin resistance. The authors commented that "...the demonstrated association between the balance of sympathetic vs. parasympathetic nervous activity and VAT can suggest that a large amount of visceral fat may activate the sympathetic and/or inactivate the parasympathetic nervous system." But they said it was also possible that autonomic dysregulation might instigate visceral fat accumulation and, thereby, promote insulin resistance. Adrenocortical function did not appear to be part of the visceral fat, autonomic nervous system, and insulin resistance association.

Ten years later, another Swedish study, led by Maria K. Svensson, provided more evidence that dominant sympathetic activity is linked to insulin resistance. This time, the researchers used 24-hour ECG monitoring as well as short-term testing during controlled breathing, tilt, and cold pressor test. They estimated abdominal adipose tissue with computed tomography and insulin resistance with the euglycemic hyperinsulinemic clamp technique. The study involved 47 healthy, non-diabetic volunteers, 23 of whom had a family history of diabetes.

Svensson et al found significant positive associations between insulin resistance, BMI, abdominal fat, and sympathetic-parasympathetic ratios from both the short-term and the 24-hour heart rate variability assessments. The 24-hour assessment showed a greater difference in heart rate variability between the controls and those with diabetes in their histories. The researchers suggest that exercise and other personal lifestyle factors may be responsible for this difference. (I don't know if they asked volunteers to record their activities during 24-hour monitoring.) ECG monitoring also showed significantly lower very low frequency power in those with a family history of diabetes, "indicating that reduced vagal activation potentially could be an early component in the development of T2D." The vagus nerve is responsible for parasympathetic control over body organs, including the heart. The authors conclude: "...the present study shows that indices of heart rate variability during everyday life are associated with insulin sensitivity, and it suggests that a higher ratio of sympathetic to parasympathetic autonomic nerve activity promotes insulin resistance."

Low heart rate variability, which indicates autonomic nervous system imbalance, was significantly associated with metabolic syndrome, according to a 2015 study that used data from the offspring cohort (n=1143) of the Framingham Heart Study. Metabolic syndrome consists of multiple risk factors,

including insulin resistance, that precede the development of metabolic disorders such as diabetes and coronary heart disease. The researchers looked at multiple risk factors associated with metabolic syndrome and found that low heart rate variability, high resting heart rate, increased age, cigarette smoking, and being male were the significant risk factors for developing metabolic syndrome: "...in terms of the risk of developing metabolic syndrome within 12 years of baseline, one standard deviation decrease in HRV (SDNN) is equal to an additional 16 years in age or nearly one pack of cigarettes per day."

We do not yet know whether autonomic imbalance causes insulin resistance and metabolic syndrome or is simply the result. The Framingham study researchers point out that exercise, biofeedback, relaxation training, β-blockers, and SSRIs are known to moderate heart rate variability and resting heart rate. (Controlled breathing practices may also help.) They suggest investigating the effect of these interventions on autonomic imbalance in clinical studies with patients at risk for developing diabetes, heart disease, and other conditions associated with metabolic syndrome.

Lindmark S, et al. Dyregulation of the Autonomic Nervous System Can Be a Link between Visceral Adiposity and Insulin Resistance. *Obesity Research.* April 2005;13(4): 717-728

Svensson MK, et al Alterations in heart rate variability during everyday life are linked to insulin resistance. A role of dominating sympathetic over parasympathetic nerve activity? *Cardiovasc Diabetol.* 2016; 15.91

Wulsin LR, et al. The Contribution of Autonomic Imbalance to the Development of Metabolic Syndrome. *Psychosomatic Medicine* 2015

Artificial Sweeteners, Gut Microbiota, and Glucose Intolerance

Non-caloric artificial sweeteners (NAS) promote glucose intolerance by changing the composition of gut bacteria, according to a 2014 *Nature* article by Jotham Suez and colleagues. Commensal gut bacteria are known to produce biochemicals that regulate all aspects of physiology, including metabolic processes and weight. These sweeteners are widely used in sugar-free processed foods and drinks—the same foods recommended to people with diabetes and obesity.

In the first of a series of animal and human experiments, Israeli researchers added commercial formulations of saccharin, sucralose, or aspartame to the drinking water of lean 10-week-old mice. After one week, the three NAS mouse groups exhibited glucose intolerance while the control groups that consumed plain water, water with glucose, or water with sucrose displayed similar glucose tolerance curves ($P<0.001$). Saccharin showed the greatest effect, so the researchers decided to use it in further studies.

Since artificial sweeteners are largely undigested and come into direct contact with gut microbes, the researchers decided to test whether a change in the microbiota accounted for the development of glucose intolerance. They fed two groups of mice normal chow and gave them water with commercial saccharin or water with glucose to drink. They then transplanted fecal microbiota from the two groups to germ-free mice: "Notably, recipients of microbiota from mice consuming commercial saccharin exhibited impaired glucose tolerance as compared to control (glucose) microbiota recipients, determined 6 days following transfer ($p<0.03$)." Microbiota from saccharin-consuming mice showed dysbiosis with significant increases in the *Bacteroides* genus and decrease in *Lactobacillus reuteri.*

Suez and colleagues also looked at non-caloric artificial sweetener consumption in humans. In one study, they used data from an ongoing clinical nutritional study involving 381 non-diabetic volunteers (44% males and 56% females; age 43.3 ± 13.2). The researchers found correlations between NAS consumption and obesity, higher fasting blood glucose, and elevated serum alanine aminotransferase (ALT, a measure of liver damage). "Moreover, the levels of glycosylated haemoglobin indicative of glucose concentration over the previous 3 months, were significantly increased when comparing a subgroup of high NAS consumers (40 individuals) to non-NAS consumers (236 individuals)," write the authors.

Suez et al also asked seven healthy volunteers who did not normally use NAS or NAS-containing foods to consume commercial saccharin for one week, using the FDA's guideline for maximal acceptable daily intake (5 mg/kg body weight). Four out of seven developed poorer glycemic response after five to seven days of saccharin consumption. Interestingly, the microbiota composition in the NAS-responders noticeably differed from the non-responders before and after saccharin consumption. The artificial sweetener had little observable effect on the microbiome of the three non-responders.

Suez and colleagues took stool samples from two NAS responders and two non-responders, before and after NAS consumption, and transplanted the samples into groups of germ-free mice. Post-NAS stool from the responders "induced significant glucose intolerance" in the mice compared to stool from the same responders taken at baseline.

The authors conclude, "Our findings suggest that NAS may have directly contributed to enhancing the exact epidemic that they themselves were intended to fight. Moreover, our results point towards the need to develop new nutritional strategies tailored to the individual while integrating personalized ➤

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differences in the composition and function of the gut microbiota."

Suez J, et al Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 2014

Plasma Manganese Levels and Type 2 Diabetes

Low and high blood levels of manganese are associated with type 2 diabetes (T2D), according to a 2016 study. Manganese (Mn) at excessive levels is toxic, but micro levels are a necessity. Manganese is required for normal immune function, blood glucose regulation, bone growth, cellular energy, and for production of the antioxidant manganese superoxide dismutase (MnSOD), which protects the mitochondria from reactive oxygen species (ROS).

The 2016 study, led by Zhilei Shan, involved 1614 newly diagnosed, drug-naïve Chinese Han patients with type 2 diabetes (T2D) and 1614 controls with normal glucose tolerance. The researchers looked for associations between plasma manganese (categorized in tertiles), polymorphisms in the MnSOD gene, and glucose tolerance. The median plasma manganese concentration for the people with diabetes was 4.37 µg/L (2.73-7.62), compared to 5.26 µg/L (3.67-8.33) for the control group.

The researchers report, "Compared with the middle tertile, the multivariate-adjusted [odds ratios] of T2D associated with the lowest tertile and the highest tertile of plasma manganese were 1.89...and 1.56 respectively." The Mn-diabetes association was stronger in people age 55 or older than in those under 55. The odds ratio of Mn-diabetes association was also affected by physical activity. People in the lowest Mn tertile who reported "no or rare" physical activity had greater odds of having diabetes than those who were physically active (1.97 vs. 1.56). Yet, in the highest Mn tertile, the opposite was true; those who reported little physical activity had an OR of 1.37 compared to 2.11 for those who were active. The researchers found the U-shaped Mn-diabetes association in all tested genotypes.

The authors point out that this case control study design cannot show whether insulin resistance and T2D affect manganese levels or manganese levels affect insulin resistance. They also say that plasma manganese may not be the best way to assess manganese status.

Corn and wheat and other cereal grains are among the food sources for manganese; yet, these foods are also the ones most likely to be exposed to glyphosate, the active ingredient in Roundup® herbicide. Glyphosate depletes Mn levels in plants, which means less manganese for animals and humans who rely on the plants for food, according to Samsel and Seneff.

Shan Z, et al U-Shaped Association between Plasma Manganese Levels and Type 2 diabetes *Environ Health Perspect* December 2016,124(12).1876-1881

Samsel A, Seneff S. glyphosate, pathways to modern diseases III: Manganese, neurological diseases, and associated pathologies *Surg Neurol Int* 2015;6.45.

Persistent Organic Pollutants and Liver Fibrosis

Environmental persistent organic pollutants (POPs), which have a long half-life and accumulate in adipose tissue and the liver, contribute to inflammation that leads to liver fibrosis in animals. In their 2017 study, French researchers exposed mice to TCDD, a POP that strongly activates the aryl hydrocarbon receptor (AhR). AhR activates enzymes that take part in the elimination of xenobiotics. It also affects lipid metabolism and has a role in the development of hepatic steatosis. Other sources of environmental AhR ligands include polychlorinated biphenyls, cigarette smoke, and diesel particles.

For their TCDD study, Caroline Duval and colleagues used two weight-matched groups of mice (n=30). One group was fed a high-fat diet (45% energy from fat) and the other ate a low-fat diet (10% energy from fat) for 14 weeks. During the last six weeks, mice from each group were injected with 5 µg/kg TCDD in corn oil (n=16) or the corn oil vehicle (n=14) once a week. The TCDD dosage was calculated to create a final blood concentration below 70 ppt, higher than that found in the general population but lower than the amounts measured in people near the Seveso industrial accident and in US Vietnam veterans (Ranch Hand cohort) exposed to Agent Orange.

TCDD exposure produced inflammation in all exposed mice. In the low-fat group, the controls injected with corn oil had normal liver histology with no sign of inflammation; but those injected with TCDD developed steatosis "with infiltration of inflammatory cells grouped in islets." Although the high-fat diet, as expected, produced steatosis, the vehicle-control mice in this group had no sign of inflammation. Exposure to TCDD, however, produced evidence of inflammation and "dramatically worsened the steatosis."

Although this study looks at the effect of just one POP on the liver of just one species, it opens the possibility that these pollutants may be contributing to the increased incidence of liver disease in humans.

Duval C, et al Chronic Exposure to Low Doses of Dioxin Promotes Liver Fibrosis Development in the C57BL/6J Diet-Induced Obesity Mouse Model. *Environ Health Perspect*. March 2017;125(3):428-436

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Literature Review & Commentary

by Alan R. Gaby, MD
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Selenium for Recurrent Hyperthyroidism

Forty-one patients with recurrent Graves' disease who had been receiving antithyroid medication (methimazole) for at least two years were randomly assigned to receive selenium (100 µg twice a day as sodium selenite) or no selenium (controls) for six months. Patients treated with radioactive iodine or thyroidectomy were excluded. At two months, mean values for free thyroxine and free triiodothyronine had decreased to a significantly greater extent, and the mean TSH value had increased to a significantly greater extent, in the selenium group than in the control group. At six months, the proportion of patients who had normal anti-TSH-receptor antibody levels was significantly higher in the selenium group than in the control group (19% vs. 0%; $p < 0.02$). During a median follow-up period of 19.5 months, the remission rate was higher in the selenium group than in the control group (52% vs. 25%; $p = 0.07$).

Comment: Selenium has been reported to have a number of different beneficial effects on thyroid disease. In some, but not all studies, selenium supplementation decreased anti-thyroid peroxidase antibody levels in patients with autoimmune thyroiditis. In addition, selenium supplementation improved quality of life, reduced ocular involvement (orbitopathy), and slowed disease progression in euthyroid patients with mild Graves' orbitopathy (Marcocci C, et al. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med.* 2011;364:1920-1931.) In the present study, selenium supplementation enhanced the effect of antithyroid drugs in patients with recurrent Graves' disease.

Wang L, et al. Effect of selenium supplementation on recurrent hyperthyroidism caused by Graves' disease. a prospective pilot study. *Horm Metab Res.* 2016;48:559-564.

N-Acetylcysteine for Obsessive-Compulsive Disorder

Forty-four patients (mean age, 33 years) with moderate-to-severe obsessive-compulsive disorder (OCD) were treated with 200 mg per day of fluvoxamine and were randomly assigned to receive, in double-blind fashion, 2,000 mg per day of N-acetylcysteine (NAC) or placebo for 10 weeks. Compared with placebo, NAC significantly improved the mean total score on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) ($p = 0.012$) and the mean score on the Y-BOCS obsession subscale ($p = 0.011$).

Comment: Hyperactivity of glutamatergic neurotransmission has been implicated in the pathogenesis of OCD. NAC is believed to reduce glutamatergic activity. In previous case reports and double-blind trials, NAC was beneficial in the treatment of OCD, including patients with trichotillomania (hair-pulling disorder). The results of the present study demonstrate that NAC is beneficial as an adjunct to fluvoxamine in the treatment of moderate-to-severe OCD.

Paydary K, et al. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther.* 2016;41.214-219.

Vitamin D for Autistic Children

One hundred nine Egyptian children (aged 3-10 years) with autism spectrum disorder were randomly assigned to receive, in double-blind fashion, vitamin D_3 (300 IU per kg of body weight per day, with a maximum of 5,000 IU per day) or placebo for four months. Autism severity and social maturity were assessed by the Childhood Autism Rating Scale, Aberrant Behavior Checklist, Social Responsiveness Scale,

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and Autism Treatment Evaluation Checklist. The mean serum 25-hydroxyvitamin D level prior to treatment was 27 ng/ml. Compared with placebo, vitamin D significantly improved symptoms of autism, including irritability, hyperactivity, social withdrawal, inappropriate speech, stereotypical behavior, and communication. No significant side effects occurred.

Comment: In this study, vitamin D supplementation improved symptoms of autism in Egyptian children. Prior to vitamin D supplementation, the mean serum 25-hydroxyvitamin D level was 27 ng/ml. The appropriate 25-hydroxyvitamin D cut-off level for diagnosing vitamin D deficiency, and the reliability of serum 25-hydroxyvitamin D as an indicator of vitamin D status remain controversial. However, it appears that it is not necessary for autistic children to have severe vitamin D deficiency in order for them to benefit from vitamin D supplementation. Further research is needed to confirm the safety and efficacy of the relatively large dose of vitamin D used in this study.

Saad K, et al. Randomized controlled trial of vitamin D supplementation in children with autism spectrum disorder. *J Child Psychol Psychiatry*. 2016 Nov 21 [Epub ahead of print].

Mediterranean Diet Improves Sexual Function in People with Type 2 Diabetes

Two hundred fifteen men and women (mean age, 52 years) with newly diagnosed type 2 diabetes were randomly assigned to consume a Mediterranean diet or a low-fat diet. The primary outcome measures were changes of erectile function according to the International Index of Erectile Function (IIEF) in men, and changes in female sexual function according to the Female Sexual Function Index (FSFI) in women. During a total follow-up of 8.1 years, sexual function decreased slightly in both sexes with both diets. The mean decline in the IIEF score was significantly less by 1.22 points ($p = 0.024$) and the mean decline in the FSFI score was significantly less by 1.18 points ($p < 0.02$) with the Mediterranean diet than with the low-fat diet.

Comment: The "Mediterranean diet" refers to the diet of olive-growing regions of the Mediterranean. In addition to olive oil, the diet emphasizes salads, legumes, wheat, fruit, nuts, and garlic. In Italy, a lot of pasta is consumed; whereas in Spain, fish consumption is high. Fat intake is around 30-40% of total energy. The results of the present study suggest that consumption of a Mediterranean diet can decrease the deterioration of sexual function in both men and women with newly diagnosed type 2 diabetes. While the mechanism of action is not certain, a Mediterranean diet may help preserve sexual function by improving cardiovascular function and overall health.

Maiorino MI, et al. Effects of Mediterranean diet on sexual function in people with newly diagnosed type 2 diabetes: The MEDITA trial. *J Diabetes Complications*. 2016;30:1519-1524.

Mediterranean Diet for Fracture Prevention?

The association between consumption of a Mediterranean diet and incidence of hip fracture was examined in two Swedish cohort studies consisting of 37,903 men and 33,403 women who were free of cardiovascular disease and cancer and who answered a food-frequency questionnaire in 1997. A modified Mediterranean diet score (mMED; range, 0-8 points) was created based on high consumption of fruits and vegetables, legumes and nuts, whole grains, fermented dairy products, fish, and olive/rapeseed oil; moderate intake of alcohol; and low intake of red and processed meat. During a 15-year follow-up period, 3,175 hip fractures occurred at a median age of 73.3 years. A 1-unit increase in the mMED score was associated with a 6% lower hip fracture rate (adjusted hazard ratio = 0.94; 95% confidence interval [CI], 0.92-0.96). Comparing the highest quintile of adherence to the mMED (6-8 points) with the lowest quintile (0-2 points), the adjusted hazard ratio of hip fracture was 0.78 (95% CI, 0.69-0.89), indicating a 22% reduction in fracture incidence. Results were similar in men and women.

Comment: Although observational studies cannot prove causation, this study raises the possibility that adherence to a Mediterranean diet can decrease the risk of hip fracture in both men and women. Mediterranean diets contain abundant amounts of micronutrients that play a role in promoting bone health, including magnesium, B vitamins, boron, and vitamin K.

Byberg L, et al. Mediterranean diet and hip fracture in Swedish men and women. *J Bone Miner Res*. 2016;31:2098-2105.

Whole Grains, Heart Disease, Cancer, and Mortality

A meta-analysis was conducted on 14 prospective cohort studies (including a total of 786,076 participants) that examined the association between intake of whole grains and mortality from all causes, cardiovascular disease, and cancer. Pooled relative risks comparing the highest and lowest categories of whole grain intake were 0.84 ($p < 0.001$) for total mortality, 0.82 ($p < 0.001$) for cardiovascular disease mortality, and 0.88 ($p < 0.001$) for cancer mortality. For each 16-g per day increase in intake of whole grains (about 1 serving per day), relative risks for total, cardiovascular disease, and cancer mortality were 0.93 ($p < 0.001$), 0.91 ($p < 0.001$), and 0.95 ($p < 0.001$), respectively.

Comment: This meta-analysis of observational studies found that increasing intake of whole grains was associated with lower overall mortality and a lower incidence of death from cardiovascular disease and cancer. Substances present in whole grains that might decrease the risk of heart disease, cancer, or both, include fiber, magnesium, vitamin E (mixed tocopherols), betaine, and B vitamins. A substantial proportion of each of these substances is lost when whole grains are refined to white flour.

Zong G, et al. Whole grain intake and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis of prospective cohort studies. *Circulation*. 2016, 133:2370-2380

Melatonin for Premedication Prior to Anesthesia

Ninety-two children (aged 5-14 years) scheduled for elective surgery were randomly assigned to receive, in double-blind fashion, premedication with oral melatonin (0.5 mg per kg) or oral midazolam (0.5 mg per kg), 40 minutes

before induction of anesthesia with propofol. Compared with midazolam, melatonin significantly decreased the dose of propofol required to induce anesthesia. No significant difference was found between groups with respect to pre- and post-anesthesia sedation, which suggests that melatonin is as effective as midazolam.

Comment: Midazolam is widely used prior to induction of anesthesia in both adults and children. Midazolam has a number of side effects including paradoxical reactions, interactions with opioids, variable bioavailability and elimination half-life, excessive sedation, disorientation, impaired psychomotor performance, and amnesia. Melatonin is recognized as an effective alternative to midazolam in adults, but data regarding its use in children are conflicting. The results of the present study demonstrate that premedication with melatonin can increase the potency of propofol, and that melatonin is an effective alternative to midazolam in children undergoing elective surgery. Use of melatonin as premedication instead of midazolam could decrease the number of adverse reactions in patients undergoing anesthesia.

Gitto E, et al. Melatonin versus midazolam premedication in children undergoing surgery: A pilot study. *J Paediatr Child Health*. 2016,52:291-295.

Vitamins B_6 and B_{12} Decrease the Concentration of *Unmetabolized Folic Acid*

Fifty-eight elderly individuals (mean age, 82 years) were randomly assigned to receive, in single-blind fashion, 400 µg per day of folic acid or folic acid plus 8 mg per day of pyridoxine and 10 µg per day of vitamin B_{12} for a median duration of 23 days. After supplementation, the median concentration of unmetabolized folic acid was significantly lower by 72% in the group receiving all three B vitamins than in those receiving folic acid alone (0.17 vs. 0.61 nmol/L; p = 0.001). The proportion of individuals who had an unmetabolized folic acid concentration of 0.21 nmol/L or greater was lower in the group receiving all three B vitamins than in those receiving folic acid alone (33% vs. 76%; p value not stated).

Comment: Unmetabolized folic acid is frequently present in the serum of people taking folic acid supplements and in elderly people receiving folic acid-fortified foods or supplements. Concerns have been raised that unmetabolized folic acid could have deleterious effects on health. However, there is as yet no convincing evidence that unmetabolized folic acid is harmful. The results of the present study suggest that the metabolism of folic acid depends on the presence of adequate amounts of other B vitamins. The clinical significance of these findings remains to be determined.

Obeid R, et al. Folic acid causes higher prevalence of detectable unmetabolized folic acid in serum than B-complex a randomized trial. *Eur J Nutr* 2016;55 1021-1028

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The Specific Carbohydrate Diet: Transforming Primary Care for Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS)

by Christine Bowen, ND

I begged the convenience store clerk to please let me use his bathroom, but he refused. I pleaded and was crying and repeated what the result would be if I couldn't use a bathroom immediately; he still said no and that is when the dam cut loose and diarrhea leaked out of my pant leg and onto his floor. I left feeling humiliated and ashamed. This was definitely a low point in my health. How could I be an otherwise healthy 26-year-old woman and yet I had this horrible condition that plagued me night and day creating endless hours of pain, missed social engagements, and this ultimate episode of mortifying proportions.

Here I was a newly practicing naturopathic doctor (ND) with all of the inspiration to help others but completely unable to help myself. As you can imagine, I had tried every allergy elimination diet, probiotic, digestive enzyme, and intestinal healing product available. I even quit my job to reduce stress, all with no positive impact in my symptoms.

Then, one day I got a random email from a former patient of a colleague asking me if I was familiar with the Specific Carbohydrate Diet. She was thinking that I should definitely know about this diet therapy that had driven her ulcerative colitis into remission 10 years prior. I hadn't heard about the Specific Carbohydrate Diet (SCD) but decided to dedicate some time and personal experience to learning the details in order to teach my patients (still holding no hope that it would do anything for me, personally). Three days into following SCD, I was symptom free for the first time since I was in my teens.

I learned SCD inside and out and never looked back. SCD removes lactose, sugar, grains, and starch from the diet. Patients who are in flare may have to modify the texture of their foods or reduce fiber to help assist healing. SCD includes some aged dairy and butter and emphasizes nutrient-dense foods such as honey (only approved and healthful sweetener allowed on this diet), nuts, seeds, protein, fruit, and vegetables. If the patient is underweight, it is important to ensure they are consuming more than adequate calories of allowed foods to make up for the calories lost from reducing starchy carbohydrates.

The theory behind this dietary approach is that by removing these foods from the diet that we shift the microbiome of the gut away from pro-inflammatory changes and toward a balanced immune system. Healthy microbial flora also helps with nutrient absorption and decreases overgrowth of unhelpful or opportunistic microbes.

SCD has been around since the 1920s, but I had not heard it mentioned in medical school – not in any of the three quarters of diet and nutrient therapy nor in any of our gastroenterology classes. Because it had helped me so profoundly, I made it my mission to use this diet therapy as first line intervention for all digestive conditions. No more probiotics, fiber, Imodium, or digestive enzymes, just diet change applied with an equal dose of compassion and knowledge and tailored to suit the needs of the patients I was seeing.

Since 2008, I have honed and refined this approach that has helped my patients with anything from autoimmunity, chronic pain, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), obesity, diabetes, mood imbalance and autism spectrum (sometimes a combination of several or all of the above). I have found that at least 80% of patients who follow a customized plan based on this dietary approach will have significant or complete symptom resolution. People have gotten off of meds, gained weight (when needed), lost weight (when needed), avoided colectomies, and regained their health and their lives after suffering for as long as 40 years prior to making this dietary change.

Despite the fact that many local gastroenterology (GI) specialists still held strongly that diet had nothing to do with these health conditions, I was reminded daily of the power of diet to transform the health of my patients with this simple, reproducible,

and powerful therapy. Now, patients who fail traditional prescription therapies (or refuse them for fear of side effects) can have hope for a much better solution than just medication or surgery. In addition to this, GI docs and other practitioners have a safe treatment approach for their patients, especially those who ask for alternative suggestions.

One of my main goals is to educate practitioners about SCD so that more patients can be helped with this foundational approach. The Specific Carbohydrate Diet was originally created in 1924 by a US pediatrician named Sydney Valentine Haas (1870-1964). He used this diet (affectionately known as the banana diet) to help children with failure to thrive, protein malnutrition associated with celiac disease, and inflammatory bowel disease. He and his son, Merrill Hass, published a book in 1951 on their dietary approach and associated case studies that was titled *The Management of Celiac Disease*.[1] One of their more than 600 patients was the daughter of a remarkable woman. This patient's mother, Elaine Gottschall, was so inspired by how much they helped her daughter that she published a book in 1987, *Breaking the Vicious Cycle: Intestinal Health Through Diet*,[2] which outlines the diet and provides guidelines and recipes. This book was and still is at the center of what grew to be a movement of patients and families helping themselves and each other to navigate diet change for management of celiac disease, IBS, IBD, and many more health conditions.

In 2014, at Children's Hospital in Seattle, Washington, Dr. David Suskind gathered several known SCD-focused providers and national SCD specialists, including myself, to discuss potential clinical application and standardization of SCD and announced that he would be publishing his first SCD retrospective study. Also in attendance were Barbara Olendzki, RD, MPH, from the University of Massachusetts Medical Center who presented the first paper cited below, and Stan Cohen, MD, who presented the paper on capsule endoscopy and SCD.

In 2014, the University of Massachusetts Medical Center conducted a study on SCD for patients with IBD.[3] They included oats and fish oil in addition to the strict SCD food list and the findings reported 100% symptom improvement in all of the study participants!!! 100%!

A pilot study from 2014 was done by Rush Medical Center.[4] It showed results of capsule endoscopies for four patients with IBD and noted bowel ulcerations of these patients at day zero and then the capsule endoscopy was repeated at the end of 12 weeks on the Specific Carbohydrate Diet. The comparisons of ulcerations at day zero and 12 weeks later showed resolution of the vast majority of these lesions and overall patient improvement across the board.

Children's Hospital publications to date: The first was a small retrospective

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study of seven children with IBD; the analysis of their health parameters over a period of time while on SCD led to the conclusion that it might be a viable treatment and would warrant another, larger SCD study which was published roughly a year later.[5] The second study was another retrospective study analyzing 26 pediatric patients with IBD who were on SCD.[6] Their labs and IBD symptoms scores were positively affected by being on SCD for 3-48 months. Across the board, patients responded favorably, and children were nourished and grew. SCD became a staple part of their treatment paradigm.

