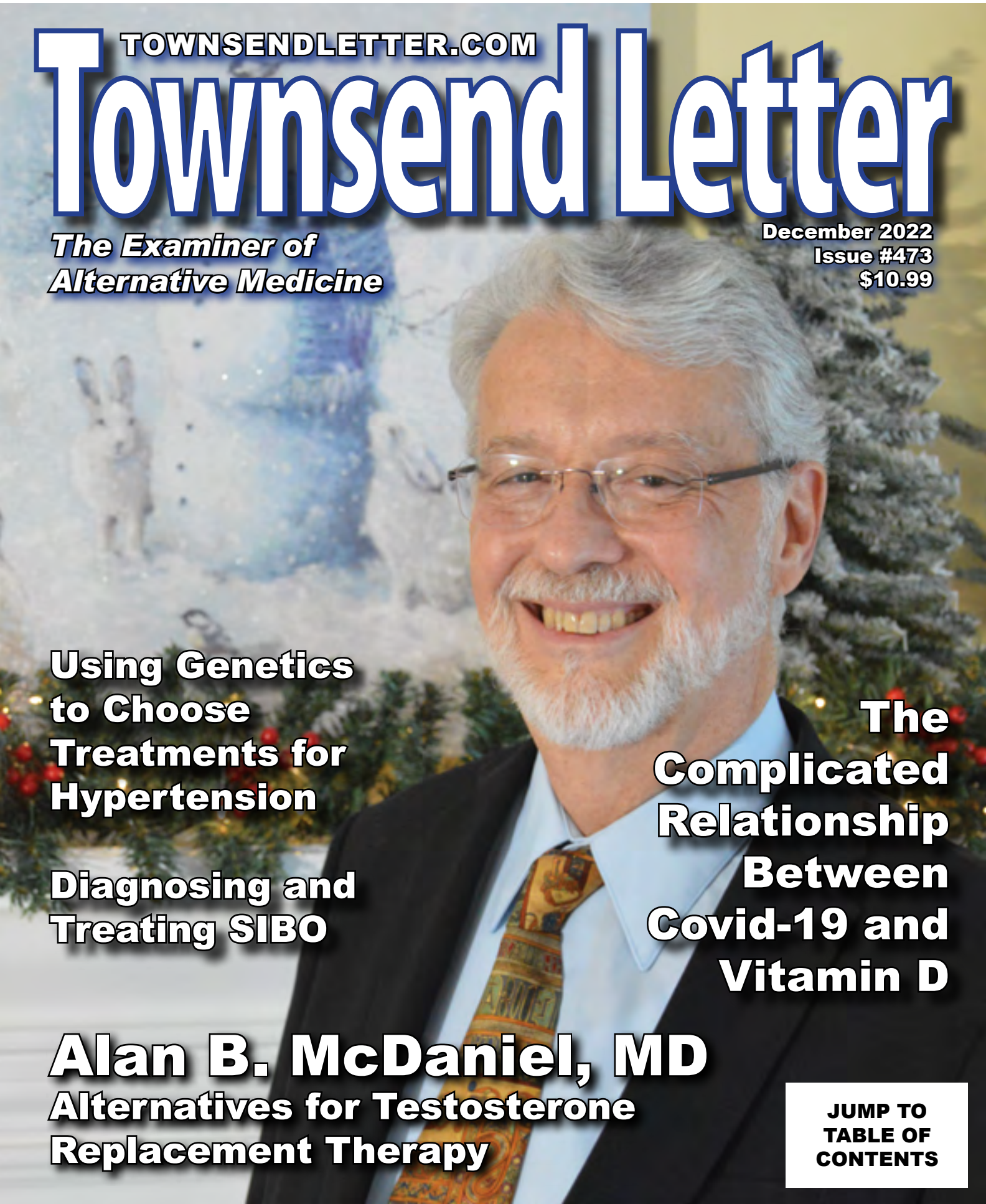
MEN'S HEALTH | ANTI-AGING

TOWNSENDLETTER.COM

Townsend Letter

The Examiner of Alternative Medicine

December 2022
Issue #473
$10.99



Using Genetics to Choose Treatments for Hypertension

Diagnosing and Treating SIBO

The Complicated Relationship Between Covid-19 and Vitamin D

Alan B. McDaniel, MD
Alternatives for Testosterone Replacement Therapy

JUMP TO TABLE OF CONTENTS

Thank you for purchasing this issue of *TOWNSEND LETTER*

On the cover (previous page) you will find a button that will take you directly to the table of contents. Once there, you can click page numbers that take you directly to articles. Click on "return to table of contents" at the bottom of each page to take you back to the TOC.

Most web and email addresses are clickable within the articles and in the calendar. We do not guarantee the accuracy of each address/URL, or that it is clickable.

Please don't overlook our advertisers, without their support *Townsend Letter* would not exist. Take the time to discover companies you might not be familiar with, many of whom offer special pricing for *Townsend Letter* subscribers. An advertiser list is printed on page 71 with clickable page numbers that will take you directly to their ad(s).

Subscription Rates and Options

Prices valid through 3/1/2023

Name _____ Email/Phone _____

Address _____

City/State/Zip _____

Payment accepted in US funds, payable by check / money order / credit card / or billed via PayPal

Payment by: Visa/MC/AMEX/Discover # _____ Expiration date: _____

Signature _____

Click here to subscribe online

	Description	Print Version	E-Edition	Combined
US Addresses (except WA state)	1-year Domestic US	$76.99	$40.00	$91.99
	2-year Domestic US	136.99	72.00	166.99
	6-month Domestic US	45.99	28.00	59.99
	1-year Student Domestic US	56.99	30.00	66.99
Washington State Residents	1-year Washington state (w/tax)	86.99	45.00	99.99
	2-year Washington state (w/tax)	146.99	79.00	183.99
	6-month Washington state (w/tax)	33.99	32.00	65.99
	1-year Washington Student (w/tax)	56.99	34.00	66.99
1st Class	1-year First Class Domestic US	96.99	40.00	111.99
	2-year First Class Domestic US	176.99	72.00	206.99
International Rates	1-year International (US$)	105.99	40.00	120.99
	2-year International (US$)	202.99	72.00	232.99
	6-month International (US$)	63.99	28.00	78.99
	1-year International student (US$)	76.99	30.00	93.99

Renew your subscription for **$76.99** and purchase a 2nd subscription for your waiting room for **$20** (Washington residents $86.99 and $22.60 – includes tax)

E-Edition Single Issue: $15.00

E-Edition Single Issue WA State (includes tax): $16.00

Single Print Issues: cover cost (for each issue), plus shipping charges, applicable taxes, and $3 per-order handling fee.

Townsend Letter

911 Tyler Street | Port Townsend WA 98368

info@townsendletter.com

360.385.6021 | 360.385.0699 (fax)

www.townsendletter.com

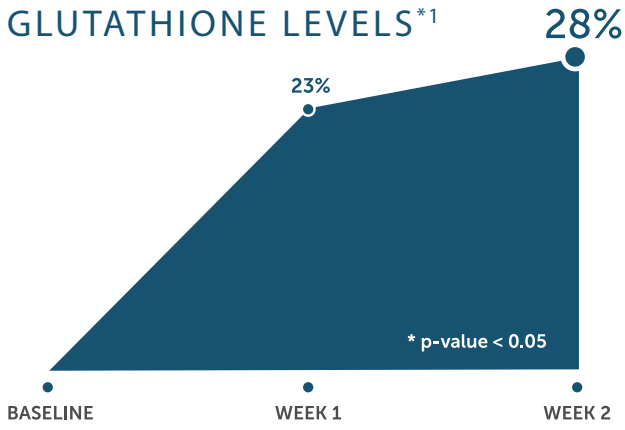
Tri-Fortify®

Liposomal Glutathione

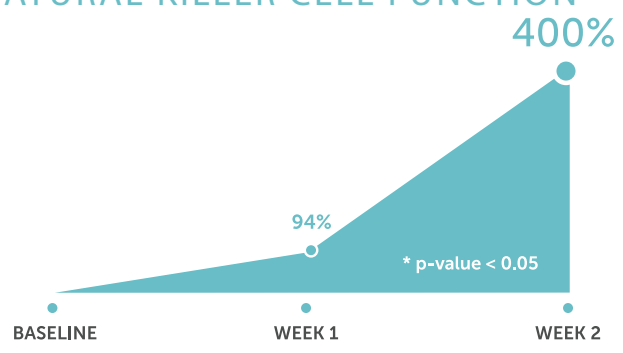
Researched Nutritionals®
solutions for life

Backed by *peer-reviewed, published* clinical research.[1]

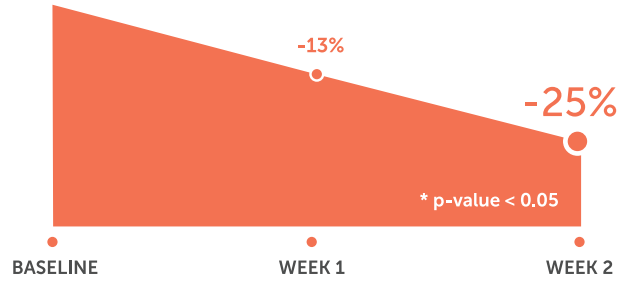
GLUTATHIONE LEVELS*[1]



NATURAL KILLER CELL FUNCTION*[1]



OXIDATIVE STRESS MARKERS*[1]



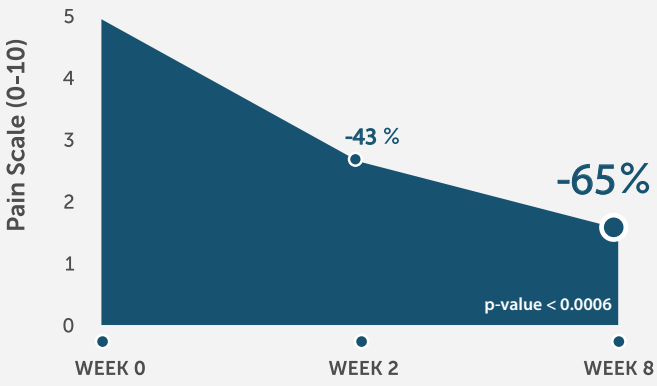
Learn more.

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

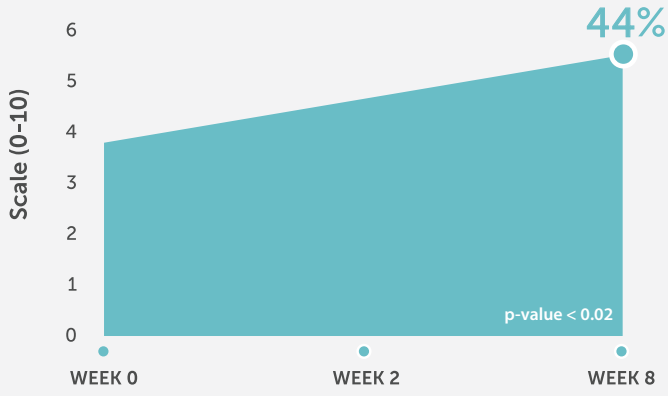
800.755.3402 • Info@ResearchedNutritionals.com • ResearchedNutritionals.com | Available only through healthcare professionals.

Research is the difference.

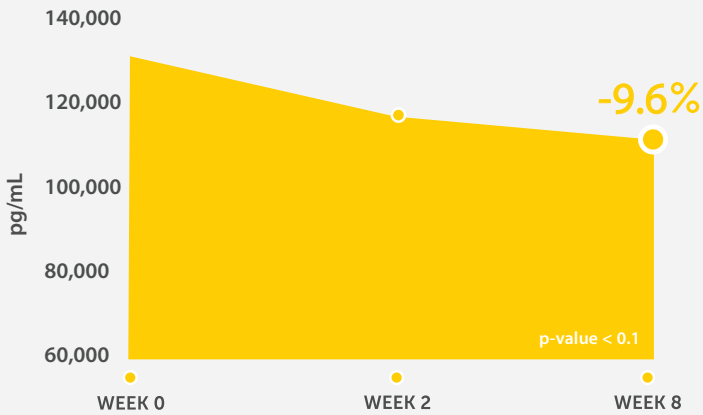
PHYSICAL DISCOMFORT*



SLEEP IMPROVEMENT*1



MMP-9*1



Learn more

Learn more: researchednutritionals.com/cytoquel

[1] Journal of Pain Research (D Hamilton, G Jensen). Pain reduction and improved vascular health associated with daily consumption of an anti-inflammatory dietary supplement blend. J Pain Res. 2019; 12: 1497–1508.

Researched Nutritionals solutions for life

800.755.3402 • Info@ResearchedNutritionals.com • ResearchedNutritionals.com | Available only through healthcare professionals.

These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

From the Publisher

Is Rapamycin the Long-Sought Fountain of Youth?

Several years ago a patient asked me about a drug that had anti-aging activities he had been reading about. When he asked if I knew anything about rapamycin (sirolimus), I admitted that I did not. He brought in a research study, which I perused and thought that the evidence appeared promising but the drug did have notable adverse effects so I remained skeptical. Ultimately, I said that I was not comfortable prescribing it. While I may have had some reasonable concerns about its use as a life extension agent, sirolimus had already been in use for nearly two decades as an immune suppressive agent for organ transplant patients. For the many kidney transplant patients, sirolimus is a very effective drug ensuring that their organ would not be rejected. Still it seemed odd to me that this drug would be appropriate to prescribe for its life extension effects. I wondered why it was not being brought up, indeed, touted at the annual A4M (Academy of Anti-Aging Medicine) meetings? Indeed, with so many articles and letters submitted to the *Townsend Letter*, why wasn't rapamycin being discussed? I don't have an answer for the paucity of discussion. However, earlier this year Ross

Pelton, "The Natural Pharmacist," wrote about rapamycin and its putative anti-aging effects in the *Townsend Letter*. Pelton has now published a short book about it: *Rapamycin, mTOR, Autophagy & Treating mTOR Syndrome.* Having just finished reading it – it is an easy, fun, fast read – Pelton lays out a compelling argument for why rapamycin may very well be our long-sought fountain of youth.

mTOR is an acronym for mechanistic target of rapamycin. However, mTOR is not a term limited to describing the pharmaceutical's mechanism of action. mTOR is a basic cellular process that is involved in how all cells function, human as well as other animals. It is essentially the organizing cellular enzyme that signals the cell to fully engage metabolically, carrying out the anabolic pathways that ensure the viability and growth of the cell. Pelton likens it to a gas pedal; if mTOR is active, cellular function is performing strongly. In contrast, when mTOR is braked, the cell is no longer synthesizing proteins and growing. Instead, with mTOR at rest, autophagy takes over, cleaning up and eliminating cellular debris. Pelton looks at the pre-modern era when we did not eat throughout the day going many hours between eating. He likens the long period of time of not eating to being a time when the body was engaged in autophagy; only during the brief time periods of eating was mTOR active. Our lifestyle of eating all day long keeps us essentially always in an mTOR state. This persistent, unstopping mTOR, according to Pelton, is responsible for our excess calories, obesity, metabolic syndrome, inflammation, diabetes, cardiovascular disease and more. He calls this hyper mTOR state the mTOR Syndrome. To counter the mTOR Syndrome we need to mimic our paleolithic ancestors eating intermittently, not eating most of the time. Of course, not eating for 14-18 hours per day is a tough go for most folks. It is, however, a definite strategy that is employed now to revitalize our health and battle cancer.

So, what does this have to do with rapamycin? The drug accomplishes essentially the same thing that intermittent fasting does. Pelton asserts it resets mTOR Syndrome putting our body in a more balanced state, emphasizing rest/autophagy while braking excess mTOR activity. Animal studies with rapamycin demonstrate an effect comparable to calorie restriction; animals tend to live longer than expected. Human studies of rapamycin's effect on longevity are scarce. However, one study at UCLA started last year to study rapamycin's effect on the aging process in humans.

There is a major difference between using rapamycin as an immunosuppressant in organ transplant patients and using it for life extension. The former requires daily use of the drug. For anti-aging, rapamycin is used only once per week. According to doctors who use rapamycin for life extension, the periodic use of it avoids the immune suppression. In fact, some think of the drug as an immune modulator, high dosing suppresses the immune system, while low dosing enhances it. Adverse effects when used weekly tend to be minimal. One challenge for patients is convincing their physician to prescribe rapamycin; a second, is having sufficient funds to pay for an expensive drug. Although Pelton makes the case that some insurance carriers will cover the cost, it appears unlikely that they will accept an anti-aging diagnosis as sufficient reason to pay for it.

From the Publisher

➤

The background story of rapamycin is fascinating. Canadian drug researchers travelled to Easter Island in 1964 to study soil organisms for possible new antibiotics or other drugs. A soil organism in the Streptomyces family was discovered in 1972 by Suren Sehgal to produce a chemical that had strong anti-fungal activity. The drug company, Ayerst, named the compound rapamycin because it was discovered on Rapa Nui, the native people's name for Easter Island. The drug was not marketed as an anti-fungal agent because it was found to have immune suppressing activity. In 1994, David Sabatini, Stuart Schreiber, and Robert Abraham separately discovered that rapamycin binds to the protein enzyme in cells that has been named mTOR. Not long after, it was observed that rapamycin's strong immunosuppressant activity would help transplant patients avoid organ rejection. Additionally, rapamycin appeared to have promising activity slowing tumor cell growth in certain cancers.

Sehgal's research work with rapamycin as reported in a May 2021, *Radiolab* (NPR) interview is quite interesting. After working with the drug for a number of years in the 1970s to 1980s, his employer, Ayerst Labs, decided to shut down the entire operation. All the research materials were being discarded. Sehgal was very devoted to his Easter Island discovery and could not bear to throw it all away. So, he took the material and stowed it in his freezer at home. When he was offered work in New Jersey he told his movers to ensure that the material in the freezer was to be shipped as well. It was in NJ that Sehgal and others conducted research on rapamycin ultimately demonstrating its effectiveness as an agent to prevent organ transplant rejection. When Sehgal developed colon cancer in the 1990s, he was informed by his oncologist that the disease had progressed so much that he would only have six months to live. Sehgal decided to take rapamycin himself – not only did he pass the six-month point, but then he lived another year and then another year surviving for five years. During this time, he travelled the world with his wife speaking at conferences and continuing bench research. He was always the scientist and decided in his fourth year of survival that he had to determine if it was chemotherapy and conventional cancer care or rapamycin that enabled his lengthy survival. He quit using the drug. Unfortunately, within months he sickened, becoming cachectic from his relapsed metastatic disease. When his wife suggested that he resume the rapamycin, he chose not to because the "experiment" he was conducting on himself could only ascertain whether it was conventional care or rapamycin that enabled his survival by remaining off the drug. Ultimately, he died, suggesting that it was, indeed, rapamycin that conveyed the survival benefit.

Metformin has been touted as an off-label anti-aging agent. Pelton makes a strong case for rapamycin being an anti-aging agent as well, perhaps the most effective one of all.

Cover Article: Alternatives to Treating Low-T with Testosterone by Alan McDaniel, MD

Townsend Letter readers are familiar with writing by Dr. McDaniel – last year he wrote a two-part series on hypothyroidism. In 2016 he wrote an extensive article for the *TL* on testosterone. In this issue McDaniel examines options

continued on page 6 ➤

Townsend Letter

ISSN 1940-5434

Subscriptions • Editorial • Advertising

360/385-6021

24 Hr. Fax – 360/385-0699

911 Tyler Street | Pt. Townsend, Washington 98368 USA

http://www.townsendletter.com | info@townsendletter.com

Editor-in-Chief	Jonathan Collin, MD
Publisher	Jonathan Collin, MD
Editor	Jule Klotter
Contributing Medical Editor	Alan Gaby, MD
Managing Editor	Barbara Smith
Circulation Manager	Joy Reuther-Costa
Managing Assistant	Julie Reuther
Advertising Projects & Accounts	Barbara Smith Joy Reuther-Costa Jonathan Collin

Columnists & Writers
Majid Ali, MD
Eleonore Blaurock-Busch, PhD
Nancy Faass, MSW, MPH
Peter A. Fields, MD, DC
Alan R. Gaby, MD
Michael Gerber, MD, HMD
Ira Goodman, MD
James Greenblatt, MD
Tori Hudson, ND
Baljit Khamba, ND, MPH
Ronald Klatz, MD, DO
Ingrid Kohlstadt, MD, MPH, FACN
Sarah A. LoBisco, ND
Marianne Marchese, ND
Alan B. McDaniel, MD
Chris Meletis, ND
Ralph W. Moss, PhD
Erik Peper, PhD
Michelle Perro, MD
Jonathan Prousky, ND, MSc
Judyth Reichenberg-Ullman, ND
Steven Sandberg-Lewis, ND
Jacob Schor, ND, FABNO
Pamela Smith, MD
Jacob Teitelbaum, MD
John Trowbridge, MD
Elaine Zablocki

Contributing Writers
Katherine Duff
Bob Frost
Gary Null, PhD

Layout & Design
Barbara Smith/Sign Me Up! Inc.