My approach is fairly standard in comparison to what is outlined in *Breaking the Vicious Cycle* but has been modified to include an introductory diet and stages of how to add more foods as the patient heals. I follow much of the information on the stages of SCD from www.pecanbread.com and gradually add foods with more texture and fiber as the patient heals and as they tolerate. The starting point is protein, broth, homemade jello, and completely overcooked (cook for four hours) and destroyed carrots. The introductory diet should be followed for no more than five days before introducing foods from stage I.

When one of my patients with IBD embarks on this diet change, I find it important to get baseline laboratory testing to establish a starting point for symptoms as well as lab work. I order a blood and stool panel, including fecal calprotectin, CMP, CBC, ESR, and CRP and patients' vitals (especially weight, BP and pulse) as baseline tests so we will have a point of comparison over the next months or years to assess progress and ensure their nutrient status and inflammatory markers are in good range. By staying on top of testing, an imminent flare may be detected and thwarted by using the intro diet as needed.

Empirical evidence and patient testimonials since the era of Dr. Sydney Hass and, later, the popularization of SCD by Elaine Gottschall weren't enough to push this therapy to the front lines of standard digestive health treatments, but some few open-minded physicians and researchers were listening and couldn't deny the stories of so many patients helped by this diet. Their collective action of testing and publishing their findings lends legitimacy to this approach in the eyes of conventional medical providers. SCD has now become integral in care of patients with IBD at a few select clinics in the United States, and I look forward to the day when it is accepted as first-line therapy for IBD around the world. If you are planning on helping your patients follow this diet, my strongest suggestion is that you do your homework or, better yet, eat this way for a period of time so you can identify the pros, cons, and troubleshooting solutions that your patients will be expecting of you.

This dietary approach is very manageable with the support of recipe resources, medical guidance, and creativity. Batch cooking makes for fewer hours spent preparing food each week. One of the largest obstacles to finding success in this diet is breaking the addiction to bread and sugar. While the diet may expand to include sweet potatoes or rice once the patient has been in remission for months, it doesn't ever really encourage these patients to return to eating the Standard American Diet.

So, it may have taken nearly 100 years, but now the medical community is starting to rediscover that food plays a vital role in digestive health and healing.

Essential SCD resources:

- **Books**: *Breaking the Vicious Cycle* by Elaine Gottschall; *Recipes for the Specific Carbohydrate Diet* by Raman Prasad
- **Websites**: www.pecanbread.com, www.btvc.com
- **Shopping**: Lucy's Kitchen Shop, Digestive Wellness, Wellbee, US Wellness Meats, Liberated Specialty Foods.

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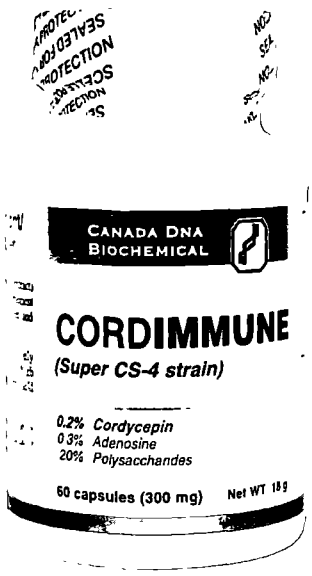

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Gut-Brain Communication: Major Mechanisms in Mental-Emotional Health and Disease

by Steven Sandberg-Lewis, ND, DHANP

> I strongly feel that it is the engagement of the gut and its microbiome that plays a major role in determining the intensity, duration, and uniqueness of our emotional feelings.
>
> Emeran A Mayer, MD, PhD
> Director, Oppenheimer Center for Neurobiology of Stress
> Professor, Medicine, Physiology & Psychiatry, UCLA School of Medicine

This article will review the gut-brain axis via the vagus nerve and microbial metabolic products including endotoxin and short-chain fatty acids, hormones, neuropeptides, and adipokines. Two-way communication between the gut brain (enteric nervous system or ENS) and the central nervous system (CNS) is a continuous process which optimizes functioning in both systems. In addition, the gut microbiota can be thought of as a distinct organ, which initiates and modifies much of this cross talk. The gut microbiota includes oral, esophageal, gastric, small intestinal, and colonic flora. The microbiome (genome of the gut flora) consists of about four million genes.

The term *holobiome* is defined as the sum of the approximately 26,000 human and the resident microbial genes. Clearly, humans are getting a free ride by relying on the gut flora to modify our genetic functions. In fact, there are over 100 microbial genes for every one human gene. The metabolome - the sum of metabolic products produced by the microbiome – comprises close to half of the total metabolites in human blood. Leo Galland, MD puts it succinctly in his 2014 review article: "The gut microbiome can be viewed as an anaerobic bioreactor programmed to synthesize molecules which direct the mammalian immune system, modify the mammalian epigenome and regulate host metabolism" (Galland, 2014). The gut microbiome is essential for the maturation and development of the enteric nervous system. These effects include both density and proper activity of the enteric neurons.

Cross talk between the gut and brain occurs through the vagus nerve, the metabolome, and cytokines. The autonomic nervous system is the major anatomical connection between the enteric nervous system (ENS) and the central nervous system (CNS). The vast majority (90%) of the impulses are sensory from ENS to CNS. The shape and consistency of the bolus as well as the pressure of the bolus against the gut mucosa is transmitted through the vagus nerve. Additional information about food composition, levels of inflammation, and quality of the microbiota is transmitted. This feedback helps to fine-tune eating behavior, mood, blood glucose, digestive secretion, absorption, and gut motility via the production of serotonin and other neuropeptides by enteroendocrine cells (EECs). Taste receptors throughout the length of the gut respond to food and stimulate production of various neuropeptides that have local and distant effects. These receptors are located on EECs and dendritic cells scattered throughout the mucosa. For example, the stimulation of bitter receptors triggers release of ghrelin, which upregulates appetite when it reaches the CNS. Mechanoreceptors are stimulated by shearing forces as the bolus moves through the gut and stimulate the EECs to release serotonin, which modifies both vagal and ENS function. As Emeran Mayer, MD, states: "the gut is the NSA... the vagus nerve is the information highway for gut-brain traffic." The ENS optimizes motility, secretion, and mucosal blood flow as well as detecting toxins and irritants.

Microbial Lipopolysaccharides, Cytokines, and Inflammation

Remarkably, forty percent of the circulating metabolites in human blood are microbiota derived. Gut microbial metabolites, such as lipopolysaccharide (LPS or endotoxin), have major effects on vagal input to the CNS with wide-ranging effects on mood, cognition, intestinal permeability, and inflammation (Grigoleit, 2011). Lipopolysaccharide is a component of the outer membrane of gram negative bacterial cell walls. There are one million copies of LPS in each gram-negative microbe (Quig, 2016), and these are released from both growing and dead bacteria (Guerville, 2016). Release may also be triggered by antibiotic therapy. Adults have approximately one gram of total gut LPS (Erridge, 2007) (Bested,

2013). Locally, LPS is a significant stimulus of the zonulin pathway, which induces hyperpermeability. When absorbed into the portal vein, LPS has major effects on the liver; and, when excessive, LPS serum levels rise and have far reaching effects. LPS and inflammatory cytokines in serum can upregulate TNF alpha, IL-1B, and IL-6 in the brain (Quig, 2016). Clearly, intestinal bacteria do not need to cross the blood brain barrier in order to influence the CNS.

Not all bacterial LPS is the same. For example, Enterobacter-derived LPS may be 1000 times more potent than LPS derived from other gram negative bacteria (Mayer, 2016). The microbial balance affects body habitus, and obesity multiplies the volume of LPS. These levels may be two to three times higher in the obese population compared to lean individuals. LPS binding protein can be measured in serum and is considered a useful inflammatory marker.

How LPS is Metabolized

In the neonate, LPS is bound and inactivated by a bacterial pattern recognition receptor CD14 found in human breast milk. CD14 is not detectable in commercial cow's milk or infant formula but is found in bovine colostrum. Lactoferrin in breast milk also binds to LPS (Guerville, 2016). After weaning, LPS binds to Toll-like receptor 4 (TLR-4) on intestinal epithelial cells. In addition, endosomal SIgA inactivates LPS, thereby reducing the NF-KB pathway and its cascade of proinflammatory cytokines: interferon, IL-6, TNF alpha (Boullier, 2009) (Fernandez, 2003). Mucins (from goblet cells) and antimicrobial peptides such as defensins (from Paneth cells) act on gram negative bacteria and, therefore, reduce exposure of intestinal epithelia to LPS. Defensins also alter the structure of developing bacterial cell walls to weaken the gram-negative microbes (Sass, 2010).

Intestinal alkaline phosphatase is a brush border enzyme secreted into blood and the intestinal lumen. It regulates lipid absorption, duodenal pH, and removal of LPS. Also, produced in the liver, phosphatase helps reduce LPS arriving via the portal vein. When LPS from gut bacteria is absorbed into the bloodstream at slightly higher levels, the alkaline phosphatase mechanism may not be adequate, and serum levels of LPS rise. The ensuing inflammatory cascade has emotional and cognitive effects. These effects may include anxiety, depression, and cognitive effects as well as visceral hypersensitivity (Grigoleit, 2011).

In addition to this LPS effect, adipose tissue in obese humans contains a tenfold increase in macrophages – 50% vs 5%. Increased systemic inflammation can trigger CNS inflammation by activating microglia (Hannestad, 2012). When CNS inflammation is initiated, it is difficult to turn off (Fenn, 2014). Inflamm-ageing is a term for the chronic inflammatory state affecting many tissues including the brain (Franceschi, 2000).

The ENS, Microbiome, and Neurotransmitter Synthesis

Gut bacteria strongly affect both the peripheral and central nervous systems by production of functionally active neurotransmitters: serotonin, dopamine, gamma-aminobutyric acid, acetylcholine, epinephrine (Bailey, 2011). Bacteria may synthesize neurotransmitters directly (e.g., gamma-amino butyric acid) or may modulate the synthesis of neurotransmitters (e.g., dopamine, norepinephrine, and brain-derived neurotropic factor).

The composition of the microbiota largely determines the levels of tryptophan in the systemic circulation and, indirectly, the levels of serotonin in the brain. Also, the composition of the microbiota determines the levels and nature of tryptophan catabolites, which in turn have profound effects on epithelial barrier integrity. This determines whether there will be an inflammatory or tolerogenic environment in the gut and other organs (Leclercq, 2016) (Galland, 2014).

Short Chain Fatty Acids – A Major Class of ENS to CNS Cross-Talk Molecules

Short-chain fatty acids (SCFAs) are produced by anaerobic bacterial fermentation of either dietary soluble fiber or intestinal mucin. Clostridia (Firmicutes phylum) are the most studied in this respect (Barcenilla, 2000), yet Lactobacillus and Bifidobacter species also produce butyrate by a "complex interspecies cross-feeding mechanisms" (Rios-Covian, 2015). The major SCFAs butyrate, propionate, and acetate are small organic acids with less than six carbon atoms. Measurement of fecal SCFAs may not fully represent concentrations in the colon because much of it is quickly taken up by colonocytes. In addition, new research is finding that certain Clostridia adhere tenaciously to the colonic mucin and are not often present in stool samples.

Butyrate is an energy source for colonocytes via beta oxidation. By this mechanism, butyrate decreases appetite and reduces the risk of immune-modulated disease by balancing inflammation. Butyrate is essential in neuroprotection and modulates microglial NF-KB signaling and optimizes apoptosis (Sun, 2016) (Ferrante, 2003). In addition to production by gut bacteria, significant quantities of butyrate are present in human breast milk as well as butter, full fat cow's milk, and most cheeses. Parmesan, as well as goat- and sheep-derived cheeses, may be especially rich in butyrate (Jaeggi, 2003).

A unique liver-specific transporter carries SCFAs into hepatocytes (Shin, 2007). Other SCFA transporters are present on the luminal aspect of enterocytes. Two types, monocarboxylate transporters and sodium coupled monocarboxylate transporters, are also located on brain neurons, astrocytes (Vijay, 2014), microglia (Moreira, 2009), oligodendrocytes (Lee, 2012), and the endothelia of the blood-brain barrier (Bergesen, 2002).

The effects of SCFAs in the gut and the brain are due to G protein coupling receptor signaling and inhibition of histone deacetylases, promoting gene expression in human cells (Stilling, 2016). SCFAs are absorbed into the systemic circulation and cross the blood-brain barrier. In the CNS, these fatty acids modulate the inflammatory cascade (Saint-Georges-Chaumet, 2015). A recent study suggests that butyrate is a major factor controlling the permeability of the blood-brain barrier via its effect on levels of the tight junction proteins claudin and occludin (Braniste, 2014).

Butyric acid is also partially responsible for the modest acidity of the colon (pH 5.7-6.7). Beta-hydroxybutyric acid and lactic acid are related molecules. A ketogenic diet induced by very low carbohydrate intake may raise the blood and cerebrospinal fluid content of beta-hydroxybutyric acid and mimic some of ➤

the effects of butyric acid (Iriki, 2009). SCFAs are mediators of the cross talk among microbes, mitochondria, and the host. Along with microbially deconjugated secondary bile metabolites, the SCFAs react with receptors on EECs. This influences serotonin levels and therefore modulates colonic motility (Yano, 2015) (Reigstad, 2015), mood (anxiety), sleep, and pain sensitivity. Some of the signaling is also mediated by more direct vagal stimulation via 5 HT3 receptors (Fukumoto, 2003).

SCFAs, Microbes, Diabesity, and CNS Inflammation

Microbial metabolites including butyrate have crucial regulatory effects on the health of nearly every organ system (O'Mahony, 2015). In experimental animals on a high-fat diet, there is a reduction in obesity and insulin resistance after dietary supplementation with butyrate (Gao, 2009). This decrease in diabesity is likely due to down-regulation of the peroxisome proliferator-activated receptor gamma (den Besten, 2015). This down-regulation promotes a shift from lipid synthesis to lipid oxidation. The SCFAs butyrate and propionate have been shown to have the most significant effects on this mechanism (Lin, 2012). When visceral adiposity enlarges, it increases production of free fatty acids and adipokines, such as tumor necrosis factor-α (TNF-α), resistin, and interleukin-6 (IL-6), and decreases levels of insulin-sensitizing adiponectin. The adipokines stimulate the tenfold increase in the percentage of macrophages in the obese visceral fat. In turn, these macrophages produce pro-inflammatory cytokines, inducing more chronic inflammation, exacerbating insulin resistance and systemic and CNS inflammation. The insulin resistance and elevated glucose can contribute to neurodegenerative changes (Cherbuin, 2012). Following high carbohydrate meals, rapid fluctuations in blood glucose deplete serotonin, dopamine, B vitamins, and magnesium. These changes contribute to glycation, insulin resistance, depression, and neurodegeneration (Geroldi, 2005) (Perlmutter, 2013).

Dr. Steven Sandberg-Lewis has been a practicing naturopathic physician for nearly 40 years in the Pacific Northwest region of the USA and a professor at the National University of Natural Medicine (NUNM) in Portland, Oregon since 1985. In 2010, he co-founded the SIBO Center at NUNM, which is one of only four centers in the USA for Small Intestine Bacterial Overgrowth diagnosis, treatment, education and research. He lectures frequently at functional medicine seminars, presents webinars, and is frequently interviewed on issues of digestive health and disease. He is the author or co-author of several *Townsend Letter* award-winning articles and the author of the medical textbook *Functional Gastroenterology: Assessing and Addressing the Causes of Functional Digestive Disorders* (NCNM Press), now in its second edition. In 2014, he was named one of the "Top Docs" in Portland monthly magazines yearly healthcare issue and in 2015 was inducted into the OANP/NUNM Hall of Fame.

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Lactobacillus fermentum ME-3: A New Era in Glutathione Therapy

by Ross Pelton, RPh, PhD, CCN

In 1995, group of scientists were testing a wide range of *Lactobacillus* bacteria for antioxidant activity. While most failed, a strain named *Lactobacillus fermentum* ME-3 exhibited extremely strong antioxidant activity. Further testing revealed that *Lactobacillus fermentum* ME-3, which is often just called ME-3, was found to synthesize glutathione. Glutathione is a tripeptide amino acid that is made in every cell throughout the body.

This article will discuss the discovery and scientific research on *Lactobacillus fermentum* ME-3 and review the functions of glutathione, including recent studies which suggest that glutathione is an effective and reliable biomarker of aging.

Since glutathione's antioxidant activity is crucial for every cell in the body, the discovery of a strain of probiotic bacteria that could synthesize glutathione and boost glutathione levels in humans has significant health and medical implications.

The history of the discovery of *L. fermentum* ME-3 began in 1994, when joint research study was initiated between the University of Linkoping in Sweden and the University of Tartu in Estonia. The purpose of this collaboration was to examine associations between allergies and intestinal microbiota in two comparative populations: Estonians with a low prevalence and Swedes with a high prevalence of allergy. As part of this study, on March 2, 1995, Professor Marika Mikelsaar isolated five strains of *Lactobacillus fermentum* from the intestinal tract of a healthy one-year old Estonian child. Overall, more than 200 human strains of *Lactobacillus* bacteria were collected for this study.[1]

In 1996, the Dutch company MONA engaged the University of Tartu to test both the MONA and the University of Tartu's department of microbiology's collection of *Lactobacillus acidophilus* strains for antioxidant properties. There was significant disappointment when none of the *L. acidophilus* strains exhibited good antioxidant activity. However, upon testing the lactobacilli strains from the previous Swedish/Estonian study, it was discovered that the *Lactobacillus fermentum* ME-3 strain isolated from one of the Estonian children exhibited extremely high antioxidant activity.

Initial studies showed that *Lactobacillus fermentum* ME-3 bacteria contain glutathione.[2] Subsequent investigation revealed that ME-3 bacteria do not just contain glutathione; the bacteria are actively synthesizing glutathione. Follow-up studies revealed that ME-3 boosts glutathione via three independent mechanisms: synthesis, transport, and redox recycling. Thus, in addition to synthesizing glutathione, ME-3 is also able to extract glutathione from the surrounding environment, and it can recycle oxidized or "used up" glutathione back to its active or reduced form. Consequently, scientists are calling *Lactobacillus fermentum* ME-3 "A Complete Glutathione System" and emphasize that nothing previously has been found to have the capability of boosting glutathione levels by three different mechanisms at the same time.[3]

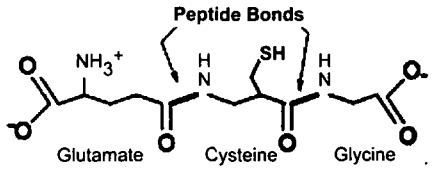
Since ME-3 produces glutathione, it makes sense that many of ME-3's benefits parallel the primary benefits of glutathione in humans.

Glutathione Overview

Glutathione is one of the most important antioxidants in the body, and it is frequently referred to as "The Master Antioxidant."[4] An increasing number of studies link glutathione depletion with an increase in oxidative stress and a greater incidence of disease and accelerated aging. For example, reduced plasma glutathione levels have been shown to represent an increased risk for cardiovascular disease.[5] Glutathione depletion has also been shown to be a primary cause of the neurodegeneration that leads to Parkinson's disease.[6] Similarly, increased oxidative stress in Alzheimer's disease has been attributed to decreased levels of glutathione in the brain.[7] In one review paper, the authors state the following:

> Glutathione (GSH) plays an important role in a multitude of cellular processes, including cell differentiation, proliferation, and apoptosis, and as a result, disturbances in GSH homeostasis are implicated in the etiology and/or progression of a number of human diseases, including cancer, diseases of aging, cystic fibrosis, and cardiovascular, inflammatory, immune, metabolic, and neurodegenerative diseases.[8]

Figure 1: Structure of Glutathione



The Benefits of *Lactobacillus fermentum* ME-3

After discovering that *Lactobacillus fermentum* ME-3 expresses strong antioxidant activity, follow-up studies began to reveal that ME-3 produces a wide range of additional health benefits. ME-3's multiple benefits fall within four

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categories: antioxidant activity, immune system support, anti-inflammatory activity, and detoxification. Consequently, scientists have been studying ME-3 for the past 20 years, and its unique health-promoting benefits are summarized below.

ME-3's Antioxidant Activity: In 1956, Denham Harmon, MD, introduced the Free Radical Theory of Aging in an article titled "Aging: a theory based on free radical and radiation chemistry."[9] Although the idea was initially met with skepticism, free radicals and free radical damage are now recognized as one of the primary causes of the aging process.[10] In fact, free radical damage is now associated with all of the common diseases of aging.[11] In addition to synthesizing glutathione, ME-3 also produces the antioxidant enzymes glutathione peroxidase and glutathione reductase, which contribute to glutathione function and regeneration.[12]

Researching *Lactobacillus fermentum* ME-3's antioxidant activity also revealed that it produces the mitochondrial antioxidant enzyme manganese superoxide dismutase (MnSOD).[13] Because mitochondria utilize about 90% of inhaled oxygen, they are highly vulnerable to free radical oxidative damage.[14] MnSOD is the primary antioxidant that neutralizes highly reactive superoxide radicals (O_2^-), which are primarily generated within mitochondrial membranes.[15] Consequently, MnSOD also plays a critical role protecting cells against free radical oxidative stress.

Lactobacillus fermentum ME-3 provides additional antioxidant support because it helps regenerate other oxidized antioxidants such as vitamin C, vitamin E, lipoic acid, and coenzyme Q10 back to their active forms. *Lactobacillus fermentum* ME-3 has the highest Total Antioxidant Activity (TAA) and the highest Total Antioxidant Status (TAS) of any probiotic tested to date.[16] Its antioxidant-related effects are listed in Table 1.

Promotes Cardiovascular Health: *Lactobacillus fermentum* ME-3 has a beneficial effect on several cardiovascular risk factors. In a two-week double-blind, placebo-controlled trial, individuals taking ME-3 achieved reductions in oxidized LDL-cholesterol (71 U/l to 63 U/l), BDC-LDL (23.8 umol/l to 22.0 umol/l), and triglycerides (2.1 mmol/l to 1.9 mmol/l) and beneficial increases in PON (110.0 U/l to 133.4 U/l) and HDL-cholesterol (1.4 mmol/l to 1.5 mmol/l).[30] At the end of this trial, these same markers had gotten slightly worse for the placebo subjects.

Enhances Detoxification: Glutathione is a critical regulator of detoxification in every cell of the body, but especially in the liver and kidneys. Glutathione detoxifies toxins in food, heavy metals, air pollutants, pharmaceuticals, and a wide range of other toxins. Because ME-3 synthesizes glutathione, scientists conclude it will increase the body's detoxification capabilities. It is important to realize that glutathione gets depleted during the process of detoxifying things that are quite common in many people's lives such as alcohol,[31] artificial sweeteners such as aspartame,[32] and tobacco smoke.[33] Acetaminophen, which is a common ingredient in many OTC and prescription analgesics, depletes glutathione very rapidly which is why acetaminophen overdose is the leading cause of acute liver failure in the United States.[34]

Promotes Liver Health: The liver is the primary organ for detoxification. There are two main phases of detoxification in the liver, which are called Phase 1 and Phase 2 detoxification pathways. A significant number of free radicals are generated during Phase 1, which can result in liver damage if adequate antioxidants (especially glutathione) are not available to quench them.[35]

Reduces Inflammation: *Lactobacillus fermentum* ME-3 has been shown to significantly inhibit levels of several key inflammatory markers, including glycated hemoglobin (HbA1c), high sensitivity C-reactive protein (hs-CRP), and interleukin 6 (IL-6); and it is also capable of stimulating production of the anti-inflammatory and anti-diabetic peptide adiponectin.[36]

Promotes Healthy Bacterial Balance: ME-3 produces significant amounts of short-chain fatty acids (SCFAs), hydrogen peroxide, and nitric oxide.[37] These postbiotic™ metabolites function in several ways to promote the growth of beneficial bacteria and suppress the growth of pathogens, which help maintain a healthy microbiome.

Detoxifies Organophosphate Pesticides: Organophosphates were developed in the 1940s as highly toxic biological warfare agents. Today, they are one of the most widely used pesticides worldwide. In addition to being sprayed on agricultural

Table 1. Antioxidant-Related Properties/Effects of ME-3.

Property/effect	Experimental (ES), animal (AS), human (HS) study
Expression of MnSOD, prolonged survival time at presence of high H_20_2, scavenging of superoxide and hydroxyl radicals	ES[17]
Characterized by high TAA and TAS values	ES[17,18]
Containing of GSH and related antioxidative enzymes	ES[18,19]
Working as natural antioxidant in soft cheese spreads with different fats	ES[20]
Maintaining its high TAA during production of probiotic cheese	ES[21]
Removal effect of metals (prooxidants) from environment	ES[22]
Elevation of blood TAS or TAA, and TAA in the gut mucosa	HS, AS[18,23,24,25,26]
Elevation of oxiresistance of LDL	HS[18,23,26]
Lowering level of oxLDL	HS[23,24,26]
Lowering level of isoprostanes	HS[23,26,27]
Lowering the glutathione redox ratio in blood, in the gut mucosa, in skin	HS, AS[18,23,24,25,28]
Lowering lipid peroxidation in the gut mucosa	AS[25,28]
Lowering level of BCD-LDL	HS[23,26,29]
Positive effects on postprandial status of OxS, blood lipoprotein's status, and urine isoprostanes	HS[26,27]

Legend: BCD-LDL, baseline diene conjugates in low density lipoprotein, GSH, reduced glutathione; H_20_2, hydrogen peroxide; LDL, low density lipoprotein; Mn-SOD, manganese superoxide dismutase; oxLLD, oxidized low density lipoprotein; OxS, oxidative stress; TAA, total antioxidative activity, TAS, total antioxidative status.

Used with permission from Professor Marika Mikelsaar. Chart originally appeared in: *Lactobacillus fermentum* ME-3 – an antimicrobial and antioxidative probiotic. *Microb Ecol Health Dis.* 2009 Apr;21(1):1-27.

food crops, they occur in many pesticide and insecticide products commonly used on residential lawns and gardens. They are also used in plasticizers, as antifoaming agents in lubricants and hydraulic fluids, and in flame retardants.

Lactobacillus fermentum ME-3 increases the activity of paraoxonase enzymes (called PON1), which helps detoxify organophosphates.[38]

In a US government-funded study titled *Fourth National Report on Human Exposure to Environmental Chemicals*, it was reported that 93% of children tested had measurable metabolites of organophosphates.[39] Also, a 2004 report stated, "Almost every person is, or has been, exposed to organophosphate insecticides in their home, work or environment."[40] These compounds are highly toxic, especially to the developing nervous system in young children. Studies have linked childhood organophosphate exposure to higher incidence of ADHD[41] and autism.[42] A probiotic such as ME-3 that improves detoxification of organophosphates may help reduce the risks to neurological diseases such as autism and ADHD.

Immune Function: Lymphocytes are a critical component of the immune system. Their primary job is to defend us against bacteria, viruses, and other foreign invaders. When faced with a challenge, the body dramatically increases the production of lymphocytes to fight the infection. Glutathione is required for the production and function of lymphocytes. Thus, glutathione levels are a critical regulator of immune function.[43]

ME-3 Stability in Humans

To be effective, a probiotic must be able to survive exposure to the highly acidic conditions in the stomach and digestive enzymes and bile acids present in the small intestine.

The results of *in vitro* studies report that *Lactobacillus fermentum* ME-3 survives at pH values ranging from 4.0 to 2.5 without a loss in viable cell count. Even at pH 2.0, the ME-3 strain survived for up to six hours. When exposed to bile acids, ME-3 survived for 24 hours without significant loss of live bacteria.[44] Although testing in the human body has not been conducted, *in vitro* testing suggests that *Lactobacillus fermentum* ME-3 may be able to tolerate exposure to harsh acidity in the stomach and exposure to bile acids in the small intestine. Hence, *Lactobacillus fermentum* ME-3 thrives and survives in conditions that simulate the harsh environments of the human gastrointestinal tract.

Human Clinical Trials

Figure 2 summarizes ME-3's antioxidant effects in human clinical trials, listed as follows:

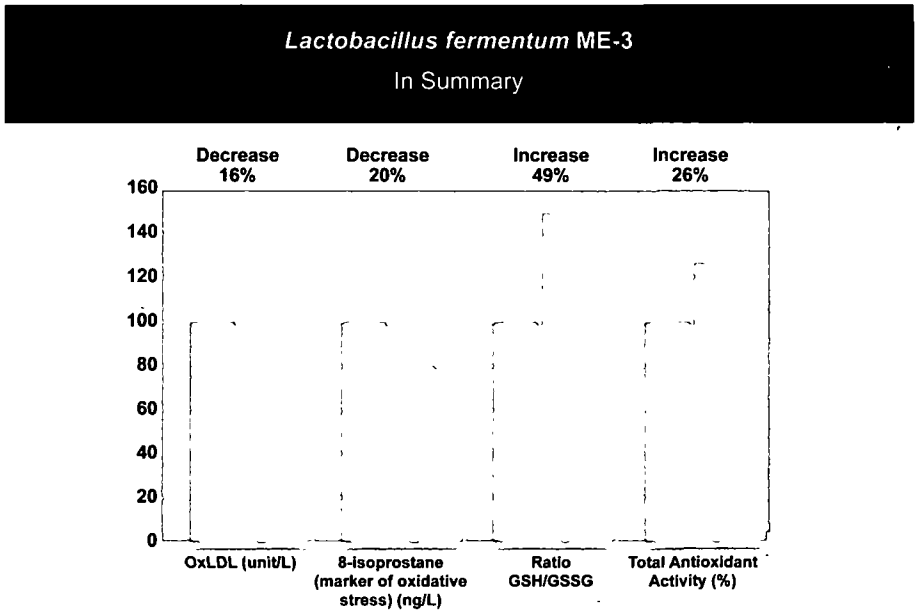
1. **Reduction in Oxidized LDL-Cholesterol:** The first column shows that individuals taking ME-3 had a 16% reduction in the levels of oxidized LDL-cholesterol compared to placebo controls.[45]
2. **Reduced 8-Isoprostanes:** The second column reports that people taking ME-3 had a 20% reduction in levels of 8-isoprostanes, which indicates reduced amounts of free radical damage due to ME-3's antioxidant activity.[46]
3. **Elevated Glutathione:** The study reported in the third column shows that people taking ME-3 had a remarkable 49% increase in the ratio of reduced to oxidized glutathione.[47]
4. **Probiotics, Oxidative Stress, Inflammation and Diseases:**[48] The fourth column reports the increase in Total Antioxidant Activity (TAA) gained by the individuals taking *Lactobacillus fermentum* ME-3. Data for this comes from the following two studies; individual results are not shown on graph.

Study 1 – Improved Atopic Dermatitis: Many patients with atopic dermatitis have genetic polymorphisms in glutathione-dependent enzymes, which results in increased oxidative stress, inflammation, and impaired skin membrane barrier function.[49] Individuals receiving ME-3 experienced significant reduction in inflammation with accompanying improvements in skin condition, blood markers, and in self-assessment rating scores.[50]

Study 2 – Improved Stroke Recovery: Stroke patients consuming ME-3 exhibited significant improvements in both the Scandinavian Stroke Scale (from 33 up to 42) and the Functional Independence Measure Inventory (from 21 up to 40). Stroke patients also experienced impressive improvements in the following blood markers: oxidized LDL-cholesterol, glutathione levels, ratio of reduced to oxidized glutathione, total antioxidant capacity, paraoxonase enzyme activity as well as reductions in markers of inflammation and free radical damage.[51]

In conclusion, new understanding that has emerged from the Human Microbiome Project is the concept of ➤

Figure 2



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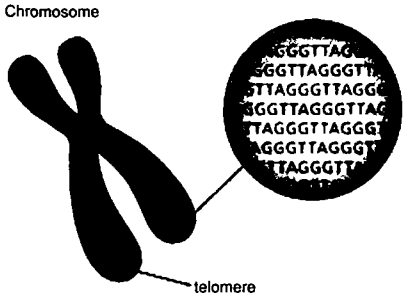
keystone strains of probiotic bacteria. Keystone strains are defined as sub-dominant strains of probiotic bacteria that are capable of exerting large biological effects. *Lactobacillus fermentum* ME-3, which produces glutathione, is a keystone strain of probiotic bacteria. When ingested by humans in doses ranging from 4 to 6 billion bacteria per daily dose, ME-3 has been shown to provide substantial reduction in inflammatory markers as well as improvements in antioxidant protection and detoxification. These biological changes are known to contribute to improvements in a wide range of health conditions. Consequently, glutathione-induced improvements in health correlate with the concept that glutathione levels are a biomarker of aging.

Figure 3: Glutathione: A Reliable Biomarker of Aging



In the late 1980s and 1990s, Drs. Calvin Lang and John Richie started studying glutathione's effect on aging. Their previous studies in mosquitoes, mice, and humans had shown that a deficiency of glutathione in many tissues and organisms is a general phenomenon of aging. They hypothesized that if glutathione deficiency could be corrected it would result in an increase in life span. In their initial study, they administered a glutathione precursor to the drinking water of mosquitoes, which resulted in a 50-100% increase in their glutathione levels. This resulted in a 30-38% increase in life span over control values.[52]

In a related study, Canadian researcher Dr. G. Buonous studied the effects of a glutathione-rich diet (whey protein) on glutathione levels and survival of 21-month-old mice (equivalent to 55-60 years old in humans) over six months, which was the equivalent of 80 years old in humans. Both tissue glutathione levels and longevity increased significantly over controls.[53] Also, paralleling the decline in glutathione levels with aging in animals, other studies reported that glutathione levels gradually decline with aging in healthy men and women ranging in age from 20 to 94.[54,55]

Glutathione reductase is an enzyme that increases levels of reduced/active glutathione. Researchers in Denmark measured levels of glutathione reductase in 41 centenarians who were 100 to 105 years old and compared them with a similar group of average individuals between the ages of 60-79. The results showed that glutathione reductase levels in centenarians were higher than those in the younger elderly subjects. Also, glutathione reductase activity was highest in the centenarians who had the highest functional capabilities. Consequently, higher glutathione reductase activity, which increases reduced glutathione levels, seems to be associated with better health and increased life span.[56]

Paralleling the fact that higher glutathione levels are associated with better health and increased longevity are studies reporting that lower glutathione levels are associated with chronic diseases and that glutathione levels are a biomarker that can be used to monitor the severity and progress of diseases.[57] In fact, lower glutathione levels are associated with a wide range of chronic degenerative diseases such as arthritis, HIV/AIDS, various cancers, cataracts, diabetes, heart disease, leukemia, kidney failure, hearing loss, macular degeneration, and urinary, GI, and musculoskeletal diseases.[58,59,60,61]

The evidence linking glutathione levels with greater health and increased longevity are causing some researchers to proclaim that glutathione is a reliable biomarker of aging. For example, a 2016 study published in *Oxidative Medicine and Cellular Longevity* is titled "Glutathione as a Biomarker in Parkinson's Disease: Associations with Aging and Disease Severity."[62]

Glutathione and Mitochondrial DNA

Low levels of glutathione have been shown to be associated with progressive loss of mitochondrial function, which results from accumulated damage to mitochondrial DNA (mtDNA).[63] In animal studies, the ability to protect mitochondrial DNA from damage is directly proportional to longevity.[64]

Glutathione, Telomeres, and Telomerase

Telomeres are repeat sections of DNA located on the ends of each chromosome. The purpose of telomeres is to protect the ends of chromosomes, which allows cells to divide without damaging our genes. However, telomere shortening is a biomarker of aging. With each cellular division, telomeres shorten slightly and telomere shortening is the main cause of age-related breakdown of cells.[65,66] In 2009, the Nobel Prize in Physiology or Medicine was awarded to three scientists for the discovery of how our chromosomes and DNA are protected by telomeres and the enzyme telomerase.[67]

Telomerase is an enzyme that can place additional DNA repeat sections on the ends of telomeres. Preliminary results from animal studies and human cell culture studies suggest that therapies which increase telomerase activity and lengthen telomeres hold the key to life extension and reducing the rate of aging.[68]

Glutathione levels have been shown to parallel telomerase activity, which is an important indicator of life span. The results of this study reveal that glutathione is a key regulator of telomerase activity. Furthermore, the authors of this study state that telomerase activity was found to be maximal when the ratio of reduced/oxidized glutathione was high.[69] A study with elderly humans revealed that higher glutathione levels are associated with a lower incidence of illnesses and higher levels of self-rated health, which is what would be expected if elevated glutathione levels are increasing telomerase activity and lengthening telomeres.[70]

Because glutathione deficiency is associated with increased risks to chronic degenerative diseases and increased glutathione levels are associated with better health and increased longevity, it has been suggested that glutathione blood levels may be an effective and reliable marker of physiological/functional aging.[70]

Conclusion

The body of research that has been reviewed in this article shows clearly that higher glutathione levels are associated with better health and life extension. Thus, one of the most effective proactive steps people can take to improve their health and their longevity is to boost their glutathione levels. *Lactobacillus fermentum* ME-3 boosts glutathione

levels. In human clinical trials, individuals taking ME-3 achieved a 49% increase in the ratio of reduced to oxidized glutathione.

Although *Lactobacillus fermentum* ME-3 is a stain of probiotic bacteria, products containing ME-3 should not be categorized as probiotics. Glutathione is so critically important to health that products containing ME-3 should be categorized as anti-aging and life extension products. Having a safe, effective way to boost glutathione levels daily has the potential to be a revolution is health and medicine.

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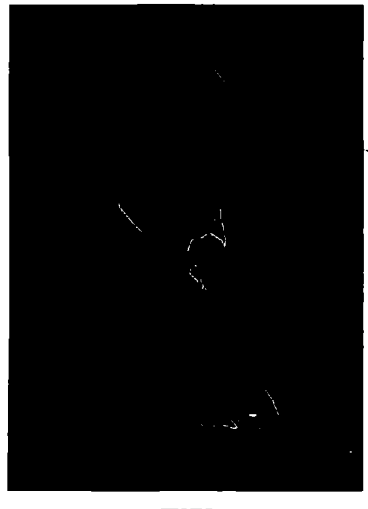

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Can Emotional Conflicts Irritate the Skin?

Psychosomatic Energetics and Urticaria

by Dr. Birgitt Holschuh-Lorang

The causes of urticaria (hives), a morbid alteration of the skin accompanied by rashes or erythema (reddening of the skin), are manifold. Physical effects such as heat, cold or pressure, food intolerances or medications are also candidate triggers. Immunological phenomena can also favor the release of histamine from mast cells, leading to the formation of rashes and erythema.

However, many cases of urticaria often remain unclear as to etiology. In such cases, psychological stress is often proposed as a possible cause.

Anyone who knows how agonizing these patients' often chronic itching is, and how much psychological harm the visible skin changes cause, will understand how desperately they search – sometimes for years – for some kind of help.

Orthodox medicine offers symptomatic treatment with antihistamines and cortisone, which is not always a solution for the affected patients – either because the efficacy of these agents is insufficient, or because concerns about side effects prevent the patients from taking them.

Looking at the cases with unresolved etiology, for which psychological stress (frequently due to emotional conflicts) might be the trigger, raises the issue of diagnostic and therapeutic options and possibilities.

In this context, Psychosomatic Energetics (PSE), a well-established complementary-medicine procedure of about 20 years' standing, offers an excellent diagnostic and therapeutic approach. From the PSE viewpoint, emotional conflicts are due to repressed psychic injuries from the past, which have stored away life energy. Life energy, along with genetic burdens and environmental influences, plays a significant role in human health and well-being.

It is thus understandable that any impairment, such as disturbance of the energy charge, energy flow, and energy intake, can have a negative influence on a person's state of health.

With the aid of the PSE method, which uses a REBA® Test Device (see Fig. 1) for diagnosis, the Vital and Emotional energy charge can be tested, providing information on the patient›s energetic well-being. Furthermore, the energy blocks (due to repressed emotional conflicts) that are at the root of the ailment can be identified. Since the repressed conflict has an energetic dimension, it can be identified and treated with the aid of special homeopathic compound remedies. The energetic conflict dissolution triggered by the homeopathic compound remedies Chavita® and Emvita® results in an increase in the amount of energy and improvement in energy uptake. Experience has shown that not only is the patient›s physical well-being (in the sense of better self-regulation) improved thereby, but emotional resilience – the patient›s emotional equilibrium – is also stabilized.

It is important – especially for patients with psychological stress – to clarify the unclear, unconscious, emotional background factors. It is necessary, however, not only to bring this into consciousness, but also, with the aid of the appropriate homeopathic compound remedy treatment, to be able to truly initiate clear physical and emotional stabilization. In these unclear cases especially, in which psychological stress is a possible cause, the PSE method offers a helpful approach to treatment.

Figure 1: PSE testing with the kinesiological arm-length test and the Reba® test device

If this treatment approach is not enough, it can be supplemented with milieu and organ testing, which can provide information about organ insufficiency related to the disease picture. Experience with skin diseases has shown that it is frequently the intestinal tract whose regulation (in the

sense of dysbiosis or – much more serious – fungal infestation) is disturbed. The corresponding disturbance can likewise be found with the aid of the REBA® Test Device and special organ and remedy test ampoules.

The following case histories are meant to demonstrate experience with PSE diagnostic and therapeutic techniques.

Case 1: Nadja, age 36, has been suffering for more than a year from an urticarial rash in the face and upper-body region. She has been taking Ceterizin® (antihistamine) constantly, otherwise the itching is intolerable. On vacation, when she is more relaxed, she can reduce the dosage somewhat. She also wants to have a child, which she is unable to do because of possible side effects of the Ceterizin®.

The initial examination with the REBA® Test Device reveals reduction in Vital energy to 50% (normal 100%) and reduction of Emotional resilience to 40% (normal 100%). In addition, in the context of hyperacidic cellular metabolism, there is organ stress of the large intestine in the form of dysbiosis.

Over 16 months of treatment time, four different conflict themes are eliminated: stress and overtaxing symptomatology (Emvita® 6), frustration and dissatisfaction (Emvita® 11), feelings of discomfort and being driven (Emvita® 24) and fear/anxiety problems (Emvita® 15). The intestinal dysbiosis is treated with Hylak plus®, Mutaflor® and Utilin S®.

In the medical conversation, the patient is well able to identify with the theme contents that were tested out. However, the crucial point is the treatment result, as shown in markedly higher energy readings of 90% for Vital and 85% for Emotional energy, along with the disappearance of the urticaria symptomatology and discontinuing the antihistamine. Her wish to have a child was fulfilled: she gave birth to a healthy girl.

Case 2: Rosemarie, age 50, has been suffering for five years from chronic pruritus (itching) with recurrent urticarial rashes over her entire body. Since it began, she has been taking Ebastin® (antihistamine), but it is not very effective. She also suffers from fatigue, despondency, and lack of drive. She is also plagued with fear.

The initial examination with the REBA® Test Device very clearly shows low values for Vital energy at 30%, as well as Emotional resilience at 25% – no wonder, considering the symptoms described. This patient has no organ disorder.

Over several months of treatment, the readings for Vital energy are raised from 30% to 85% and Emotional from 25% to 90%. These improved values are accompanied by a feeling of greater satisfaction and, above all, healing of the tormenting skin problem. The emotional conflicts are treated: suppressed rage (Emvita® 9), a fear/anxiety symptomatology (Emvita® 15) and a stress problem complex with severe inner restlessness (Emvita® 22).

Case 3: Helmut, age 71, has had a generalized and nearly unbearable pruritus with urticarial rash for more than a year. The skin surface is so hypersensitive all over his body that just wearing normal clothing is agonizing. His patient history has for the last 10 years included COPD and constipation with hemorrhoidal suffering. Various dermatological therapies, some performed in a university dermatology clinic, have brought no relief.

The initial examination with the REBA® Test Device measures a significant reduction of Vital energy to 45% and Emotional resilience to 30%. The patient exhibits a markedly hyperacidic milieu due to fungal infestation of the intestinal tract.

In the months that follow, there are a number of conflict themes to eliminate in this case as well, due to repressed frustration (Emvita® 10), a stress and overtaxing symptomatology (Emvita® 6), severe inner drivenness and restlessness (Emvita® 22). The fungal infestation is treated conventionally with Itroconazol twice daily for seven days at four-week intervals, followed by regulation of the intestinal flora with Mutaflor®.

After a total of 15 months of treatment, the energy readings have risen to 100% for Vital and 95% for Emotional energy. The patient feels noticeably stabilized, the itching has disappeared; only on his legs is the skin still somewhat sensitive. This course of treatment also succeeded in regularizing bowel movements.

Summary

These case histories show that, from the standpoint of holistic medicine, a mainstream diagnosis (of urticaria in these cases) does not necessarily call for a standardized one-size-fits-all-patients therapy. On the contrary, experience has shown that, with the aid of Psychosomatic Energetics, it is possible to put together a personalized diagnostic and therapeutic plan for each patient. This of course also includes, as the third case history describes, mainstream-medical treatment which at the same time enables more targeted treatment and, as a rule, quicker therapeutic results.

As a general practitioner, this approach to treatment on the physical and psychological level – which is what holistic medicine signifies, in the best sense of the word – has for me become the most important part of my everyday work. As a basic approach, it should not be restricted just to dermatological problems in daily therapeutic clinical practice.

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The Clinical Importance of 5-Alpha-Reductase in Human Health and Pathology

Part 2: Women, Polycystic Ovarian Syndrome, Premenstrual Dysphoric Disorder, Hormone Replacement Therapy, and Beyond

by Alan B. McDaniel, MD

Introduction

Men and women have the same sex hormones, made from cholesterol by our ovaries or testicles and adrenal glands, also the brain...and even the skin! The body assumes male and female forms depending on how much of which hormone we make. This net effect is determined by enzymes, which produce our hormones and then alter them, to subtly "fine-tune" the messages they deliver. One such critical enzyme is 5-alpha-reductase (5α-R): When its effects go awry, the consequences can be dramatic – altering the body *via* sex hormones and nervous system function through its neurosteroids.

This report describes women whose sex hormones are inappropriately 5α-reduced. The actions and effects of the involved hormones are discussed, as are the causes of the problems and various solutions. The new frontier of 5alpha-reduced neurosteroids is introduced. We examine the causal link between 5α-R and the significant health issues of premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS); painful menstruation; postpartum depression; "progesterone resistance" in hormone replacement therapy; and even migraine headaches and seizures. Treatment options are presented and illustrated by these cases with references to published literature.

Women's Hormone Replacement: Case 1

Case 1 is a petite (5 ft. 1 in., 96 lbs.) woman who at age 41, in 2002, first saw Doc for thyroid trouble. Her history suggested she was insulin-resistant: In her teens, she had both menstrual irregularities requiring suppression with oral contraceptives (OCP)[1] and fibrocystic breast disease.[2] These problems worsened in her late 30s when, after three children and a tubal ligation, she developed menorrhagia with large clots, severe cramps, and "alarming" mood swings. Her symptoms were mitigated by resuming the OCP, but she never felt safe in using it.

Her hair was thinning excessively in '02 – initially attributed to her thyroid problem. Symptoms of hypoglycemia sometimes interrupted her activities and forced her to snack. Her first degree-relatives' history of obesity, hyperlipidemia, stroke, ovarian cysts, and uterine fibroids also suggested inherited insulin resistance. These factors and symptoms implying the controversial diagnosis of "adrenal fatigue" indicated a workup beyond thyroid tests.

A 24-hour-urine adrenal steroid profile by GC-mass spectrometry showed robust cortisol and cortisone but low precursors and, significantly, excessive 5α-R activity by increased androsterone relative to etiocholanolone. On four-hour oral glucose tolerance test with insulin, her fasting values of glucose (90 mg/dL) and insulin (3.2μU) were normal, but her 30-minute insulin response was sluggish; the two-hour glucose was excessive at 151, and she "felt like passing out" at the fourth hour, with glucose only 59 – a weak counter-regulatory response.[3] *Alas!* The lab missed the "key" two-hour insulin test, which if elevated might help explain this hypoglycemia.

Case 1 responded well to thyroid treatment combining T3 with T4; nutritional supplements and a healthy diet for insulin resistance (low glycemic index; slowly-accessible glucose and low insulinemic index). Her mental clarity was restored, her hair became normally thick, and PMS and dysmenorrhea symptoms eased – until 2007, at age 46, when her gynecologist (GYN) said she must stop the OCP. Without the OCP, menorrhagia relapsed – heavy to "flooding." Serious mood swings resumed, described as "outbursts." Menstrual-related problems caused her to miss work *every* month. Her GYN prescribed conjugated equine estrogens and medroxyprogesterone (PremPro®). This failed: Case 1 felt worse and gained 10 lbs. (a *lot* when you weigh only 96!). Next, a surgical approach was recommended: The patient underwent endometrial ablation in 2008. She felt better postoperatively.

However, she did not feel well. In 2009, despite tests showing her ovarian cycles continued and produced normal and balanced amounts of steroid sex hormones, oral progesterone 100 mg daily was prescribed. This, too, was unsuccessful: It worsened symptoms and caused weight gain and so was discontinued. The GYN next recommended changing thyroid treatment to T4-only, which certainly failed to improve the situation.

Case 1 again consulted Doc in 2016. Now age 54, in addition to symptoms of thyroid dysfunction, she also had those of menopause: vulvar atrophy, reduced libido, insomnia and cognitive difficulty.

This was in spite of taking HRT from her GYN: Oral progesterone (Prometrium®) 100 mg at bedtime; transdermal estradiol (Evamist®) one spray, and DHEA 10 mg every AM – and oral testosterone 3 mg every other morning. *She added this clue*: Her tests "always" showed low testosterone – but any more than her current dose caused her "serious acne" and undesirable hair growth!

Her blood was tested. Thyroid tests reaffirmed her dysfunctional deiodination – for which replacing some T4 with T3 compensated. Her sex hormones were unbalanced: Estradiol was 31.4 pg/mL, an "early follicular" value for cycling women. However, progesterone at 4.5 ng/mL is normal only in luteal phase. Her observation about low testosterone was *almost* true: Testosterone was immeasurably low (total <3 ng/dL and free <0.2 pg/mL) but dihydrotestosterone (DHT) was 3.5 ng/dL. Women usually have about half as much DHT as total testosterone; Case 1's DHT was the greater – a *decidedly* non-physiological balance – showing abnormally induced 5α-R.

Hormones 101: Testosterone, DHT, and Estradiol

The differences between the sexes are determined in-utero and subsequently at adolescence through various factors, amongst which the enzyme 5α-reductase (5α-R) is important. Testosterone is not, as some believe, the Avatar of All Things Masculine. It is a pre-hormone, as noted in the companion to this paper.[4]

Although the *essence* of testosterone is androgenic (*literally:* "makes men"), it quickly can be converted to the most powerfully feminizing hormone – estradiol. While men change a small but important fraction of their testosterone to estradiol,[5] women perform this step "wholesale," giving them (at ovulation) up to ten times more estradiol than healthy men ever have.

Conversely, men generously convert testosterone to DHT– while women should not. This difference is remarkably important, since DHT stimulates the Androgen Receptor (AR) in the cell nucleus approximately *ten times* more potently than does testosterone[6,7] The AR, in turn, promotes the activation of all DNA programs that create the "masculine." Normal men's DHT can vary from 30-85 ng/dL, while women's is considerably lower, between 4-22 ng/dL.[8] In women, excessive DHT can produce such undesirable results as acne, unwanted facial and body hair, and male-pattern hair loss – as Case 1 experienced.

Enzymes 101: 5α-Reductase (5α-R) and Women

Enzymes are responsible for these normal – *and* abnormal – hormone effects. Enzymes are expediters of biochemical reactions. Generally proteins, they hasten the conversion of a raw material (or "substrate") into something *else*, a "product." The DNA genome encodes "blueprints" for enzymes. By transcribing, synthesizing, activating, and degrading these enzymes – many of which have opposing or synergistic effects – our body makes products that manifest its structure, function and, indeed, the continued existence of itself and its species.

Enzymes are "specialists." The enzyme aromatase (CYP19A1, or estrogen synthase) converts testosterone to estradiol. As implied above, women normally make a lot of this enzyme, and men not so much. The "title enzyme" 5α-reductase, to the contrary, reduces testosterone to DHT – *this* enzyme is abundant in men, while healthy women produce little of it.

5α-Reductase exists to cut a double-bond between the carbon atoms #4 and #5 in the "A" ring of its substrates. These targets of 5α-R are formally called "3-keto, Δ 4, 5 steroids" (Figure 1). As above, one substrate is the hormone testosterone. Other hormones include aldosterone, cortisol and – *drum-roll, Maestro* – **progesterone**. More substrates include hormone precursors (androstenedione, deoxycorticosterone) and "metabolites" (epi-testosterone).[6]

A more detailed review of 5α-R is presented in my earlier article (Part 1),[4] and this is the clinical essence: There are three isoforms of 5α-reductase (different *genomic encoding;* dissimilar *structure* but nearly identical *function*)[9,10] and two other very different proteins also have similar effects. These five are so important they are found in *all* eukaryotic cells.[6] The most recently discovered "type-3" isoform *also* seems to have an important role in glycosylation, and genetically deficient-humans are *severely* impaired.[11]

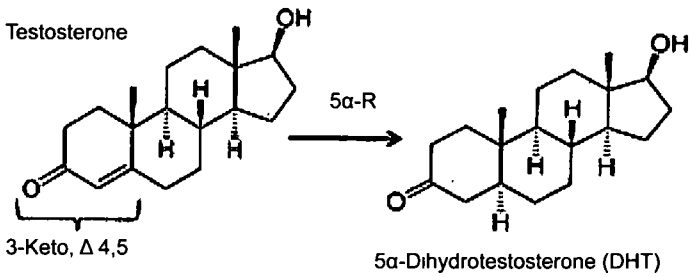
Isoforms of 5α-reductase are expressed in various tissues beginning rather shortly after conception, and their appearance is orchestrated for quite specific moments in development. The products of 5α-R help direct the orderly differentiation of the brain and body into healthy men and women (psychosexual differentiation).[12] For example, men lacking the genetic program for type-2 5α-R have pseudo-hermaphroditism, with ambiguous external genitalia and absent prostate gland. Women with the same defect, though, show but little evidence: reduced body hair; freedom from acne; and on blood tests, high total testosterone/ DHT ratio.[13]

Enzyme production and function can be *inappropriately* increased. This paper focuses upon women in whom 5α-R is detrimentally over-produced. The author regrets that the reader must endure the following didactics to appreciate the consequences of this unfortunate situation – and to rejoice in the fact that blocking or inhibiting abnormal enzyme actions can give great relief.