Design Team
Jonathan Collin
Joy Reuther-Costa
Barbara Smith

Cover Photo Credit
Natalie J. McDaniel

Printing
Dartmouth Printing Company

Website Design & Maintenance
Joy Reuther-Costa

Published by
Townsend Letter for Doctors & Patients, Inc.
Jonathan Collin, President
Deborah Nissen-Collin, Vice-President

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

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

Corn-Free Vitamin C

Buffered Cassava Vitamin C
now available from Allergy Research Group

Allergy Research Group pioneered the use of buffered vitamin C supplements in the United States, and we continue to offer the purest, least allergenic vitamin C formulas on the market.

Our newest offering, Buffered Cassava Vitamin C, provides high-purity, Non-GMO ascorbic acid derived from cassava root, not corn. This formula is enhanced with calcium and magnesium, and is safe for vegetarians, vegans, and those sensitive to corn.*

- CORN FREE
- NON-GMO
- VEGAN
- NON-GLUTEN
- DAIRY FREE

AllergyResearchGroup®

Fullscript

Call or order online
800.545.9960
allergyresearchgroup.com

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

From the Publisher

➤ *continued from page 4*

that may be employed to stimulate endogenous production of testosterone in patients with low-T. Of course, longevity clinics prescribe testosterone, but McDaniel asks why should this be done if a patient's testosterone level can be adequately raised without prescribing hormone? A major concern that goes largely unaddressed is the prospect of developing smaller testes. For the younger men this may mean that there is a decreased production of sperm and a smaller ejaculate volume. Other concerns may be development of gynecomastia and polycythemia – not to mention the administration and expense of testosterone therapy can be burdensome.

McDaniel considers lab testing for these patients to be paramount. Not only are testosterone and estradiol measured but also the gonadotrophins, LH and FSH, are as well. Why would a patient having a low testosterone level also have low LH and FSH? Typically, LH and FSH are increased if the testosterone level is low, and one should explore whether excess estradiol is shutting down the gonadotrophin production. Excess weight is probably the leading cause for excess aromatase activity converting testosterone to estrogen. For such a patient a weight loss program, including diet, exercise, and support for insulin resistance, is in order. However, the best approach to countering high estrogen is the prescription of an aromatase inhibitor. There is a challenge in prescribing these drugs – one does not wish to excessively lower the patient's estrogen level. What if the gonadotrophins remain relatively low following treatment with an aromatase inhibitor. McDaniel advises the use of selective estrogen-receptor modifiers (SERMs) to reduce the effect of estradiol on the hypothalamus, enabling greater production of gonadotrophin releasing hormone to stimulate increased LH and FSH.

McDaniel illustrates management of four patients experiencing low-T using aromatase inhibitor and/or SERM, demonstrating changes over time to testosterone, estradiol, LH/FSH and related labs that are monitored. This article is a great take-away for use in the office.

Valued Reader: We Need Your Support!

The *Townsend Letter* has been in print since 1983. Back in the day, it was pretty much the only forum for integrative doctors and the nutraceutical industry. While there was the occasional medical convention where docs and reps could get together and share the newest technologies and supplement products, there was no media for folks to share information. Basically, we fit that niche. Of course, in the 1990s a few other print publications began to appear and then the internet's appearance in the 2000s led to the media digital revolution. It is true that there is prolific e-publishing appearing on the net by doctors, supplement companies and laboratories on all sorts of platforms, including YouTube, Google Search, podcasts, and websites. The *Townsend Letter* continues as a print magazine as well as an e-magazine, and e-newsletter.

Now nearing its 40th year of publication the *Townsend Letter* is facing tremendous difficulties without adequate support from the nutritional community. Everyone seems to think editorial content is deserved on a free basis and that serving the functional medicine community can be accomplished without funding. So, yes, this is a plea asking each of you to step up and support the *Townsend Letter.* We have faithfully provided a forum for four decades and that forum is in danger of not being able to sustain itself. Ask yourself, do I want the *Townsend Letter* forum to be able to survive the challenges of e-publishing and digital advertising?

Here's how you can support us: Renew your subscription today for the rate of $76.99 and for $20 more we will send you a second copy to place in your office reception area (Washington State residents renewal rate and reception copy is $86.99 + $22.60.) Yes, it is quite an ask we are making for your support but it is vital now. For those who wish to provide sustaining support beyond the subscription fee, we are most appreciative. Thank you so much for your support!

Jonathan Collin, MD

Immune Support from our Maitake Family For Your Family*

Prepare your family for the change in seasons with Maitake D-Fraction®! As the days grow shorter and cooler, life on the home-front picks up the pace – getting the kids to school on time, rushing to meet that work deadline, driving in traffic... and most of all, the concern of your and your family's immune health.* It's time to introduce our Maitake D-Fraction for the continued health and support of their immune system.*

Maitake D-Fraction is a standardized extract from the fruiting body of the Maitake mushroom and is available in a family of strengths and forms. Visit the Mushroom Wisdom website or search Maitake D-Fraction to learn more and choose this unique and patented extract product of choice in liquid, capsule or tablet.

Bringing You Nature's Gifts for Over 30 Years

MUSHROOM FRUITING BODY + NO STARCH + NO GRAINS

Available to Practitioners at:
Fullscript™

MUSHROOM WISDOM®

Available to Practitioners at:
emerson ECOLOGICS®

1-800-747-7418 • www.MushroomWisdom.com

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

Shorts

briefed by Jule Klotter
jule@townsendletter.com

Hormetic Stress and Aging

"Our stress responses are not typically thought of as basic mechanisms of aging," writes Elissa S. Epel in a 2020 review article, "but indeed they are actively shaping rate of aging." Her article looks at physiological, psychological, and social stresses and the need to develop "stress resilience" and use beneficial hormetic stress as a way to slow biological aging and decrease age-related disease. Over the eons, humans have adapted, physiologically and psychologically, to acute stresses from environmental changes, periodic food depravation, and other survival threats. In a very real sense, what didn't kill them made them stronger. But too much of a "good stress" can also cause harm.

Repeated exposure to *short-term*, *low or moderate* stressors – such as exercise, fasting, and high or low temperature exposure (such as from a sauna or cold shower) – can produce a beneficial hormetic response. Epel defines hormesis as "the set of evolutionary well-preserved mechanisms of biological plasticity to survive and thrive when exposed to harsh circumstances and substances." During hormesis, cells do "housecleaning" and rejuvenate, and new neural pathways form. Scientists are investigating the types of exposures (e.g., moderate aerobic exercise vs. high-intensity intermitment exercise – see this month's Curmudgeon's Corner, page 71) and the exact timing that produces this beneficial response. When a stress continues for too long and/or a person does not have the psychological/social resources to cope with the stress, the mechanisms designed to help us adapt and recover become entrenched, leading to organ damage and aging. In short, stress becomes toxic.

Low socio-economic status, minority status, trauma and adverse life events, poor health behaviors, and poor mental health are all known to be factors in toxic stress and premature aging. But *under-exposure* to stresses is also a negative because people do not develop the resources that help them recover from stressful conditions. "Ideal exposure to sufficient numbers of manageable challenges throughout life," says Epel, "stimulate cognitive growth, coping skills, and emotion regulation skills, as well as the need for supportive social networks." A person's ability to respond to stressors, which is tied to how fast their body ages, depends upon their reserve capacity – i.e., their physiological fitness, access to social support, and psychological aspects (e.g., optimism/positive affect, mindfulness, sense of purpose). "One can build reserve capacity by increasing physiological buffers (fitness, or antioxidant diets)," writes, Epel, "or psychological stress resilience, through psychological trainings that might decrease chronic stress arousal and shape one's mental filter so they habitually perceive less threat."

Epel's article contains a chart with examples of factors that support resilience and rejuvenation and those that accelerate aging. Biological factors that produce a physiological hormetic response include intermittent hyperthermia or hypothermia, intermittent hypoxia, intermittent high intensity exercise, and intermittent fasting; phytochemicals from foods help the body protect itself from oxidative stress. Psychological factors that lead to rejuvenation include exposure to intermittent, manageable stressors (as opposed to chronic or no stress), a "challenge" rather than "threat" mindset, a purpose in life, and intermittent cognitive challenges. Social factors that support stress resilience include a safe, cohesive neighborhood, food security, and a sense of belonging. "Resilience may develop over time, "she says, "leading to more mastery, purpose, faith, self esteem, and thus more resilient responses to future stressors."

Epel says, "It remains to be seen how much resilience is merely a characteristic of healthy aging or a causal factor, although much evidence reviewed here suggests it is at least partly causal." Chronic psychological stress, for example, has been shown to shorten telomere length in animal studies. Telomeres, which protect the ends of chromosomes, indicate biological age. Every time a cell replicates, the telomere becomes shorter; eventually the shortened telomere length triggers the Hayflick limit, the point at which the aging cell no longer divides. A 2021 Columbian review article found that some of the interventions in Epel's article – such as regular moderate physical activity, vegetable- and antioxidant-rich diets, and stress control techniques (e.g., tai chi, yoga, and

meditation) – are linked to longer telomere length in the peripheral blood mononuclear cells of humans. In contrast, sedentary behavior correlates to shorter telomere length as well as reduced mitochondrial activity. But these were primarily epidemiological, not intervention, studies.

Epel and colleagues at University of California-San Francisco are testing a hormetic protocol similar to the Wim Hof Method, which uses intermittent hypoxia and cold (see "Shorts," *TL* June 2022), to see if it improves autonomic and neuroendocrine responses, leading to a quicker recovery from acute stress.

Epel ES. The geroscience agenda: Toxic stress, hormetic stress, and the rate of aging. *Ageing Research Reviews.* September 28, 2020.

Espinos-Otalora RE, et al. Lifestyle effects on telomeric shortening as a factor associated with biological aging: A systematic review. *Nutrition and Healthy Aging.* 2021;6:95-103.

Another Way to Assess Age

According to a 2021 study, DNA methylation patterns are "the best biochemical markers of an individual's age." In a randomized pilot study, Kara N. Fitzgerald and colleagues used a methylation-based clock and saliva samples to assess the effect of a diet and lifestyle intervention on healthy adult males (age 50-72). DNA methylation is an epigenetic mechanism that controls gene expression; it is the addition of a methyl group to cytosine residues on a chromosome. The researchers used Horvath's DNAmAge clock that, they say, "predicts all-cause mortality and multiple morbidities better than chronological age." It shows "about 60% of CpG sites losing methylation with age and 40% gaining methylation." These changes can, for example, promote inflammatory cytokine expression and decrease tumor suppression activity. The Horvath clock is available at https://dnamage.genetics.ucla.edu/.

In this eight-week study, the participants in the treatment group (n=18) were given a detailed diet that included three servings of liver (3 oz) and 5-10 eggs each week along with 6 oz of animal protein, and over seven cups of vegetables daily. In addition, they were given a fruit and vegetable powder (PhytoGanix®) and probiotic (UltraFlora®) as supplements. (Both products are made by Metagenics, Inc., which supported the study with "an unrestricted grant."). Participants in the treatment group were also asked to engage in at least 30 minutes of exercise at least 5 days per week, average a minimum of seven hours of sleep each night, and use the breathing exercise developed by Herbert Benson, MD, twice a day.

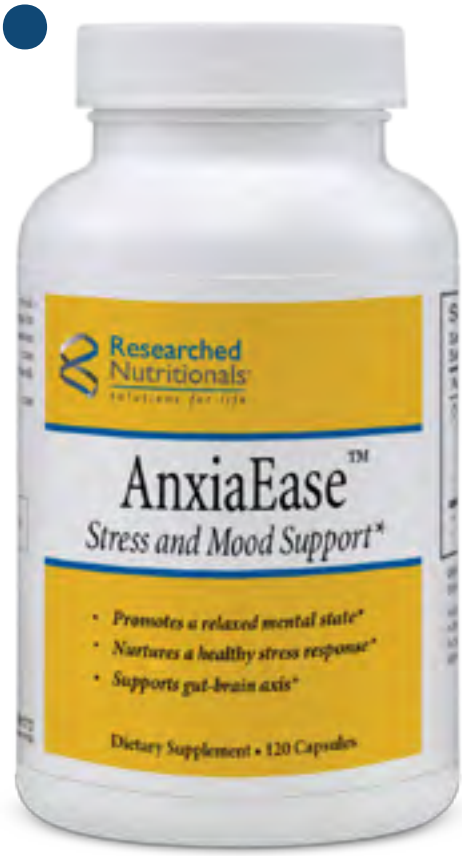
All participants had to agree to discontinue nutrition and herbal supplements not prescribed by a healthcare provider for a medical condition (some low-dose supplements were allowed) during a three-week washout period. They also had to avoid any recreational substance. Saliva samples were taken at baseline, week 5, and week 9.

At the end of the eight weeks, the treatment group scored an average 1.96 years younger, according the the DNAmAge clock (p=0.066). Controls averaged 1.27 years older (p=0.153). The small sample size limited the statistical power. The authors say larger study groups – and more diverse populations – are needed to confirm a beneficial effect.

continued on page 12 ➤

Stressed?

Support the brain and the gut for a healthy, systemic stress response.



Mechanisms of Action:

- Optimizes the gut-brain axis via targeted probiotics*
- Supports healthy cytokine, serotonin, and cortisol function*
- Adaptogenic herbs promote a healthy biological response to stress*

Supplement Facts

Serving Size: 2 capsules
Servings per Container: 60

Amount Per Serving		%Daily Value**
Vitamin B-6 (as pyridoxal 5-phosphate)	25 mg	1471%
Magnesium (as magnesium taurate)	25 mg	6%
Healthy Stress Response	460 mg	†
Holy Basil Extract (*Ocimum sanctum*) (leaf), Ashwagandha Extract (*Withania somnifera*) (whole plant), Sharp-PS® Green Phosphatidylserine (from sunflower)		
Calming Complex	610 mg	†
Lemon Balm Extract (*Melissa officinalis*) (aerial), English lavender Extract (*Lavandula officinalis*) (aerial), Passionflower Extract (*Passiflora incarnata*) (aerial)		
Gut-Brain Soother	1.5 Billion CFU I 60 mg	†
Lactobacillus helveticus Rosell®-52, *Bifidobacterium longum* Rosell®-175		

** Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Other Ingredients: Hypromellose (veggie capsule), leucine.
Contains: Trace amounts of soy and milk used in the fermentation of the probiotic strains

Manufactured without eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, corn and gluten. Produced in a facility that may process other ingredients containing these allergens.

Learn more

Learn more: ResearchedNutritionals.com/AnxiaEase

Researched Nutritionals solutions for life

800.755.3402 • Info@ResearchedNutritionals.com • ResearchedNutritionals.com | Available only through healthcare professionals.

These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

In this Issue

December 2022 | #473

ONLINE ONLY

ON THE COVER: Alan B. McDaniel, MD – Alternatives for Testosterone Replacement Therapy (pg. 24); Using Genetics to Choose Treatments for Hypertension (pg. 48); The Complicated Relationship Between Covid-19 and Vitamin D (pg. 44); Diagnosing and Treating SIBO (pg. 52)

Shorts

➤ *continued from page 9*

The authors write, "It is not yet fully established whether interventions that slow any of the 'methylation clocks' necessarily curtail risks of age-related diseases." That will take more research. But what an interesting way to assess biological age and the effects of lifestyle interventions – if it pans out!

Fitzgerald KN, et al. Potential reversal of epigenetic age using a diet and lifestyle intervention: a pilot randomized clinical trial. *Aging.* 2021;13(7):9419-9431.

Periodontal Inflammation and the Immune Response

In 2020, Canadian researchers reported evidence that periodontal inflammation does not just affect the mouth; it can exacerbate the immune response and actually contribute to systemic disease. The researchers developed a flow cytometric testing approach to assess polymorphonuclear neutrophil (PMN) activity. PMNs, which are normally found at mucosal sites in the mouth, help contain biofilm formation between the tooth and gingival crevice. During periodontal inflammation, cytokines signal the bone marrow to produce more PMNs and prime them for action. Although PMNs provide "first-line" immune defense during inflammation, hyperactive PMN activity in the mouth elevates phagocytosis, degranulation, and reactive oxygen species production, which can damage tissue. The response is not confined to inflamed tissue in the mouth: "This hyperactive PMN response to oral pathogens is accompanied by an upregulation of proinflammatory cytokines in tissues and the circulation."

In an experiment with mice, the researchers found that periodontal inflammation (caused by surgical installation of a nylon ligature) primed the immune system to produce significantly higher PMN levels in response to peritonitis (caused by intraperitoneal injection of *E. coli*). A "hyperinflammatory PMN response" occurred in mice with periodontal inflammation that did not occur in the controls that were also injected with *E. coli.*

In a human experiment, healthy volunteers stopped normal oral care for three weeks to produce gingival inflammation and resumed care for the following two weeks. Blood and saliva were collected on days 0, 4, 7, 14, and 21 (no care) and on days 28 and 35 (care resumed). Also, bleeding on probing, gingival index, and oral PMN counts were assessed at each visit. As expected, bleeding, gingival index, and oral PMN counts all increased without oral care. While bleeding and gingival index declined to near baseline by the end of the five weeks, oral PMN count was still high.

Blood testing showed that the cytokine IL-6 significantly increased by day 21 and returned to baseline by day 35. IL-6 is a granulopoietic factor and effective PMN priming agent. Also, the researchers found increased CD11b expression during the gingivitis phase when blood samples were stimulated with a bacterial peptide. CD11b, contained in PMN membranes, is involved with degranulation (release of granules, such as mast cells and basophils, from the cell). CD11b returned to normal after two weeks of oral care.

The authors write: "Our study reinforces the ramifications of oral hygiene and oral health for systemic health and specifically implicates PMNs as an important axis for crosstalk between oral disease and other systemic inflammatory conditions."

Fine N, et al. Periodontal Inflammation Primes the Systemic Innate Immune Response. *J Dental Research.* 2020;1-8.

Paul Marik and Septic Shock

Septic shock, usually preceded by signs of severe infection, is the leading cause of death worldwide – about one in five deaths, according to a 2020 *Lancet* study. Standard care is antibiotic administration; yet, too often, these patients die. Globally, over 10 million people die from sepsis each year. In 2016, Paul Marik, MD, an internationally acknowledged pulmonary and critical care specialist with over 500 peer-reviewed articles to his name, was faced with a 30-year-old female patient with multi-organ failure who was dying from sepsis. He had read a paper by A.A. Fowler, MD, on the use of intravenous vitamin C to treat the condition and decided to give it a try. As he told Del Bigtree in a September 23, 2022, interview, it was safe and there was nothing to lose – but he didn't have much hope. The next morning, he was "dumfounded" to learn she no longer needed the drugs that supported blood pressure, her kidney function had improved, and they were able to get her off the ventilator. She walked out of ICU three days later. Astounded at the response, Marik began using intravenous infusions of C along with thiamine and hydrocortisone; and more patients survived.

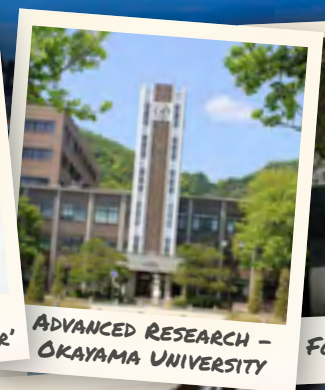
The Vice Dean for Research at Eastern Virginia Medical School, the President and Provost at Eastern Virginia Medical School, and the Corporate Vice President and President for Sentara Norfolk General Hospital (primary teaching hospital for EVMS) took part in a video heralding Marik's use of the three agents. Even though the treatment had not yet gone through a placebo-controlled trial, the hospital had decided it would be unethical to not use it for septic patients. John Catravas, PhD, then Interim Executive Director at Old Dominion University's Reidy Center for Bioelectrics, confirmed in the laboratory that vitamin C and hydrocortisone have a synergistic effect in protecting cells from bacterial toxins by restoring cells' barrier function.