Laboratory Tests for 5α-Reductase Function

Practitioners cannot order an assay for 5α-R. Instead, commercially-available laboratory measures can indicate whether a person's 5α-R *activity* is appropriate for their sex. Blood tests are used to find the absolute amounts and calculate the ratio of total – free *and* bound – testosterone (tTest) to total DHT. From normal reference intervals and clinical observation, it may be argued that women's normal tTest/ DHT value is about "2." ➤

Figure 1: 5-Alpha-Reductase Acts on 3-Keto, Δ 4, 5 Steroids



5-Alpha-Reductase

A second laboratory metric is the balance of 5alpha- to 5*beta*-reduced steroid metabolites (e.g. androsterone to etiocholanolone) in GC/mass-spec studies of 24 hour-urine specimens. Men are expected to have more 5alpha-reduced products and women to show more 5beta. This method has been employed in published research[14,15] and these tests are available from several American reference laboratories – at least some of which have for years *routinely* report a calculated 5α/5β balance.[16,17]

Case 1 Revisited

Tests showed Case 1 excessively converts her testosterone to DHT (<3 ng/dL to 3.5 ng/dL; ratio tTest/DHT < 0.86). This explains her acne and crops of new hair growth with attempted testosterone replacement. Although a "backdoor pathway" to DHT has been demonstrated,[18,19] her unduly great amount is more likely the result of conversion by increased 5alpha-reduction.

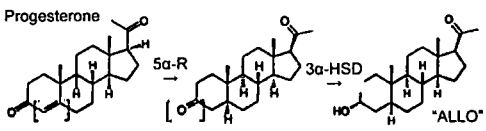
The evidence? Excessive 5α-R activity was shown years before in her 24-hour-urine adrenal steroids: She had relatively high 5α-androsterone compared to the 5beta-reduced etiocholanolone. Her insulin resistance provides a causal mechanism, as follows. Moreover, her difficulties with progesterone also can be attributed to 5α-R. It is time to broaden our focus.

Enzymes 201: 5-Alpha-Reductase (5α-R) *Beyond* Testosterone

5α-Reductase acts on substrates *other* than testosterone: Aldosterone, like testosterone, may be more potent at its (single) receptor when 5alpha-reduced.[6,20] Cortisol, in contrast, is weakened at *its* sole receptor – with important physiological effects.[21] The benefits of "diversifying signaling at a single nuclear receptor" can be invoked in all of these actions.[22] Progesterone, though, is neither intensified nor weakened by 5α-R but changed into something completely different, a neurosteroid.

The first – and *rate-limiting* step – by which progesterone becomes a neurosteroid is performed by 5α-R. The second is via the unstinting cooperation of another enzyme, 3α-hydroxysteroid dehydrogenase (3α-HSD). This neurosteroid product has the unreasonably long proper name, 3α,5α-tetrahydro-progesterone (allopregnanolone), shortened hereafter to simply "ALLO" (Figure 2). The same two enzymes send an aldosterone precursor (deoxycorticosterone) to a similar neurosteroid, mercifully abbreviated THDOC.

Figure 2: 5α-Reductase and 3α-HSD Convert Progesterone to ALLO



Hormones 201: Neurosteroids

Neurosteroids are fairly recent arrivals upon the stage of physiological cognizance and merit careful attention. These are not the steroid hormones made in our body, which themselves will easily cross the blood-brain barrier to be "neuro-active" in the brain.

Neuro-active steroids such as testosterone and estrogens vary by sex, of course, and parents of adolescents know they are behavior-altering. They are also importantly neuro-protective.[23,24] This helps explain the sex-differences in the onset, symptoms and outcomes of various neurological diseases such as Alzheimer's; Parkinson's; Huntington's; multiple sclerosis; stroke; traumatic injury to brain and spinal cord; diabetic encephalopathy; peripheral neuropathy; seizures; and psychiatric disorders.

Yet, the brain doesn't simply receive second-hand steroid hormones. Like the skin, it too has all the synthetic enzymes to make steroids *de-novo* from cholesterol – and this production is regulated by local factors, *not* the hypothalamic-pituitary axis.[25,26] "Neurosteroid" is the term applied to the neutrally-active steroids **made within** the brain. Importantly, the amount of ALLO within the brain depends upon the availability of progesterone and the activity of 5α-R – the "rate-limiting" enzyme.[26]

Brain cells containing this important pair of enzymes (5α-R, 3α-HSD) are found in regions critical for mood, emotion, and sexual function. Their neurosteroid products, ALLO and THDOC, act on the brain's $GABA_A$-receptor, once known to medical students as "the diazepam receptor." Indeed, the neurotransmitter GABA, 5α-reduced neurosteroids, benzodiazepines, barbiturates, and ethanol *all* exert similar and *synergistic* "mellowing" effects there – and more.[27]

Hormones 301: Neurosteroids Balance the Brain – *or Not*

At the $GABA_A$-receptor, ALLO and THDOC potently increase the inhibitory effects of GABA in its yin/ yang balance with glutamatergic stimulation.[26] This balance is necessary for maintaining a network that successfully integrates stimuli with appropriate forebrain, limbic, and HPA-axis responses. This also influences metabolic balance: The glucose counter-regulatory response is inhibited by hypothalamic $GABA_A$-R; *increasing* this receptor's output inhibits glucagon release with resulting hypoglycemia.[28,29] The modulation of $GABA_A$-receptor function by neurosteroids is important.[25]

In acute stress, the proper amounts of ALLO and THDOC protectively reduce anxiety and stress-behavior.[30–32] In chronic stress, inappropriate neurosteroids are associated with dysfunctional GABAergic transmission and increased susceptibility to stress and to develop psychiatric disorders.[25] Premenstrual dysphoric disorder (PMDD) and the milder premenstrual syndrome (PMS), migraines and even catamenial epilepsy are importantly involved with ALLO and THDOC.[33–35]

The effects of ALLO and THDOC are modified by counteracting neurosteroids (e.g. 3β-THP; DHEA-S and pregnenolone-S)[26,36,37] and opposing effects of neuro-active steroids.[24,38–40] Ultimately, neurosteroids are deactivated and degraded by local enzymes.[25]

It must be noted that *receptors* themselves can adaptively change their structure, function, and even numbers (subunit composition, phosphorylation state and population) in response to different amounts and types of stimulation by steroids or drugs.[41,42] These changes cannot be measured, but their effects explain some clinical "paradoxes," such as the role of neurosteroids in postpartum depression.

Why Does Case 1 Have Too Much 5α-R Activity?

Insulin resistance is the likely answer to this question. This is certainly the case amongst women with polycystic ovary syndrome (PCOS), of which insulin

resistance is a hallmark.[43,44] Like Case 1, women with PCOS overproduce 5α-R – largely type-1 – and this is a "key" cause of their diagnostic virilization.[45] Indeed, the similarly diagnostic infertility of PCOS *also* results from excessive 5α-R production in the ovary.[45–47] *Now hear this*: **High insulin causes excessive 5α-R activity**.

A number of reports convincingly correlate elevated insulin with higher 5α-R – and have even identified 5α-reductase as a treatment-target.[20,48,49] A definitive study incubated cultured human ovarian granulosa cells with insulin in varying concentrations: In a dose-dependent manner, insulin stimulates the ovary to increase 5α-R production.[46] Repeating for emphasis: As more insulin is applied, more 5α-reductase is made.

Many women fall victim to this. It is estimated up to 18% of Western women have PCOS.[50] Far more women are insulin-resistant and therefore have elevated insulin – up to 40% of the U.S. population and over 50% of some ethnic groups.[51] We shall now see why this is associated with the incidence in some 3-8% of women of PMDD and up to 25% with the milder version, PMS.[27]

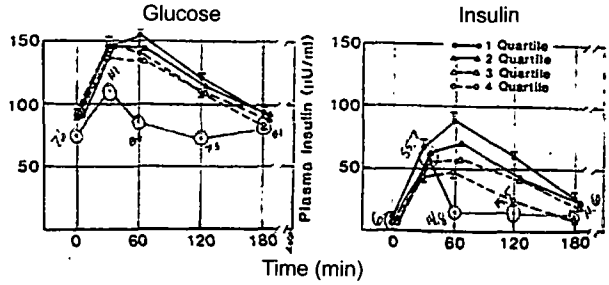
Why Do Luteal Levels of Progesterone Bother Women Like Case 1?

The answer is founded upon this basic fact: *Too much* ALLO causes distressing neurological symptoms. Most women tolerate even robust amounts of progesterone (e.g. during luteal phase or pregnancy) without problem because their normal 5α-R *limits* its conversion to ALLO. However, when women like Case 1 make too much 5α-R, their ALLO production is now restricted only by the availability of progesterone. Hence, the occasions of high progesterone in luteal phase or pregnancy can become associated with distressing neurological symptoms.

An apparent paradox must be acknowledged: Research in rodents and the observations of men indicate that *low* ALLO is associated with anxiety behavior and increased pain perception.[26,52] However, further valid studies show *excessive* ALLO is also related to similar neurological symptoms. Understanding now that the response to neurosteroids is bi-phasic, an old puzzle can be solved: For decades, the obvious association of sex hormone changes with PMDD, PMS, and postpartum depression was studied – and the only outcome was a "frustrating lack of evidence."[53] The neurosteroids offer an explanation.

Women with these problems overly produce 5α-R, thus excessively make ALLO when progesterone is available. Researchers able to measure ALLO find women with PMDD have higher ALLO compared to progesterone (ALLO/progesterone ratio);[53] and, on taking oral progesterone, these women produce the *most* ALLO of anyone.[54] Their blood levels of ALLO consistently reflect those of progesterone: Lowest in follicular and highest in luteal (when symptoms emerge) and then low again at the onset of menses (when symptoms remit).[55,56] Furthermore, symptoms are absent when progesterone fails to rise during anovulatory cycles[57,58] and taking progesterone can worsen their symptoms.[53] We are now prepared to consider treatment for these problems.

Figure 3: Case 2 Oral Glucose Tolerance Test with Insulin (July 2000); Taking Divalproex



Results are graphed against published normal values for her age. *J Clin Endocrinol Metab.* 1987; 64:1169-73

Case 2: Treatment of Premenstrual Dysphoric Disorder

This woman is a 38-year-old, 5 ft. 9 in., 140 lb., nulligravida with PMDD. Although a varsity athlete, she needed antibiotics for adolescent acne. In her early twenties, she was diagnosed with "atypical" or type-2 bipolar disorder. She has taken many psychoactive medications, including SSRI drugs, clonazepam, bupropion, and divalproex – often in combination but affording little relief. Her family history is positive for PTSD and alcoholism (*1st Marines WWII*), cardiovascular disease, PCOS, depression, and hypothyroidism.

In her mid-20s, incapacitating premenstrual dysphoria and severe dysmenorrhea forced her to drop out of Harvard graduate school. She had noticeable alopecia related to her cycle. Evaluation (July 2000) showed free T3 at the first-centile of the reference interval. Her 24-hour-urine steroids were consistent either with stress and adrenal fatigue or 11β-HSD dysfunction (her 5α and 5β-reductase products balanced normally). Her oGTT with insulin was abnormal, with but little glycemic response and insulin resistance revealed by the areas under the curves (AUC) (Figure 3).

Fifteen years later (August 2015), her PMDD still bothered her greatly. One week every month found her disabled by fatigue, pain, mood swings, and irritability – straining the relationship with her co-habiting Significant Other. She said: "I've tried all the anxiety meds, all the psych. meds" and none helped much. She had tried "every" oral contraceptive, and all seemed too strong: "They flipped me out" and made her feel angry.

After an appropriate informed consent-talk (Doc trained as a surgeon), she began a 5α-reductase inhibitor, saw palmetto extract (SPE) 320 mg twice daily. Asked about the results, she effused: "It was amazing!" Within two weeks, she felt happier and "more level." Through the entire next menstrual cycle, she had remarkably reduced physical and emotional distress that had characterized her previous 15-plus years.

After taking SPE 320 mg bid for five months, she estimated she had 50% relief of her overall PMDD and 70% improved mood. Some symptoms persisted at that dose of saw palmetto: She missed one work day each month due to fatigue, *not* pain; she slept nearly all that day. She stopped this herbal drug for one month and had "horrible" PMDD!

She was happy to learn she could increase her dose to 450 mg BID, which improved her relief to 75%. She still misses one day of work *not every* month but the majority. Her Significant Other commented he no longer has to "move out one week every month." In fact, they are planning to marry. She knows saw palmetto is contraindicated in pregnancy so has no plan ever to become pregnant. Her evaluation: Saw palmetto is "the best thing ever." ➤

5-Alpha-Reductase

➤

Conventional Endocrine Treatments for PMDD/ PMS

Treatment with oral contraceptives is commonly employed to relieve menstrual problems, which are significantly (up to 95%) associated with insulin resistance.[1,59] Doc originally thought the OCP simply suppressed the ovaries but the progestin it contains *indeed* acts differently than progesterone.[60] Progestins inhibit the normally acquiescent 3α-HSD, so that *this* enzyme assumes from 5αR the role of rate-limiting "barrier" and limits ALLO production.[61] Progestins even alter $GABA_A$-receptors.[61, 62] This treatment was satisfactory for Case 1 but did not help Case 2.

In order to relieve PMDD/ PMS among PCOS patients while maintaining fertility, insulin resistance is addressed. In addition to diet (per Case 1), metformin is commonly used.[63] This drug improves insulin-sensitivity and reduces long-term complications of insulin resistance while remaining weight-neutral.[64] However, metformin is not reliably effective in controlling the 5α-R related problem of hirsutism.[65]

Novel Treatment: 5α-Reductase Blockade

The trail of evidence impressively implicates insulin-induced overproduction of 5α-R and, thereby, ALLO with PMDD and PMS. If 5α-reductase excess causes PMDD/ PMS, treatment with 5α-R blockers offers an effective alternative, ***barring pregnancy***. Indeed, the relationship between 5α-R and PMDD has been proven to be cause-and-effect by a lovely small study, the *first* of its kind.[66] In this NIH-supported report, the drug dutasteride – which blocks all three 5α-R isoforms and is *not* approved for use in women – both inhibited the luteal-phase increase of ALLO *and* prevented symptoms of PMDD in six of the eight women treated.

5α-Reductase Blockers

Two classes of agents block the action of 5α-R.[66] First are steroidal agents, the drugs finasteride and dutasteride. Both have long been approved for men's use in benign prostatic hypertrophy and the former also for male-pattern hair loss.[67] Dutasteride is now shown to help women with PMDD, though it is not approved for their use *and* it has a rather remarkably long working half-life of five weeks.[66] Although effective in rodents,[68,69] finasteride should *not* be used to treat women's PMDD because it cannot block the version of type-1 5α-R active in human brains.[70]

The second class, non-steroidal 5α-R blockers may offer advantages in effectiveness, availability, and price. This is a broad and diverse group, including saw palmetto and reishi ("Chinese mushrooms")[71] and also benzoquinolones; nonsteroidal aryl acids; butanoid acid derivatives; polyunsaturated fatty acids (esp. linolenic acid); zinc; and green tea.[6]

What Is Saw Palmetto and How Could It Help PMDD?

Saw palmetto (*Serenoa repens*) is a dwarf palm indigenous to the southeastern US.[72] Its berries yield the medicinal extract – of which the active ingredients are various fatty acids.[73,74] Saw palmetto has long been an American folk medicine, used as a "nerve sedative" and for its effects on reproductive organs and urinary symptoms.[75,76] These statements could describe treatment for PMDD/ PMS.

The fatty acids in saw palmetto extract (SPE) vary in potency by tissue type[77] and individual 5α-R isoform.[74] SPE inhibits both types 1 and 2 5α-reductase.[77,78] Its action on type-1 5α-R is most relevant for PMDD, since the human brain uses *this* isoform.[78]

Saw palmetto extract relieved Case 2's PMDD because it inhibits human type 1 5α-R very well – some ten times more potently than does finasteride.[79] In comparison, dutasteride is said to block human type 1 5α-R 100 times-more potently than finasteride.[80]

The side effects of saw palmetto extract are few. A meta-analysis of blinded studies found the withdrawal rate from SPE was 9%, midway between that from finasteride (11%) and from placebo (7%).[81] Its most significant side-effect may be a reduced libido,[39] although various others have been reported.[73] Healthy women make little 5α-R and congenitally deficient women are little-affected, so one might expect its inhibition not to be objectionable. However, it is *absolutely contraindicated* in pregnancy *and* nursing a child: Its effects could mimic the male pseudo-hermaphroditism of type-2 5α-R deficiency.

Saw palmetto extract has few human hepatic-drug interactions,[82] though some have been suggested.[83] Due to effects on cortisol and neurosteroids, it seems prudent to monitor liver insulin sensitivity and blood lipid levels during treatment with any 5α-R blocker.[84, 85] A knowledgeable reviewer endorses SPE as safe for long-term use.[73]

Progesterone Treatment for PMDD/PMS

The informed reader is excused for resisting the statement: "Too much progesterone causes PMDD/ PMS when added to excessive 5α-R." Many practitioners understand that PMDD/ PMS is caused by "estrogen dominance," meaning too *little* progesterone.[86] After all, Dalton proved women with PMS respond to added progesterone[87]; but relevant for this paper, she later stated doses had to be of pharmacological-strength (supra-physiological) and that testing blood progesterone revealed nothing significant.[88,89]

Dalton's methods are still applied. At (integrative) meetings, practitioners state some patients require 400 mg (or even *more*) oral progesterone daily to relieve their PMDD/ PMS symptoms. Blood tests show the resulting progesterone levels are consistent with advanced pregnancy. The term "Progesterone Resistance" is applied. These observations are valid, and it seems 5α-R excess and ALLO can explain this "resistance," also.

There Is a Bi-Modal Relationship Between Serum ALLO and Women's Mood.

In a well-designed study, investigators found serum ALLO values between 1.5 and 2.0 nmol/L are associated with significantly *negative mood*; but a woman's mood is good when concentrations are either lower *or higher* (Figure 4) – a bi-modal effect.[90] The researchers had given menopausal women various doses of progesterone orally and, in so doing, also found the progesterone blood levels producing the "dysphoric" amounts of ALLO are those of normal endogenous *luteal* phase. Either lower or significantly greater blood levels were better tolerated. Upholding Dalton, the fact is that the ill-effects of "too much" progesterone producing "too much" ALLO can be overcome by giving *more* progesterone (Figure 4). There are several possible explanations but none are proven.

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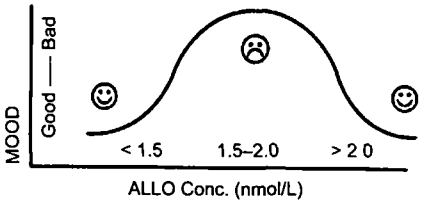
Figure 4: The Biphasic Association of Blood ALLO Concentration and Mood in Women



Derived from data in Andréen L *et al Psychopharmacology (Berl)* 2006 Aug, 187(2):209-21.

These biphasic effects of ALLO may be explained by invoking altered receptor function, perhaps an acute adaptation to "saturation" by ALLO. Some researchers strongly advocate such a mechanism.[27] It is possible that receptor adaptation could explain catamenial seizures,[91] menstrual migraine, and perhaps postpartum depression with its incomplete response to therapeutic progesterone.[53]

Alternately, the biphasic response could be related to a yin/ yang balancing-act of ALLO with progesterone. Functional MRI studies correlated significant variations in amygdala activity with changes in the ratio of ALLO-to-progesterone. Specifically, the effects of a lower ALLO/progesterone ratio resembled benzodiazepine treatment, while higher ratios mimic anxiety reactions.[27] How is this balance altered?

Simply, the ALLO/ progesterone ratio depends upon two variables: activity of 5α-R and availability of progesterone substrate. Higher, luteal levels of progesterone and increased 5α-reductase combine to produce elevated ALLO and a high ALLO/ progesterone balance. When more progesterone is added, by Dalton's method for instance, the maximum reaction rate (Vmax) of 5α-R *may* be exceeded, whereupon the ALLO/ progesterone ratio is expected to decline towards normal.

Are Pharmacological Doses of Progesterone Desirable?

With this knowledge of 5α-R and neurosteroids, which Dalton lacked, reconsidering her progesterone treatment introduces concerns about the disadvantages of supra-physiological dosing. High, pregnancy-levels of ALLO alter $GABA_A$-receptors; it is appropriate to feel apprehensive regarding "withdrawal" symptoms – like postpartum depression, seizures or migraines. Secondly, progesterone is a hormone with many effects (such as weight gain), which high levels may express in excess. Thirdly, progesterone can be metabolized into other steroids, including via the "backdoor pathway" to DHT. When fertility is not desired, blocking 5α-R is an attractive alternative.

Case 3: Dysmenorrhea and 5-Alpha-Reductase

In 2005, this 34-year-old, 5 ft. 8 in. and 170 lbs. nulligravida woman had monthly severe dysmenorrhea attributed to her laparoscopically-proven endometriosis (at tubal ligation). She was able to continue working only by taking celecoxib 200 mg in doses of 6-8 daily for two-to-three days. Her family history is positive for type-2 diabetes, obesity, hypertension, stroke, and heart attack. She has Hashimoto's disease with dysfunctional deiodination that responded to desiccated thyroid (USP) but not to levothyroxine.

She had earlier been evaluated for symptoms considered "hormone imbalance" and her 24-hour-urine adrenal steroid profile showed excessive 5α-R in the high androsterone to etiocholanolone balance. This was validated by her subsequent response to an unwise (*in retrospect*) supplementation with DHEA 12.5 mg twice-daily: Her facial acne worsened and hypogastric midline hirsutism appeared. Prior to stopping the DHEA, she collected a second 24-hour-urine which proved her excessive 5-alpha-reduction produced high androsterone values.

She later performed a four-hour-oral glucose tolerance test with insulin to evaluate her insulin resistance. Her glycemic counter-regulatory response was poor – indeed, she became hypoglycemic to 49 at two hours – and her areas under the curves prove insulin resistance (Figure 5). Dietary and lifestyle measures were recommended.

5-Alpha-Reductase

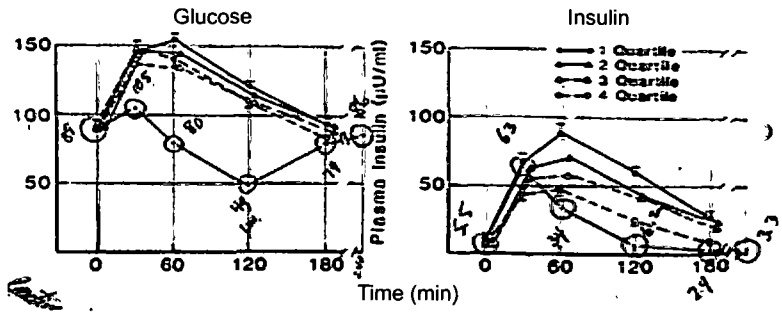
In 2005, her symptoms were consistent with "estrogen dominance," but blood tests instead showed estradiol was *low* relative to progesterone – in two consecutive menstrual cycles and during her symptoms of PMS! Did she have "progesterone dominance"? Or, was her PMS and subsequent *severe* dysmenorrhea somehow related to her demonstrated excessive 5α-R activity, acne and sensitivity to the virilizing effects of DHEA? Doc guessed "yes" and thinking too much DHT might be to blame, suggested saw palmetto – the right thing for the wrong reason.

Case 3 started saw palmetto extract 160 mg twice daily; and at her next menses two weeks later, breast tenderness was reduced *but* her menses were heavier, longer, and cramping was worse. By the second and third months, SPE treatment clearly was helping: She estimated her cramps were reduced by 75%; her flow was lighter and shorter; her cycle had lengthened from 26 to 28 days; and her breast tenderness was 75% better.

As the "index patient" for this treatment, she agreed to stop SPE – *briefly*. Her first month saw a 25-day cycle with heavier bleeding and "hideous cramps." Her breast pain also returned to baseline severity, and she resumed saw palmetto.

Taking 320 mg saw palmetto extract twice daily, she needs only 400 mg ibuprofen once on day 2 to control her pain. However, her best SPE dose is 450 mg twice daily, on which she needs no analgesics at all. Her flow is less on 450 mg bid than with the lower dose, and her cycle is now consistently 27-28 days. Her sensation of pelvic inflammation is relieved completely by the higher dose. ➤

Figure 5: Case 3 Oral Glucose Tolerance Test with Insulin (March 2003)



Results are graphed against published normal adult values *J Clin Endocrinol Metab* 1987; 64.1169-73

She reports: "That sh-t is fabulous."

Her androgenic signs were most appreciated after their remission with saw palmetto: On the higher dose, she has no facial acne and her hair is thicker in front (father and maternal grandfather both were bald). She realized that the annoying axillary odor for which she had consulted two dermatologists has disappeared with SPE. Why? Apocrine axillary secretions contain pheromones – "fragrant" 5α-reduced androgens including her demonstrably excessive androsterone and androstenone.[92,93]

She offers this caution to women: Take SPE without interruption! When she stopped it for three weeks, "all hell broke loose" with her next menses; she was "right back where I started." Doc adds a second warning: It cannot be taken when breastfeeding or during a pregnancy, else Junior may be born without his "pieces-parts."

5-Alpha-Reductase and Pain

Pain was Case 4's primary complaint, and it responded dramatically to the 5α-R inhibitor. In addition to affecting mood, neurosteroids alter pain transmission in the spinal cord and in neuropathic conditions.[94] Here again, we see the "biphasic response," because *normal* amounts of ALLO have analgesic and neuro-protective effects.[61] Indeed, among male veterans who served in war zones, low ALLO blood levels are significantly associated with low-back and chest pain.[52]

However, women in luteal phase – when progesterone far exceeds men's – have increased sensitivity to pain that correlates with higher ALLO concentrations.[95] The authors of this study invoked the biphasic effect of ALLO as they observed that very high ALLO may be analgesic (as in pregnancy) but luteal phase ALLO levels can be associated with *heightened* sensitivity to pain.

Case 4: Migraine Headaches

Case 4 is a woman with migraine headaches and positive family history for type-2 diabetes. She was a sickly child with allergies and other issues including hypoglycemia. She got migraine headaches with her menses. Progestin did not help these – nor did it help her premenstrual dysphoria, clumsiness, and dysmenorrhea. Ultrasound demonstrated multiple ovarian cysts, and endometriosis was suspected. She became hypothyroid from Hashimoto's disease; her symptoms responded better to desiccated thyroid (USP) than to levothyroxine treatment.

In her early 40s, a 24-hour-urine adrenal steroid profile confirmed excessive 5α-R activity with high androsterone/ etiocholanolone ratio. The "Yeast Connection" diet became the most successful she had ever tried, and she lost an almost worrisome amount of weight. Eating this low glycemic-index, low insulinemic-index and slowly accessible-glucose (no-sugar, no-starch and no-fruit) diet, she had "the best period of my life" with no PMS whatsoever. With incomplete adherence, though, PMS symptoms relapsed.

Her breast cancer was found in 1997: Both estrogen and progesterone receptors were positive. Post-operative chemotherapy hastened her menopause. She developed hot flashes; felt stressed and fatigued; spacey and forgetful and she couldn't sleep. Polyarthralgia began, and she lost bone density; taking raloxifene helped only the latter. Persisting insomnia became a real problem. In 2001, she briefly tried HRT with estriol and progesterone cream based on salivary tests but felt *neither* well nor safe using them. She began cultivating black cohosh in her backyard.

Seventeen years post-breast cancer, she used estradiol vaginal suppositories (Vagifem®). Her insomnia persisted, featuring prolonged 3 AM awakenings. Her energy was variably poor. Migraine-severity headaches with nausea occurred at waking twice-monthly and could last for days. For these, she needed opiate medication. More frequently, milder and brief headaches began later in the day. A variety of antidepressants had not improved her mood, just made her feel "fuzzy." Her therapist said she should consider starting HRT.

On Doc's evaluation, her diet was "clean." Her adrenals seemed adequately supported, and "natural" thyroid replacement gave her good thyroid blood levels. Blood tests (8.4.2014) showed estradiol = 7.1 pg/mL (menopause reference interval < 55); progesterone 0.2 ng/mL (0.1-0.8) and total testosterone 23 ng/dL (3-41). They had a detailed informed-consent talk about the risks and benefits of resuming HRT in her circumstances. After several months of deliberation, she chose to try transdermal estradiol, balanced with progesterone derived from oral pregnenolone – with the goal of recapitulating mid-follicular blood levels to improve her symptoms.

This was achieved with Vivelle Dot® estradiol patch 0.0375 mg twice-weekly; pregnenolone 20 mg at bedtime, and neonatal bovine adrenal cortex. Her sleep was significantly improved, but her headaches worsened. She awoke with pulsating retro-orbital pain associated with nausea – as formerly associated with her menstrual cycles – on average twice and up to *four* times-weekly. The pain could last three days; it might be aborted if she promptly took sumatryptan with ibuprofen. During this time, her blood tests showed estradiol= 49.4 pg/mL; progesterone 0.7 ng/mL; tTest 18 ng/dL; and free testosterone 1.6 pg/mL (0.0-4.2).

Doc recommended a 5-alpha-reductase blocker, and she preferred saw palmetto. He offered a few samples of his wife's 450 mg, and these were too strong, upsetting her stomach. She switched to 160 mg once daily and soon reported five consecutive pain-free days. After three months, saw palmetto extract, 160 mg three-times-daily, was relieving about two-thirds of her migraines – in fact, headaches were better than ever.

Further Clinical Applications

The experiences of Cases 1 and 4 offer another useful lesson: The design of women's hormone replacement therapy (HRT) should consider their history for increased 5α-R and accommodate for it. A number of menopausal women shun progesterone treatment because it causes headaches and other symptoms. Doc sets therapeutic goals at *follicular* blood levels, for progesterone as well as estradiol – thereby avoiding the risk of reproducing PMS symptoms from luteal progesterone levels. Oral pregnenolone can easily and inexpensively achieve progesterone values about 1.0 ng/mL to balance follicular estradiol levels. It is also theoretically possible pregnenolone sulfate may balance ALLO; but clearly, it does not always.

Although even a modest dose of progesterone or pregnenolone causes some women distress, Doc learned these women often can tolerate only a small initial dose of SPE – or else their pain and symptoms worsen. In this way, they

seem to resemble the male veterans cited above.[52] By slowly increasing their doses of both pregnenolone and saw palmetto extract, they may achieve follicular progesterone values without distress. The requisite SPE dose is usually 320 mg twice daily or less.

Can Induction of 5-Alpha-Reductase in the Skin Affect Transdermal Progesterone?

The companion to this article described a man who suffered a spectacular failure of his transdermal testosterone replacement after an overdose of the applied hormone caused his skin to make 5-alpha-reductase excessively. Blood tests showed the enzyme destroyed his testosterone by converting it to DHT.[4] Progesterone also is a substrate for 5α-R. It is logical to suspect that, in a similar fashion, topical progesterone may stimulate women's skin to over-produce 5α-R.

Doc has heard reports of women who after prolonged use of topical progesterone could "no longer absorb it." Their skin is said to be "saturated"; and no matter how much progesterone they apply (2% cream gives 20 mg progesterone per gram *and* 10% delivers 100 mg/gm), no increase in salivary or blood progesterone can be measured.

Long puzzled by this, Doc can now offer an hypothesis: Topical progesterone can induce skin to make 5α-R; and if "men's Case 1" is a guide, the more progesterone is applied, the faster 5α-R is induced. The skin is not "saturated" but is equipped to rapidly destroy absorbed progesterone – by 5alpha-reduction. Progesterone *is* absorbed – *and killed*. If so, then women, like men, have a "first-pass effect" in both the skin and the liver.

Is 5α-R Involved with Hypoglycemia?

For some years, the American Academy of Environmental Medicine's new endocrinology course has presented a peculiar observation: A group of young women with symptoms of insulin resistance and mood disturbances from mild anhedonia to type-2 bipolar disorder show a peculiar response to oral GTT with insulin tests: They have a blunted, sometimes virtually absent, glycemic response with just enough excessive insulin response to indicate its greater AUC.

After reviewing these test results from Cases 2 and 3, Doc recalled Case 1's hypoglycemia and went to Pub Med. These "flat" glucose responses may be related to dysfunctional hypothalamic $GABA_A$-receptor function, which impairs the counter-regulatory glycemic response.[28,29]

Finally, is there a link between neurosteroids and fibromyalgia? Certainly, neurosteroids are involved with pain transmission, and fibromyalgia is properly described as central nociceptive hyperesthesia – heightened perception of pain within the central nervous system. Fibromyalgia is strongly associated with elevated cytokines and the PubMed search field "neurosteroids AND cytokines" yields over 30,000 citations. Lastly, the drug most commonly given for fibromyalgia is gabapentin...the GABA receptor, *right?* Further investigations into a possible connection between 5α-R and fibromyalgia may be productive – as might treatment trials with saw palmetto extract for selected patients.

Conclusion

5α-R and its neurosteroid products are significant for some of our patients, as indicated by these "anecdotal" case studies and a small but high-quality NIH-sponsored trial using a 5α-reductase inhibitor (dutasteride).[66] When *conventional* treatments for problems related to 5α-R excess such as PMDD, postpartum depression, catamenial seizures, menstrual migraine and alopecia, acne and hirsutism are ineffective (or unsuitable *or* simply not the patient's preference), the use of a 5α-R blocker can be considered if fertility is not desired.

Saw palmetto in this century has been considered a "man's treatment," but it offers more. It can be used successfully for PMDD/PMS and dysmenorrhea – perhaps other neurosteroid-related problems as well – but do so wisely: It is contraindicated in pregnancy and nursing.

5-Alpha-Reductase

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The Cannabis Revolution: Medical Benefits

by Stephen Holt, MD, DSc

Distinguished Professor of Medicine (Emeritus), author of *The Cannabis Revolution*

Medicinal Benefits of Cannabis

Favorable opinions on the health benefits of cannabis have recently triggered the escalating medicinal use of cannabis. This situation has been reinforced by promising reports of the clinical outcome of the treatment of many diseases, even though many of these reports involve anecdotal experiences. Media reports describe thought leaders who have changed their minds about the value of cannabis as a medicinal agent. Most notable among this group is the positive opinion about medical marijuana expressed by medical correspondents. These individuals have highlighted the fact that until recently only approximately six percent of studies examined the health benefits of cannabis. In comparison, there is a much larger amount of research on its adverse effects. This situation has created "skewed" opinions that influence the evaluation of cannabis-use outcomes.

The health benefits of marijuana use have been summarized by several authors.[5-7, 9, 10-13] These disease state or condition specific applications of cannabis are summarized in Table 1 and reviewed in reference 13.

Table 1. A List of Some of the Principal Health Benefits of Cannabis (adapted from references[1-4, 10-13]). Comprehensive review at reference 13.

Disease/Disorder	Comment
Glaucoma	Lowers intraocular pressure and may inhibit disease progression in glaucoma
Lung Disorders	Arguments prevail but some studies imply that cannabis does not affect lung function in an adverse manner and may increase lung capacity. Overall, smoking is best avoided as the primary mode of cannabis delivery, and vaping is becoming very popular
Epilepsy	The anti-epileptic effects of cannabis are well described with a potential role for CBD and THC. These components of cannabis may be useful in refractory epilepsy e.g. Dravet Syndrome, with variable outcome
Anti-Metastatic Effect	Tumor spread may be inhibited by CBD, which turns off the gene id-1. Other tumor-killing mechanisms may be promoted by cannabis (CBD) e.g. apoptosis, anti-angiogenesis etc.
Anxiety Relief	"A double edged" sword May be sedative at low dosages but THC may precipitate anxiety and paranoia
Pain Relief/ Anti-Nausea Effects	Valuable with chemotherapy-induced nausea and vomiting and some other causes of upper digestive upset.
Alzheimer's Disease	Interference with amyloid plaque formation by enzymatic inhibition.
Pain in Multiple Sclerosis	Marijuana smoking may relieve painful muscle contractions (spasms). Other causes of painful muscle contractions or myoclonus may respond.
Hepatitis C	Standard treatment of Hepatitis C causes several adverse effects Cannabis use can result in reduction of side effects and improve patient compliance with Hepatitis C treatments. Cannabis may have an antiviral effect, but some studies suggest that cannabis may promote hepatic fibrosis (arguable).
Inflammatory Bowel Disease	THC and CBD have benefits on gut function and immune activities. Enhanced intestinal permeability (leaky gut) may be present due to endocannabinoids, which can be modulated by phytocannabinoids. Specific benefits noted in reducing Crohn's disease activity and ulcerative colitis.
Arthritis	Value described in several types of arthritis e.g rheumatoid disease and osteoarthritis. Main effect is pain reduction with variable improvements in mobility.
Metabolic Support	Improved glucose tolerance with cannabis and weight control, despite increased calorie intake as a consequence of the munchies.
Autoimmune Disease	Reduces the autoimmune attack on tissues (immune suppression) and assists with general symptoms of pain, nausea, and loss of appetite.
Positive Effect on Creativity, but Negative Effect on Short-Term Memory	Along with loss of short-term memory, individuals may make mental associations more efficiently when not in the status of being "high"
Parkinson's Disease	Smoking marijuana relieves pain and tremors with associated improvements in sleep and fine (motor) movements (tremors).
PTSD	Post traumatic stress disorder causes fear, anxiety, and flashbacks. Improvement in symptoms, undergoing further substantiation.
Post Stroke Protection	Neuroprotective effects of cannabis are well documented in animals Cannabis may also reduce ischemic injury to heart muscle
Brain Trauma, Concussions, and Chronic Traumatic Encephalopathy	Rodent studies show a benefit in cerebral healing after traumatic injury Strong recommendations made to permit low-dose cannabis use to treat or prevent concussions (or toxic or vascular brain injuries)
Sleep Disturbances	Cannabis disturbs sleep cycles by interrupting REM sleep, but serious nightmares can be abolished, e g in PTSD patients Also, variably effective in stopping sleep apnea.
Alcohol Intake Reduction	Substitution of cannabis for alcohol may result in harm reduction, but it is not a cure for alcohol addiction
Appetite Stimulation in Wasting Syndromes, Vomiting, and Adverse Effects of Chemotherapy	Marijuana and certain drugs (e.g. Marinol®) can relieve nausea and vomiting with appetite-stimulating effects Evidence for these effects is strong.

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Cannabis Revolution

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Medicinal Futures of Cannabis

Medical cannabis use and further research on new cannabis drugs has produced encouraging results and some concerns. Cannabis contains a highly complex collection of different chemicals with diverse clinical effects. This knowledge has been used to support the preferential use of cannabis (marijuana) in its more natural (whole herbal) form, rather than when it is taken as isolated components of the plant (e.g. THC or its analogues or CBD, available alone in certain pharmaceuticals). It appears that the inevitable development of many regulatory-approved pharmaceutical-types of cannabinoid products will occur within five to ten years. Protagonists of cannabis use argue that its safety and effectiveness have been substantiated in a variety of medical or recreational circumstances, but no pharmaceutical agent is completely without adverse effects, especially if used inappropriately. Claims of universal safety of cannabis serve to mislead the public because, at present, we cannot define many of the potential outcomes of the widespread use of cannabis in society, especially with its long-term use in young people.

Thoughtful physicians and regulators have proposed that the ideal scientific and regulatory approaches to cannabis use should stress that it is shown to be safe and effective for each of the indications for which it is considered to have potential benefit. The emerging legislation that governs marijuana availability makes these prudent approaches in approval processes appear impractical or of diminished importance; and they are claimed by some to be increasingly redundant. These circumstances have generated much disagreement, especially among scientists and physicians.

Several scholarly articles have appeared on the future of cannabis as medicine.[1-7] Some of these articles argue that cannabis is much safer than many commonly available medications. Furthermore, cannabis use has been considered to be relatively safe in comparison with the adverse effects of chronic alcohol intake. However, there is inherent fallacy in using examples of "worse" substances of potential abuse, e.g. alcohol, to justify cannabis use itself. It is the outcome of the use of cannabis itself that is the real issue to be examined in risk/benefit assessments.

Modern trends to "pharmaceuticalize" cannabis have not tended to result in the development of drugs that can out-perform the complex actions of intact, whole, herbal marijuana. As noted earlier, such differences are dependent to a major degree on the content of various cannabinoids and other compounds that account for the overall "entourage effects" of herbal cannabis. As mentioned previously, the "entourage effect" means, in simple terms, that the many natural components of cannabis work best together (synergy).[8]

Many scientists and physicians express their confidence that herbal marijuana use is now well established with adequate justification in certain circumstances.[1-7,10-13] In addition, it is predicted that pharmaceutical discoveries of the actions of cannabinoids will lead to the development of a range of drugs with diverse, beneficial, therapeutic applications. That said, there is some residual doubt that these "cannabinoid pharmaceuticals" will be able to have the same degree of applicability, effectiveness, and safety that has been experienced with whole herbal cannabis. While a current public perception of the superior effects of cannabis smoking often exists, the downside risks are the vascular and pulmonary effects of smoking and other problems.

Cannabis: Research Problems

Studies of the health benefits or adverse consequences of cannabis use are clouded often by confounding factors. The heavy cannabis user is likely to engage in adverse lifestyle, compounded by common types of substance abuse such as tobacco, alcohol and use of other illicit drugs. To separate out contributory factors that alter health status in cannabis research has proven to be difficult. As discussed earlier, studies that show correlation of cannabis use with disease often fail to establish causal links. Furthermore, there is often a concern that adverse health findings could antedate cannabis use or even operate in a causal manner to drive cannabis use.

Associations between cannabis use and adverse health effects are clear in many studies, but it is stressed repeatedly in medical literature that evidence of causality is often missing.[1-12] This situation can only be cured by prospective or longitudinal studies that have been difficult to perform previously because of the many years of prohibition of cannabis use. There is difficulty in being able to define clear, cause-and-effect relationships in many studies, especially when research has been retrospective.

W. Hall and L. Degenhardt[9] have reviewed the adverse effects of chronic cannabis use and summarized them by probability of occurrences. See Table 2.

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Table 2. The Adverse Effects of Cannabis Use, Stratified by Existing Evidence to Invoke Causal Relationships (adapted with modifications from Hall and Degenhardt).[8]

Most Probable Adverse Effects of Chronic Cannabis Use	• Dependence in one in nine users • Cardiorespiratory problems • Psychosis • Low educational progress • Cognitive problems
Possible Adverse Effects of Regular Cannabis Use	• Lung cancer • Depression • Mania • Suicide • Use of other drugs

Summary of Problems with Cannabis Research

Several problems exist with medical cannabis research.[1-12] These problems must be kept in mind when interpreting study outcome data. Studies about the health consequences of cannabis use often display disadvantages and limitations that interfere with the development of firm conclusions. As mentioned earlier and repeatedly, in most circumstances, studies are based upon "associations" or correlations of varying strength. This means that several factors may account for the study outcome and the demonstration of a clear cause and effect relationship cannot be defined. Other circumstances operate with "chicken and egg arguments" about what came first. For example, outcomes may be related to the presence of pre-existing disorders or diseases in the study populations.

Prospective or longitudinal studies that examine potential causal relationships are much more valuable than correlative studies. Of course, these types of studies to show cause and effect are increasing but difficult to perform. The "prohibition" of cannabis use in the past has restricted this type of valuable research.[1-7,13]

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Hiking, Mindfulness, and the Healing Power of Nature

by Douglas Lobay, BSc, ND

> A human being is a part of the whole, called by us universe, a part limited in time and space. He experiences himself, his thoughts and feeling as something separated from the rest, a kind of optical delusion of his consciousness. This delusion is a kind of prison for us, restricting us to our personal desires and to affection for a few persons nearest to us. Our task must be to free ourselves from this prison by widening our circle of compassion to embrace all living creatures and the whole of nature in its beauty.
>
> Albert Einstein

I love hiking. I am passionate about being outside in the temple of nature. I feel alive; it energizes and rejuvenates me. When I was in naturopathic school, I went hiking to the south rim of the Grand Canyon. Our group hiked down and camped at the foot of the Colorado River as it etched its way through the canyon. I remember sitting back each afternoon and just looking in awe at this wonder of nature. The opposite side of the canyon was layered like a cake with different levels of stratification that represented millions of years of geological time. The setting sun enhanced the browns, reds, and yellows and reflected the hues across the canyon. Except for the occasional activity of members of our group, the canyon was quiet. The only movement was the mellifluous flow of the river as it ebbed by our campsite. I remember just sitting there for hours absorbing the vastness of this natural phenomenon. As the evening progressed, the twinkling of the stars above began to illuminate the night sky. There was vast silence and immense stillness. It was invigorating to tap into this incredible healing power of nature.

When you are hiking, you can practice mindful meditation. Mindfulness is the practice of bringing one's attention to the present moment. It is a mental state of focus and awareness on what is happening right now in front of you. It allows for calming and quieting the mind and bringing stillness to wandering thoughts. It acknowledges and accepts one's feelings, thoughts, and bodily sensations.

Just by being and moving in a natural outdoor setting, you bring your awareness and focus to the present moment. You help to calm and still the rumination of an active mind and the endless rambling of many thoughts. You free yourself from the endless activities of urban living. You free your concentration from the incessant inclusion of digital devices on your mind and consciousness. You open and accept that you are a smaller part of an immense universe. You allow the energy and life-giving force of Mother Nature to flow into you. You accept and receive the healing power of nature.

Science is beginning to validate the healing power of nature. Several studies support this notion that is one of the foundations of naturopathic medicine. In this article, I focus particularly on the mental and emotional impact of nature on human health.

G.N. Bratman from Stanford University evaluated brain activity and scores on a questionnaire in 38 subjects. Nineteen participants walked 90 minutes in a natural lush green setting around Stanford University, and 19 other participants walked for the same amount of time through an urban setting with heavy traffic. Functional MRIs showing blood flow and brain activity were performed in each group of volunteers. The MRIs showed that those who walked in an urban setting had markedly increased activity in the subgenual prefrontal cortex. This was associated with increased stress, anxiety, and rumination of thoughts. Those who walked in the natural setting showed decreased activity in this area of the brain. These participants also reported less rumination, anxiety and showed more attentiveness and were happier than those who walked in the urban setting.[1]

In an evaluation of three other independent studies, imaging tests showed that urban living increases the activity of the perigenual anterior cingulate cortex, which surrounds the corpus callosum in the frontal lobe, and the amygdala in the brain. The anterior cingulate cortex is believed to be involved in a wide variety of autonomic functions including blood pressure, heart rate, and certain higher level functions such as decision making, impulse control, and emotion. The amygdala consists of two almond-size regions in the deeper brain and is involved in emotional reaction, decision making, and memory. Increased activity of the amygdala was associated with increased levels of stress hormones, increased anxiety, increased mood disorder, and increased depression.[2] No other areas of the brain were affected or showed increased activity with urban living.

In 2016, *National Geographic* published an expose of the positive effects of nature on human health. Psychologist David Strayer from the University of Utah showed that being in a natural environment decreased brain

theta wave activity. This was associated with decreased heart rate, decreased stress hormones, and decreased protein biomarkers of stress. Swedish researchers showed that scenes of nature decreased heart rate variability quicker and allowed the heart rate to return to normal after a complex math test. Japanese researchers showed that those subjects who strolled in forests versus urban city centres had 16% less levels of the stress hormone cortisol and showed slight decreases in heart rate and blood pressure. Korean researchers used functional MRIs to evaluate blood flow in different parts of the brain after viewing different pictures. Pictures of urban scenes increased blood flow to the amygdala, which is typically associated with fear and anxiety. Pictures of nature scenes increased blood flow to the anterior cingulate and insula, which are associated with empathy and altruism.[3]

Nature-based physical activity, including countryside walks, hiking and horseback riding, has been found to be an effective way to improve the health of people with mental illness.[4] A 2005 study showed that walking 35 minutes per day, five times per week, or 60 minutes three times per week significantly improved symptoms of depression. Walking 15 minutes per day did not have such an effect on mood. Other reported symptoms included lower blood pressure, protection against heart disease, and boosting self-esteem.[5] In another study, 20 British participants compared hiking outdoors in a natural setting to walking in an indoor urban shopping mall. Seventy-one percent of those who hiked outside reported a decrease in depressive symptoms while 22% reported increased depression when walking indoors. Ninety percent reported an increase in self-esteem while in nature, and 44% said self-esteem decreased when walking indoors.[6] Many observational and interventional studies show that regular exercise reduces symptoms of depression. In one study, 156 people with depression were divided into three groups; those who did aerobic exercise, those who took the SSRI medicine Zoloft (Sertraline), and those who exercised and took Zoloft. After 16 weeks, all three groups showed an equal response with a 70% improvement of symptoms. The group that took the prescription medicine improved quicker than the group that just did aerobic exercise.[7]

The experiences of four American veterans who suffered from stress and/or post-traumatic distress were examined in a clinical setting. The veterans incorporated nature-based activities into their recovery programs including farming, fishing, gardening, hiking, and caring for pets. While some of veterans continued with medication therapy, they all discovered that the addition of nature therapy provided an additional outlet for recovery. The author concluded that the positive beneficial effects of nature-based pursuits should be further explored and utilized in the recovery of military veterans who suffer from post-traumatic stress.[8]

In one study, 56 adults of an average age of 28 years participated in an evaluation of creative reasoning after exposure to natural settings. The 28 males and 28 females were evaluated through Remote Associates Testing (RAT) before and then just after participation in an Outward Bound outdoor program. Performance on the RAT test increased by 50% after just four days of Outward Bound.[9] In another study, green outdoor activities reduced symptoms of attention-deficit/hyperactivity disorder and had more positive effects on symptoms than other indoor activities; 96 parents of children with confirmed ADHD reported that "fresh air" and the ability to be outside in light, open spaces was better at reducing ADHD symptoms.[10]

A meeting of the American Heart Association in New Orleans discussed the results of an Austrian study of 45 volunteers who went hiking three to five hours per week, up and down a ski mountain in summer over a two-month period. Blood sugar significantly decreased, and glucose tolerance measurably improved while total cholesterol, LDL cholesterol, and triglycerides also significantly decreased.[11] In a 2011 study, 12 female breast cancer patients and six male prostate cancer patients measured oxidative stress and antioxidant capacity before and after a long hiking trip. The generation of free radicals and oxidative stress is believed to be an important factor in the genesis and promulgation of cancer. Oxidative stress decreased, especially in the male prostate cancer patients, and antioxidant capacity significantly increased in both groups after the hike.[12]

Twenty-four Norwegian families with children were interviewed after their experiences of hiking together in a natural environment. The researchers concluded that incorporation of nature-based activities helped to improve family bonding and cohesion of the family unit.[13] An evaluation of 30 males and 16 females from Norway, aged 30 to 79 years, showed that two-thirds reported an increase in overall health status, quality of life, and function after engaging in outdoor nature activities. They also reported an increase in self-efficacy and self-esteem due to outdoor activities that included hiking.[14]

Clearly, there is a vast and largely untapped healing power to nature. The positive impact on human health, particularly the mental and emotional aspects are incredible. For me, hiking has been the conduit to access this immense source of energy. Doctors should routinely prescribe a dose of nature for many common ailments that are currently treated by pharmaceuticals. The cost is low, and the health benefits are vast.

John Muir once said, "Climb the mountains and get their good tidings. Nature's peace will flow into you as sunshine flows into trees. The winds will blow their own freshness into you, and the storms their energy, while cares will drop away from you like the leaves of autumn. The mountains are calling and I must go."

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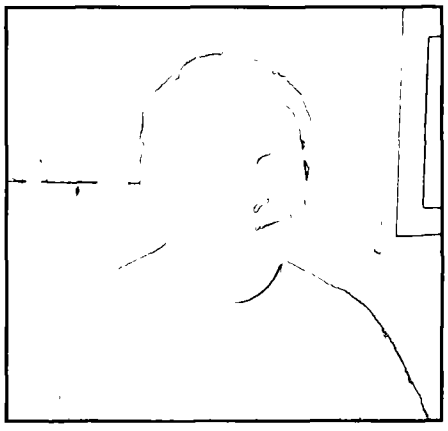
Douglas G. Lobay is a practicing naturopathic physician in Kelowna, British Columbia. Dr. Lobay graduated with a bachelor of science degree from the University of British Columbia in 1987. He then attended Bastyr College of Health Sciences in Seattle, Washington, and graduated with a doctorate of naturopathic medicine in 1991. While attending Bastyr College, he began researching the scientific information on the use of food, nutrition, and natural healing. Dr. Lobay enjoys research, writing, and teaching others about good health and good nutrition. He is the author of four books and numerous articles in magazines. He also enjoys hockey, skiing, hiking, tennis, and playing guitar.



The Healing Power of Nature

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Depression: A Personalized Treatment

review by Katherine Duff

Breakthrough Depression Solution: Mastering Your Mood with Nutrition, Diet and Supplementation
by James M. Greenblatt, MD, with Winnie To, BS
Sunrise River Press, 838 Lake Street South, Forest Lake, Minnesota 55025
©2016, softcover, $16.95, ebook edition $9.99, 285pp.

"At last we have an objective and truly balanced approach to finding relief from depression."

When it comes to depression, a condition for which there is no definitive test, patients and physicians must often pick their own lane. The patient's treatment may be dictated by their insurance coverage or cash in the bank. A psychotherapist may seek remedy through talk therapy. A physician, more often than not, will start the process of antidepressant prescriptions in hope of finding one or a combination that will help. James M. Greenblatt, MD, says that is not good enough. As an integrative physician, he reminds us that the mind and body are one and there could be many contributing factors to one's depression. His book, *Breakthrough Depression Solution,* offers an examination of the many influences on our mental health that are rarely addressed.

The list of contributing factors includes biochemical dysregulation, physical issues such as illnesses, genetic factors, nutrient deficiencies or excesses, and psychological factors. The book addresses all of these factors in detail so convincing it becomes evident a more thorough workup is needed rather than just symptom matching through the *Diagnostic and Statistical Manual of Mental Disorders*. The truth is, the causes of depression are different for each individual.

The investigation into the causes of depression begins with questions that are not usually part of the diagnostic exam. Is the patient taking any of a long list of drugs that can cause depression? Does the patient have an illness that may predispose them to depression? Are there signs of an over-active immune system? Have hormone levels been checked to see if thyroid conditions, low testosterone, or estrogen levels may be affecting mood? Is there a family history of depression, including grandparents? What is the diet and nutritional status of the patient? Is the patient exposed to toxic chemicals?

Greenblatt has coined a mnemonic to describe his personalized approach to treating depression: THE ZEEBRA. It is around this term the book is organized to include helpful supplements and herbs, investigations of underlying illnesses, and appropriate therapies. To start, the T stands for Take Care of Yourself. Topics include diet, which can point to unhealthy diets of too much sugar and the wrong fats that can affect proteins necessary for brain development. Digestive enzymes may be lacking in the patient who could see improvement through the use of enzyme supplements. Inadequate sleep plays a large role in mood disorders, and it may be necessary to treat for insomnia or apnea.

A skip to the "Z" leads us to the all-important role of minerals in the proper functioning of the brain. The author notes that zinc is one of the most important minerals for mental health. He calls zinc the "metabolic spark plug" for its role in over 200 different enzyme reactions. In the discussion of the role zinc may have on depression, he notes studies that have found low zinc levels to be linked to depression. As with many substances, the reasons for that have not been proven; but he does discuss the many theories that could explain it. There are similar discussions of other minerals that play a role in depression through levels too high or too low. Among these are magnesium, copper, lithium, and chromium.

Other topics addressed in the book include the importance of exercise, the B and D vitamins, and amino acids and proteins. A chapter about restoring gut health (R-Restore) is especially good for its explanation of how the brain and gut are connected. This newly discovered two-way street between the intestines and the brain has become an interest for psychiatric research. This and other chapters are detailed in their explanations of how mood may be affected and possible remedies.