When Marik was thinking about conducting a placebo-controlled study, the hospital nurses objected, saying it was unethical to deny dying patients such an effective treatment that has so little negative effect. Instead, Marik published a retrospective study in *CHEST* (June 2017) that compared patients with a primary diagnosis of sepsis or septic shock and a procalcitonin level of ≥2 ng/mL, treated with the protocol between January 2016 and July 2016, to patients with the same inclusion parameters, who were treated between June 2015 and December 2015, and did not get the IVC, thiamine, or hydrocortisone infusions. In March 2022, Kyle Sheldrick made *MedPageToday* headlines by claiming the study was a fraud. Sheldrick's post, which was roundly criticized by statistician Mathew Crawford and Norman Fenton (an expert in risk management), is no longer online; but *MedPageToday*'s article is still available.

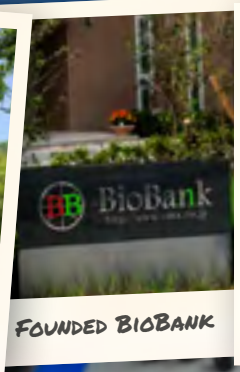
continued on page 14 ➤

Dr. Iichiroh Ohhira: A Pioneering Genius in Probiotic Science

MALAYSIAN MYSTERY – 'DRINKING FERMENTED ELIXIR'



ADVANCED RESEARCH – OKAYAMA UNIVERSITY



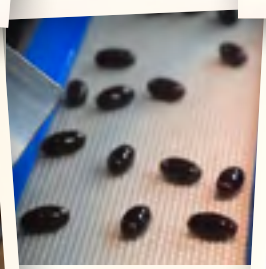
FOUNDED BIOBANK

DISCOVERY LAB TH-10

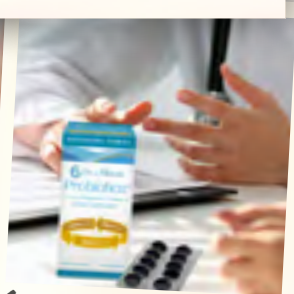
TESTING FOODS FOR PEAK NUTRITION

EXCLUSIVE 5-YEAR FERMENTATION

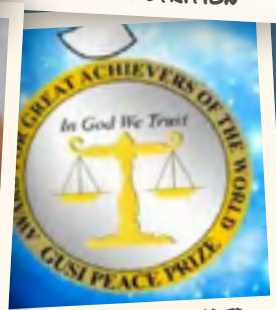
NATURE'S PERFECT PROBIOTIC W/POSTBIOTICS



PATENTED ENCAPSULATION



OFFERING "LONG LIFE AND GOOD HEALTH TO ALL!"



DR. OHHIRA AWARDED GUSI PEACE PRIZE

Developed Natures 'Perfect Probiotic' over 40 Years ago!

Dr. Ohhira has proven to be one of the world's most influential researchers in the history of probiotic science as his discoveries continue to be confirmed. He intrinsically understood restorative timeline when developing a 5-year natural temperature fermentation method that produces herculean strains of probiotics as well as therapeutic **Postbiotics Metabolites**, recently proven to be the most beneficial aspect of probiotic supplementation. Recent research on Dr. Ohhira's Probiotics revealed that his formula contains over 400 kinds of these health-promoting postbiotic metabolites!

Discover the Dr. Ohhira's Difference!™

ESSENTIAL FORMULAS®

www.EssentialFormulas.com • (972) 255-3918

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

Shorts

➤ *continued from page 12*

In January 2020, Dr. Marik was invited to respond to the VITAMINS Randomized Clinical Trial, a large Australian clinical trial of the protocol to be published in *JAMA,* at an international critical care conference in Belfast, North Ireland. Dr. Marik was sure that this study would confirm the empirical results he and other specialists had observed. Instead, the study – which organizers did not let him read until 16 hours before the presentation – was negative. It was, Dr. Marik told Bigtree, "a scientific ambush."

As Marik and Pierre Kory, MD, (who met for the first time at the conference) told Bigtree, the study was designed to fail. Septic shock is "the most time sensitive of any disease." As Kory discovered in his own use of the protocol as critical care service chief at University of Wisconsin's hospital, the protocol had no benefit if started after 12 hours of presentation. Video clips from the conference show Kory asking the lead author, Tomoto Fugii, why they delayed; the first vitamin C dose was given 5.7-19.0 hours (median 12.1 hours) after identifying sepsis. Moreover, hydrocortisone was given to the "control" group but not the treatment group, according to the authors' slide presented at the conference.

At the conference, Marik charged the audience of doctors, "My question is to you, if your daughter was in the ICU dying of septic shock, would you deny her a therapy that we know, we know absolutely for a fact, is safe and that may potentially save her life?...There are no downsides....The only downside is you may save the patient's life." When the moderator asked for a show of hands, only a few were willing to use the protocol; most wanted to wait for more research. Dr. Marik told Bigtree he has no hope that future large studies will support the use of this simple protocol for septic shock because of the prejudice against vitamin therapy.

Drs. Marik and Kory co-founded the FLCCC protocols for treating covid-19, protocols that use vitamins and already approved drugs with known safety profiles. As a result of going against federal guidelines for covid treatment, Sentara Norfolk General Hospital conducted a sham peer review, suspended Dr. Marik's hospital privileges, and reported him to the National Practitioner Databank. A sham (or malicious) peer review, according to the American College of Emergency Physicians, is "'the practice of using a medical peer review process to remove a doctor who is seen to be disruptive, is too great an advocate for changes or is competitive with doctors within the same institution.'"

Academia's War on Dr. Paul Marik. *The Highwire.* September 23, 2022. https://thehighwire.com/videos/academias-war-on-dr-paul-marik/ (Sepsis discussion begins at 28:35).
Crawford M. The Meta-Analytical Fixers, Part 111: Defamation of Paul Marik, Take Two. March 26, 2022. https://roundingtheearth.substack.com/p/the-meta-analytical-fixers-part-iii-4e8?s=r
Fenton N. The curious perfect p-value: a case study in defamation and ignorance. June 25, 2022 (Updated) https://www.normanfenton.com/post/the-curious-perfect-p-value-a-case-study-in-defamation-and-ignorance
Rudd KE, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet.* January 18, 2020.

◆

A4M MMI REDEFINING MEDICINE®

Longevity FEST 2022

30TH ANNUAL WORLD CONGRESS

This year's Annual World Congress in Anti-Aging Medicine will be extraordinary in many ways, as we celebrate our past while building on the foundation of 30 years of excellence.

FEATURED SPEAKERS

As we seek to further extend longevity, how can we simultaneously help patients live longer and delay age-related health issues?

To explore this key question, the World Congress will bring together physicians, researchers and scientists from a variety of fields including genetics, biology of aging, endocrinology, clinical psychology, physiology, and more.


Charles Brenner, PhD


Kara Fitzgerald, ND


Thierry Hertoghe, MD


Mark Houston, MD, MS, FACP, ABAARM


Gordon Lauc, PhD


Daved Rosensweet, MD


Erika Schwartz, MD


Pamela W. Smith, MD, MPH

HOTEL INFORMATION

THE VENETIAN AND PALAZZO RESORT

3355 S. Las Vegas Blvd. Las Vegas, NV 89109

SAVE $200

Use coupon code Townsend 200

www.a4m.com

Literature Review & Commentary

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

Pregnant Women Are Not Getting Enough Iodine

The authors reviewed 61 studies (including a total of 163,021 pregnant women) that estimated the prevalence of insufficient iodine intake during pregnancy in different regions of the world. The overall prevalence of insufficient iodine intake was 53%. The prevalence was 46% in the Americas (North and South America combined). Pregnant women living in countries with insufficient iodine status had a higher prevalence of inadequate iodine intake (86%) than women living in countries with sufficient iodine intake (51% prevalence).

Comment: Iodine deficiency in pregnant women can lead to impaired fetal growth and development. Low iodine status *in utero* and during infancy has been associated with lower IQ in later childhood. Although increased use of iodized salt has decreased the worldwide prevalence of iodine deficiency, an estimated 2 billion people around the world have insufficient iodine intake. The Endocrine Society, the American Thyroid Association, the Teratology Society, and the American Academy of Pediatrics recommend that women receive prenatal vitamins containing 150 µg per day of iodine during preconception, pregnancy, and lactation. Some prenatal vitamin products contain iodine, but others do not.

Patriota ES, et al. Prevalence of insufficient iodine intake in pregnancy worldwide: a systematic review and meta-analysis. *Eur J Clin Nutr*. 2022;76:703-715.

Melatonin Improves Sleep in Children with Autism Spectrum Disorder

This study enrolled 198 Japanese children (mean age, 11.2 years) with autism spectrum disorder who had average sleep onset latency of at least 30 minutes (i.e., it took them at least 30 minutes to fall asleep). The children were randomly assigned to receive, in double-blind fashion, melatonin (1 mg or 4 mg) or placebo before bedtime for 14 days. The primary outcome was sleep onset latency, as assessed with an electronic sleep diary. Sleep onset latency shortened significantly in the 1-mg and 4-mg melatonin groups compared with the placebo group (-22.0, -28.0, and -5.0 minutes, respectively; $p < 0.0001$ for each melatonin dose compared with placebo). No serious adverse events were reported.

Comment: This study found that melatonin can improve the ability of children with autism spectrum disorder to fall asleep. The lower dose (1 mg) was nearly as effective as the higher dose (4 mg). Although melatonin was generally well tolerated, it is important to remember that melatonin is a hormone, and that its long-term safety in children has not been well studied. Studies in elderly individuals with insomnia have found that, once melatonin resets the biological clock, it can be discontinued in many cases without causing a return of abnormal sleep patterns. An attempt should also be made to wean children from melatonin after it has achieved the desired benefit.

Hayashi M, et al. Melatonin treatment and adequate sleep hygiene interventions in children with autism spectrum disorder: a randomized controlled trial. *J Autism Dev Disord*. 2022;52:2784-2793.

Unexplained Iron Deficiency? Consider *Helicobacter pylori* Infection

The records were reviewed on 60 children (aged 2-18 years; mean, 14.8 years) in Israel with *Helicobacter pylori* infection and non-anemic iron deficiency (n = 39) or iron-deficiency anemia (n = 21). Hemoglobin and ferritin levels were measured before and 6 to 9 months after successful eradication of *H. pylori*. None of the children had recently been given iron supplements, and iron supplements were not given during the trial. The mean ferritin level increased from 6.3 µg/L at baseline to 15.1 µg/L at 6 to 9 months after eradication therapy, and became normal in 60% of the children. The mean hemoglobin concentration increased significantly in the group as a whole, and also among those with iron-deficiency anemia. In multiple logistic regression analysis, older age was the only factor associated with resolution of anemia following eradication therapy (odds ratio = 1.65; $p = 0.005$).

Comment: *H. pylori* is a well-known cause of peptic ulcers. It is not as well known that *H. pylori* can impair the capacity of the stomach to secrete hydrochloric acid. *H. pylori*-associated

hypochlorhydria is frequently reversible once the infection has been eradicated. Hydrochloric acid plays a key role in the absorption of nonheme iron, and hypochlorhydria can increase the risk of developing iron deficiency. In the present study, eradication of *H. pylori* improved iron status in children with iron deficiency. *H. pylori* infection should be considered in the differential diagnosis of unexplained iron deficiency, particularly if iron supplementation fails to correct the deficiency or if ongoing iron therapy is needed to prevent a recurrence of iron deficiency.

Tanous O, et al. Resolution of iron deficiency following successful eradication of Helicobacter pylori in children. *Acta Paediatr*. 2022;111:1075-1082.

Evening Primrose Oil for Diabetic Neuropathy

One hundred patients (mean age, 60.7 years) at one of 11 clinics in South Korea who had painful diabetic peripheral neuropathy were randomly assigned to receive, in double-blind fashion, 320 mg per day of gamma-linolenic acid (GLA) from 3.6 g per day of evening primrose oil or 600 mg per day of alpha-lipoic acid for 12 weeks. The treatments were taken in two divided doses, 30 minutes before breakfast and dinner. Among the 73 patients who completed the trial, significant decreases (improvements) were seen in both groups in the mean visual analogue scale score for pain and in the total symptom score (a composite of stabbing pain, burning pain, paresthesias, and numbness). Evening primrose oil was nonsignificantly more effective than alpha-lipoic acid. For evening primrose oil, the mean visual analogue scale score (on a scale of 0 to 10) improved from 5.26 at baseline to 2.94 after 12 weeks ($p < 0.0001$), and the mean total symptom score (on a scale of 0 to 14.64) improved from 3.86 to 2.18.

Comment: Diabetic neuropathy is a disorder of peripheral nerves associated with diabetes. In animals with experimentally induced diabetes, supplementation with GLA or evening primrose oil (which contains GLA) prevented the development of nerve conduction velocity deficits without affecting the severity of the diabetes. In two double-blind trials conducted in the 1990s, treatment with 4.0 g to 5.3 g per day of evening primrose oil for 6 to 12 months resulted in significant improvements in subjective and objective signs of diabetic neuropathy, compared with placebo.[1,2] However, the principal investigator who conducted these clinical trials was subsequently found by the professional conduct committee of the General Medical Council (United Kingdom) to have falsified the results of the research.[3] Now, some 30 years later, Korean researchers have demonstrated that evening primrose oil is indeed an effective treatment for painful diabetic neuropathy. In their study, evening primrose oil was at least as effective as alpha-lipoic acid, which has been demonstrated in multiple studies to be beneficial in the treatment of diabetic neuropathy.

Won JC, et al. gamma-Linolenic acid versus alpha-lipoic acid for treating painful diabetic neuropathy in adults: a 12-week, double-placebo, randomized, noninferiority trial. *Diabetes Metab J*. 2020;44:542-554.

Pickle Juice Relieves Muscle Cramps in People with Cirrhosis

Eighty-two patients (mean age, 57 years) with cirrhosis and more than four muscle cramps in the previous month were randomly assigned to consume one tablespoon of pickle juice or tap water at the onset of cramps. Participants were allowed to use pickle juice from the brine of dill or kosher pickles, but not from the brine of sweet pickles or bread and butter pickles. Patients on a sodium-restricted diet were instructed to consume no more than three tablespoons of pickle juice per day, in order to prevent volume overload. Cramp severity was assessed by a visual analogue scale with a range of 0 to 10, with higher numbers indicating worse cramps. At baseline, the medium number of cramps per month was 11 to 12, and average cramp severity was greater than 4. The primary outcome measure was the change in cramp severity after 28 days compared with baseline. The mean improvement on the visual analogue scale was greater with pickle juice than with tap water (-2.25 vs. -0.36; $p = 0.03$). More patients in the pickle juice group reported that cramps were aborted by the intervention (69% vs. 40%; p value not stated). Compared with tap water, pickle juice did not cause weight gain, either in patients with or without ascites.

Comment: Muscle cramps affect about two-thirds of patients with cirrhosis. The cramps cause pain and interfere with mobility and sleep, and are associated with poor health-related quality of life. Treatment options are limited. The results of the present study demonstrate that consumption of small amounts of pickle juice can improve the severity of cramps, without causing any significant adverse effects. The authors of this study suggested that the active ingredient in pickle juice is acetic acid, which increases vagal tone by acidic stimulation of oropharyngeal nerves. They further suggested that, if the mechanism of action is acid-related, then other acidic liquids such as apple cider vinegar might also be effective.

Tapper EB, et al. Pickle juice intervention for cirrhotic cramps reduction: the PICCLES randomized controlled trial. *Am J Gastroenterol*. 2022;117:895-901.

Intravenous Magnesium and Myasthenia Gravis

A woman in her 90s with a history of myasthenia gravis and atrial fibrillation presented to an emergency department after falling down. She was given intravenous magnesium to treat atrial fibrillation and the associated rapid ventricular rate. Shortly thereafter she developed acute respiratory failure, which required intubation and ventilation. Her respiratory function recovered quickly, and she was extubated the next day. On subsequent days, the patient received two further doses of intravenous magnesium, and on both of those occasions she again developed transient respiratory failure.

Comment: Myasthenia gravis is an autoimmune disorder characterized by skeletal muscle weakness that increases with exertion and improves with rest. Most people with myasthenia gravis have antibodies that damage or interfere with acetylcholine receptors at the neuromuscular junction, which results in a decrease in cholinergic stimulation of muscle contraction. Magnesium acts at the neuromuscular junction, where it competes with calcium and inhibits the release of acetylcholine. Magnesium therefore has the potential to exacerbate the deficiency of cholinergic stimulation that occurs in patients with myasthenia gravis. There have been several previous case reports in which intravenous administration of

➤

➤

magnesium triggered a crisis (including respiratory failure) in patients with myasthenia gravis. Intravenous magnesium is therefore contraindicated in patients with this disease.

Jessop K. Intravenous magnesium sulfate inducing acute respiratory failure in a patient with myasthenia gravis. *BMJ Case Rep*. 2022;15:e250455.

Coenzyme Q10 and Alpha-Lipoic Acid for "Long Covid"

One hundred seventy-four Italian patients with chronic fatigue syndrome that had developed after a Covid-19 infection were treated at a clinic that provided multiple interventions, including analgesic and anti-inflammatory medications, antidepressants (mostly for treatment of pain), anticonvulsants that have an analgesic effect (pregabalin and gabapentin), psychological counselling, physio-kinesotherapy, physical reconditioning, and yoga/pilates. Two-thirds of the patients also received coenzyme Q10 and alpha-lipoic acid (100 mg per day of each) for two months, while 58 patients did not receive these supplements (control group). The treatment assignments were apparently not randomized. The proportion of patients who had a complete response (defined as at least a 50% improvement in the Fatigue Severity Scale score) was higher in the supplement group than in the control group (53.5% vs. 3.5%).

Comment: These findings suggest that the addition of coenzyme Q10 and alpha-lipoic acid to a comprehensive treatment program can improve outcomes in patients with "long covid." The difference in complete-response rates between groups may at first glance seem implausibly large (53% vs. 3.5%). It should be noted, however, that 73% of the patients in the control group who failed to have a complete response did have an improvement of 20-50% on the Fatigue Severity Scale. Randomized controlled trials are needed to confirm the results of this study.

Barletta MA, et al. Coenzyme Q10 + alpha lipoic acid for chronic COVID syndrome. *Clin Exp Med*. 2022 Aug 22 [Online ahead of print].

Vitamin B12 for Diabetic Neuropathy: Revisiting an Old Iranian Paper

One hundred patients (mean age, 35 years) with symptomatic diabetic neuropathy without vitamin B12 deficiency were randomly assigned to receive, in single-blind fashion, vitamin B12 (2,000 µg intramuscularly twice a week for 3 months) or nortriptyline (10 mg once a day at night). The mean scores for pain ($p < 0.001$), paresthesias ($p < 0.001$), and tingling sensation ($p < 0.001$) improved to a significantly greater extent in the vitamin B12 group than in the nortriptyline group. Changes in vibration sensation, position sensation, pinprick sensation, and nerve conduction parameters did not differ significantly between groups. The authors concluded that vitamin B12 is more effective than nortriptyline for the treatment of painful diabetic neuropathy.

Comment: In my writings during the past 10 to 15 years, I cited a number of research papers from Iran. Over the past several years I developed concerns about the credibility of much of the nutrition research coming from that country. I have therefore begun taking another look at some of the research I cited in the past. The study described above, which was published in 2009, has a number of concerning issues. I have written to the journal that published this paper, and they stated that they will conduct an investigation.

Concerns about Talaei A, et al. Vitamin B12 may be more effective than nortriptyline in improving painful diabetic neuropathy. *Int J Food Sci Nutr*. 2009;60(Suppl 5):71-76.