This is a book of questions that need answers to form a comprehensive treatment plan for patients with depression. One important question that has been touched upon but needs more discussion is that of exposure to toxic chemicals. Tons of neurotoxins are put into our living environment every year but are rarely acknowledged as a source of illness. Shouldn't we be asking if patients have moved into a new home or had remodeling done? Are they having monthly pesticide applications done in or on their homes? Are they exposed to neurotoxic chemicals in their work or hobbies? Do they have neighbors who use yard chemicals? Defense attorneys in toxic tort cases have long known the multitude of chemical exposures in everyday life that can cause health problems. In depositions, they use questionnaires that seek to identify those exposures in hope of confounding their client's culpability. Those questionnaires may be a place to start for all illnesses including depression.

As the author makes clear, depression is a serious illness that is projected to be the number one cause of disability in wealthy countries and number two globally in twenty years. Current drug treatments for this common illness are not proving successful in the long run, which is not surprising since the drug trials generally last just six weeks. The side effects can be self-defeating with some increasing the risk of suicide. The social stigma of having depression is further complicated by the fact that when drugs do not work, or the side effects become unbearable, the patients end up blaming themselves. Greenblatt offers the alternative.

The book is directed to the patient but not as a treatment. A knowledgeable physician willing to pursue this course is essential. Patients in the throes of depression may find themselves swimming in the details, and many of the recommendations require medical supervision. So, whereas this book offers the patient the "tools to ask the right questions," the physician would be wise to read the book as well. Greenblatt provides extensive references, a list of relevant tests, an index of nutritional supplements with dosages, and a resource list that includes labs and sources for supplements.

With twenty-five years of psychiatric practice, Dr. Greenblatt has seen the suffering of those with depression and the effects of failed drug treatments. His passion for a new approach for treatment is palpable in this book. As he says, the science is there and it is time.

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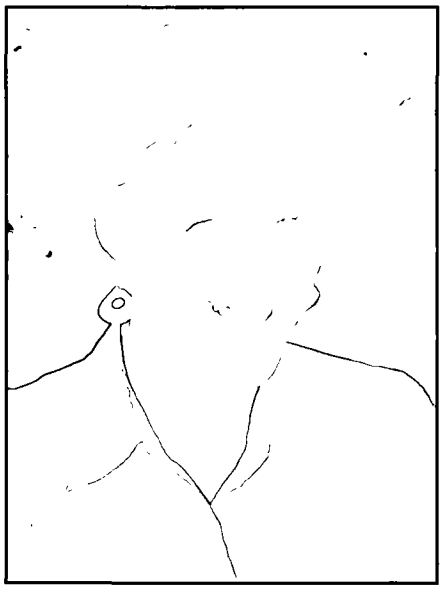

Optimizing Metabolism

by Ingrid Kohlstadt, MD, MPH
www.INGRIDients.com

Fascia: Clearing the Metabolic Traffic Jam

Orthopedic surgeon and integrative medicine physician, Dr. Ken Cintron comments on Western medicine's understanding of fascia: "Let me tell you, fascia is an obscure organ for orthopedists. As surgeons, we only release it after injury or repair it during a reconstruction. However, once you consider it, fascia's importance for musculoskeletal health is profound." This column addresses fascia in musculoskeletal pain, the metabolic implications and the scientific basis for integrative therapies.

Introduction

Medical school anatomy lab included fascia as a structure; but in the physiology course, fascia dropped off the syllabus. In surgical and emergency room clinics, the thinking was make sure the fascia is attached, except when there is risk of compartment syndrome. It turns out general contractors take that approach, too, which leads me to a story.

My house is built in Queen Anne style with ornate wooden trim. But there's one piece of wood no one notices. It's the vertical frieze below the roof. The rain gutter is nailed to it and it's called the fascia. One time a fascia board worked itself loose and no one noticed, until a raccoon woke me up at 2 am attempting to occupy the crawlspace created by the separated fascia. The next day we reattached the fascia in orthopedic style and sprinkled cayenne pepper in the vicinity to further discourage the raccoon, and that was that.

When it comes to human fascia, the raccoon in the story got it right: Pay attention to the fascia and how it moves.

Fascia's Form Explains Its Functions

Fascia is commonly described to look like a knit sweater covering the body. I think that's a good comparison because a sweater confers both form and function. By enwrapping the body, fascia can help coordinate its functions as the name "connective tissue" implies. Like a well-knit sweater, the fascia has some elasticity or spring. One might think of fascia as an inner trampoline. The connective tissue creates a somewhat penetrable boundary, and the means by which heat and nutrients navigate it remains a research frontier.

Fascia has several times more sensory neuronal receptors than does muscle. This finding, made possible by recent advances in technology, suggests that research doesn't yet fully understand fascia's key roles in spatial orientation and pain sensation. It also adds science to patients' perceived pain relief from manual fascia-oriented therapies.

Research on the Move

Fascia is about movement and so are its clinical researchers. There is an International Fascia Research Congress, and its

fifth gathering is already on the schedule for November 2018 in Berlin, Germany. I was impressed with the accumulation of basic science and clinical research, towards the eventual study of the movement of metabolites in fascia.

A research team led by Dr. Meltzer published an in vitro study in 2010 where fibroblast cells underwent biomechanical strain similar to repetitive motion. The fibroblasts, which were then subjected to mechanical simulation of myofascial release, demonstrated recovery and less apoptosis. Subsequent studies have reproduced these findings.

Another line of evidence was presented by the International College of Acupuncture and Electro-therapeutics at their 2016 Seminar (icaet.org). Using a novel biomedical assay called the Bi-Digital O-Ring Test, physicians well-versed in the technique detected improved uptake of medications when the medication was taken along with fascia-oriented manual therapies. In other words, manipulating fascia improved the uptake and distribution of oral medications such as antibiotics and vitamin D.

Manual Therapies Which Improve Fascial Movement

My study of fascia introduced me to David Lesonak, KMI, LMT, of the Center for Integrative Medicine at University of Pittsburgh Medical Center. I previewed a chapter excerpted from his forthcoming book *Fascia: What It Is and Why It Matters* (ISBN-10: 1909141550). The chapter is entitled "Fascia-oriented Therapies." The presented modalities include acupuncture, fascial fitness, fascial manipulation, fascial stretch therapy, myofascial release, fascial movement, myofascial trigger point therapy, structural integration, visceral manipulation, and yin yoga. While there is overlap among the fascia-oriented therapies, each is different with distinct advantages. With the author's permission, I excerpt the section on acupuncture from David Lesondak's forthcoming book.

Acupuncture

Origin: According to archeological evidence, acupuncture dates back to the Neolithic Age, somewhere between 10,000–2,000 B.C., and the original needles were made of stone (LiangYue, D., et al., 2003). From there and to suit our purpose, we need to time travel considerably into the future, to 2001 and the lab of Helene Langevin. She has long been intrigued by the grasping sensation often associated with acupuncture. This is the physiologic sensation felt by the fingers of the practitioner of the acupuncture needle being sucked into the body by the tissue. It has no biological explanation, or at least not until very recently (Langevin, 2001).

What was observed under the microscope was loose connective tissue wrapping itself around the acupuncture needle. Every time the needle was twisted, the loose connective tissue would further entwine itself, like "spaghetti around a fork" (Langevin, 2013). Furthermore, this phenomenon also occurs in living tissue (Langevin, 2004). It is precisely this kind of stretch that activates mechanotransduction and has an effect on the shape of nearby fibroblasts (Langevin, 2011).

Methods: In acupuncture, very fine needles, about the width of a human hair, are inserted into the skin. The insertion is not at random, the acupuncture points occur along twenty specific lines throughout the body called meridians. These meridians are the conveyors of qi, often spelled, and pronounced, "chi." In traditional Chinese medicine, qi is the essential energy of the human body. Qi maintains all the vital and functional activities of tissues and organs.

The meridians themselves seem to have a deeper connection to the fascia, as they seem to be preferentially located along fascial planes. More than 80% of the acupuncture points in the arm are located along fascial planes (Langevin & Yandow, 2002).

Research is at the beginning stages of providing the science behind the commonly perceived benefit of manual therapies. How the therapies interact with fascia may be a large part of the explanation.

Orthopedic surgeon Dr. Ken Cintron again summed it up: "David Lesondak's clinical research brings light and logistic to implement new strategies in orthopedic practice and rehabilitation."

In Summary

Fascia is about freedom of movement. Among the roles of this aptly named "connective tissue" is coordination of nutrient delivery and toxin removal across organ systems. Yet, restrictions in fascial movement arise commonly, partly from the demands of modern day living. Several manual therapies confer their perceived benefit through restoring fascial movement and clearing up the metabolic traffic jams. ◆

Anti-Aging Medicine

by Ronald Klatz, MD, DO, and
Robert Goldman, MD, PhD, DO, FAASP
www.worldhealth.net

Anti-Aging Guide to Maintaining a Healthy Gut Microbiome

The gastrointestinal tract contains the largest amount and concentration of microbes found in the human body. Changes occurring in the gut microbiome during aging can have a negative impact on health and contain a high degree of variability. A major controllable factor that influences the composition of the microbiome is diet. The nutritional value of food is determined in part by the gut microbial community, or microbiota, and its component genes (microbiome). Switching from a low-fat, plant-rich diet to one containing high-fat and high-sugar (otherwise known as the "Western" diet) changes the structure of the microbiota within 24 hours, altering the representation of metabolic pathways and the genes in the microbiome. In this column, we review recent studies that suggest natural methods of maintaining a healthy digestive system.

Turnbaugh PJ, et al. The Effect of Diet on the Human Gut Microbiome: A Metagenomic Analysis in Humanized Gnotobiotic Mice, *Sci Transl Med.* 11 Nov 2009;1(6).

Gut Microbes, Diet, and Host Gene Expression

New research has found that changes in diet affect our gut microbe population and our health. More evidence has shown the important role bacteria plays in our gut and how they alter gene expression depending on diet preferences. Researchers discovered that Western diets, poor in fiber-rich whole plant food, do not provide nourishment for the microbes. The number of microbes in our guts can reach in the trillions and weigh as much as 2 kilograms (4 or 5 pounds). Through fermentation, they help to digest food and produce compounds called metabolites that help the immune system and act as a barrier to infections. The report was published in the journal *Molecular Cell* by a team of researchers from the University of Wisconsin-Madison.

Genes in our DNA make up the code that makes life possible. However, genes can be altered by many environmental factors that switch some genes on or off. The complete set of genes that make up our entire DNA is called the genome, and molecules called epigenome communicate with the genome.

In the study, the researchers found small levels of molecules that were communicating with cells of the mice through the epigenome. UW-Madison professor John M. Denu suggests that metabolites (compounds created by gut microbes) and possibly many other compounds were communicating with the epigenome.

The researchers used lab mice in two groups with different diets. One group was fed plant food high in carbohydrates to mimic a human diet rich in fiber, and the other group was fed a diet of sugar and fat to mimic a typical Western diet. The team then compared the mice fed the Western-style diet to those fed the plant-food diet and discovered the Western diet deterred many epigenetic changes that occur naturally with the plant diet. The researchers then supplemented the diet of the mice that were fed fats and sugars with metabolites. This supplementation restored the proper epigenetic changes seen in the group of mice fed plant food.

Professor Denu and his colleagues suggest the study helped to prove that metabolites that are produced by microbes in the gut when fed a plant-based diet are the major communicators to the epigenome. They call the microbe functions "microbial metabolism." It turns out that food rich in sugar or fat are easily digested but are not a good source of nutrients for the gut bacteria. When the microbes are starved under this diet, the result is a less diverse microbiome with poorer communication with the epigenome.

A surprising result of the study was the discovery that these complex communications in the gut microbiome are not confined to the colon but also between liver cells and fatty tissue inside the gut. This study has profound implications for future studies of the complex interactions between different diets and a healthy gut microbiota.

Scientists are beginning to understand the mechanisms of the bacteria in the microbiome. This study has revealed that gut microbes that are fed a fiber-rich diet of fruits and vegetables produce metabolites that can positively affect our health. But the underlying mechanisms are still poorly understood, and

further research in this area could give scientists the tools to create microbiota supplements. This would be a breakthrough for people who eat a Western-style diet because microbes in the gut help digest excess food thus helping to maintain a healthy weight.

Krautkramer KA, et al Diet-microbiota interactions mediate global epigenetic programming in multiple host tissues. *Molecular Cell*, doi:10.1016/j molcel 2016 10.025, published online 23 November 2016.

Pineapples Halt Harmful Gut Bacteria

Scientists working to find new ways to treat antibiotic-resistant superbugs have discovered a possibility in the stems and roots of pineapples. A group of three enzymes known as bromelain were initially discovered in the 1930s, but the uncovering of their antibiotic qualities happened only a few decades ago, with Australian scientists now using the enzymes to cure diarrhea in piglets. While antibiotics target bacteria, bromelain works with the cells in the gut by making it difficult for the bacteria to stick to the cells. The chance of bacteria evolving and becoming resistant is limited by the three enzymes targeting gut cells. According to Rob Pike, a biochemist from LaTrobe University located in Melbourne, Australia, since pigs and humans are anatomically and physiologically similar in several ways, the enzymes have the potential to provide an alternative treatment for people. Scientists hope this will be the case in humans, so diarrhea will not occur.

It is crucial to find alternative treatments for superbugs because they are predicted to kill about 10 million people a year by 2050, more than the number of people killed by cancer. Scientists hope the new enzymes from pineapple can be used as another weapon to fight bacteria, as many antibiotics do not work as well as they used to. "The momentum to develop alternatives to antibiotics is there now because people believe antibiotics are on the way out and we need something to replace them," said Pike.

Professor Pike and his colleague Lakshmi Wijeyewickrema are presently developing the alternative treatment to antibiotics along with Anatara Life Science, which also conducted the animal trials.

Palmer D. Pineapples Can Stop Harmful Bacteria in the Gut *Parent Herald*. June 27, 2016
Smith B. Pineapples could play key role in global superbug battle. *Sydney Morning Herald* June 23, 2016.

Agave Extracts Help Improve GI Health

Prebiotics are digestion-resistant compounds that feed the "good bacteria" in the GI tract. The agave plant contains inulin, a polysaccharide for which some previous studies suggest a physiologic effect. Kelly Swanson, from the University of Illinois (Illinois, USA), and colleagues enrolled 29 healthy adults in a three-period crossover double-blind study in which subjects were randomized to one of three groups: 0, 5.0, or 7.5 grams per day of agave inulin. Each period was followed by a seven-day washout before crossover. Fecal samples

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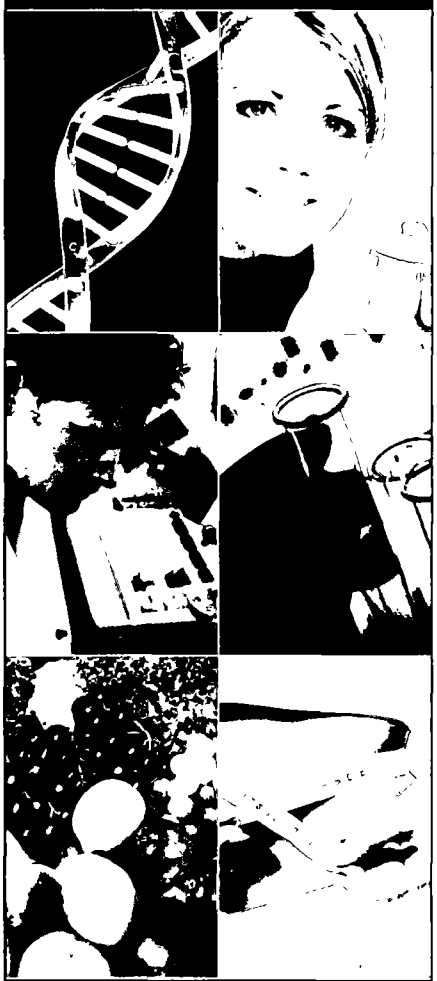

Anti-Aging Medicine

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were collected and fermented, then analyzed to determine gut bacteria populations. Data analysis revealed that Bifidobacterium levels increased four-fold after 5.0 and 7.5 grams per day agave inulin, and Desultivibrio (anaerobic sulfate-reducing bacteria) levels decreased 40%. Agave inulin consumption was also associated with reduced fecal pH and increased butyrate – suggesting increased saccharolytic fermentation and reduced proteolytic fermentation. The study authors observe, "Agave inulin supplementation shifted the gastrointestinal microbiota composition and activity in healthy adults."

Holscher HD, et al. Agave Inulin Supplementation Affects the Fecal Microbiota of Healthy Adults Participating in a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. *J Nutr.* 2015 Jul 22. pii: jn217331.

A Pair of Benefits of Pears

A fruit of the Rosacie family of trees, the pear is abundant in antioxidants, flavonoids, and dietary fiber while being fat- and cholesterol-free and low in calories. Dipayan Sarkar, from the University of Massachusetts (Massachusetts, USA), and colleagues analyzed the pulp and skin of the Bartlett and Starkrimson varieties of pear to ascertain the probiotic potential of the compounds present in the fruit. The researchers found that the peel (as compared to pulp) of the pear exhibited a high phenolic content; whereas the pulp was high in antioxidant activity. As well, the team observed that fermented whole pear juice exerted an inhibitory effect on the stomach ulcer bacterium, *Helicobacter pylori*. Observing that "[p]ear has potential for phenolic-linked management of type 2 diabetes associated hyperglycemia and hypertension," the study authors submit, "This in vitro study provides conceptual foundation for animal and clinical studies involving pear to combat type 2 diabetes."

Sarkar D, et al. Dietary functional benefits of Bartlett and Starkrimson pears for potential management of hyperglycemia, hypertension and ulcer bacteria Helicobacter pylori while supporting beneficial probiotic bacterial response. *Food Research International*. March 2015;69:80-90.

Gut Bacteria Linked to Age-Related Diseases

New research suggests that treating a leaky gut may promote longevity. Alterations in the intestinal microbiota have been linked with aging and measures of frailty in the elderly. To investigate this, Dr Rebecca Clark, a UCLA postdoctoral scholar when the research was conducted and now a lecturer at Durham University (England), and colleagues analyzed the gut bacteria of more than 10,000 female fruit flies, to see if their microbiota had any impact upon lifespan. Previous research by the same group had revealed that fruit flies develop a leaky gut five or six days before they die. Study results showed that the scientists were able to detect changes in the intestinal microbiota, characterized by an expansion of the Gammaproteobacteria, which occurred just prior to the development of leaky gut. The researchers then went on to show that it is possible to reduce bacterial levels in the intestine and prevent the flies from developing leaky gut by treating them with antibiotics. Results also revealed that using antibiotics to reduce bacterial levels can significantly prolong the flies' lifespan. Flies treated with antibiotics as soon as changes in their microbiota were detected lived for an average of 20 days, whereas untreated flies with leaky intestines died within a week. "The health of the intestine – in particular the maintenance of the barrier protecting the rest of the body from the contents of the gut – is very important and might break down with aging," said Dr. Clark.

Clark RI, et al. Distinct shifts in microbiota composition during drosophila aging impair intestinal function and drive mortality. *Cell Rep*. 2015,12:1656-1667.

To stay updated on the latest breakthroughs in natural approaches to maintain a healthy gut microbiome, visit the World Health Network (www.worldhealth.net), the official educational website of the A4M and your one-stop resource for authoritative anti-aging information. Be sure to sign up for the free *Longevity Magazine* e-journal, your weekly health newsletter featuring wellness, prevention, and biotech advancements in longevity.

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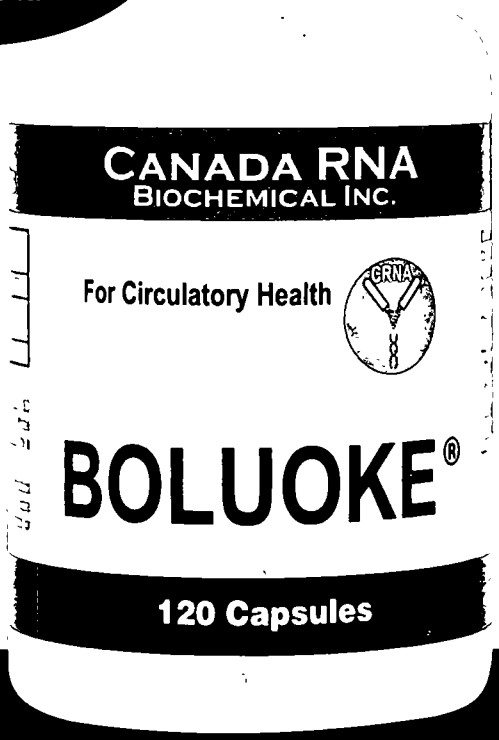

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Pathways to Healing

by Elaine Zablocki

Integrative Health and Medicine: Still Rising

I've just been leafing through a remarkable book, *The Rise of Integrative Health & Medicine: the Milestones – 1963 to Present*. It includes brief descriptions of 125 key events in the history of the integrative health and medicine movement, ranging from 1963, when Delaware enacted the first state mandate for chiropractic insurance coverage, up to 2016, when Medicaid increased its use of integrative methods as first-line treatments for pain and chronic conditions.

We have this book thanks to the work of Glenn Sabin, founder and principal of FON Consulting, who came up with the idea and acted as publisher, and Taylor Walsh, an experienced integrative health consultant and writer, who gathered and curated nuggets of history for the book. They have partnered on several integrative health projects, and the book is now available as a free download from the FON Consulting website. (See Resources section for details.)

Some specific events listed in *The Rise* caught my eye because I was a participant. For example, I remember exactly how I felt when I first read the 1993 article by Harvard's David Eisenberg, MD, reporting that a third of the adults in the USA used "unconventional medicine" to treat their health problems and were spending over $3.7-billion per year out-of-pocket to do so. That issue of the *New England Journal of Medicine* stayed on my reference shelf for two decades.

And I remember when the prestigious Institute of Medicine (IOM) began its assessment of Americans' reliance on complementary and alternative medicine (CAM), published in 2005. Initially, I was concerned that the IOM might weight its scales and denounce any "alternative" methods. However, they produced a balanced and informative report, calling for new research methods that would appropriately measure the clinical effectiveness of complementary and alternative medicine.

The *Townsend Letter* itself, founded in 1983 by Jonathan Collin MD, is listed as milestone number 10 in the initial pages of this book. I suspect that many *Townsend Letter* readers, as they leaf through the book's pages, will recognize professional associations and research consortiums that have affected their own lives.

As we all know, this story did not end in 2016. The advent of functional medicine more completely embeds integrative thinking into healthcare. Sabin and Walsh strongly encourage readers to send in information about the latest developments in integrative health and medicine, to be included in the next edition of *The Rise*. "This is a work in progress, and we would love to hear from anyone who has something to add to the timeline," Walsh says.

John Weeks Describes Five Eras in Integrative Health

We have this new book in large part thanks to the decades-long work of John Weeks, publisher and editor of the Integrator Blog News & Reports and of several precursor publications. Weeks began his work as a chronicler of the field through a column he wrote for the *Townsend Letter* during the 1990s called "Charting the Mainstream." These archives yielded many historical moments, and Walsh and Sabin selected and summarized the most important events.

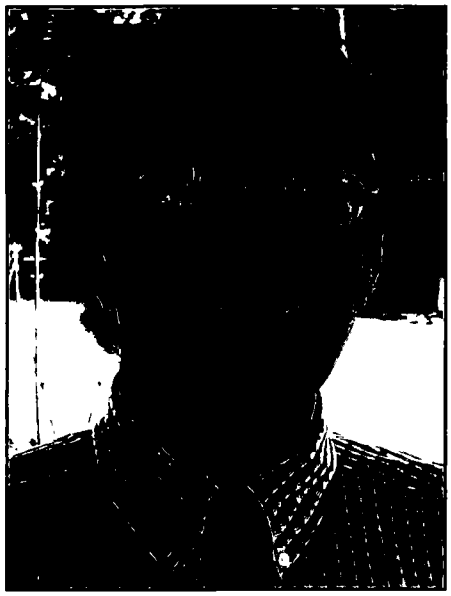
Weeks wrote an introduction for the book, and last fall he wrote an article for the Huffington Post looking at the 125 milestones, saying he finds it most useful to think of the integrative health and medicine movement in terms of "5 Eras":

Era #1: Formation. From the "amniotic stew" of the 1960s to the remarkable era of organizational creation from 1977-1979, many organizations arose to advance new whole-person ideas: the American Holistic Medicine Association, the American Holistic Nurses Association, and the predecessor to the American Herbal Products Association.

Era #2: Advancing in Silos. There were many new holistic organizations, and they focused on their own foundational needs. Holistic nurses and doctors created separate communities. Acupuncturists and naturopathic doctors, and later massage therapists and midwives, worked on professional formation, including schools, accrediting bodies, state licensure, and national professional organizations.

Era #3: Non-Integrated Integration. The 1993 Eisenberg article captured the attention of hospitals and other mainstream organizations, which used nominally "integrative programs" to attract new customers, but didn't plan to include integrative methods throughout their services. Instead, hospitals sponsored stand-alone clinics, as a "extra" service.

Era #4: Advancing in Collaboration. During 2000 to 2003, we see active movement-wide collaborations designed to stimulate increased impact on mainstream healthcare. They include the first Integrative Medicine Industry Leadership Summits and National Policy Dialogue, formation of the Bravewell Collaborative of philanthropists, the Integrative Health Policy Consortium, the Academic Consortium for Integrative Medicine and Health, and the Academic Collaborative for Integrative Health. A consensus had arrived that working in ever larger consortia would be key to making transformative impact.



Taylor Walsh
photo by David C Walsh, www pixwords com

Era #5: Convergence in Health Creation. Some aspects of the Affordable Care Act, designed to move "from volume to value" (and to cut costs while increasing quality) "offered a first chance for real integrative alignment," Weeks writes. "Integrative medicine leader Tracy Gaudet, MD is named as a key transformational officer at the VA.... Integrative strategies are embedded in major systems like Allina, the VA, and the DoD. National strategies for pain, for prevention and health promotion, highlight the value of integrative approaches." For a link to his complete article, see the Resources section.

Integrative Health and Medicine: Still Growing

As principal of Integrative Health Strategies in Washington, DC, and while consulting and writing on the emergence of integrative health care, including *The Rise*, Walsh has had an opportunity to think deeply about decades of development in integrative health, and where we are now.

We observe significant progress in recent years, he notes, but one remaining gap is that the general public – whose interest in and use of integrative health has driven its growth since the very beginning and which relies on integrative care approaches – isn't fully involved in the national policy dialogue. "We're at a stage when integrative therapies and approaches are becoming used in many care settings and are winning recognition as potential solutions to difficult health challenges," he says. "But there isn't yet a major organization focused on providing education and communication with and to the public."

Walsh says this as the originator and manager of one of the first efforts to engage the public on access to integrative health, CoverMyCare.org (milestone 120), a web-based project of his client Integrative Health Policy Consortium (IHPC), which has been primarily concerned with policy issues. Provisions of the Affordable Care Act direct insurers to end discrimination against licensed integrative providers. CoverMyCare extended IHPC's mission to grassroots advocacy in the states, where compliance must be directed by regulators.

Walsh sees this as another stage in the development in the fields, noting the formation of a strong national intellectual infrastructure in complementary and alternative methods. "This way of thinking is being implemented within medical schools and the NIH and the military," he says. "There are several hundred thousand practitioners in the marketplace. Millions of people have benefitted from these therapies, but it has been difficult to tap that experience with an effective public voice."