1. The study was conducted over a three-month period, and the treatment lasted three months. That would mean that all 100 patients in the study would have had to start the study at the same time. That is very unusual for a clinical trial.
2. One of the inclusion criteria was having had type 2 diabetes for at least three years (type 1 diabetics were excluded). The paper reported that the mean age of the study participants was 35 years, which means the mean age at diagnosis of diabetes was 32 or younger. It would be very unusual to have such a young population of type 2 diabetics.
3. The control group received 10 mg per day of nortriptyline, which is usually a sub-therapeutic dose in the treatment of diabetic neuropathy. A typical treatment regimen is to start with 10 mg per day of nortriptyline and to increase progressively, according to response and tolerance, to a maximum of 75 mg per day. One wonders whether it is unethical to give the subjects in this study a treatment that is not likely to be effective.
4. All of the patients had been referred to a single clinic in Arak, Iran, for evaluation of diabetic neuropathy. However, only one of the four study authors was from Arak; the other three were from Isfahan, which is 3.5 hours away by car.
5. Implausibly large degree of improvement: Symptoms such as pain and tingling were measured on a 5-point visual analogue scale. In the group receiving vitamin B12, the mean improvement in pain was 3.66 points, with a range of 3.06 to 4.25. Most people would consider an improvement of 3.06 points on a 5-point scale to be a very large or even dramatic improvement. Thus, all 50 patients given vitamin B12 had a very large improvement. I cannot think of any treatment for any health condition that produces a very large benefit 100% of the time.
6. The paper stated, "All patients before, during and after the study were under their usual protocols and were managed appropriately." However, since these patients had been referred from other clinics, one wonders how the researchers could have known that the patients had been managed appropriately before they were referred.

Talaei A, et al. Vitamin B_{12} may be more effective than nortriptyline in improving painful diabetic neuropathy. *Int J Food Sci Nutr*. 2009;60(Suppl 5):71-76.

References

1. Jamal GA, Carmichael H. The effect of gamma-linolenic acid on human diabetic peripheral neuropathy: a double-blind placebo-controlled trial. *Diabet Med*. 1990;7:319-323.
2. Keen H, et al. Treatment of diabetic neuropathy with gamma-linolenic acid. *Diabetes Care*. 1993;16:8-15.
3. Dyer O. GMC reprimands doctor for research fraud. *BMJ*. 2003;326:730.

◆

A Comprehensive Approach to Sexual Function

by Judson Brandeis, MD

During my 25 years as a urologist, I have had the privilege of taking care of thousands of men. When you surgically remove a man's cancerous prostate or even perform a vasectomy on him, you get to know a man on a deeper level that goes beyond medicine. I came to realize that one of my strengths as a clinician is my comprehensive and personal approach to evaluating and treating sexual dysfunction. What follows is the discussion and thought process I use when evaluating a new patient.

The experience starts when patients enter my office. I create a relaxing and masculine environment where men feel comfortable opening up to me. The setting is critical because I can only help someone if they put all their cards on the table. For example, I recently met with a 55-year-old otherwise healthy and prosperous man with ED, but his story did not match his erectile function. I communicated that I was having a difficult time making sense of his overall picture. At that point in our relationship, he felt comfortable enough to tell me about his history of drug abuse in his twenties. Finally, the pieces of the puzzle fell into place, and I could begin the process of helping him. It is essential that patients form a therapeutic relationship with their doctor and be honest about their medical history.

Assessing Cardiovascular Health

Most erectile dysfunction is related to issues with blood vessels. Of course, any history of smoking, diabetes, high cholesterol, or high blood pressure must be addressed, and the ability to have physical intimacy is a strong motivator for change.

Loss of sexual function is often concrete proof that there is something physically wrong.

By improving blood flow to the penis, we are improving the entire circulatory system.

Going deeper, I look for a family history of cardiovascular disease in men with early erectile dysfunction, since ED often precedes heart disease by five to ten years. I frequently send patients for heart scans, which can now predict early cardiovascular disease with great accuracy. I also send patients for vascular ultrasounds and find aneurysms and blood vessel blockages. If something does not make sense to me, I always try to find the underlying cause by ordering the appropriate tests.

I explain to men that blood pressure medications limit blood flow to the genitals. Nitric oxide boosters and stress reduction can reduce a man's dependence on blood pressure medications and improve erectile function.

Many of my patients have Kaiser as their insurance. The Kaiser system is excellent at taking care of a large population of Americans at a reasonable cost, but when I have a man sitting in front of me, my only concern is his wellbeing, not cost containment or the millions of other patients in the system. So, my approach is to optimize the performance of the individual I accept as my patient.

Conserving Nerve Function

Some men have erectile dysfunction because of nerve damage, especially those who have undergone prostate cancer surgery or radiation. Even when there is nerve-sparing surgery, men will rarely regain 100% of their presurgical potency. I put these patients immediately on a nitric oxide booster, a daily dose of Cialis, and daily treatment with a vacuum erection device to stretch and adequately oxygenate the penis. Early use of low-intensity shockwave therapy and platelet-rich plasma (PRP) are also important therapies I use to restore erectile function in the post-surgical period. Without early intervention, there is little hope of regaining potency.

Another common but overlooked medical issue that causes ED is lumbar spine problems. The squeezing of the lower sacral nerves that causes back pain can also compromise the nerve signals to the penis. I had a 44-year-old patient with lumbar disc herniation who had ED that resolved after spine surgery.

Chemistry

I need to rule out any unrecognized health issues, so my patients get lab work to check their kidneys, liver, blood count, vitamin D, B12, PSA, and electrolytes. Normal thyroid function is essential for erectile function. I check testosterone and free testosterone as well. Testosterone is critical for libido and

➤

➤

energy, concentration, sleep, athletic performance, muscle building, and fat burning. I used to be conservative about replacing testosterone, getting men back to "normal" levels, but I have discovered that men do much better when their testosterone levels are around 1000, and I have seen very few adverse effects. Of course, some men have their prostates grow and have difficulty urinating, while others complain about hair loss. However, optimizing testosterone plays a critical role in helping men get back into shape and regain their libido. For every one man with a complaint about testosterone replacement, I have 20 who swear by it.

Optimizing Physical Health

I put all my patients on a body composition scale and discuss weight loss, nutrition, and muscle building. Excess fat limits a man's ability to exercise and can increase estrogen levels in men. I work with my patients to get their percentage of body fat under 20%. To do this, we need to restrict calories, and as a result, men need to make all of their calories count. I explain that the healthiest way to lose weight is by dropping one pound of fat per week, which is much harder than it sounds. Often this means significantly reducing alcohol consumption because those calories come with no nutritional value.

Physical optimization requires determination and a long-term commitment. I do not shame or judge patients because everyone needs a different approach. My office is within an hour of the headquarters of Google, Facebook, Apple, Oracle, Tesla, and the Lawrence Livermore Lab. I attract engineers as patients, and they need data to change habits. Other men need a wake-up call. For example, I had a 68-year-old patient who was CEO of a successful company. I could sense that he and his younger wife were moving in different directions, and that he was occupying himself with work to avoid the discomfort of getting back into shape and reconnecting with her. I brought him into my office, looked him in the eyes, and sternly said, "What the *** are you doing! You are going to mess up the best thing you have going!" The next time I saw him, he told me that no one had ever talked to him like that before, but that was what he needed to make a shift. Within three months, he had lost 15 pounds of fat and had started taking his beautiful wife on hikes all over Northern California.

I also discuss physical fitness with my patients. Men over 40 need two or three days of cardio and two or three days of strength-building every week. I especially like circuit training with lighter weights and more reps, reducing the risk of injury, and augmenting cardiovascular fitness. I discuss the importance of avoiding injury that will set men back and the need for consistency. Increased muscle mass will boost a man's basal metabolic rate, which is the number of calories a man burns every day just by

being alive. Men also feel better about themselves when they are leaner and more muscular, and this boosts libido. I recommend the Emsculpt machine to men with financial resources to quickly increase muscle mass and get back into shape.

Optimizing Relationships

I always explore relationship issues with my patients. I see many recently divorced men who have difficulties with erectile function, so much so that I joke with them and my staff that there is a divorce hex I need to break.

One aspect of relationships that needs to be addressed is the health of the partner's genitalia. I vividly remember the disappointment on my patient's face. We had worked together to restore his erectile function, and he was finally able to have penetrative intercourse with his 68-year-old wife. But unfortunately, she had a history of breast cancer and could not use estrogen, so her vagina was narrow and dry. Intercourse was painful for her and stirred up bleeding, so she refused to attempt intercourse again. As a result, I always supply my patients with a silicone-based lubricant such as UberLube and encourage them to discuss estrogen replacement with their spouses.

Everyone has a story, whether they are a widower getting back into the dating pool, a monogamous couple getting older, or a couple rediscovering each other when the nest is finally empty. I believe it is essential to understand my patients' goals and give them realistic expectations.

Psychological issues certainly affect erectile function. For example, anxiety produces adrenaline which works against erections. Depression can dramatically reduce libido. Medications for depression, especially SSRIs such as Zoloft and Paxil, are also acknowledged to reduce erectile function and orgasm. Sometimes by changing antidepressants, the ED will resolve. This can be true of a surprising number of other medications as well.

Specific Treatments

Many of my patients also have difficulty with clogged and narrow blood vessels. Fortunately, several regenerative treatments can help grow new blood vessels.

Shockwave therapy. I was an early adopter of shockwave therapy to treat erectile dysfunction. This technology uses pulsed high-pressure acoustic waves to stress the blood vessels in the penis. Mechanical stress in the body creates an injury response that activates stem cells and promotes the secretion of growth factors, leading to additional blood vessels that can increase blood flow to the penis. Using this technology, men with mild erectile dysfunction no longer need to rely on Viagra, men with moderate erectile dysfunction get better results from Viagra, and men with more severe erectile dysfunction are able to function without injection therapy.

Nitric oxide is a critically important and frequently overlooked solution to erectile dysfunction. As men age, their nitric oxide production slowly declines, affecting the delivery of blood throughout their body. Replacing nitric oxide improves circulation to the muscles, so many elite endurance athletes supplement with nitric oxide boosters. Studies on nitric oxide have shown a small but noticeable improvement in athletic performance. Furthermore, there are more nitric oxide receptors in the brain than in any other organ in the body, so elevating nitric oxide levels improves mental sharpness. When I learned more about the effects of nitric oxide on erectile function, I created a supplement called AFFIRM (affirmscience.com), which utilizes both pathways in the body that boost nitric oxide. My patients and I have seen great results from supplementing nitric oxide.

PDE-5 inhibitors such as Viagra (sildenafil), Cialis (tadalafil), and Levitra (vardenafil) work together with nitric oxide boosters to improve the nerve signals that dilate blood vessels. The PDE-5 enzyme is only present in the penis, which is why these medications are so effective in shunting blood specifically to the genitals. I put many of my patients on 5 mg of tadalafil every evening to improve their nighttime erections, which I feel are key to long-term erectile health.

Trimix. Men with erectile dysfunction related to nerve problems or severe narrowing of blood vessels are candidates for injection of medication into the penis. This therapy is called Trimix because typically the injection consists of three medications: papaverine, phentolamine, and prostaglandin E-1. It is necessary to teach my patients how to inject the medication properly. We always start with a low trial dose because this medication can cause priapism (an erection that will not go away without medical attention). Injection therapy lacks spontaneity, but it is the only option for some patients.

Vacuum erection device. For men who are not experiencing nighttime erections, I recommend using a penis pump, also known as a vacuum erection device. Men are supposed to get 30 to 60 minutes of erections every night, which maintains the elasticity of the erectile bodies' lining and oxygenation of the erectile tissue. When the body no longer does this naturally, men need to replace nighttime erections with artificial erections using a penis pump. I recommend a series of five one-minute cycles in the morning and the evening. The pump is the least expensive, most effective intervention men can use to maintain penile size and function. Men who are comfortable using a penis pump can apply a silicone ring on the base of the penis to maintain an erection for penetrative intercourse.

The P-Shot. I frequently recommend a P-Shot to follow a course of shockwave therapy, which introduces platelet-rich plasma into the erectile bodies of the penis. Platelets have two functions in the body. The first is to form blood clots if we are bleeding, but the second and less well-known function is to release growth factors at the injury site. Therefore, injured tissue grows back more quickly than the surrounding tissue. Platelets contain 140 different growth factors, including vascular growth factors that stimulate the growth of blood vessels. To prepare a P-Shot,

➤

➤

we draw blood, and then spin the blood in a centrifuge. The red blood cells are heavy and gather at the bottom. Next, we extract the platelets and inject the platelets into the penis with a tiny needle using ultrasound guidance. PRP is like fertilizer for stem cells stimulated by shockwave therapy, and recent data demonstrate that P-Shots also improve erectile function independently. In addition, I am conducting a clinical research study at BrandeisMD using a combination of PRP, penile traction, a penile suction device, and an AFFIRM nitric oxide booster to improve both the length and girth of a man's penis.

An implant. Another option I discuss with my patients, especially younger men with a history of prostate cancer surgery or diabetes, is placing an inflatable penile prosthesis. This curative treatment for erectile dysfunction allows men to get an erection on demand and maintain an erection for as long as they desire. For many men, the idea of placing a synthetic implant is a substantial psychological hurdle that they need to overcome. However, once the implant is placed, it is all internal, and the quality-of-life questionnaires show a high satisfaction rate with penile implants. I refer all my patients desiring penile implants to Dr. Ed Karpman in San Jose, California. In his hands, this procedure typically takes 20 minutes and is done on an outpatient basis.

Pleasure aids. Also known as sex toys, I now recommend high-end devices to patients who need additional stimulation to reach climax. The reality is that as we age, our nerves become less sensitive, and we need extra stimulation. The Fun Factory was founded by an engineer who used his expertise to create high-quality sex toys manufactured in Germany. I encourage my patients, reminding them that there is no shame in getting a little help. Women use vibrators without any social stigma. Why not men?

Creative Solutions. Not everyone can achieve an erection firm enough for penetrative intercourse. However, some of my happiest and most sexually satisfied patients have found ways to be creative in assuring their pleasure and that of their partner.

In summary, it is important to me that my patients feel good, look good, and have great physical intimacy. I try to create a comprehensive, long-term plan not only to restore erectile function, but to set men on a path for lifelong health and fitness that includes erectile fitness. By improving blood flow to the penis, we are improving the entire circulatory system. By helping men engage in physical intimacy, we boost their happiness and the strength of their intimate relationships. Happy, healthy men make great husbands, fathers, professionals, leaders, and neighbors.

This article is excerpted from *The 21st Century Man,* a comprehensive work of leading-edge perspectives on men's health that includes contributions by sixty physicians and experts. Curated by Judson Brandeis, MD, the book provides research and clinical insight on sexual health and healing, and rejuvenation medicine.

Judson Brandeis, MD, is a urologist, researcher, physician educator, clinician, and surgeon. A graduate of Brown University and Vanderbilt University School of Medicine, with a urologic surgery residency at UCLA and a post-doc fellowship at Harvard, today he specializes in the emerging fields of men's health and sexual medicine.

Brandeis MD Male Rejuvenation Center
and AFFIRM SCIENCE Supplements
100 Park Place, Suite 140
San Ramon, California 94583
Email: contact@brandeismd.com
Phone: 925-255-7867
Web: BrandeisMD.com
Book: thetwentyfirstcenturyman.com
Supplements: affirmscience.com

◆

Simply the Best

It's so good the FDA uses Boluoke® as the gold standard for lumbrokinase research!

Your Patients.
Your Reputation.
Trust Nothing Less!

Boluoke® (lumbrokinase)

- the original lumbrokinase used in trials
- highest fibrinolytic strength on the market
- over 30 years of clinical safety/efficacy records
- does not affect INR or aPTT testing

Hypercoagulation, a central issue in:

- conditions with an impaired circulation
- growth and spread of rogue cells
- biofilm-associated states
- poor healing due to tissue hypoxia
- hyper-inflammatory or -immune response

Dragon's www.dragonsmedicalbulletin.com
Medical Bulletin
Your Quick Stop for Integrated Clinical Research Updates

CRNA

1-866-287-4986
www.canadaRNA.com

Boluoke® is also available through:

Researched Nutritionals · Pro Health Network · Nature 2 Health · antiaging-systems.com · M•P · NaturoDoc · BIORESOURCE

On the Cover

Stimulate Endogenous Testosterone in Late-Onset Hypogonadism

by Alan B. McDaniel, MD

Preface

This review focuses on older men with secondary, or late-onset hypogonadism (LOH, colloquially "low-T"). The author resists the temptation to present a flood of information (delightful to some but *dreary* to most) about the definition of LOH[1] and the prevalence of this problem[2]; the rate of decline of aging men's testosterone levels[3] and the danger this poses to their longevity[4]; its diagnostic criteria and the contraindications to testosterone therapy[5]; the success of testosterone replacement and proper precautions for its monitoring.[6] Some suitable references are offered, with the Editor's permission.

Introduction

This commentary briefly examines the options for restoring testosterone and even fertility in men with LOH whose aging testicles remain (mostly) normal. Testosterone replacement therapy is the only solution for primary testicular failure and is our current mainstay for all causes of low testosterone. However, proven therapeutic options exist that can engage men's remaining testicular function to produce endogenous testosterone.

Men's testosterone may be low because of hypothalamic or pituitary dysfunction, so that the glands are not sufficiently stimulated (secondary hypogonadism). Other men make plenty of testosterone but their body over-produces aromatase and excessively converts testosterone to estradiol: Low-T can result and the surplus estradiol feeds back to depress the hypothalamus. This exaggerates the testosterone deficiency and produces a clinical picture very similar to hypothalamic and pituitary dysfunction.

Treatment options *other* than testosterone will be presented briefly. Preliminary nutritional remediation with neonatal bovine adrenal cortex and DHEA has been described previously.[7] In the selection of therapy, the ease, convenience, success and safety of the patients' usage are important considerations. The costs are also – and they vary significantly. The readers' indulgence is begged: Prices have been rising rapidly and the costs cited here may soon be obsolete.

Testosterone Replacement – "The Industry Standard"

Thanks to recent studies,[6] the success of testosterone replacement therapy (TRT) is well documented. Safety concerns regarding prostate, heart and cardiovascular risks have been examined by meta-analyses, showing there is little risk when patient selection and monitoring guidelines are followed.[8] Why is there any need to consider changes to this practice?

Testosterone replacement therapy depresses the hypothalamic release of gonadotropin releasing hormone (GnRH). Thus, the unstimulated pituitary releases little to no luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Lacking gonadotropic stimulation, endogenous testosterone production lapses, sperm production falls, and the gonads atrophy.

Many men are disconcerted to see their testicles becoming unnaturally small, and some men complain of low volumes of ejaculate as well. The lack of sperm production from atrophic testicles is a serious issue for men who wish to retain normal fertility. Providers may notice the inconvenience of prescribing a schedule-III drug.

The cost of TRT is also an important issue, which has driven patients to alternative treatments. The monthly price of transdermal gel is robust and climbing, even the generic. Calculating from online pricelists, the monthly cost of *four* pumps-daily of generic 1.62% testosterone gel ranges from $75 to $289. Even one pump-daily creates a monthly expense from $19 to $72.[9]

Oral testosterone undecanoate is surprisingly costly for a drug so long available abroad. The price of one month's treatment is $479 at the lowest dose and $950 at the highest.[10] In addition, the wisdom of using the oral route for steroid sex hormone administration may be questioned for men, as it is for women.

Injected testosterone cypionate is the most affordable; the average monthly dose (2 mL of testosterone cypionate 200 mcg/mL) costs from $10 to $214.[11] However, the injections are undesirable: Few men gladly embrace the opportunity to inject themselves even twice a month, let alone the once or twice-weekly regimens that many practitioners recommend to prevent "roller-coaster blood levels."[8]

Finally, clinicians are expected to properly diagnose the cause(s) of their patients' problems and to successfully apply treatments that best address the underlying pathology. It seems desirable to use the safest, least expensive treatments that are directed to the basic cause(s) of the problem – and when possible, that preserve men's normal function. In fact, the author feels chuffed when he accomplishes this.

"Generic" Laboratory Workup to Diagnose Late-Onset Hypogonadism

An untreated patient's history and examination lead his practitioner to the appropriate initial workup. Suspecting LOH or previous (mis)use of anabolic steroids, it is often prudent to obtain blood tests for LH and FSH; total estradiol (tE2) and total testosterone (tT) by LC/MS-MS method; free testosterone (fT), bioavailable or by equilibrium dialysis (ED); and PSA (a baseline is essential!). His total DHT, also by LC/MS-MS, may be useful.

Men with LOH may have normal or low serum LH and FSH concentrations, *and* normal gonadotropin values are inappropriate when associated with low serum testosterone.[12] Research has shown that ratios can aid us in clinical diagnosis. The LH/ FSH can be elevated >1 from insulin resistance.[13] Aromatase excess reduces the tTest/ tE2 balance. Occasionally, the tTest/ DHT is important.[14]

It is always easier to evaluate an *un*treated patient. If your man is using testosterone replacement treatment when you first attend him, seek his baseline, untreated laboratory records – they can help identify the nature of his problem. It can be disappointing, though, when one finds few tests were obtained before TRT was begun.

A review of nine organizations' clinical practice guidelines reported that their (orthodox) recommendations for pre-treatment workup were generally uniform.[15] Remember: The diagnosis is not always simple. Research has shown that some prostate cancers produce fragmentary androgens, which are not functioning hormones but can suppress the hypothalamic-pituitary-gonadal (HP-G) axis.

Remain suspicious of a pituitary tumor; prolactin particularly inhibits testosterone production. HIV infection frequently causes hypothalamic hypogonadism.[16] Drugs, especially opioids and methadone, can suppress the HP-axis' proopiomelanocortin-receptors. The past use of anabolic steroids, which may not be admitted, causes prolonged (some say permanent) HPG-axis depression. "Just" stress can be causative![17]

Treat Low-T and Testosterone/Estradiol Ratio Due to Aromatase Excess

Obesity is the greatest factor contributing to low-T in adults. Recent papers have focused on the causes of obesity-related late-onset hypothalamic hypogonadism, including decreased sex hormone binding globulin, inflammatory cytokines, leptin resistance, and elevated insulin levels.[18] Fewer report on the importance of excessive aromatase production by the visceral fat.[19,20] The author finds this problem is common.

The enzyme aromatase (CYP-19, "Aro") converts testosterone to estradiol. Insulin resistance and obesity cause

Obesity is the greatest factor contributing to low-T in adults.

visceral fat to produce aromatase excessively.[21,22] This increases men's conversion of testosterone to estradiol. Testing obese men often shows low-T (about 40% of men with metabolic syndrome) and sometimes high estradiol – but the *most* useful laboratory indicator is the **ratio** of total testosterone to total estradiol (tT/ tE2).

Derive the tT/tE2 ratio by dividing the values as reported by your lab; mine gives tT in ng/dL and tE2 in pg/mL. By *not* reconciling units, much time is saved – though to purists, this shortcut is a bit vulgar (follow your bliss). Among younger healthy men, tT/tE2 (units *not* reconciled) is generally >30 and in healthy older men, it shall be >20. Virtually all writers agree that values <10 are bad. Many clinicians, including the author, consider starting aromatase-inhibitor treatment when the ratio is less than 15.[23]

Since this problem is strongly related to obesity, treatment starts with recommendations for proper diet, lifestyle interventions, supplements and perhaps metformin or berberine, or other treatments. While the magnitude of weight loss is linearly associated with the increase in testosterone levels,[24] the response to these efforts is usually slow. From the outset, it is appropriate to consider starting aromatase inhibitors (Aro-I). Then, look forward to reducing and perhaps stopping Aro-I treatment as the patient's metabolic health improves.

Even when LH and FSH seem inappropriately low for the testosterone level, an aromatase inhibitor can be a good choice for initial therapy. Remember that estradiol strongly feeds-back upon the hypothalamus to reduce GnRH and thusly, impairs the production of LH and FSH. Aromatase excess can mimic the picture of hypothalamic hypogonadism and treatment can improve this.[25] Watch the tT/tE2 ratio!

Many natural products have aromatase-inhibitory effects.[26] Chrysin is usually successful,[27] but doses of 300 mg, two or three times daily, are usually needed, costing $30 to $45 a month.[28] Even so, some patients prefer chrysin over any other aromatase inhibitor. Other herbal treatments include Myomin®, *Astragalus m*., *Curcuma z*. and *Cyperus r*. – *none* of which the author has any practical experience with.

Prescription aromatase inhibitors are stronger anti-estrogenic drugs than are estrogen-receptor blockers like tamoxifen. Aro-Is are indicated to eradicate estradiol production in people with estrogen-sensitive cancers.

➤

➤

Therefore, prescriptions of "third generation" aromatase-inhibiting anastrozole (GF: Arimidex) and letrozole (GF: Femara) for men with LOH are off-label. The author's experiences with anastrozole have been good.

Anastrozole increases circulating testosterone and lowers estradiol, improving the tT/tE2 ratio and often increasing LH and FSH (Table 1). Taken alone, it can also improve spermatogenesis.[29] Young men start at 0.25 mg (¼ tablet) every other day – usually in the morning. On occasion, their mood and behavior become so altered (they get "testy") that they must take it less often. Older men are more sensitive to the sudden rise in androgens and seem more likely to develop low estradiol values; they should begin taking anastrozole 0.25 mg every third or even fourth day.

The cost of this treatment is astonishingly low. Men who are willing to cut their tablets into quarters pay on average about $5 a month without using their insurance.[30] Compounding the drug will cost more; how could it not? Letrozole is usually dosed 2.5 mg daily, to as few as three times a week.[31] The monthly cost of every-other-day use can be as low as $14.[32]

The risks of Aro-I treatment are largely related to a lack of estradiol. The PDR supplies a long list of them.[33] Aromatase inhibitors *effectively* block estradiol production in a dose-related fashion. *Caution*: When physicians treating men heed published research articles and prescribe anastrozole 1 mg daily (women's dose for cancer therapy) to men, their estradiol levels usually become immeasurably low, even by LC/MS-MS. This is undesirable, for everyone needs proper amounts of estradiol.

Many beneficial effects attributed to testosterone are *actually* due to its conversion to estradiol. For instance, testosterone is trophic for bones largely because local aromatase changes it to estradiol. No, DHT can't be converted to estradiol and is *not* trophic for bones. Estradiol is protective for the brain and cognition, for articular cartilage (up to 61% of women taking Aro-Is for cancer develop arthralgia[34]) and for cardiovascular health – and each of these tissues makes its own aromatase. To avoid complications and side-effects, keep your man's estradiol level within the normal range: Above 12 to 15 pg/mL seems adequate with a good tT/tE2 ratio.

Table 1. Patient 1. Anastrozole to treat late onset hypogonadism

Patient 1, age 70, had low free T and poor tT/tE2 ratio. On treatment including anastrozole 0.25mg every 2 or 3 days, his fT, tT, tE2, ratio of tT/E2 and LH & FSH were improved. **Abbreviations:** CytPT and CytAD are proprietary glandulars: PT is lamb pituitary and hypothalamus. AD is neonatal bovine adrenal cortex (*The patient initially purchased the wrong product*). Arimidex ¼ is 0.25mg anastrozole.

Test	6.29.15	10.23.15	12.18.15	4.26.16
Estrone Reference Interval		**129 H** 12--72	63	**83 H** Same
Estradiol Ref. Int.	25.6 7.6-42.6	37 Same	14.1	14.1
Progesterone Ref. Int.	0.3 0.2--1.4	**5.3 H** Same	**1.7 H**	**2.1 H**
Total Testosterone Ref. Int.	**330 L** 348-1197	404 Same	435	401
Free Testosterone Ref. Int.	**4.1 L** 6.6-18.1	12.2 Same	8.8	9
DHT Ref. Int.	38 30-85	47 Same		38
Ratio E1/E2 E2/P4*	 85.3 (H)	3.5 7.0 (L)	4.5 8.3 (L)	5.9 (H) 6.7 (L)
Ratio tTest/E2* DHT/ E2	12.9 (L) 1.5	10.9 (L) 1.3	30.9	28.4 2.7
Other: LH/ FSH	**1.6L**/ 3.1 tT/DHT=8.7	2.2/ 3.1 tT/DHT=8.6	2.5/ 4.0 DHEA 98 (31--701)	 tT/DHT=10.6
Taking: *Units Not Reconciled		CytPT* 5/d DHEA50+50 (brand) *wrong glandular	CytPT* 5/d DHEA25+25 (Same) Arimidex 1/4 q 2d	CytAD2+1+2 Same (Same) Arimidex 1/4 q3d, 28h

Treat Hypogonadotropic Hypogonadism

Symptomatic men with late-onset hypogonadism due to the lack of LH and FSH may or may *not* have frankly low values for these pituitary gonadotropins. When the hypothalamic-pituitary-gonadal axis fails to *sufficiently* stimulate relatively healthy gonadal testosterone and spermatogenesis, it can be stimulated to restore normal function – or nearly so. Clomiphene has long been used (off label) to successfully stimulate men's HP-G axis.

SERMs: Clomiphene and Tamoxifen for LOH

We have seen that aromatase inhibitors can increase testosterone production: By lowering estradiol, the inhibitory effect on the hypothalamus is mitigated. Selective estrogen-receptor modifiers (SERMs) effectively reduce estradiol's negative feedback on the hypothalamus, enabling greater production of GnRH – and they have the same action on the pituitary's inhibitory estrogen receptors as well.

Being both more stimulated *and* disinhibited, the pituitary then releases more LH and FSH. These hormones are trophic for the testicles, increasing their testosterone and sperm production (unless there is primary hypogonadism).[35] As a bonus, it is observed that clomiphene also can improve the tT/tE2 ratio.

Infertile men have been treated with SERMs – clomiphene or tamoxifen – since the early 1970s. From the first studies, both of these have produced moderate increases in LH, FSH, testosterone and estradiol – as well as improving some parameters

of sperm health.[36] Therapeutic response is generally rapid and enduring: Clomiphene maintained symptom improvement in 77% of 400 men with low-T who were treated for at least three years.[37]

A meta-analysis of eleven RCTs (1980-2009; n=903 men, ages 20-49) using tamoxifen or clomiphene validated their benefits. Across these trials, treatment with the SERMs (compared to controls) significantly increased FSH (p= 0.0001), testosterone (p= 0.006), sperm concentration and motility, and pregnancy rates (by 2.4 times).[38] A more recent meta-analysis of 17 studies including 1,279 patients treated with clomiphene added confirmation.[39]

Tamoxifen is supplied in tablets of 10 and 20 mg. Clinical trials usually give 20 to 30 mg daily, which is expected to cost between $4 and $47 per month, varying by pharmacy.[40] It is possible the adverse effects of tamoxifen are greater than those of clomiphene.[41]

The author prescribes clomiphene, starting with 25 mg (½ tablet) every other day (QOD). There is no clear evidence whether it is more effective at bedtime or in the morning and the patient is allowed to choose. If the testicles have become atrophic, slower response should be expected and larger doses may be required. On occasion, clomiphene 50 mg QOD is needed but when LH and FSH have responded, prolonging the treatment seems more successful than giving higher doses.

After gonadal atrophy is improved – particularly after any exogenous testosterone replacement has been discontinued – the clomiphene dose may be reduced as tolerated. The cost of clomiphene 25 mg every other day now ranges from $4 to $20 month.[42] Patient 2 (Table 2) responded well to clomiphene every other day and has met the goals of therapy.[5]

Research studies often use daily doses of clomiphene, from 25 mg to 50 mg. Internet writers mention doses up to 100 mg daily. Because cells' receptor populations vary in response both to hormone levels and to receptor blockade, the daily use of clomiphene or tamoxifen causes some concern about up-regulating the estrogen-receptor population. Every *other* day dosing seems preferable if it works.

Clomiphene has few reported side-effects. A meta-analysis above reported there was *no* difference in adverse events between treated patients and controls.[38] Among 120 men treated for more than 3 years, 8% reported side effects (mood changes, blurred vision and breast tenderness); there was no "significant" adverse event.[37] Treatment with enclomiphene (the more active of two stereoisomers) had no noteworthy effect on the levels of TSH, ACTH, cortisol, lipids or bone markers.[43]

This paucity of side-effects is generally consistent across published studies. The freedom from erythrocytosis is important. Some writers express concerns about possible neoplastic effects of elevated gonadotrophic hormones, though menopausal women have far greater amounts for decades. A risk of thromboembolic events has been stated.[44] A few men will complain of testicular tenderness, which seems related to testicular growth within the previously atrophic tunica – a compartment syndrome? The discomfort responds to dose reduction.

Stimulate Testicles with Gonadotrophs: LH/ hCG

The success of clomiphene and tamoxifen treatment depends upon an intact hypothalamic-pituitary connection, ➤

Table 2. Patient 2. Clomiphene to treat late onset hypogonadism.

Patient 2, age 48 had symptoms and repeatedly low total testosterone with inappropriately low-normal LH and FSH. His tT/tE2 ratio was acceptable. On clomiphene 25mg QOD, his testosterone responded well; LH briefly became a bit high, as often the case. The tT/tE2 ratio has improved.

Abbreviation: CytAD is desiccated neonatal adrenal cortex.

Test	9.15.16	11.14.16	1.26.17	7.17.19	11.25.20
Estrone Reference Interval			**125 H** 12--72		
Estradiol Ref. Int.	11.4 Same	38.1 7.6--42.6	37.8 Same	LCMS 33	LCMS 20
Progesterone Ref. Int.	**0.2** "H" "< 0.2"	**0.4** "H" Same	**0.3** "H"	IA 0.5 Same	IA 0.2
total Testosterone Ref. Int.	**206** L Same	649	593	LCMS 711.8	LCMS 616
free Testosterone Ref. Int.	7.1 6.8--21.5	**22.3** H Same	17.4	ED 20.0 5.0-21.0	ED **21.9H** Same
DHT Ref. Int.	LCMS **25** L 30--85	LCMS 49 Same	LCMS 59		
Ratio* E1/E2 E2/P4	57	95.3 (?)	3.3 126 (H)	66	100
Ratio* tTest/E2 LH/ FSH	18.1 3.6/ 2.8	17.03 **10.9**H/5.5	15.7 8.5/ 5.2	21.6 5.8/ 4.7	30.8
Other:	DHT/E2 2.2 tT/DHT 8.2	DHT/E2 1.3 tT/DHT 13.2	DHT/E2 1.6 tT/DHT 10.1	DHEA 295 (31--701)	
Taking: *Units Not Reconciled		CytAD2+2 Clomiph 25mg qod.	CytAD 2+2 Clom 25qod 24h p dose	CytAD 2+2 Clom 25qod	CytAD 2+2 Clom 25qod

➤

which some patients lack! Pituitary lesions, from tumors to transections of the stalk, can reduce or eliminate the gland's response to hypothalamic GnRH. In such cases, SERMs will fail – but gonadotrophs can work because they replace hormones the pituitary cannot provide.

With impaired pituitary function, luteinizing hormone (LH) and follicle stimulating-hormone (FSH) are deficient. These hormones act synergistically upon responsive testicles to produce testosterone, sperm and to maintain the gonads (i.e.: gonadotrophic). Via three key enzymes, LH regulates Leydig cells' secretion of testosterone. FSH works cooperatively to promote spermatogenesis.[45] Replacing LH and sometimes also FSH can restore testicular function. The FDA has approved hCG products as LH-substitutes for "select hormonal treatment in males."[46]

Table 3. Patient 3.
Transition from Testosterone cyp. to clomiphene, then anastrozole

Patient 3, age 36 is Patient 2's brother. He chose to switch from injected testosterone to oral clomiphene. Anastrozole was added twice-weekly for a healthy tT/tE2 balance. **Abbreviations**: T cyp is testosterone cypionate, 60mg per week. CytAD is desiccated neonatal adrenal cortex. Anast .25 is 0.25mg anastrozole. "24h p dose" notes the blood was drawn 24 hours after the previous dose of clomiphene. "6 hr p dose" indicates the blood was taken six hours after the last dose.

Test	8.25.15	10.11.16.	2.28.22
Estrone Reference Interval			
Estradiol Ref. Int.	14.9 7.6-42.6	42.5 Same	LCMS 18
Progesterone Ref. Int.	0.8 0.2--1.4	0.3* "H" 0.0--0.2*	IA 0.3
total Testosterone Ref. Int.	591 Same	599	LCMS 571.9
free Testosterone Ref. Int.	14.6 8.7-25.1	15.2 Same	LCMS 10.18
DHT Ref. Int.	30 30--85	44 Same	
Ratio* E1/E2 E2/P4	18.6	141.7 (H)	60
Ratio* tTest/E2 LH/ FSH	39.7 **0.1**L**/<.2 L**	14.1 (L) **14.9**H/11.6	31.8
Other:	DHT/E2 2.0 tT/DHT 19.7	DHT/E2 1.0 tT/DHT 13.6	
Taking: *Units Not Reconciled	T cyp q wk 0.3cc-60mg Day #4 1/2 Mid-dose	No T cyp CytAD 2.1.0 No DHEA Clom 25OD 24h p dose	CytAD 2.1.0 Clom 12.5OD 6 hr p dose Anast .25 QTu&Fr.**4d**

A meta-analysis of 30 studies including 440 azoospermic (no viable sperm) human males receiving hCG with or without FSH proved spermatogenesis was successful in 75% of patients.[47] After treatment for 12-24 months, one can expect spermatogenesis (as above), testicular growth, and about 50% of men can contribute to a pregnancy. Furthermore, studies have reported the enduring resolution of hypothalamic hypogonadism in 10% of patients after their treatment has been stopped.[48]

Clinicians and patients should know that certain factors influence the outcomes of hCG therapy: Success is greater in patients with post-pubertal hypogonadism, in men with larger initial testicular volume, with higher baseline serum inhibin-B concentrations and in men who previously had repeated cycles of therapy.[49] Response is likely to be less favorable in previously cryptorchid men and with prepubertal testes (volume <4mL); their success is no better than 50%.

Recombinant LH (rLH, from Chinese hamster ovaries) was approved by the U.S. FDA in 2004. Before its advent, purified human chorionic gonadotropin (hCG, from pregnant women's urine) was substituted for LH, as the two are very similar in form and function, and act upon the same receptor.[48,50] Purified hCG is less expensive than rLH and of the two, is still the most frequently used. Some researchers believe that rLH offers no significant advantage over hCG.[47]

Treatment with hCG to restore testicular function and fertility usually begins with doses of 1,000 to 2,000 IU, given intramuscularly (IM) or subcutaneously (SC) from once[2] to three times a week.[45] Studies commonly report doses of 5,000 IU per week. During follow-up, the hCG dose will be titrated, based on trough testosterone levels and testicular growth. As the testes enlarge, the dose can be reduced.[48] Because 10% of patients enter remission after a period of treatment, hCG may (should?) be stopped for re-evaluation after a good response to hCG.[48]

The typical monthly cost of the hormone is $676 for men taking 5,000 IU hCG/week, calculated from the quote on Drugs.com.[51] However, a compounding pharmacy near the author will charge only $280 for this monthly dose. The retail cost of recombinant LH (lutropin alfa, Luveris®) is $61 per 75 IU vial.[52]

Perhaps the greatest drawback of hCG and rLH therapy is that these must be injected.[53] Patients' adherence to treatment improves when it is given SC, rather than IM.[54]

Potential side effects of gonadotropin therapy include gynecomastia, from increased estrogen production; headache; fatigue; and mood changes.[55] The package insert for rLH states gastrointestinal upset is common, also. To minimize these side effects and the risk of erythrocytosis, the dosage of hCG therapy should be kept as low as possible. Providers have been encouraged to aim for testosterone levels in the low-normal range.[56]

Combinations of Treatments

The treatments herein reviewed are not exclusive of each other. They may be used in combination to achieve clinical goals. Men treated with testosterone are often seen to "spill" their TRT into excessive estradiol. They are likely to benefit

from adding an aromatase-inhibitor. Thus, their tT/tE2 ratio is improved – and if estradiol had suppressed their HP-G axis, this will be lessened.

Negative feedback from testosterone treatment inhibits gonadotropin release and shrinks men's testicles, which raises some objections. As above, an Aro-I might improve this issue. hCG works well: An all-star baseball slugger illicitly using anabolic steroids used hCG to maintain the trophic stimulation of his testicles. When his urine test revealed he was "pregnant" (hCG), further investigation led to his suspension.[57]

Some users of testosterone add hCG to maintain their fertility. A small series (n=26) of such men using topical testosterone gel received hCG 500 IU intramuscular injections every other day. They maintained normal semen parameters and 9 men contributed to pregnancies during the study.[58]

Continued injection of testosterone can lose its appeal. Patient 3 (Table 3) is Patient 2's brother. He was "Case 1" in *Townsend Letter*, December 2016.[14] He had an unusual complication from overdosing transdermal T-gel. He switched to injected testosterone cypionate and was happy – for a few years. Wearying of self-injection, he switched to oral clomiphene, making an easy transition. He needed to add anastrozole to restore and maintain a satisfactory tT/tE2 balance.

The use of an aromatase inhibitor may be simply insufficient to restore desirable blood levels of testosterone. Clomiphene can be added to Aro-Is in the usual doses. Patient 4 (Table 4) has insulin resistance; he is not obese but has high postprandial insulin-spikes. Previously, gel-TRT did not help him and was stopped. At age 53, anastrozole restored a good tT/tE2 ratio but his testosterone remained low until clomiphene was added.