Another important theme is the growing capability of science and technology. "We're starting to see explanations for why acupuncture works," Walsh says. Western culture needs to see everything through a rational viewpoint, and in fact we are gathering new information on the reasons various healing traditions work so effectively. In addition, there is the special role played by the Army. The military has this great attitude that 'If something works and it's safe, we're going to use it.' This has been an important factor in demonstrating the actual effectiveness of integrative methods."

Until now modern technology hasn't been closely involved in the expansion of integrative health, but that's going to change, Walsh predicts. "Some Silicon Valley tech companies are quite interested in wellness and self-care, and connections are starting to form. It's obvious that technical apps could play a valuable role in supporting health-related behavior change. The integrative health community could make important contributions in helping to design these apps and target the most appropriate healing outcomes."

Resources:

For a copy of *The Rise of Integrative Health and Medicine*, go to https://fonconsulting.com/resources/the-rise/ and request a free copy.

Taylor Walsh's website and blog:
http://www.integrativestrategies.us/

For John Weeks' Huffington Post article go to: http://www.huffingtonpost.com/john-weeks/free-ebook-rise-documents_b_13109712.html

For the Integrator Blog go to http://theintegratorblog.com/

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

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Magnesium and Hot Flashes: The Ethics of Placebos

The American Medical Association has struggled to come to grips with the use of placebos for years. In 2006, the AMA's Council on Ethical and Judicial Affairs (CEJA) decided that it is unethical for a physician to use a placebo in the guise of therapy without the "knowledge and cooperation of the patient."[1] This opinion remains in place; a 2008 publication by the Council in the *Journal of Clinical Ethics* declared the following:

> Ultimately, the deceptive use of placebos is not ethically acceptable because it may harm patients to a greater degree than it helps them. This is particularly true in cases when placebos are utilized to serve the convenience of the physician rather than to promote the welfare of the patient. Perhaps the most pernicious use of placebos is for mollifying a patient who is demanding, displays a difficult personality, or has a complex problem that has become frustrating to the physician. Placebos should never be used in this way because it is fundamentally inconsistent with physicians' professional obligations to promote patients' welfare and respect the autonomy of patients.[2]

Some people live in a world where ethical decisions are black and white choices. Some of us find we live in a more complex world, not just many shades of grey, but full rainbows of color, and ethical decisions are less clear. Prescribing a placebo is one of such area.

As an example of a placebo that isn't clear cut, consider the changing status of magnesium for hot flashes. For the last half-decade, we've suggested it to breast cancer patients. And it seems that taking magnesium often helped.

The idea to use magnesium oxide originated about six years ago when two pilot studies reported that doing so reduced the number and intensity of hot flashes experienced by women taking either tamoxifen or aromatase inhibitors.

The first of these studies was presented in 2010, at the American Society of Clinical Oncology (ASCO) meeting in Chicago. Herrada reported on a pilot study of 22 women who received 400 mg of magnesium oxide three times a day for a month. All the women were receiving adjuvant treatment for breast cancer. "Ten (45%) pts achieved a complete resolution of hot flashes. Ten (45%) pts experienced at least a 50% reduction in the number of hot flashes per day. In two (10%) patients, no changes in the number of hot flashes were noted."[3]

Results of a second pilot study were reported in 2011. A group of 25 breast cancer patients, also receiving some form of adjuvant treatment, were given 400 mg of magnesium oxide per day for four weeks, escalating to 800 mg if needed. Hot flash scores were significantly reduced. "Of 25 patients, 14 (56%) had a >50% reduction in hot flash score, and 19 (76%) had a >25% reduction. Fatigue, sweating, and distress were all significantly reduced."[4]

Together these two studies, albeit small, were enough to suggest potential benefit. Thus, for the last five years we have recommended that women in similar situations try taking magnesium; it seemed helpful in about the same proportion of cases as hinted by these studies.

Then last year, in 2015, something confusing happened. A large placebo-controlled randomized trial was published that called these early results into question. The lead author of this new and far more comprehensive trial is Haeseong Park, the lead investigator from the 2011 pilot study.

Park's new study enrolled 289 women between December 2011 and March 2013. All the women were postmenopausal with a history of breast cancer and had bothersome hot flashes. They were randomized into treatment groups who were given either magnesium oxide 800 mg or 1,200 mg daily or placebo. Treatment lasted a total of eight weeks.

Mean hot flash scores, mean hot flash frequencies, and associated changes during the treatment period were similar for all groups, including those receiving placebo. Taking magnesium increased incidence of diarrhea, not a

surprise as this is a well-known side effect. There was no statistically significant difference in other toxicities or quality-of-life measures observed, in other words all the women did equally well.[5] The study concluded that magnesium didn't do anything. The reality is more complicated. Hot flashes dropped steadily during the study. But they dropped equally in the placebo group and the magnesium-taking groups. Magnesium oxide did not offer any more benefit than placebo did. Hot flash intensity and frequency changed by a bit more than 30% during the eight-weeks of the trial for both magnesium and placebo groups. See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4442087/figure/F2/

It is not that magnesium wasn't associated with improvement; it was. The problem is that the placebo worked just as well. These data suggest that the benefit of taking magnesium oxide for hot flashes is a placebo effect. Both of the earlier pilot studies were open label without placebo arms.

When we simply had data from the 2010 and 2011 trials, we could honestly tell patients that the evidence suggests that magnesium is helpful for hot flashes. What should we tell them now? Should we tell patients that magnesium works no better than a placebo, but that it still may help them? What about patients who have taken magnesium for years and think it helps? Do we tell them to stop taking it as its benefit is only as a placebo? Or to keep taking it because for them a placebo appears to work?

This brings to mind Ted Kaptchuk's somewhat mind boggling study from 2010 on placebo effect in irritable bowel syndrome (IBS) that suggested it doesn't matter what patients know. In Kaptchuk's study, 80 women with IBS were given either "placebo pills" or no treatment. Despite the fact that those receiving placebo knew they were placebo, they still nevertheless did significantly better than the no-treatment control group.[6]

Some will point out that magnesium oxide is typically not our first choice for magnesium supplementation as it is poorly absorbed and tends to have a laxative effect. As the first two studies demonstrated benefit, this might not matter. The magnesium oxide seemed to work well enough. The fact that magnesium oxide is a laxative may enhance its placebo effect, and we should think twice before switching to "better forms" of magnesium. Benefit may have nothing to do with absorption.

Hot flashes appear to be quite responsive to placebo intervention.[7] Placebo benefit has been reported in several prior randomized studies. In Boekhout's 2006 review, about 25% of 1174 patients who received placebo or the intervention reported hot flashes reduced by at least 50%, and 15% had greater than 75% reduction.[8] In Sloan's 2001 review of seven randomized trials, the 375 patients who received placebo had an average 25% decrease in hot flash frequency and intensity.[9] Hot flashes may just be particularly sensitive to placebo effect.

The steady decrease in hot flashes seen in the 2015 Park study may not be the result of placebo or magnesium at all; it may be the natural course of the symptoms. Hot flashes may simply improve over time, or the improvement may be a limitation of using diaries to record intensity and frequency. Women recorded their symptoms, and one might imagine that mere habituation and tedium led to a decrease in symptom recording.

We should also note that this same research group has a history of investigating several hot flash treatments and proving them ineffective, including vitamin E in 1998,[10] soy in 2000,[11] black cohosh in 2006,[12] acupuncture in 2007,[13] flax seed lignins in 2012,[14] and paced breathing in 2013.[15] Like magnesium oxide, black cohosh had shown benefit in an earlier pilot study.[16]

There is, in all likelihood, a "...psychological component of hot flashes. In fact, a previous small study demonstrated that distressing or problematic hot flashes were predicted by depression, anxiety, and low self-image, but not frequency of hot flashes. Therefore, women with equal numbers, and perhaps severity, of hot flashes may have very different emotional responses to their hot flashes; some desiring treatment, considering the symptoms bothersome, and others, not."[17]

The more women perceive that they 'have control over their symptoms' the less bothersome hot flashes seem to be.[18] Thus, taking magnesium or anything else that offers a sense of control over those 'bothersome hot flashes', even if the sense of control is an illusion, may in a way prove useful to take.

We should also consider that women with a history of breast cancer whose hot flashes are treated using the commonly prescribed drugs, venlafaxine, gabapentin or clonidine, are at high risk for adverse events. A November 2016 Cochrane review of 12 studies with a total of 1467 participants, reports that 81% of those women in the treatment group and only 19 % in the control group had adverse reactions.[19] With this in mind, trying magnesium, even if it is only a placebo, might be a safer first option. Yet, ethically, it would now be considered a placebo and a violation of the patient's autonomy. Perhaps, the ethically correct thing to do is to tell the patient magnesium is a placebo and suggest they take it anyway? Their symptoms might drop by 30%. I have yet to suggest this in this way to a patient but am looking forward to the conversation that follows.

Some conservative elements in the medical community think that any and all treatments prescribed by complementary and alternative medicine (CAM) practitioners are efficacious only because they elicit a placebo response. This opinion was harshly echoed in an online posting by Valerie Jones: "As far as I can tell, no CAM treatment has been proven effective beyond placebo.... Therefore, the effects of these treatments cannot be explained by inherent mechanisms of action, but rather the mind's perception of their value. In essence, the majority of CAM treatments are likely to be placebo therapies, with different levels of associated ritual."[20]

While, to us, this seems to be a ludicrous generalization, it is a perception worth noting, as this is how many medical practitioners view our therapies. Being aware of this should make us more mindful of the evidence that does recommend what we do and more conscious of when the claims of benefit are well founded and when they are weak.

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Curmudgeon's Corner

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When confronted with lack of solid evidence, I have a catch phrase that helps me keep it all in perspective: "prunes, parachutes and poppies." Prunes, because until quite recently there were no randomized controlled trials that prove they had laxative action yet they worked fine.[21] Parachutes because we will never have a placebo controlled randomized trial to prove they are helpful, yet we are fairly certain they work. And poppies are worth remembering as an example of an herbal medicine whose effect is clearly not placebo.

In the case of hot flashes, it appears that placebos have relatively strong effect; that has left us with many remedies that work some but not all of the time.

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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.

MAY 24-28: AUTISM ONE 2017 in Colorado Springs, Colorado. CONTACT: www.autismone.org/

JUNE 1-3: THE INSTITUTE FOR FUNCTIONAL MEDICINE'S 2017 ANNUAL INTERNATIONAL CONFERENCE in Los Angeles, California. CONTACT: www.functionalmedicine.org/AIC

JUNE 2-3: SOUTHEAST REGIONAL INTEGRATIVE MEDICAL CONFERENCE in Asheville, NC. CONTACT: https://www.ncims.com

JUNE 2-4: PHYSICIANS ROUNDTABLE ON MIND, BODY, SPIRIT in Orlando, Florida. CONTACT: 717-254-1953; https://www.facebook.com/2017-Physicians-Round-Table-Conference-Orlando-376833002674820/

JUNE 2-5: MEDICINES FROM THE EARTH HERB SYMPOSIUM in Black Mountain, North Carolina. CEs for health professionals. CONTACT: (541) 482-3016; https://www.botanicalmedicine.org/

JUNE 3-4: VIATREXX TRAINING-Putting It All Together with Andreanna Rainville in Scottsdale, Arizona. What is the body asking for? CONTACT: 888-337-8427; info@viatrexx.com; Viatrexx.com

JUNE 8-10: 10th WORLD CONGRESS INDIGENOUS MEDICINE in Nevis, West Indies. CONTACT: panamint@sisterisles.kn; www.smoch.org

JUNE 9-11: 5th INTERNATIONAL WORKSHOP ON BIOBRAN @ Andel's by Vienna House in Krakow, Poland. Lectures by top researchers and doctors about Biobran, a powerful immunomodulator and anticancer agent made from bran rice modified on shitake culture. Presenters include Prof. Serge Jurasunas, ND, and Joseph Brenner, MD. CONTACT: Monika Ebertova, monika@dhdeurope.com; phone 421 254630314; fax 421 254603014.

JUNE 9-11: 3rd HRI INTERNATIONAL HOMEOPATHY RESEARCH CONFERENCE in Malta. CONTACT: www.HRIMalta2017.org

JUNE 9-11: 13th INTERNATIONAL HERB SYMPOSIUM @Wheaton College in Norton, Massachusetts. CONTACT: www.internationalherbsymposium.com

JUNE 15-17: SOPMED (Society of Progressive Medical Education) ANNUAL CONFERENCE & TRAINING in Colorado Springs, Colorado. CONTACT: 517-242-5813; info@sopmed.org; www.sopmed.org

JUNE 16-18: ADVANCED JOINT INJECTION (Module 2) in Vancouver, Canada. CNBPC recognized for certification. Also, **DECEMBER 1-3.** CONTACT: 1-888-337-8427; info@viatrexx.com; www.Viatrexx.com

JUNE 16-18: PERINEURAL INJECTION TREATMENT with John Lyftogt, MD, (New Zealand) in Seattle, Washington. Effective pain treatment at the level of the cutaneous nerves. CONTACT: Jeff Harris, ND at 206-517-4748; www.jeffharrisnd.com

JUNE 17-24: CLINICAL & COMPARATIVE MATERIA MEDICA with Dr. Subrata K. Banerjea in Great Baddow, Chelmsford, UK. Class room or interactive video. CONTACT: www.homeopathy-course.com/index.php/training-courses/england-homoeopathy-training/7-day-summer-school

JUNE 22-24: 14th INTERNATIONAL SOCIETY OF SPORTS NUTRITION (ISSN) ANNUAL CONFERENCE & EXPO in Phoenix, Arizona. CONTACT: https://www.sportsnutritionsociety.org

JUNE 24-25: MEDICAL CANNABIS CONFERENCE & EXPO with International Canna Pro Expo in Philadelphia, Pennsylvania. CME/CNE/CLE's offered. Montel Williams keynote and other expert speakers. CONTACT: https://internationalcannaproexpo.com/?utm_source=Townsend&utm_campaign=RegPromo&utm_medium=Calendar&utm_content=Event

JUNE 30-JULY 2: INTERNATIONAL CONGRESS ON NATUROPATHIC MEDICINE – ICNM 2017 in London, UK. CONTACT: secretariat@icnmnaturopathy.eu; icnmnaturopathy.eu

JULY 12-15: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS ANNUAL CONVENTION & EXPOSITION in Phoenix, Arizona. CONTACT: www.naturopathic.org/aanp2017

JULY 13-15: HORMONE ADVANCED PRACTICE MODULE – RE-ESTABLISHING HORMONAL BALANCE in Chicago, Illinois. CONTACT: www.functionalmedicine.org/Hormone

JULY 14-16: GPL MASTER PRACTITIONER WORKSHOP in Kansas City, Missouri. Tests covered in this workshop include the Organic Acids Test, GPL-TOX (Toxic Non-Metal Chemical Profile), Glyphosate Test, GPL-SNP1000 (DNA Sequencing Profile), GPL Mycotox, and more. CONTACT: 913-341-8949; www.GPLUniversity.com

JULY 16-18: ENERGY REGULATION ADVANCED PRACTICE MODULE – ILLUMINATING THE ENERGY SPECTRUM in Chicago, Illinois. CONTACT: www.functionalmedicine.org/Energy

JULY 29-30: MEDICAL CANNABIS CONFERENCE @ National University of Natural Medicine in Portland, Oregon. CONTACT: 503-552-1555; career-alumni.nunm.edu/2017-medical-cannabis-conference/

AUGUST 11-12: INTRAVENOUS NUTRITIONAL THERAPIES SYMPOSIUM in Las Vegas, Nevada. CONTACT: 561-997-0112 or 888-997-0112; info@a4m.com; a4m.com

AUGUST 11-13: NEW WORLD CONSCIOUSNESS CONFERENCE & EXPO in Orlando, Florida. CONTACT: 855-606-2733; www.newworldconsciousness.com/

AUGUST 17-20: HEALING SKIES NATUROPATHIC CONFERENCE (SANP) at Manitou Beach, Saskatchewan, Canada. Special session: Advanced IV Therapy Techniques. CONTACT: sanp.ca/healing-skies-conference.html.

AUGUST 18-20: 11th INTERNATIONAL HYPERBARIC SYMPOSIUM in New Orleans, Louisiana. CONTACT: hbot2017.com/

SEPTEMBER 6-9: 18th ANNUAL FALL CONFERENCE ON INTEGRATIVE MEDICINE IN WOMEN'S HEALTH in Ojai, California. CONTACT: www.symposiamedicus.org

SEPTEMBER 11-15: APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE – 5-day foundational course in Dallas, Texas. CONTACT: www.functionalmedicine.org/AFMCP

SEPTEMBER 14-16: BHRT SYMPOSIUM in Chicago, Illinois. CONTACT: https://www.a4m.com/bhrt-symposium-chicago-2017.html

SEPTEMBER 14-16: CRITICAL UPDATES AND APPLICATIONS IN FUNCTIONAL MEDICINE in San Juan, Puerto Rico. CONTACT: 800-531-3688; www.acam.org/?page=Events

SEPTEMBER 15-17: ADVANCED JOINT INJECTION (Module 1) in Vancouver, Canada. CNBPC recognized for certification. CONTACT: 1-888-337-8427; info@viatrexx.com; www.Viatrexx.com

SEPTEMBER 15-22: KLINGHARDT IMMERSION WEEK in Kenmore, Washington. Neural therapy, Autonomic Response Testing (all levels), Applied Psycho-Neurobiology, Integrative protocols. CONTACT: 908-899-1650; info@klinghardtacademy.com; www.klinghardtacademy.com

SEPTEMBER 22-24: ADVANCED JOINT INJECTION (Module 3) in Vancouver, Canada. CNBPC recognized for certification. Also, **APRIL 13-15, 2018**. CONTACT: 1-888-337-8427; info@viatrexx.com; www.Viatrexx.com

SEPTEMBER 22-24: LOW DOSE NALTREXONE 2017 CONFERENCE in Portland, Oregon. CONTACT: www.ldnresearchtrust.org

SEPTEMBER 28-OCTOBER 1: 8th ANNUAL INTEGRATIVE MEDICINE FOR MENTAL HEALTH CONFERENCE (IMMH) in Orange County, California. CONTACT: www.IMMH.org

SEPTEMBER 29-OCTOBER 1: 10th INTERNATIONAL MEDICAL CONFERENCE-Curing the Incurable, the Fungal, Parasites, Dental Conundrum in St. Louis, Missouri. CONTACT: www.iamconf.com/

SEPTEMBER 30-OCTOBER 1: WASHINGTON ASSOCIATION OF NATUROPATHIC PHYSICIANS (WANP) ANNUAL CONFERENCE -Primary Care Update in Lynnwood, Washington. CONTACT: www.wanp.org

OCTOBER 4-8: NEURODEGENERATION-THE IMPACT OF ENVIRONMENTAL INSULT in Grand Rapids, Michigan. CONTACT: icimed.com/conferences/

OCTOBER 5-8: 15th ANNUAL INTERNATIONAL RESTORATIVE MEDICINE CONFERENCE in Tucson, Arizona. With T3 Certification and Botanical Medicine Intensive with Tieraona Low Dog, MD. CONTACT: restorativemedicine.org/conferences/tucson/ or jen@restorativemedicine.org

OCTOBER 7-8: NEVADA HOMEOPATHIC AND INTEGRATIVE MEDICAL ASSOCIATION (NHIMA) CONFERENCE in Reno, Nevada. CONTACT: 775-742-4695; info@nevadahomeopathy.org; www.nevadahomeopathy.org

OCTOBER 12-14: 26th ANNUAL IAACN SCIENTIFIC SYMPOSIUM – Solving the Disease Crises Caused by Our Toxic Environment in Plano, Texas. CONTACT: 972-407-9089; khenry@clinicalnutrition.com; www.iaacn.org

OCTOBER 19-21: GI ADVANCED PRACTICE MODULE – RESTORING GASTROINTESTINAL EQUILIBRIUM in Denver, Colorado. CONTACT: www.functionalmedicine.org/GI

OCTOBER 22-24: DETOX ADVANCED PRACTICE MODULE – BIOTRANSFORMATION AND TOXICITY in Denver, Colorado. Live Streaming Available. CONTACT: www.functionalmedicine.org/Detox

OCTOBER 22-25: LIFESTYLE MEDICINE 2017 – Transforming Health, Redefining Healthcare in Tucson, Arizona. CONTACT: 971-983-5383; events@lifestylemedicine.org; https://lifestylemedicineconference.org.

OCTOBER 22-26: AIHM ANNUAL CONFERENCE – PEOPLE, PLANET, PURPOSE in San Diego, California. CONTACT: https://www.aihm.org/aihm-conference/

OCTOBER 26-NOVEMBER 1: 44th BIOLOGICAL MEDICINE TOUR TO GERMANY & BADEN BADEN MEDICINE WEEK – "Putting It All Together: A Comprehensive Overview of Effective Modalities in Biological Medicine. CONTACT: Occidental Institute, 800-663-8342 or 250-490-3318; oirf.com/

NOVEMBER 11-12: GREAT PLAINS LABORATORY PRACTITIONER WORKSHOP in West Palm Beach, FL. This workshop reviews organic acids testing, genetic testing, and toxic chemical testing. CONTACT: 913-341-8949; www.GPLUniversity.com

DECEMBER 14-16: A4M & MMI WORLD CONGRESS in Las Vegas, Nevada. CONTACT: 561-997-0112; www.A4M.com

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Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

Regulating Toxic Substances – Who's Keeping Us Safe?

Introduction

Every day, people are exposed to toxic chemicals through the air, water, food, beverages, cosmetics, grooming products, cleaning products, and more. Although these chemicals may be considered low-dose exposure to toxins, they still have adverse health effects. There are many resources available online to help consumers figure out which products have harmful chemicals and which do not. But why does the consumer have to do so much work to try and avoid chemicals in products? Why are these chemicals in consumer products and food to begin with and who is regulating them?

Most assume that either the Environmental Protection Agency (EPA) or the Food and Drug Administration (FDA) are regulating chemicals in our air, water, food, and products. This isn't necessarily true. The Food and Drug Administration regulates the safety of chemicals in our products, but loopholes in federal laws allow the cosmetics industry to put virtually any chemical into a cosmetic or personal care product without any pre-market FDA safety testing or review, and no monitoring of health effects. The Environmental Protection Agency is operating under an old outdated law from 1976. The Toxic Substances Control Act of 1976 provides the EPA with authority to require reporting, record-keeping, testing requirements, and restrictions relating to chemical substances. Food, drugs, cosmetics, and pesticides are excluded from this list. Under the outdated law, around 64,000 chemicals are not subject to environmental testing or regulation.

Why Do We Need Regulation?

Harmful toxins are everywhere, making it almost impossible for even the informed consumer to avoid them. Here are just a few recent examples of toxic chemicals found in common foods and drinks.

Lead in turmeric: Lead is a heavy metal linked to harmful effects in children and adults. Water is the most common source of exposure, and most don't expect lead to be found in food products. Recently, several brands of turmeric spice were recalled due to high lead levels. Random sampling by New York Department of Agriculture found the high lead levels. The company Gel Spice Inc. produces Fresh Finds turmeric along with Spice Select, Market Pantry, Gel, Clear Value, Lieber's, and Spice Supreme turmeric.[1]

Pesticides in tea: Green tea, black tea, and oolong tea are known for their health benefits. Millions around the world drink tea on a daily basis. Most don't realize that tea can be a source of pesticide exposure. A 2015 study published in the *Journal of Agriculture and Food Chemistry* revealed that over 50% of teas have pesticides.[2] The EPA has no established level of tolerance for pesticides in tea. Due to lack of regulation, no one knows if there is an acceptable level of pesticide residue in tea.

More Regulation Is Starting to Happen

Perhaps due to pressure from consumers and environmental groups, there seems to be a change in regard to regulation. Many states have taken it upon themselves to ban certain chemicals from products or require labeling of products with warnings to consumer. Even the FDA and EPA have taken measures to ban chemicals or put out warnings. Many environmental groups have been putting pressure on the US Senate and Congress to create tighter regulations. It seems some of this has paid off. Here's a sampling of recent changes in regulation. Perhaps the tide is turning.

The Senate approves update of toxic chemical regulation. In June 2016, the US Senate finally approved a bill that would update the 1976 Toxic Substances Control Act.[3] This

40-year-old Act is the sole source of regulation of chemicals in everyday household products such as cleaners and detergents. Under this law about 64,000 chemicals are not subject to environmental testing or regulation. These untested and unregulated chemicals end up in products Americans use daily. This new bill just passed by Congress and Senate would require the EPA to begin conducting tests on those 64,000 chemicals, but at a very slow pace. It would examine about 20 chemicals at a time, with a deadline of seven years per chemical. Although many environmental groups wanted a stronger bill that would have required the EPA to test more than 100 chemicals a year and allowed states to enact stronger regulations, this new bill is a start in the right direction.

EPA regulates formaldehyde. Just a month after the Senate approves a bill requiring the EPA to test and regulate more toxic chemicals than in the past, the EPA finally put limits on formaldehyde exposure. According to the Agency for Toxic Substances and Disease Registry, ATSDR, formaldehyde is a chemical used in many products including fertilizer, paper, plywood, urea-formaldehyde resins, anti-septics, medicines, and cosmetics. It is also used as a preservative in some foods. It off-gasses from wood products (such as particle-board, plywood, and furniture), auto exhaust, cigarette smoke, paints, carpet, and permanent press fabrics. We are mostly exposed through inhalation. In 2011, the Department of Health and Human Services determined that formaldehyde is a known human carcinogen.[4]

Until July 2016, the EPA had not regulated formaldehyde. But new testing and certification requirements go into effect in 2017. One example of the regulation involves companies that laminate wood. They must prove that they have purchased manufactured wood from a company that complies with the new rules. Laminators also have seven years to switch to a non- or low-formaldehyde-emitting glue or meet some of the more expansive testing requirements.[5] Although environmental groups hoped for even tighter restriction, this is a start to limit a previously unregulated chemical present in almost every home.

FDA bans ingredients in antibacterial soaps. Many Americans use antibacterial soap in hopes of fighting off germs and staying healthy. Most are not aware that antibacterial soaps contain harmful ingredients including one called triclosan. In September 2016, the FDA took the unusual step of banning triclosan and 18 ingredients found in liquid and bar soaps. These chemicals could pose health risks, such as bacterial resistance or hormonal effects.[6] According to the FDA, companies will no longer be able to market antibacterial washes with these ingredients because they didn't show that the ingredients are both safe for long-term use and more effective than plain soap and water.[6] Companies have one year to comply with the new regulation.

The following 19 ingredients are now banned:

- Cloflucarban
- Fluorosalan
- Hexachlorophene
- Hexylresorcinol
- Iodophors (Iodine-containing ingredients)
  - Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
  - Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
  - Nonylphenoxypoly (ethyleneoxy) ethanoliodine
  - Poloxamer—iodine complex
  - Povidone-iodine 5 to 10 percent
  - Undecoylium chloride iodine complex
- Methylbenzethonium chloride
- Phenol (greater than 1.5 percent)
- Phenol (less than 1.5 percent)
- Secondary amyltricresols
- Sodium oxychlorosene
- Tribromsalan
- Triclocarban
- Triclosan
- Triple dye

FDA issues safety alert for WEN haircare products. WEN hair care products by Chaz Dean are a line of popular hair products including cleansing conditioner, styling cream, mouse, straightening gloss, and replenishing mist. In July 2016, the FDA started investigating the company after reports of hair loss, hair breakage, itching, balding, and rashes. As of July 7, the FDA had received 127 adverse event reports directly from consumers about WEN products, the largest number of reports ever related to a cosmetic hair cleansing product.[7] This prompted the FDA to issue a rare *safety alert* for the product ➤

Dear readers,

It is time I close a chapter in my career and say goodbye to writing the Environmental Medicine column. We launched the column in 2009 to educate readers on the link between our health and toxins in the environment. It has been both an honor and a privilege to be a voice for the Townsend Letter. I encourage everyone to continue to push for awareness, research, and regulation of environmental issues that affect health and disease.