Clomiphene can improve the ratio of testosterone to estradiol – but sometimes not adequately. Patient 3 was taking clomiphene but needed anastrozole to improve his tT/tE2 balance, as have others. In the author's limited experience, the two drugs are compatible. Drugs.com reports no interactions between the two.

When clomiphene fails to achieve the desired results, hCG can be substituted. For the restoration of fertility, this still may be insufficient: hCG treatment can plateau at around six months. If results are suboptimal, therapy with some form of FSH can be added, starting with 75 IU every other day. Then, if needed, FSH is gradually increased to 150 IU daily.[59]

Men with low-volume testicles or prior cryptorchidism who desire fertility should be treated with planned combined LH and FSH. In difficult cases, FSH "gonadal priming" is given for 4 months before pulsative GnRH is added for another two years.[45] Pulsatile GnRH is expensive, technically challenging and "high maintenance"; thus, its use is generally restricted to specialist centers.[48]

➤

➤

Gynecomastia is the most common side-effect of hCG treatment. hCG stimulates aromatase, which converts testosterone to estradiol.[49] While the use of the lowest successful hCG dose is recommended,[48] anastrozole or other Aro-I would be helpful to prevent or treat this problem.

Limitations

The author feels confident in the accuracy of this review – *but* lacks experience with hCG, rLH, FSH and pulsed GnRH therapy. Dosing and treatment regimens for these agents were extracted from the medical literature. Observably, the doses used in some studies, particularly in early innings, can be clinically inappropriate – e.g., giving men anastrozole 1 mg daily, discussed above. The author and the Editor invite readers' comments based on their personal experiences. It is desirable to have an interchange of ideas in this forum.

Conclusions

Most men with late-onset hypogonadism have secondary gonadal failure, not primary. With proper stimulation – and the removal of suppressive amounts of estrogen – the potential for normal testicular function remains. Some men produce plenty of testosterone, but they promptly convert it to estradiol – visualize pumping water into a bucket with lots of holes in the bottom. Aromatase inhibitors plug the "holes" through which testosterone is lost and this removes the inhibiting feedback exerted by the excessive estradiol.

More frequently than having aromatase excess, men lack the pituitary hormones that drive testicular function. This deficiency can arise in the hypothalamus or from pituitary lesions. Hypothalamic depression usually responds to SERMs like clomiphene, letrozole, and tamoxifen. If the pituitary is unresponsive, the gonadotrophic hormones that it cannot make are replaced with LH or hCG and sometimes FSH.

Because problems of various types can simultaneously exist at several levels, the informed and persistent practitioner has a high likelihood of success inducing and balancing endogenous hormone production and even restoring fertility to these men. The choice of treatments is determined by the patient's medical diagnosis, his preferences, his budget – and of course, his initial response to the treatment. Early failure is often later corrected. Both patient and practitioner are advised to be optimistic and relentless in the pursuit of their goals.

Table 4. Patient 4 Clomiphene is added to anastrozole.

Patient 4, age 53 had received no benefit from transdermal TRT. Anastrozole restored a good tT/tE2 ratio but adding clomiphene produced better results, improving symptoms, function, and blood tests.
Abbreviations: Dess.Adr is desiccated adrenal cortex by LEF, discontinued on 11.2015. DHEA 50/D indicates 50mg daily.

Test	9.10.15	10.20.15	11.25.15	2.22.16	7.14.16
Estrone Reference Interval					
Estradiol Ref. Int.	13.9 Same	**< 5** L 7.6--42.6	**6.9** L Same	16.8	17
Progesterone Ref. Int.	1.2	1.2	1.3	**4.0** H	1
total Testosterone Ref. Int.	**330** L	**302** L 348--1197	**304** L Same	529 Same	516
free Testosterone Ref. Int.	7.2	**6.5** L 7.2--24.0	**3.3** L Same	16.6 Same	12.3
DHT Ref. Int.	**26** L	**19** L 30--85	**25** L Same	30 Same	33
Ratio E1/E2 E2/P4	11.6	< 4.2 (L)	5.3 (L)	4.2 (L)	17
Ratio tTest/E2 DHT/ E2	23.7 1.9	> 60.4 (H)	44.1	31.5 1.8	30.4 1.9
Other: tTest/DHT (1.7--8.6) (1.5--12.4)	12.7 LH 5.4 FSH 4.8	15.9 DHEA 143 31--701	12.2 DHEA 180 LH 4.8 FSH 5.6	17.6 DHEA 212 LH **9.7**H FSH 7.8	tT/DHT 15.6 LH 7.5 FSH 8.5
Taking:	**LH/FSH ratio 1.1H**	CytAD Dess.Adr DHEA 75/d Arimidex .25mg q3d day #2	CytAD 5/d No LEF Ad DHEA 100/d Arimidex Same	Same - Same Same Clomid 25 qod	Same DHEA 50/D Same?

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

He has presented at various national meetings in the US (AAO-HNS, AAOA, ANS, AAEM, IFM, PAAS, ACAM, ICIM) and in Mexico. Topics of his lectures and publications have included general surgery and otolaryngology; otology and neurotology; allergy; chronic fatigue and endocrinology. He has been a faculty member for the American Academy of Otolaryngic Allergy, both basic and advanced courses, and for the American Academy of Environmental Medicine. His two-day course "New Endocrinology" has been presented at the AAEM and elsewhere since 2005, to physicians from five continents.

Work with dizziness and allergy in the 1980s led him to seek solutions for chronic fatigue syndrome. These clinical investigations were extended to the endocrine aspects of this and related conditions. Because basic surgical training emphasizes the need to know several alternative approaches to an operation, he saw the logic of studying integrative and controversial medical methods. He has endeavored to understand these in the light of new facts from research, mindful that medical history shows innovation begins as a minority opinion.

He is excited that applying new research to patient care offers solutions to many of the chronic and worsening problems that are epidemic in modern society.

◆

References are available online at www.townsendletter.com.

Still the Best

A Must Have for Kidney Function Support!

CORDIMMUNE ™

The only cordyceps product that is standardized for and declares its cordycepin content

- Supports mitochondrial function and ATP production
- Modulates immune system
- Enhances athletic performance safely
- An excellent adaptogen and adrenal support
- Supports bone marrow function
- 0.2% Cordycepin
- 0.3% Adenosine
- 22% Polysaccharides

Immune Support Beyond Just Polysaccharides!

CORIO PSP ™

The most clinically researched mushroom in Japan and China

- Protects and maintains healthy liver functions
- Supports and maintains the quality of life
- Raises the activities of NK cells and macrophages
- Maintains optimal thymus weight
- Contains no less than 38% polysaccharides

The statements herein have not been evaluated by the FDA. This product is not intended to diagnose, treat, or prevent any disease.

CANADA RNA BIOCHEMICAL INC.
Tel: (604) 273-2233 • **www.canadaRNA.com**

1-866-287-4986

Mortality Reduction in Diabetics with PDE5 Inhibitor, Statin, and Testosterone Combination

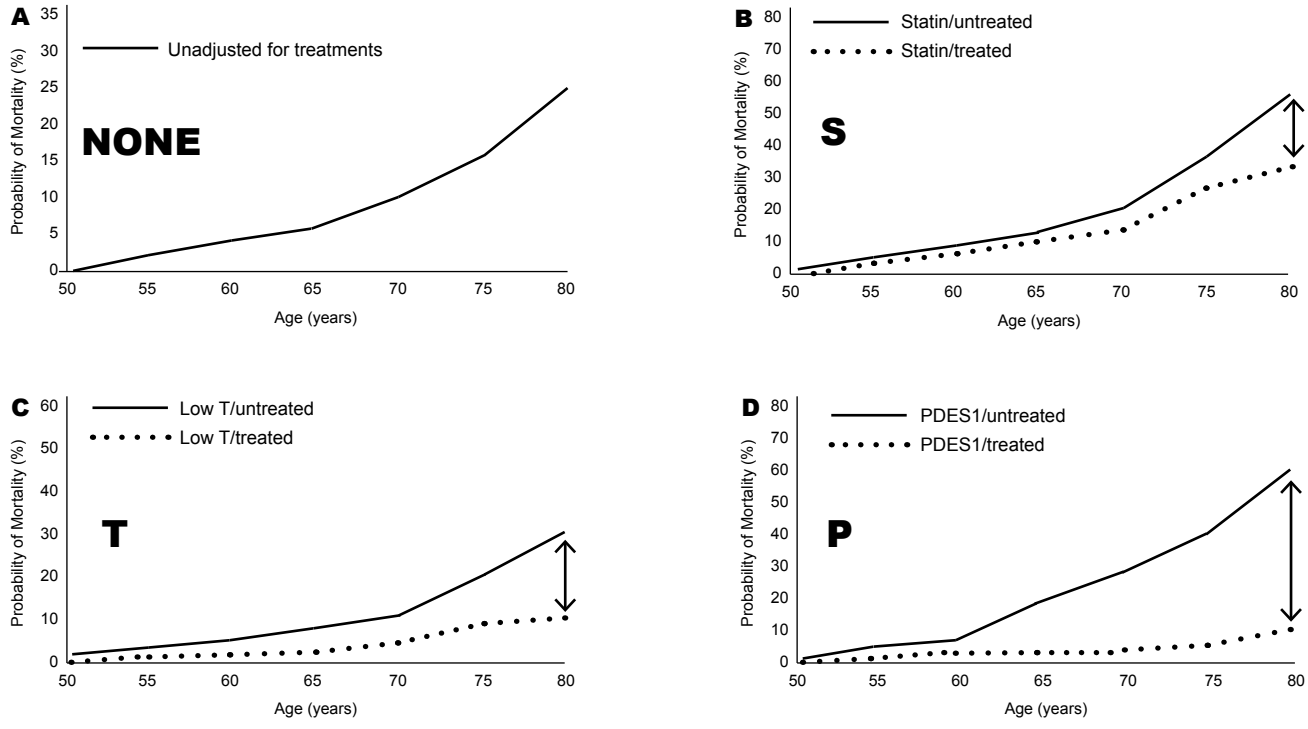
by Jeffrey Dach, MD

While researching nitric oxide and the plant-based diet, I came across this 2017 study by Geoffrey Hackett in the *World Journal of Diabetes*, "Statin, testosterone and phosphodiesterase 5-inhibitor treatments and age-related mortality in diabetes."[1] Well-known complications of diabetes are peripheral neuropathy, diabetic renal disease, accelerated coronary artery disease, and erectile dysfunction, all related to nitric oxide deficiency commonly found in diabetics.[2-12] It is also well known that both testosterone therapy and statin therapy are beneficial for diabetics, providing a reduction in all-cause mortality of 20-60%, depending on the study.

Statin Drugs for Diabetics

The recommendation of prescribing a statin drug for diabetics is regardless of cholesterol levels. In my opinion, the benefit of a statin drug for diabetics is not due to the cholesterol-lowering effect of the drug. The benefit is due to pleomorphic effects, the anti-inflammatory and anti-microbial effects. For example, see the 2007 study by Zhang in which one-to-two years of statin use in diabetics is associated with 24-29% reduced all-cause mortality.[13] There are many others.[14-16] On the other hand, it is admitted that not everyone is in agreement that statins are beneficial for diabetics.[17,18]

Figure 1. **Mortality Results in Hackett Study (courtesy of Hackett). Group A ("None")** shows probability of mortality in untreated group. **Group B ("S")** shows the difference (see arrow) in mortality between men receiving statin and those not receiving statin. **Group C ("T")** shows the difference (see arrow) between men with low testosterone who did not receive testosterone and those with low testosterone who did get testosterone treatment. **Group D ("P")** shows the difference between the men receiving PDE5 inhibitor Cialis and the untreated group. Note the dramatic separation distance compared to other two treatment charts.[1]



Testosterone for Diabetics

The benefits of testosterone for diabetics were demonstrated nicely in a 2013 study by Muraleedharan, et al.[17] In 2019, Hackett published another more recent study of diabetic men with low testosterone. For untreated men, mortality was 16.9%. However, when these men were given testosterone then discontinued, mortality was reduced to 6.2%. If the men were treated continuously with testosterone, mortality over 3.8 years was reduced to ZERO!![18]

Even Greater Benefits for PDE5 Inhibitor Tadalafil

As impressive as the benefits of testosterone and statins are for diabetics, the benefit of a PDE5 inhibitor, such as Cialis (tadalafil) 5 mg daily, is even greater. This was demonstrated nicely by Dr Geoffrey Hackett in the UK who found profound reduction in mortality in diabetics taking Cialis 5 mg daily (See Figures 1 and 2).[1]

Figure 2. All three treatments together in combination.
Courtesy of Hackett: Bold line is mortality of untreated group. Dotted line is mortality of treated group using all three modalities: statin, testosterone and PDE5 inhibitor. Note dramatic reduction in mortality denoted by arrows in the treated group.[1]

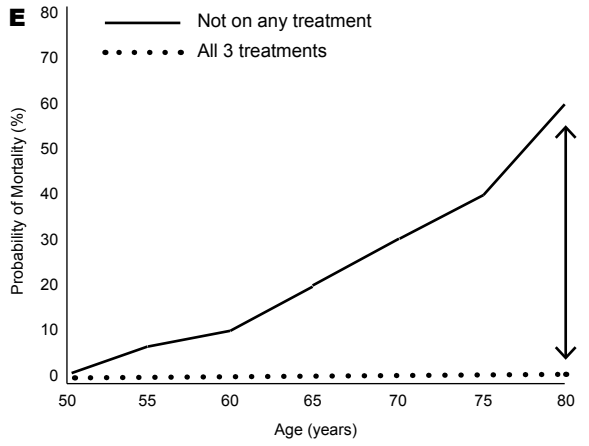
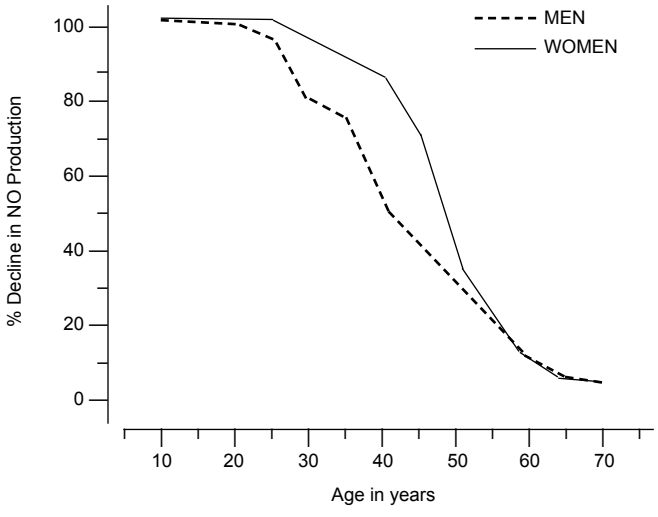


Figure 3. Nitric Oxide and Aging.



What Is the Connection to Nitric Oxide, Erectile Dysfunction, and PDE5 inhibitors?

Nitric oxide production declines with age. This decline is directly related to erectile dysfunction, endothelial dysfunction and vascular disease (See Figure 3).[17-29]

*Mechanism of Action***.** In 1998, The Nobel Prize in Medicine was awarded to Robert F. Furchgott, Ferid Murad and Louis Ignarro for work on nitric oxide in smooth muscle vasodilation. The key messenger molecule producing vasodilatation is cyclic guanosine monophosphate (cGMP), which is downstream to nitric oxide. The PDE5 inhibitors do not directly increase nitric oxide. They prevent degradation of the cyclic guanosine monophosphate (cGMP) induced by nitric oxide, thus producing vasodilatation, and relieving erectile dysfunction.[30-32]

PDE5 Inhibitors

BPH and Chronic Prostatitis. In addition to their benefit for diabetics, Cialis (tadalafil) 5 mg daily has been found beneficial for benign prostatic hypertrophy (BPH), and chronic prostatitis patients.[33-36] Of the PDE5 inhibitor drugs, tadalafil has the longest duration of action (36 hours) making the drug suitable for daily dosing.[37-38]

Cognitive Function and Neuropathy. Increases in micro circulation and blood flow induced by PDE5 inhibitors provide benefit in peripheral neuropathy, cognitive function, and neuroprotection.[39-47]

As a Repurposed Cancer Drug. A large volume of clinical and pre-clinical studies suggests PDE5 Inhibitors may be repurposed as highly effective anti-cancer drugs.[21,22]

Other Benefits of PDE5 Inhibitors. Other suggested benefits of PDE5 Inhibitors include use in atherosclerotic heart disease, Alzheimer's dementia, Duchene muscular dystrophy, and of course, the drug is approved for treatment of pulmonary hypertension.[19,20,26,48-54]

Conclusion

The dramatic benefit of PDE5 inhibition with tadalafil in diabetics is even greater when used in combination with testosterone and statin drugs. ◆

References are available online at www.townsendletter.com.

Dr Dach was originially trained in clinical medicine, and worked as an emergency room doctor in Illinois. He then worked 25 years as a hospital-based physician as a diagnostic and interventional radiologist. After retiring from radiology in 2004, Dr. Dach returned to clinical medicine and founded a new clinic specializing in bioidentical hormones and natural thyroid for the low thyroid condition. Dr. Dach also prescribes low dose naltrexone (LDN) for a variety of inflammatory and autoimmune conditions.

Why 5-Alpha Reductase Inhibitors Should Be Avoided for Prostate Urinary Problems and Nutraceutical Options

by Geo Espinosa, ND, LAc

As a urology naturopathic clinician, I have been against the clinical use of 5-alpha-reductase-inhibitors (5ARIs), the category of drugs that include finasteride (Proscar) and dutasteride (Avodart), as I've noticed significant adverse effects (discussed further down) from the use of these drugs. While there may be some moderate prostate benefits from using 5ARIs, to me the risk outweighs the benefits.

5-Alpha-Reductase Inhibitors and How They Work

Let's reverse engineer how 5ARIs work and then discuss why it might be a problem. ARIs inhibit the production of dihydrotestosterone (DHT), a by-product of testosterone (T), by blocking the enzyme 5-alpha-reductase (5-AR). Under normal circumstances, testosterone uses the enzyme 5-AR to make dihydrotestosterone, but by inhibiting this enzyme with a 5ARI like finasteride or dutasteride, there is less DHT in the body.

What Does Dihydrotestosterone Do in the Body?

DHT is responsible for forming the penis, prostate, and scrotum during fetal development. If DHT production is inhibited (as occurs with genetic abnormalities), then what would have been a penis becomes a clitoris. This highlights the importance of DHT during fetal development in the masculinization of boys in the womb.[1] While there is much less circulating DHT in adult males, it binds to androgen receptors stronger and longer than testosterone.[2]

DHT is one of four principal androgens in humans and is synthesized primarily via the irreversible action of the 5-alpha-reductase enzyme. There are different types of 5-AR in prostate tissue (type I and II), skin (type I), liver (types I and II), and hair follicles (primarily type I).

Conversion of T to DHT via the 5-AR activity in peripheral tissue is the primary source of circulating DHT. Little DHT is synthesized in the prostate or liver; but when it enters the general circulation, much metabolism of DHT occur in these tissues.[3]

Despite false beliefs, there is no evidence that higher DHT increases the risk of prostate cancer.[3]

Why Stop the Production of Dihydrotestosterone?

DHT seems to have two effects on the body that many men would want to avoid. One, it stimulates the muscular part of the prostate to grow (the prostate is 70% glandular, 30% muscle); and two, it promotes male pattern baldness. Do you ever wonder why most guys who have a full head of hair often have very little to no hair on their bodies? Every strand of hair on the male body grows from a hair follicle. Once it's freely flowing through your bloodstream, DHT can then link to receptors on hair follicles in the male scalp, causing them to shrink and become less capable of supporting a healthy head of hair. The progression of hair loss can be very gradual and continuous or episodic. Paradoxically, DHT can stimulate hair growth on the face, chest, and genital area, while inhibiting hair growth on the scalp's skin.[4]

The Development of 5-Alpha Reductase Inhibitors

In the early 1970s, a rare genetic mutation that inhibits the production of 5-alpha-reductase was discovered in a group of boys from the Dominican Republic. The boys do not produce DHT. With no DHT, there is no development of the penis, prostate, and scrotum until roughly age 12.