Sincerely,
Dr. Marianne Marchese

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line. According to the FDA, WEN did not address safety concerns after the company received over 21,000 complaints of side effects.[7] Although WEN states it is cooperating with the FDA by providing a full list of ingredients, the company doesn't have to prove safety of any of its ingredients. No company under current law has to prove their ingredients have been tested and are safe. Currently, the FDA does do pre-market testing on the safety of ingredients in cosmetic products. The FDA has no ability to access companies' safety records and testing results. Only Congress can give them the power to demand access to safety records, that's if the company has any of course. So in the meantime, WEN products remain in the stores, and the most the FDA can do is issue a *safety alert.*

Summary

Toxic chemicals are present in cosmetics, food, water, and household products. Many people are not aware that even in small amounts some of these chemicals may be harmful and have adverse health effects. The FDA and the EPA are the government agencies responsible for monitoring and regulating toxic substances. Due to outdated laws and loop holes in new laws, many chemicals end up in our homes, products, food, and eventually our bodies. Although these agencies have recently begun the process of more rigorous testing and monitoring, pressure needs to continue on Congress and the Senate. Recent advances in regulation have come from consumer demands and environmental watch groups. It's important for both physicians and patients to continue educating each other about the harmful effects of these chemicals and how to take action to make companies accountable.

Dr. Marchese is the author of *8 Weeks to Women's Wellness.* She maintains private practice in Phoenix Arizona, and teaches gynecology at Southwest College of Naturopathic Medicine. She was named in *Phoenix Magazine*'s Top Doctor Issue as one of the top naturopathic physicians in Phoenix. www.drmarchese.com

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Kyowa Hakko Bio Launches Global Kyowa Quality Web Site

Kyowa Hakko Bio is introducing a new website for products made with Kyowa Hakko's ingredients backed by its Kyowa Quality® mark.

Kyowa Hakko Bio is an international health ingredients manufacturer whose primary goal is to provide health solutions that support optimal health for improved quality of life. Pioneers in the development and application of patented fermentation technology, Kyowa's ingredients meet the most demanding quality assurance standards in place within the dietary supplement, health food, cosmetic and pharmaceuticals industries. Kyowa Hakko represents a line of well-researched, branded ingredients and an extensive line of quality-assured, ultra-pure amino acids that are guaranteed with the Kyowa Quality name or seal.

The brand essence behind the Kyowa Quality® mark is nature, health, and science. **Nature:** Kyowa's products are plant based, produced through a natural fermentation process. **Health:** Kyowa's products contribute to the health and well-being of people around the world. **Science:** Kyowa's products are scientifically tested and provide world class quality. For over 60 years, Kyowa has been at the forefront of research and development of high-quality ingredients.

In recent years, the advent of the internet has allowed consumers to become increasingly knowledgeable, and they are now looking not just for brand names they know but also for key ingredients from manufacturers they can trust. "No one is positioned better to help consumers find products containing Kyowa ingredients than Kyowa. We have therefore announced the launch of www.KyowaQuality.com, a new website for products containing our ingredients and backed by our Kyowa Quality mark." said Elyse Lovett, marketing manager at Kyowa Hakko USA.

The site features Kyowa's line of Kyowa Quality ingredients as well as products that hold the KQ Logo from around the world. Kyowa's Quality ingredients include strategically branded ingredients and amino acids, pharmaceutical-grade ingredients, food-grade ingredients, and industrial grade ingredients.

About Kyowa Hakko Bio Co. Ltd

Kyowa Hakko Bio employs leading-edge fermentation technology to develop innovative manufacturing processes for producing various useful substances and is offering ingredients ranging from amino acids, nucleic acid-related compounds, vitamins, and organic acids to oligosaccharides and dipeptides globally to customers in the pharmaceutical, nutrition and healthcare markets. Our primary objective is to organically integrate fermentation and synthesis by fully leveraging the fundamental technological capabilities, human resources, and assets we have developed and perfected since pioneering the method to manufacture glutamic acid by fermentation 60 years ago.

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Fish Oil Capsules Get Blamed for Unreported Drug Interactions

by Bill Sardi

Orthomolecular Medicine News Service | www.orthomolecular.org

In what is getting to be known as the anti-dietary supplement journal, *JAMA Internal Medicine* is at it yet again. The journal recently reported on changes in prescription drug and dietary supplements from 2005 to 2011, with prescription drug use rising from 84.1% to 87.7% and dietary supplements from 51.8% to 63.7% over that time.[1]

The authors were quick to blame the increase that could result in serious side effects (a rise in risk from 8.4% to 15.1%) on the use of fish oil capsules when combined with blood thinners. This could pose bleeding problems. Fish oil use rose from 4.7% to 18.6% during the study period.

"This is a major public health problem," said the report's lead author in the *New York Times*.[2] She added that she was stunned to discover that the use of omega-3 fish oil supplements had quadrupled over five years (about 1 in 5 Americans now take fish oil capsules) as they can cause bleeding in patients taking blood "thinners" like warfarin (Coumadin). However, there are few case reports and scant evidence.[3-6]

In fact, EPA (eicosapentaenoic acid), a component of fish oil, reduces arterial calcification (stiffness) induced by vitamin K depletion caused by the drug warfarin.[7] Furthermore, concomitant use of fish oil with blood thinning drugs also is documented to reduce the risk for drug-induced gastrointestinal injury.[8]

With use of blood thinning drugs rising from 32.8% to 43.0%, there certainly would be a massive number of adverse event reports if fish oil pills even resulted in 1% of patients taking blood thinners experiencing a bleeding episode.

JAMA Internal Medicine's Bias Against Dietary Supplements

JAMA Internal Medicine published a scathing report on what it called valueless vitamin pills in its headline report published late in 2013 entitled "Enough is Enough:

Drug & Dietary Supplement Usage 2005-2011 with Comparison Listing of Nutrients Depleted by Drugs and Percentage Who Supplement with That Nutrient

Drug	Estimated Usage 2005 - 06	Estimated Usage 2010 - 11	Nutrients Depleted	Usage of Depleted Nutrient*
Statins	37.3%	50.1%	Coenzyme Q10	3 0%
Simvastatin (Zocor)	10.3%	22.5%	Vitamin K	Nil
Atorvastatin (Lipitor)	13.8%	9.7%	Selenium	Nil
Pravastatin (Pravachol)	2.8%	4.9%		
Rosuvastatin (Crestor)	1.1%	4.9%		
Zetia (ezetimibe)	5.6%	4.6%		
Beta blockers	27.1%	31.2%	Coenzyme Q10	3.0%
Atenolol	9.5%	8.5%		
Metaprolol	11.7%	14.9%		
Carvedilol (Coreg)	2.3%	4.5%		
ACE inhibitors	24.5%	30.4%	Zinc	1.5%
Lisinopril	12.9%	19.9%		
Angiotensin antagonist	13.5%	13.2%	Potassium	8.5%
(Diovan, Valsartan)			Magnesium	2.9%
			Zinc	1.5%
Calcium blockers	17.8%	19.5%	Potassium	8.5%
Norvasc	8.5%	13.4%		
Anti-diabetic drugs	8.5%	7.9	Vitamin B12	9.8-34.9%
Non-sulfonylureas				
Metformin	9.3%	12.6%		
Antiplatelet (blood thinners)	32.8	43.0	Vitamin K	Nil
Clopidogrel (Plavix)	4.5%	7.1%		
Warfarin (Coumadin)	5.3%	6.4%		
Acid blockers	15.7%	18.5%	Vitamin B12	9.8%
(proton pump inhibitors)			Folic acid B9	4.2%
Omeprazole (Prilosec)	8.2%	14.2%	Iron	1.8%
			Zinc	1.5%
			Calcium	24 1%
			Vitamin C	9.5%
			Vitamin D	15.6%
Anti-inflammatory	10.1%	13.7%	Vitamin B6	9.8%
NSAIDS			Folic acid	4.2%
Acetaminophen (Tylenol)	8.1%	8.7%	Iron	1.8%
Naproxen (Aleve)	3.5%	4.7%	Vitamin C	9.5%
Aspirin	30.3%	40.4%	Iron	1.8%
			Vitamin C	9.5%
			Folic acid	4.2%
Diuretics	36.9%	47.6%	Potassium	8.5%
Thiazide	17.1%	19.3%	Magnesium	2.9%
Furosemide	7.3%	8.2%	Thiamin B1	9.8%

Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011 JAMA Internal Medicine April 1, 2016.

* not counting multivitamins

Many other articles by journalist and radio host Bill Sardi will be found at his educational website, http //knowledgeofhealth com .

Fish Oil Capsules

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Stop Wasting Money on Vitamin and Mineral Supplements,"[9] which prompted this reporter to write a rebuttal entitled: "Vitamins: Enough of 'Enough is Enough'."[10]

JAMA Internal Medicine's most recent report takes a similar swipe at supplements by saying "Despite no evidence of any clinical benefits, dietary supplement use is increasingly common among older adults, with almost a 50% increase in the use of multiple supplements." Before authors of this nonsense are allowed to go any further with their false claim that there is "no evidence" for the benefits of dietary supplements, let's take a look at the strong ***need*** for dietary supplements among senior adults.

Researchers have recently done a meticulous job of documenting the progressive shrinkage (atrophy) of the human brain with advancing age, a process that is slowed by provision of vitamin B12 supplements.[11,12] By the way, the B12 vitamin cure for this problem does not work without co-consumption of fish oil or other excellent sources of omega-3 fatty acids such as walnuts, flax oil, and grass-fed beef.[13]

Brain shrinkage is a universal part of aging. No brain scans or diagnoses are needed before embarking upon a dietary supplement regimen that includes B12 and fish oil. Should one have to wait until brain shrinkage is noted to start taking B vitamins and fish oil? I think not. And why aren't *JAMA Internal Medicine* editors unanimously urging their physician readers to prescribe fish oil and vitamin B12 for their senior patients?

The Real Problem: Drug-Induced Nutrient Depletion

Statin drugs are the most used class of drugs, taken by half of senior Americans. I guess American doctors haven't read the shocking report by investigators in Japan that claims, by virtue of statin drugs' inhibition of vitamin K, coenzyme Q10 and the trace mineral selenium, they hasten heart failure.[14] This makes dupes (a victim of deception) out of every naive statin drug user.

The larger problem is the potential for prescription drugs to deplete essential nutrients from the body, which results in disease substitution rather than disease treatment. Pharmaceutical drugs are notorious for their ability to deplete patients of nutrients, meaning the patient will never get well. There is long-term profit there, and lots of it.

Thanks to the *JAMA Internal Medicine* report, we can get a rough idea what proportion of medication users are at risk for nutrient depletion because we can compare the data side-by-side. The chart below shows drug use (percent use by subjects in survey) that can be compared with a list of nutrients these drugs deplete and the percent of nutrient usage.

Nearly half of the subjects in the survey took statin drugs and only 3% of those surveyed take coenzyme Q10. That is a lot of people at unnecessary risk. For most individuals, proper doses of vitamins such as vitamins C, D, E, B-complex, and essential nutrients such as magnesium can obviate the need for statins. Nutrients are a far better way to prevent and reverse heart disease.[15,16]

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Women's Health Update

by Tori Hudson, ND
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Coronary Artery Calcium Testing in Women

Coronary artery calcium (CAC) is associated with an elevated risk for coronary heart disease (CHD), but the question is whether or not CAC testing predicts cardiovascular outcomes in women who are considered at low risk for cardiovascular disease. To investigate this relationship between CAC and cardiovascular disease, researchers conducted a meta-analysis of five large studies involving 6739 women, ranging in ages 44 to 63, with an estimated 10-year risk for cardiovascular disease of less than 7.5%.

A total of 36.1% of the women analyzed in all the studies had coronary artery calcium present. With an average follow-up ranging from 7.0 to 11.6 years, the risk for atherosclerotic cardiovascular disease events, including non-fatal heart attacks, coronary heart disease death, or stroke, was significantly higher in women with coronary artery calcium (4.33 per 1,000 person years) than in those without (1.41 per 1,000 person years). When coronary artery calcium was added to traditional cardiovascular risk factors, the ability to reclassify low-risk women into other risk groups improved but only modestly.

Comment: The results of this meta-analysis suggest that coronary artery calcium testing is fairly common in women who are at low risk for cardiovascular disease and that it may be used to classify their risk more precisely. However, that does not necessarily mean that there would be more effective prevention strategies in women who are otherwise at low risk for cardiovascular disease. There are women who have risk factors that may not be identified in the usual screening. For example, someone may appear to have a reasonable basic lipid panel, but if she were to have advanced lipid testing with testing of other cardiovascular risk markers such as C-reactive protein, homocysteine, lipid subfractions and more, we might reclassify her risk; and in this case, a coronary artery calcium

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test may elucidate the need to be more pro-active in her prevention strategies. True, we do not have data on each prevention strategy and each data point. There are patients and clinicians who are willing to fine tune the prevention program with optimal natural therapeutics that improve these markers with the intention of lowering cardiovascular disease risk further.

Kavousi M, et al Prevalence and prognostic implications of coronary artery calcification in low-risk women· A meta-analysis. *JAMA*. Nov 12, 2016 (e-pub)

Exercise and All-Cause Mortality

Current physical activity guidelines recommend moderate-intensity exercise for 30 minutes most days of the week for a total of 150 minutes/week, or vigorous exercise for 75 minutes per week, spread out over at least three sessions per week. In a report published in January 2017, researchers evaluated more than 63,000 men and women over age 40, inquiring about their moderate to vigorous physical activity. The research participants were classified into four groups: 1) individuals who did no moderate or vigorous physical activity 2) those who met the 150 minutes/week of moderate intensity or 75 minutes/week guidelines for of vigorous intensity and divided over at least three times weekly 3) those who met those total amount of minutes per week but did so within one to two sessions/week and 4) and those who did some moderate to vigorous exercise but less than the guidelines.

The results demonstrated that all of the active groups, compared with those having no moderate to vigorous activity, had substantial reductions in cardiovascular disease and all-cause mortality. Those individuals who met the guidelines and exercised at least three sessions per week had a 35% reduction in all-cause mortality. All three active groups had approximately a 40% reduction in cardiovascular mortality compared with those who did not report any moderate to vigorous activity.

O'Donovan G, et al. Association of weekend warrior and other leisure time physical activity patterns with risks for all cause, cardiovascular disease and cancer mortality. *JAMA Intern Med*. Jan 9, 2017 Epub ahead of print.

Marjoram Tea and PCOS

This pilot study was a randomized, double-blind, placebo-controlled trial. A group of 28 women diagnosed with PCOS were recruited from a gynecology clinic at the University of Jordan Hospital. Women were randomized to either the treatment group of marjoram tea or placebo tea twice daily for one month, with 15 in the marjoram tea group and 13 in the placebo group. Participants maintained their usual dietary habits and physical activity level during the study. One woman withdrew from the treatment group and two from the placebo group for noncompliance and inability to follow-up.

Dried leaves of marjoram were placed in storage bags containing 1.3-1.5 gm of herb, equivalent to one heaped teaspoon. The placebo material was prepared from the hard stems of thyme herb but was subjected to prolonged boiling for five hours to assure very poor content of the water-soluble components. Participants steeped the content of the marjoram bag in 250 mL of boiled water for 20 minutes, and then strained. Each woman drank one cup of 250 mL of assigned tea, unsweetened, twice daily and were told to not consume any food or beverage before or after the tea for at least one hour.

Blood samples were taken on days 2-4 of a spontaneous menstrual cycle or on a random day for those who were oligomenorrheic or amenorrhoeic and then again within five days after the end of the one-month study period. Serum samples included follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, total testosterone, DHEA-S, insulin, and glucose. For all tests but the testosterone or DHEA-S, the phase of the menstrual cycle was taken into account in the analysis of the results.

Marjoram tea significantly reduced fasting insulin levels and DHEA-S by a mean of 1.9 and 1.4 respectively. There was also an improvement in HOMA-IR and glucose to insulin ratio although it was not significant. Compared to the placebo, marjoram tea resulted in a significant reduction in DHEA-S levels and HOMA-IR values although the changes in insulin levels did not reach significance. Changes in the phase dependent hormones (all those but total testosterone and DHEA-S), showed no significant differences.

Comment: Marjoram or sweet marjoram is a perennial plant of the mint family, native to eastern Mediterranean countries. In those regions, it has been used in traditional medicine to help restore hormonal balance. I believe this is the first published study investigating the therapeutic use of the herb in women with PCOS. Marjoram has been shown to activate the peroxisome proliferator-activated receptors (PPARs); and the activation of these receptors has an established role in the improvement of insulin sensitivity. The herb is also rich in flavonoids and phenolic compounds with antioxidant activity.

The results of this study show the benefits of marjoram tea in women with PCOS by reducing adrenal androgens and improving insulin sensitivity. Add this simple herbal tea therapy to another simple therapy with positive androgen lowering results in PCOS women: spearmint tea, one cup twice per day.

Haj-Husein I, et al. The effect of marjoram tea on the hormonal profile of women with polycystic ovary syndrome: a randomised controlled pilot study *J Human Nutrition and Dietetics*. 2016; 29 105-111.

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not have the same negative effects, and might even be beneficial.

Possible Implications for Prostate Cancer

Basic-science research and observational studies in humans suggest that alpha- and gamma-tocopherol might each help prevent prostate cancer. However, randomized controlled trials of alpha-tocopherol have produced conflicting results. In a randomized study of male smokers, supplementation with 50 IU per day of alpha-tocopherol for 5-8 years significantly decreased the incidence of prostate cancer by 31%.[15] In contrast, in other double-blind trials, alpha-tocopherol at a dose of 200 IU per day had no effect on prostate cancer incidence,[16] and at a dose of 400 IU per day for 5.5 years (with a total follow-up period of seven years) alpha-tocopherol significantly increased the incidence of prostate cancer by 17% compared with placebo ($p < 0.01$).[17] These apparently contradictory findings might be explainable by a dose-related depletion of gamma-tocopherol by alpha-tocopherol. That possibility is supported by the dose-response relationship in the randomized controlled trials of alpha-tocopherol mentioned above: a protective effect with 50 IU per day, no effect with 200 IU per day, and a deleterious effect with 400 IU per day. Vitamin E might be more effective for cancer prevention if it is administered in the form of mixed tocopherols (which contain all four isomers of vitamin E) than if alpha-tocopherol alone is used.

Future Directions

Future studies of vitamin E for prevention of heart disease and cancer should use mixed tocopherols, rather than pure alpha-tocopherol. Furthermore, although much of the evidence is at present circumstantial, it would be reasonable to recommend mixed tocopherols instead of alpha-tocopherol when using vitamin E therapeutically.

Mixed tocopherols are more expensive to produce than alpha-tocopherol, and some products labeled as vitamin E "with mixed tocopherols" contain only token amounts of mixed tocopherols. Reputable mixed-tocopherols products should specify the amount of gamma-tocopherol present. It has been my practice to recommend products that contain 50-100 mg of gamma-tocopherol per 400 IU (268 mg) of D-alpha-tocopherol. That ratio is in line with the ratio of gamma- to alpha-tocopherol in the European diet, although it is lower than the ratio in the American diet.

Alan R. Gaby, MD

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Vitamin E: The Importance of Gamma-Tocopherol

Vitamin E: Nomenclature

"Vitamin E" refers to a group of eight naturally occurring compounds with antioxidant activity: alpha-, beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma-, and delta-tocotrienol. Tocotrienols have demonstrated some beneficial effects in humans, but they have not been well studied and will not be discussed in this article. Vitamin E was named "tocopherol," from Greek words meaning "to bear young," because it was found to be an essential nutrient for fertility in rats.

According to a standard assay (the rat fetal resorption assay), alpha-tocopherol has the highest biological activity of the four tocopherols, and it is the only form of vitamin E that is officially recognized as being capable of meeting human requirements. In addition, the vast majority of clinical research on vitamin E has used alpha-tocopherol. For these reasons, alpha-tocopherol is often considered to be synonymous with vitamin E. In this article, "vitamin E" generally refers to alpha-tocopherol unless otherwise specified.

Biological Effects of Gamma-Tocopherol

In contrast to alpha-tocopherol, gamma-tocopherol has very low vitamin E activity according to the rat fetal resorption assay.[1] For that reason, its potential importance for human health has been largely overlooked. However, gamma-tocopherol has a number of other important biological effects, some of which are more pronounced than those of alpha-tocopherol. For example, gamma-tocopherol was more effective than alpha-tocopherol in inhibiting prostate cancer cell growth, reducing oxidative DNA damage, and increasing superoxide dismutase activity.[2] Gamma-tocopherol or mixed tocopherols (which contain a high proportion of gamma-tocopherol) also inhibited platelet aggregation to a greater extent than did alpha-tocopherol.[3,4] In addition, gamma-tocopherol was more effective than alpha-tocopherol at scavenging peroxynitrite. Peroxynitrite is a powerful mutagenic nitrating and oxidizing agent formed during the activation of phagocytes. It is believed to play a role in the pathogenesis of cardiovascular disease, cancer, and neurodegenerative diseases.[5] Moreover, a metabolite of gamma-tocopherol – 2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman (gamma-CEHC) – appears to function as a natriuretic hormone, in that it is involved in the body's response to sodium-induced plasma volume expansion.[6,7,8,9] This action as a natriuretic hormone raises the possibility that gamma-tocopherol could useful for preventing and treating congestive heart failure. In addition, according to a recent study in mice with experimentally induced diabetes, gamma-tocopherol has anti-inflammatory activity and enhances wound healing.[10] Thus, while gamma-tocopherol is not capable of preventing classical manifestations of vitamin E deficiency, it appears to have useful functions.

Alpha-Tocopherol Depletes Gamma-Tocopherol

The importance of considering gamma-tocopherol in human nutrition is underscored by reports that supplementation with alpha-tocopherol in doses of 200-1,200 IU per day decreased serum levels of gamma-tocopherol by accelerating its metabolism.[2,11,12,13] As suggested below, it is possible that some of the adverse effects attributed to long-term vitamin E supplementation are due to alpha-tocopherol-induced gamma-tocopherol depletion.

Possible Implications for Heart Failure

In a double-blind study of patients with vascular disease or diabetes, supplementation with 400 IU per day of alpha-tocopherol for seven years resulted in a significant 19% increase in the incidence of heart failure compared with placebo.[14] This adverse effect may have been due to alpha-tocopherol-induced gamma-tocopherol depletion, resulting in a deficiency of the natriuretic hormone, gamma-CEHC. If high-dose alpha-tocopherol does adversely affect cardiac function in some people, one might reasonably expect that mixed tocopherols, which contain all four isomers of vitamin E, would

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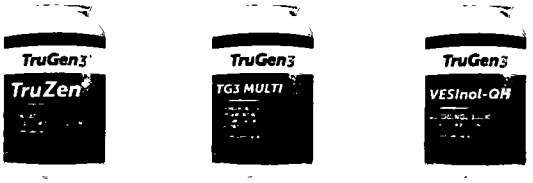

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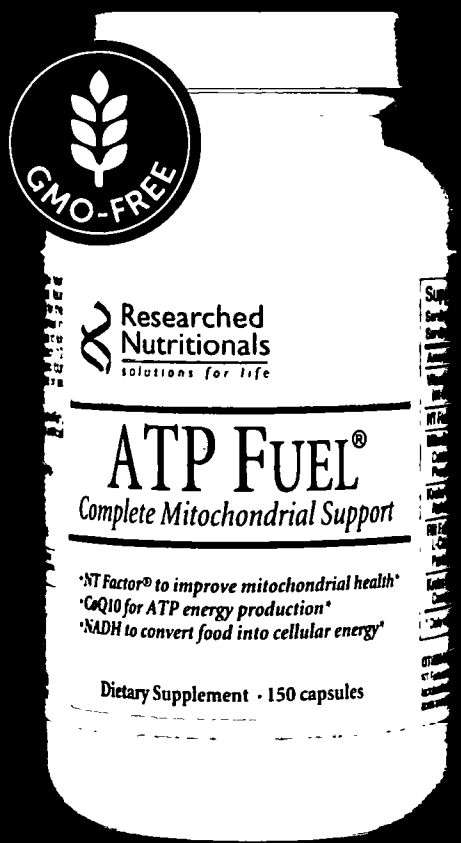

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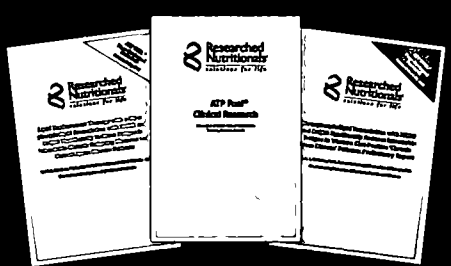

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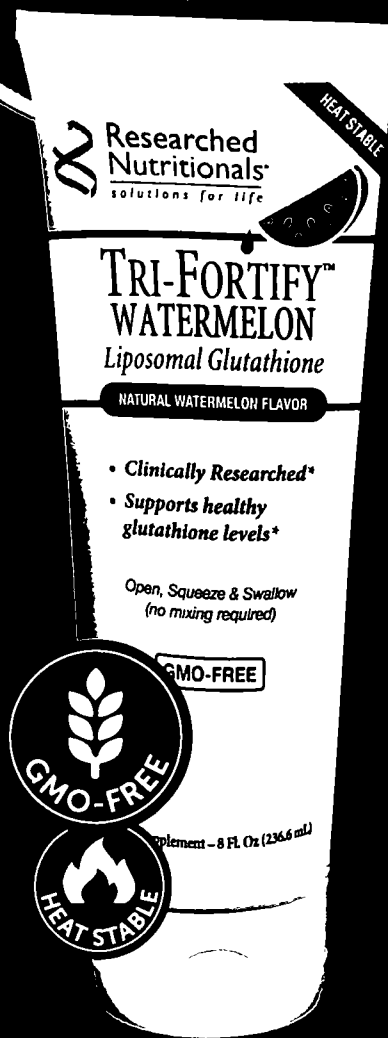

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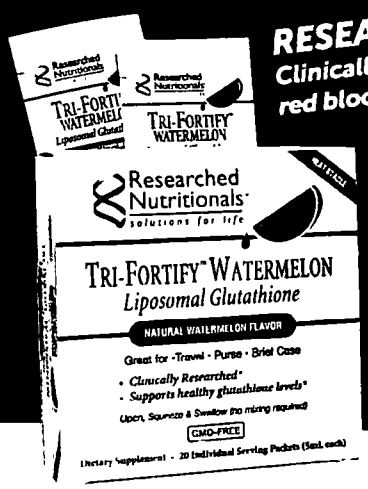

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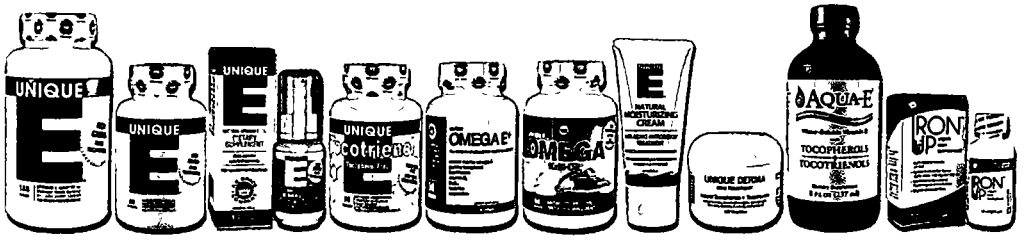

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