The condition, known as Guevodoces (Spanish for *guevo* – penis, *doces*-twelve or penis at twelve), affects males born with unusual genitals—female-like labial folds with scrotal appearance, ambiguous vagina, and a clitoral-like phallus. These kids were initially raised as girls. So, the boys, despite having an XY chromosome, appear female. After a T surge at around twelve years old, their genitals form, they develop body muscle mass, their voices deepen, their phallus enlarges into a functional penis, testes descend, and there's no breast development. Researcher Imperato-McGinley and team observed that most Guevedoces kids live out their lives as men. However, some go through an operation and remain female, and, interestingly, they tend to have small prostates.[5]

Imperato-McGinley's observation, made in 1974, was picked up by Roy Vagelos, head of research at the multinational pharmaceutical giant Merck who thought this was extremely interesting and set in progress research that led to the development of what has become a best-selling drug, finasteride, which blocks the action of 5-alpha-reductase, mimicking the lack of dihydro-testosterone seen in the Guevedoces. Finasteride (Proscar), a 5-AR1 inhibitor, was approved by the FDA in 1992 for treating benign prostate hyperplasia (BPH).[6] Proscar is used at 5 mg per day to reduce prostate size to treat lower urinary tract symptoms (LUTS), and Propecia, the other tradename for finasteride, is used at 1 mg a day for male pattern baldness.

Can 5-Alpha Reductase Inhibitors Lower Prostate Cancer Risk and Help Lower Urinary Tract Symptoms?

It was once falsely thought (still thought in some cases) that DHT causes prostate cancer. A study published in 2003 in the *NEJM* reported a 24.8% reduction in low-grade prostate cancer in the experiment group of men taking finasteride; however, a 27% increased risk of developing high-grade prostate cancer was found in those taking the drug versus the placebo group.[7] Finasteride can also cross the blood-brain barrier and might induce a deficit in neurosteroid metabolism in the central nervous system.[8]

Dutasteride is the other popular 5ARI and goes by the trade name Avodart. Dutasteride, a 5-AR1 and 5-AR2 inhibitor, was found to reduce the risk of low-grade prostate cancer in a study involving over 6,000 men. In this trial using dutasteride, the incidence of high-grade prostate cancer during the four years of the study was not significantly increased. However, it is essential to note that the number of men diagnosed with high-grade prostate cancer using dutasteride was significantly higher at 29, versus only one in the placebo group.[9] Finasteride and dutasteride may increase the risk of potentially life-threatening prostate cancer, which is the type we care about most since most men die with the disease rather than from it. Further, a byproduct of DHT is 3β-androstanediol, also known as 5α-androstane-3β,17β-diol, and often shortened to 3β-diol, an endogenous steroid hormone. 3β-diol binds to estrogen receptor beta (Erβ) and, in doing so, possesses anti-proliferative effects against prostate cancer cells.[10] 3β-diol has been found to have beneficial neuronal effects in the brain, including antidepressant, anxiolytic, cognitive-enhancing, and stress-relieving effects. However, anti-prostate cancer and psychiatric benefits may be reduced by 5-ARIs, or intake of these pharmaceuticals may induce post-finasteride syndrome (PFS), which we will discuss shortly.[11] Lastly, 5ARI therapy effectively reduces prostate volume by approximately 20% in many patients; however, about 25%-30% of patients do not experience any improvement in their urinary symptoms, and another 5%-7% develop worse symptoms and may ultimately require surgery.[12] In my clinical experience, an enlarged prostate only occasionally causes LUTS as I have seen many men with big prostates with no LUTS and quite a few cases of men with small prostates and much LUTS.

Omega 3-fatty acids, curcumin, Boswellia, ginger extract, and quercetin are my clinical "go-to" for addressing inflammation of the prostate.

Post-Finasteride Syndrome

Post-finasteride syndrome (PFS) is a controversial and ill-defined spectrum of symptoms in three categories (sexual, physical, and psychological) that putatively arise and persist despite finasteride exposure and cessation. The FDA mandated a label change on finasteride advising a risk of libido loss, erectile dysfunction (ED), ejaculatory disorders, gynecomastia, and other adverse experiences based on low-level evidence reports lacking validated questionnaires.[13]

From April 1, 2011, to October 27, 2014, 2048 cases spanning a 43-month period received monotherapy: finasteride/Propecia 1 mg (1581 cases); finasteride/Proscar 5 mg (240 cases); dutasteride/Avodart (1 case); finasteride unreported dose (226 cases). The 1 mg dose showed significantly higher frequencies for sexual dysfunction, libido decrease, ejaculation disorder, erectile dysfunction, testicular atrophy, orgasmic disorder, hypogonadism, skin rash, metabolism abnormalities, self-harm, slow cognition, psychological pathology, change in emotional affect, and sleep disturbances. Breast enlargement (gynecomastia) was the only symptom reported as more prevalent for 5 mg versus 1 mg. Interestingly there were no PFS symptoms reported for dutasteride in the 1 monotherapy case in the FAERS database.[14] Dutasteride is often "guilty by association" since the two drugs share the same mechanism of action, but I have not found any reliable data to show its cause of PFS similar to finasteride. That said, one study shows dutasteride having sexual and libido adverse events similar to finasteride.[15]

Nutraceutical Management of BPH-Related Lower Urinary Tract Symptoms

Treating BPH successfully with nutraceutical interventions focuses on lowering chronic inflammation, reducing oxidative stress, and relaxing hyperactive nerves and tight muscles.

An inflammatory microenvironment contributes to an enlarged prostate and associated LUTS.[16] Omega 3-fatty acids, curcumin, Boswellia, ginger extract, and quercetin are my clinical "go-to" for addressing inflammation of the prostate. Rye pollen extract (Cernilton) seems to have a beneficial anti-inflammatory and anti-proliferative effect on prostate cells and improves quality of life in men with LUTS.[17] White blood cell activity, mainly macrophages and neutrophils, may induce oxidative stress, which then leads to excess cell proliferation of the prostate.[18] To address oxidative stress to the prostate, I clinically use vitamin C,

➤

➤

vitamin E with high gamma-tocopherol, alpha lipoic acid, and grape seed extract. The prostate is 30% smooth muscle[19] and like any smooth muscle (think blood vessels), unmanaged stress causes tightening and constriction.

My natural prescription here is deep diaphragmatic breathing, magnesium, and botanicals that relax smooth muscles, mainly ginger extract and Chinese skullcap (*Scutellaria*), which also relaxes overactive nerves. Reishi mushroom (*Ganoderma lucidum*) exhibits a significant reduction in prostate-related urinary problems at 6 mg daily without acting as 5-ARI but how it is beneficial to the prostate is unclear.[20] Lastly, the use of cranberry extract (*Vaccinium macrocarpon)* has also shown promise in the management of LUTS and BPH in men. Cranberry significantly improves urinary function in men while also reducing prostate specific antigen (PSA) in men.[21] I have found such combination of nutrients and botanicals found in Regimen 01 targeted prostate packets (XYWellness.com) or in a single bottle formula of Mr. Happy prostate support (https://iammrhappy.com/) to be clinically effective in reducing prostate-related urinary frequency, urgency, and nighttime urination along with a moderate drop in PSA. For full disclosure I am chief medical officer and formulator of both companies.

Closing Thoughts

The likelihood of my clinically recommending 5-ARIs is minimal, and some of the reasons might be based on my clinical experience suggesting that an enlarged prostate rarely induces LUTS or the fact that natural, nutritional, and lifestyle methods when prescribed work well in reducing symptoms. Additional natural prescriptions for prostate-related LUTS includes meditation, physical exercise, other botanicals, and a plant-based, Mediterranean diet. If a pharmaceutical drug is required, I find alpha-blockers such as tamsulosin or alfuzosin work well with minimal side effects. If a big size prostate (BPH) contributes to urinary problems (often the bladder is the culprit), a surgical procedure may be necessary to open the prostate for better flow. In most cases, however, even when the patient has a history of urinary retention, relief with the natural interventions recommended above reduces the risk of future urinary obstruction and helps avoid aggressive medical interventions.

References

1. Walsh PC, et al. Familial incomplete male pseudohermaphroditism, type 2: decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. *N Engl J Med*. 1974; 291:944–949.
2. Gao W, et al. Chemistry and structural biology of androgen receptor. *Chem Rev*. 2005;105(9):3352–3370.
3. Swerdloff RS, et al. Dihydrotestosterone: Biochemistry, Physiology, and Clinical Implications of Elevated Blood Levels. *Endocr Rev*. 2017;38(3):220-254. doi:10.1210/er.2016-1067
4. Urysiak-Czubatka I, et al. Assessment of the usefulness of dihydrotestosterone in the diagnostics of patients with androgenetic alopecia. *Postepy Dermatol Alergol*. 2014 Aug;31(4):207-15. doi: 10.5114/pdia.2014.40925.
5. Imperato-McGinley J, et al. Steroid 5alpha-reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science*. 1974 Dec 27;186(4170):1213-5.
6. Marks LS. 5α-Reductase: History and Clinical Importance. *Rev Urol.* 2004; 6(Suppl 9): S11–S21.
7. Thompson IM, et al, The Influence of Finasteride on the Development of Prostate Cancer. *N Engl J Med* 2003; 349:215-224
8. Rahimi-Ardabili B, et al. Finasteride induced depression: a prospective study; *BMC Clin Pharmacol*, 6 (2006), p. 7
9. Andriole GL, et al. Effect of Dutasteride on the Risk of Prostate Cancer. *N Engl J Med* 2010; 362:1192-1202.
10. Weihua Z, et al. An endocrine pathway in the prostate, ERbeta, AR, 5alpha-androstane-3beta,17beta-diol, and CYP7B1, regulates prostate growth. *Proceedings of the National Academy of Sciences of the United States of America*. October 2002;99 (21): 13589–94.
11. Handa RJ, et al. A Role for the Androgen Metabolite, 5alpha Androstane 3beta, 17beta Diol (3?-Diol) in the Regulation of the Hypothalamo-Pituitary?Adrenal Axis. *Frontiers in Endocrinology*. 2011.
12. Bechis SK, Otsetov AG, Ge R, Olumi AF. Personalized medicine for the management of benign prostatic hyperplasia. *J Urol*. 2014 Jul;192(1):16-23.
13. Ganzer CA, Jacobs AR, Iqbal F. Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. *Am J Men Health*. 9 (2015), pp. 222-228
14. Adverse events with Finasteride or Dutasteride: FAERS. *Reactions Weekly* **1710,** 5 (2018). https://doi.org/10.1007/s40278-018-48679-z
15. Zhou Z, et al. The efficacy and safety of Dutasteride compared with Finasteride in treating men with androgenetic alopecia: a systematic review and meta-analysis. *Clin Interv Aging*. 2019 Feb 20;14:399-406.
16. Cai T, et al. Current Knowledge of the Potential Links between Inflammation and Prostate Cancer. *Int. J Mol Sci*. 2019;20:3833
17. Loschen G, Ebeling L. Inhibition of arachidonic acid cascade by extract of rye pollen. *Arzneimittelforschung*. 1991;41(2):162–7.
18. Sugar LM. Inflammation and prostate cancer. *Can J Urol.* 2006;13(suppl 1):46–47.
19. Berry SJ, et al. (1984) The development of human benign prostatic hyperplasia with age. *J Urol* 132:474–479
20. Noguchi M, Kakuma T, Tomiyasu K. Effect of an extract of Ganoderma lucidum in men with lower urinary tract symptoms: a double-blind, placebo-controlled randomized and dose-ranging study. *Asian J Androl*. 2008;10:651-658.
21. Vidlar A, et al. The effectiveness of dried cranberries (Vaccinium macrocarpon) in men with lower urinary tract symptoms. *Br J Nutr*. 2010;104:1181-1189.

◆

Dr. Geo Espinosa (Dr. Geo) is a naturopathic functional medicine doctor recognized as an authority in urology and men's health. He has a faculty position at New York University Langone Health and the Institute for Functional Medicine (IFM). Dr. Geo is the chief medical officer and formulator at the male-focused nutraceutical company XY Wellness, LLC, and its sister company Mr. Happy. He is co-founder and producer of the popular male health website, DrGeo.com, and *The Dr. Geo Podcast*. Dr. Geo is the co-founder of the Integrative and Functional Urology Institute (IFUI), an online program to train health care practitioners in science-based integrative methods to treat urological conditions. When he is not working on his craft, Dr. Geo enjoys family time and training in the Israeli martial art, Krav Maga.

Testicular Cancer: An Update

by Pamela W. Smith, MD, MPH, MS

Testicular cancer is the most common solid tumor among males 15 to 34 years of age, with an estimated 8,850 new cases and 410 deaths during 2017 in the United States. With effective treatment, the overall five-year survival rate is 97%. The signs and symptoms of testicular cancer include scrotal swelling, scrotal heaviness, painless, solid testicular mass, firmness of the testis, dull ache in the scrotum or abdomen, acute pain in the testis or scrotum. Epididymitis is an important part of the differential diagnosis of a scrotal mass. Epididymitis is an inflammation of the coiled tube (epididymis) at the back of the testicle that stores and carries sperm. If tenderness, swelling, or examination abnormalities persist after antibiotic treatment, further evaluation is necessary to rule out testicular cancer. Individuals with symptoms of metastatic disease (about 5 percent of patients with testicular cancer) may present with a neck mass, abdominal mass, lumbar back pain, cough, hemoptysis, dyspnea, or gastrointestinal symptoms. Approximately 10 percent of men with testicular cancer have gynecomastia from tumors that secrete beta subunit of human chorionic gonadotropin.

The high survival rate and young age of patients with testicular cancer result in long periods of survivorship with multiple sources of potential morbidity

Risk factors for testicular cancer are numerous.

- In patients with undescended testis (cryptorchidism), the relative risk of developing testicular cancer ranges from 2.9 to 6.3; the risk is increased in both testes, although the risk is much higher in the ipsilateral (same side) testis. Among these patients, the risk of cancer increases when orchiopexy is delayed until after puberty or never performed compared with early orchiopexy. Orchiopexy describes the operation to surgically correct an undescended testicle to move and/or permanently fix a testicle into the scrotum. Even after early orchiopexy, the risk of testicular cancer remains elevated compared with the general population.
- Patients with a personal history of testicular cancer have a 12-times greater risk of developing a contralateral (opposite side) testicular cancer than the general population. However, the greatest risk is in the first five years after diagnosis, and the 15-year cumulative risk is 1.9%. In addition, patients with a father or brother with testicular cancer have a significantly great risk of developing the disease.
- Moreover, men with infertility have an increased risk of developing testicular cancer, although the underlying mechanism is unclear.
- Associations between testicular cancer and marijuana use, inguinal hernia, diet, maternal smoking, and body size are inconclusive.
- Infections with human papillomavirus (HPV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus B-19, and human immunodeficiency virus (HIV) increase an individual's risk.
- In addition, trauma to the testicle is a risk factor.
- Furthermore, high maternal estrogen levels are also a risk factor.

However, testicular microlithiasis and vasectomy are not risk factors for testicular cancer.

Conventional Therapies

If a solid intratesticular mass is discovered, orchiectomy is both diagnostic and therapeutic. Radical inguinal orchiectomy is a surgical procedure in which one or both testicles are removed, including removal of the spermatic cord to the internal inguinal ring. It is the primary treatment for any malignant tumor found on surgical exploration of a testicular mass. Testis-sparing surgery is generally not recommended but may be performed for a small tumor in one testis or for small bilateral tumors. Orchiectomy may be delayed if life-threatening metastases require more urgent attention. Treatment after orchiectomy is based on histology, staging, prognosis, and an individualized discussion with the patient on the benefits and risks of treatment options. Additional therapies may include radiation and/or chemotherapy.

The high survival rate and young age of patients with testicular cancer result in long periods of survivorship with multiple sources of potential morbidity and mortality. Complications arise from both the disease process and treatment and vary according to each individual.

Secondary malignancy may be a concern in these individuals. Testicular cancer survivors treated with radiotherapy or chemotherapy are at increased risk of secondary malignant neoplasms. There is a threefold increased risk of leukemia among testicular cancer survivors treated with radiotherapy to

➤

➤

the abdomen and pelvis. Cisplatin and etoposide therapies also increase the risk of secondary leukemia. Radiotherapy and chemotherapy increase the risk of solid cancers beginning five years after treatment. Sites of secondary malignancy included stomach, pancreas, pleura, bladder, colon, and esophagus.

Infertility and hypogonadism should be addressed. Cancer alone may affect fertility. A systematic review found that up to 50% of patients with testicular cancer have semen abnormalities prior to orchiectomy. Orchiectomy and the effects of chemotherapy and radiation also carry significant risks of future infertility. Retrograde ejaculation (when the semen travels backwards into the bladder) or anejaculation (inability to ejaculate) may occur but advances in surgical techniques have reduced this risk.

Adjuvant therapy increases the short- and long-term risks of cardiovascular disease in testicular cancer survivors. A recent population-based study of more than 15,000 testicular cancer survivors found a fivefold increased risk of cardiovascular mortality within the first year after chemotherapy compared with orchiectomy alone. This cardiovascular risk was not significant beyond the first year. A retrospective study of testicular cancer survivors compared with age-matched control patients showed that radiotherapy or chemotherapy imposes greater than a twofold increased long-term risk (after 10 years posttreatment) for atherosclerotic heart disease; combined therapy increased the risk to almost fivefold. Mediastinal irradiation carries more risk than subphrenic irradiation. There are no evidence-based recommendations for heart disease screening in testicular cancer survivors. Patients and their health care providers should be aware of potential cardiovascular risk in testicular cancer survivors.

Precision Medicine Therapies

Precision medicine therapies include all the conventional approaches discussed previously along with the following treatments.

Smoking. Stop smoking! Smoking cessation therapies have been shown to be helpful for many people.

Stress. Stress from any cause is known to modify the immune response and can partially suppress certain aspects of immune function. In addition, prolonged psychological stress appears to be correlated with cellular aging, inducing characteristic senescence features such as increased oxidative stress, reduced telomere length, chronic exposure to glucocorticoids, decreased thymus, changes in cell trafficking, decreased cell-mediated immune response, steroid resistance, and chronic low-grade inflammation. In fact, immunosenescence (alteration of immune function due to aging) has been widely reported in older individuals, as a result of the chronic antigen stimulation and cellular stress encountered throughout life. Furthermore, both biological and psychological stress experienced during cancer therapy may be responsible for stimulating molecular processes that induce premature aging and deterioration of immune system in testicular cancer survivors, leading to an increased susceptibility to infections, cancer, and autoimmune diseases.

The increasing evidence described above that some cancer treatments may induce cellular senescence and aging of the immune system, may have implications on the development of secondary medical conditions later in life. Testicular cancer survivors have an increased risk of suffering late adverse events, including hypogonadism, infertility, metabolic syndromes, neurotoxicity, lower cognitive functions, reduced renal function, heart disease, and secondary cancers. Hypogonadism also increases the risk of developing metabolic syndrome, including cardiovascular complications and diabetes, which appears to be greater after combination therapy (chemo-radiotherapy). In addition, testicular cancer survivors struggle with high rates of anxiety and post-traumatic stress disorder (PTSD).

Inflammation. One study hypothesized a correlation between low testosterone levels and increased secretion of pro-inflammatory cytokines as the cause and maintenance of chronic diseases. The inflammatory component in the body can be lowered with EPA/DHA (fish oil) and curcumin. Compounded prescription low-dose naltrexone is also a fabulous anti-inflammatory agent, and it also has other positive anti-cancer effects.

Low-Dose Naltrexone (LDN). The results of increasing studies indicate that LDN exerts its immunoregulatory activity by binding to opioid receptors in or on immune cells and tumor cells. Consequently, these new discoveries indicate that LDN is a promising immunomodulatory agent in the therapy for cancer and many immune-related diseases. It has also been reported that LDN is able to reduce tumor growth by interfering with cell signaling as well as by modifying the immune system. This data supports further the idea that LDN possesses anticancer activity.

Testosterone Replacement. A recent study is the first to investigate the effect of testosterone replacement in testicular cancer survivors with mild Leydig cell insufficiency. Increasing testosterone levels decreases the risk of developing other long-term diseases such as hypercholesterolemia, insulin resistance, diabetes, metabolic syndrome, weight gain, and sexual dysfunction.

Conclusion

As you have seen there are both conventional and precision/anti-aging medicine treatments that are successful for testicular cancer. The increasing evidence that some cancer treatments may induce cellular senescence and aging of the immune system may have implications on the development of secondary medical conditions later in

Pamela Wartian Smith, MD, MPH, MS, spent her first 20 years of practice as an emergency room physician with the Detroit Medical Center and then 26 years as an anti-aging/functional medicine specialist. She is a diplomat of the board of the American Academy of Anti-Aging Physicians, and is an internationally known speaker and author on the subject of personalized medicine. She also holds a master's in public health degree along with a master's degree in metabolic and nutritional medicine. She has been featured on CNN, PBS, and many other television networks, has been interviewed in numerous consumer magazines, and has hosted two of her own radio shows. Dr. Smith was one of the featured physicians on the PBS series "The Embrace of Aging" as well as the online medical series "Awakening from Alzheimer's" and "Regain Your Brain." Dr. Pamela Smith is the founder of The Fellowship in Anti-Aging, Regenerative, and Functional Medicine, and is professor emeritus from the Morsani College of Medicine, University of South Florida. She is the author of ten best-selling books. Her book: *What You Must Know About Vitamins, Minerals, Herbs, and So Much More* was published last year. Her newest book: *How to Maximize Your Immune System*.

life. Testicular cancer survivors have an increased risk of suffering late adverse events, including hypogonadism (when the testes produce little or no hormones), infertility, metabolic syndromes, neurotoxicity, lower cognitive functions, reduced renal function, heart disease, and secondary cancers. Hypogonadism also increases a person's risk of developing metabolic syndrome, including cardiovascular complications and diabetes, which appears to be greater after combination therapy (chemo-radiotherapy). In addition, testicular cancer survivors struggle with high rates of anxiety and post-traumatic stress disorder (PTSD). Many of these disease processes can be mitigated by a precision medicine approach to healthcare.

References

Baird, D., et al., "Testicular Cancer: Diagnosis and Treatment," *Amer Fam Physician* 2018; 97(4):261-68.

Shaw, J., et al., "Diagnosis and treatment of testicular cancer," *Amer Fam Physician* 2008; 77(4):470.

McConaghy, J., et al., "Epididymitis: an overview," *Amer Fam Physician* 2016; 94(9):723–26.

Lip, S., et al., "A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life," *Arch Dis Child* 2013; 98(1):20–6.

Akre, O., et al., "Risk of contralateral testicular cancer among men with unilaterally undescended testis: a meta analysis," *Int Jour Cancer* 2009; 124(3):687–89.

Walsh, T., et al., "Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer," *Jour Urol* 2007; 178(4 pt 1):1440–46.

Chan, E., et al., "FRCSC for Canadian Association of Pediatric Surgeon Evidence-Based Resource. Ideal timing of orchiopexy: a systematic review," *Pediatr Surg* 2014; 30(1):87–97.

Pettersson, A., et al., "Age at surgery for undescended testis and risk of testicular cancer," *NEJM* 2007; 356(18):1835–41.

Fossa, S., et al., "Risk of contralateral testicular cancer," *Jour Nat; Cancer Inst* 2005; 97(14):1056–66.

Hemminki, K., et al., "Familial risk in testicular cancer as a clue to a heritable and environmental aetiology," *Brit Jour Cancer* 2004; 90(9):1765–70.

Del Risco Kollerud, R., et al., "Family history of cancer and risk of paediatric and young adult's testicular cancer: A Norwegian cohort study," *Brit Jour Cancer* 2019; 120(10):1007-14.

Hemminki, K., et al., "Familial risks in testicular cancer as aetiological clues," *Int Jour Androl* 2006; 29(1):205-10.

Jacobsen, R., et al., "Risk of testicular cancer in men with abnormal semen characteristics: cohort study," *BMJ* 2000; 321(7264):789–92.

Walsh, T., et al., "Increased risk of testicular germ cell cancer among infertile men," *Arch Intern Med* 2009; 169(4):351–56.

Eisenberg, M., et al., "Increased risk of cancer in infertile men," *Jour Urol* 2015; 193(5):1596–1601.

Goedert, J., et al., "Risk of germ cell tumors among men with HIV/acquired immunodeficiency syndrome," *Cancer Epidemiol Biomarkers Prev* 2007; 16(6):1266–69.

Gurney, J., et al., "Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis," *BMC Cancer* 2015; 15:897.

Manecksha, R., et al., "Epidemiology of testicular cancer," *BJU Int* 2009; 104(9 part B):1329–33.

Lerro, C., et al., "A systematic review and meta-analysis of the relationship between body size and testicular cancer," *Brit Jour Cancer* 2010; 103(9):1467–74.

Garolla, A., et al., "Role of viral infections in testicular cancer etiology: Evidence from a systematic review and meta-analysis," *Front Endocrinol* (Lausanne) 2019; 10:355.

Coupland, C., et al., "Risk factors for testicular germ cell tumours by histological tumour type. United Kingdom Testicular Cancer Study Group," *Brit Jour Cancer* 1999; 80(11):1859-63.

Haughey, B., et al., "The epidemiology of testicular cancer in upstate New York," *Amer Jour Epidemiol* 1989; 130(1):25-36.

Depue, R., et al., "Estrogen exposure during gestation and risk of testicular cancer," *Jour Natl Cancer Inst* 1983; 71(6):1151-55.

Gaddam, S., et al., Testicle Cancer, StatPearls (Internet). Nov. 7, 2021.

European Association of Urology. Guidelines. Testicular cancer. 2015. https://uroweb.org/guideline/testicular-cancer. Accessed August 1, 2022.

American Cancer Society. Can testicular cancer be found early? http://www.cancer.org/cancer/testicularcancer/detailed guide/testicular-cancer-detection. Accessed August 8, 2022.

Albers, P., et al., "European Association of Urology. Guidelines on testicular cancer: 2015 update," *Eur Urol* 2015; 68(6):1054–68.

Fung, C., et al., "Long-term morbidity of testicular cancer treatment," *Urol Clin North Amer* 2015; 42(3):393–408.

Travis, L., et al., "Second cancers among 40,576 testicular cancer patients: focus on long-term survivors," *Jour Nat Cancer Inst* 2005; 97(18):1354–65.

Djaladat, H., et al., "The association between testis cancer and semen abnormalities before orchiectomy: a systematic review," *Jour Adolesc Young Adults Oncol* 2014; 3(4):153–59.

Ostrowski, K., et al., "Infertility with testicular cancer," *Urol Clin North Amer* 2015; 42(3):409–20.

Fung, C., et al., "cardiovascular disease mortality after chemo-therapy or surgery for testicular nonseminoma: a population-based study," *Jour Clin Oncol* 2015; 33(28):3105–15.

Haugnes, H., et al., "Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study," *Jour Clin Oncol* 2010; 28(30):4649–57.

van den Belt-Dusebout, A., et al., "Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer," *Jour Clin Oncol* 2006; 24(3):467–75.

Glaser, R., et al., "Stress-induced immune dysfunction: Implications for health," *Nat Rev Immunol* 2005; 3:243–51.

Bauer, M., "Chronic stress and immunosenescence: a review," Neuroimmunomodulation 2008; 15:241-50.

Reed, R., "Stress and immunological aging," *Curr Opin Behav Sci* 2019; 28:38–43.

Epel, E., "Psychological and metabolic stress: a recipe for accelerated cellular aging?" *Hormones* 2009; 8(1):7–22.

DePadova, S., et al., "Immunosenescence in testicular cancer survivors: Potential implications of cancer therapies and psychological distress," *Front Oncol* 2020; 10:564346.

Smith, P., *Max Your Immunity*. Garden City Park, NY: Square One Publishers, 2021.

Bauer, M., et al., "The role of stress factors during aging of the immune system," *Ann NY Acad Sci* 2009; 1153:139–52.

Cupit-Link, M., et al., "Biology of premature ageing in survivors of cancer," *ESMO Open* 2017; 2:e000250.

Lubberts, S., et al., "Early ageing after cytotoxic treatment for testicular cancer and cellular senescence: Time to act," *Crit Rev Oncol Hematol* 2020; 151:102963.

Haugnes, H., et al., "Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study," *Jour Clin Oncol* 2010; 28:4649–57.

La Vignera, S., et al., "Hypogonadism and sexual dysfunction in testicular tumor survivors: A systematic review," *Front Endocrinol Lausanne* 2019; 10:264.

Smith, A., et al., "The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study," *Jour Cancer Surviv* 2016; 10(2):223–33.

Kreiberg, M., et al., "Psychological stress in long-term testicular cancer survivors: a Danish nationwide cohort study," *Jour Cancer Surv* 2020; 14(1):72–9.

Dahl, A., et al., "Aspects of posttraumatic stress disorder in long-term testicular cancer survivors: cross-sectional and longitudinal findings," *Jour Cancer Surviv* 2016; 410(5):842–9.

Maggio, M., et al., "Correlation between testosterone and the inflammatory marker soluble interleukin-6 receptor in older men," *Jour Clin Endocrinol Metabol* 2006; 91(1):345-47.

Li, Z., et al., "Low-dose naltrexone (LCN): A promising treatment in immune-related diseases and cancer therapy," *Int Immunopharmacol* 2018; 61: 178-84.

Liu, W., et al., "Naltrexone at low doses upregulates a unique gene expression not seen with normal doses: Implications for its use in cancer therapy," *Int Jour Oncol* 2016; 4992):793-802.

Bandak, M., et al., "A randomized double-blind study of testosterone replacement therapy or placebo in testicular cancer survivors with mild Leydig cell insufficiency (Einstein-intervention)," *BMC Cancer* 2017; 17:461.

Habous, M., et al., "Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short course randomized study," *BJU Int* 2018; 122(5):889-97.

Tseng, A., et al., "Gynecomastia in testicular cancer patients. Prognostic and therapeutic implications," *Cancer* 1985; 56(10):2534-538.

◆

Atherosclerosis I: Reduction, Nattokinase, Digital Pulse Wave Analysis

by Davis W. Lamson, MS, ND

Tahoma Clinic, Tukwila, Washington

Abstract: A 2017 report showed the removal of arterial soft plaque in 76 individuals by the enzyme nattokinase. A comparison study was run using Digital Pulsewave Analysis instrumentation, shown to reliably detect arterial stiffness and atherosclerosis of the major arteries. The present study confirms that nattokinase (an inexpensive, safe, over-the-counter enzyme supplement) can remove soft arterial plaque over a few months.

Introduction

Cardiovascular disease is considered the leading cause of death in the United States. Atherosclerosis is defined as a thickening or hardening of the artery walls with loss of elasticity that occurs with formation of plaques within the arterial intima. These plaques can be either calcified or "soft" and result in narrowed arteries that obstruct blood circulation.

Limited circulation to some areas of the body may give recognizable symptoms that signal for attention (e.g., intermittent claudication in the legs). Obstruction of cardiac vessels can be silent until a result of myocardial infarction, which may or may not be survived.

If there is reason to suspect significant atherosclerosis, a physician can order a CT scan of cardiac arteries and obtain a calcium score that evaluates the extent of calcified plaque in that area. By injection of contrast medium, hard and soft plaque can both be evaluated.

If there appears substantial plaque build-up, various strategies are employed in standard medicine, perhaps anticoagulants or statin drugs in less concerning cases. If more threatening blockages exist, there are stents, various methods of angioplasty, and even coronary artery bypass, all quite invasive.

What if atherosclerotic build-up could be determined easily, inexpensively, and non-invasively and then removed at low cost by an over-the counter supplement? You wouldn't likely hear of it from a pharmaceutical company. An answer to the question is suggested in the remaining text.

Soft Plaque Removal

In 2017 a Chinese research report was listed on PubMed, but only the abstract is available in English: A clinical study on the effect of nattokinase on carotid artery atherosclerosis and hyperlipidaemia.[1]

Seventy-six patients with atherosclerosis in the common carotid artery were evaluated for intimal medial thickness and carotid artery plaque size by ultrasound, along with usual measurements of blood lipids. Group 1 was treated with 6000 units of nattokinase daily and Group 2 with simvastatin 20 mg daily.

Some of the findings after 26 weeks of nattokinase therapy:

1. Reduction in intimal medial thickness and carotid plaque size in both groups; plaque reduction in the nattokinase group was 36.6% versus 11.5% in the statin group.
2. Both treatments reduced total cholesterol, low-density lipoprotein cholesterol and triglyceride, with greater reduction in the statin group.
3. Nattokinase increased the level of HDL-C; in contrast HDL-C in the statin group did not change.
4. Lipid lowering by nattokinase was not correlated to reduction of intimal medial thickness and carotid artery plaque size.
5. The mechanism underlying reduction of carotid atherosclerosis by nattokinase may be independent from its lipid-lowering effect, which is different from that of statins.

No reference was located showing nattokinase activity against calcification. It is presently presumed that the effect demonstrated is by removal of soft

plaque, unless calcified plaque reduces as a result of soft plaque removal.

Nattokinase enzyme has many benefits to health and was found safe for humans at substantial dose. Nattokinase was first isolated from the Japanese "soul food" Natto (bacterially fermented soy beans) and well described in the references cited.

Some nattokinase activities from literature include:

1. Satisfactory oral absorption[2]
2. Mild anti-coagulant[2]
3. Strong antifibrinolytic, reducing clots[2]
4. No side effect of bleeding[2]
5. Safe for use in humans[2,3]
6. Anti-hypertensive, decreasing angiotensin II[4]
7. Shrinks nasal polyp tissue and decreases mucus viscosity[5]
8. Completely removed amyloid plaque from the brain in animals[6]
9. Heals oral mucositis *in vivo*[7]

Digital Pulse Wave Analysis (DPA)

Over decades there has been an evolution in instruments externally measuring the stiffness of arteries. That has been related to the degree of atherosclerosis and extensively documented in many publications.[8-10]

The instrument used at Tahoma Clinic for the determinations described is the Digital Pulse Wave Analysis instrument manufactured by the Meridian Co., Ltd of Korea. It functions by passing red light (an LED) through the fingertip to a receiver. Absorption of red light by hemoglobin is the basic measurement. The subtleties of the shape of the pulse wave (affected by atherosclerosis in the major arteries) allows calculation of several cardiovascular factors, including heart rate variability and arterial stiffness. For evaluation of patients, three separate fingers are used to document consistency.

The device grades arterial stiffness from A to G. Generally, only the very young seem to score an A grade, so B and C are acceptable adult grades. Grades of D to G show increasingly advanced arterial stiffness. While all new patients are evaluated by DPA, only one G grade has been recorded at the clinic. It was decided to use the DPA instrument to "proof" the Chinese report on nattokinase featured above.

In-Office Research

Four patients with grades of E or F were selected for the trial along with one with a D grade (chosen because of multiple medical problems possibly related to circulation). Patients agreed to take 2000 units of nattokinase before breakfast and before bed. (From knowledge of nattokinase it seems likely that the 6000 units in the Chinese study was given as 2000 units three times daily. Since dosing in the middle of the day can be problematic for many persons, a twice daily schedule was chosen.)

Re-evaluation by DPA at eight weeks showed no differences from original measurements (presumably meaning that any effect was not substantial enough to register instrumentally, not that nattokinase had no effect).

At 16 weeks, three of the original four patients had improved by a letter grade in stiffness. The fourth improved by two letter grades from F to D. The fifth patient did not return until 20 weeks. His stiffness score had improved by two letter grades from D to B.

While this study has the obvious weaknesses of a small population and no alternate method of atherosclerosis evaluation, the result agrees with the Chinese research report and seems convincing as to removal of soft arterial plaque by nattokinase. The study will continue on the particular patients to observe how much the stiffness score reduces and over what period of time.

Nattokinase, isolated from bacterially fermented soybeans, has several health benefits.

References

1. Ren NN, Chen HJ, Li Y, Mcgowan GW, Lin YG. A clinical study on the effect of nattokinase on carotid artery atherosclerosis and hyperlipidaemia. *Zhonghua Yi Xue Za Zhi* 2017;97(26):2038-2042.
2. Weng Y, Yao J, Sparks S' Wang KY. Nattokinase: An Oral Antithrombotic Agent for the Prevention of Cardiovascular Disease. *Int J Mol Sci* 2017;18(3): 523.
3. Chen H, et.al. Nattokinase: A Promising Alternative in Prevention and Treatment of Cardiovascular Diseases. *Biomark Insights*. 2018;13:1-8.
4. Kim JY, et al. Effects of Nattokinase on Blood Pressure: A Randomized, Controlled Trial. *Hypertens Res* 2008;(8):1583-8.
5. Takabayashi T, et al. Nattokinase, profibrinolytic enzyme, effectively shrinks the nasal polyp tissue and decreases viscosity of mucus. *Allergol Int*. 2017;66(4):594-602.
6. Fadl NN, Ahmed HH, Booles HF, Sayed AH. Serrapeptase and nattokinase intervention for relieving Alzheimer's disease pathophysiology in rat model. *Hum Exp Toxicol* 2013 Jul;32(7):721-35.
7. Zhang J, et. al. Nattokinase crude extract enhances oral mucositis healing. *BMC Oral Health* 2012;21(1):555.
8. Cockcroft JR, Wilkinson IB. Arterial stiffness and pulse contour analysis: an age old concept revisited. *Clin Sci* (Lond) 2002;103(4):379-80.
9. Millasseau SC, Kelly RP, Ritter JM, Chowienczyk PJ. Determination of age-related increases in large artery stiffness by digital pulse contour analysis. *Clin Sci* (Lond) 2002;103(4):371-7.
10. Wilkinson IB, et al. Pulse-wave analysis: clinical evaluation of a noninvasive, widely applicable method for assessing endothelial function. *Arterioscler Thromb Vasc Biol* 2002;22(1):147-52. ◆

Dr. Lamson has been a staff physician at Tahoma Clinic and received a naturopathic doctor degree from Bastyr University in 1982. His original training was as a research chemist and prior to practicing at Tahoma Clinic, he held positions in teaching and/or research at Iowa State University, Drexel University, and the University of Pennsylvania School of Medicine. He believes this initial training to be a major benefit in locating underlying causes of medical problems for his patients.

The Effectiveness of Platelet Rich Plasma for Joint Injury Repair

by Peter A. Fields, MD, DC

When patients are faced with a joint injury and the possibility of surgery, they frequently look for an alternative. PRP treatments are effective non-surgical options for joint injury repair. This non-surgical option is a great way for patients to avoid the pain, complications, and recovery time associated with joint surgery.

What Does PRP Mean?

PRP stands for platelet rich plasma. Plasma is the fluid portion of blood that contains cellular components such as red cells, white blood cells, and platelets. The method that OrthoRegen® and Peter A. Fields, MD, DC, use concentrates the platelets 7-10 times of what is normally found in the blood. Other systems concentrate them but to a lesser extent.

PRP For Joint and Spine Repair

With PRP, your own blood platelets are used as one of the treatment solutions. Why are blood platelets used? Blood platelets contain potent growth factors effective at repairing tissue and regenerating the injury site. The platelets are concentrated to provide a large reservoir of these growth factors resulting in a great boost to the body's normal healing process.

Joint repair using PRP is an exciting and cutting-edge therapy for the stimulation of tissue repair and the regeneration of weakened, torn, or damaged ligaments and tendons.

What Can Be Expected with a PRP Treatment?

- A blood draw similar to a blood draw for a blood test.
- Concentration of the blood drawn via a special centrifuge
- Injection of the concentrated solution into the areas of joint injury or degeneration
- Boosting of recovery by your own healing growth factors at the site of your soft tissue injury

PRP vs. Dextrose Prolotherapy

The main difference between PRP treatment and dextrose prolotherapy treatment is the solution being used. Dextrose prolotherapy involves the injection of a dextrose solution.

By contrast, the PRP treatment solution is derived from your own blood. A small amount of your own blood is drawn, and after filtering out the rest of the cells and plasma, the platelets that remain are then concentrated.

What Conditions Are Helped with PRP?

PRP is very effective at repairing musculoskeletal tissue conditions such as moderate to severe tendon and ligament problems as well as meniscus and labrum tears. It also works well in smaller areas such as with carpel tunnel, Achilles tendon, tennis elbow, and more. Due to the huge amount of growth factors contained in platelets, PRP has an enormous amount of potential for repair in so many joint and spine conditions.

PRP is promising in sports medicine, including the treatment of tendon injuries, pain reduction, and improved function for articular injuries of the ankle, knee, and hip. Plus, it is advocated as a safe procedure with negligible adverse effects.[1] PRP is readily available and has minimal risk of reactivity compared to other compounds due to the autologous (from your own body) nature of PRP injections.

Is PRP a New Therapy?

Although platelet rich plasma has recently gained quite a bit of popularity, it has been around for decades. In 2012, the medical journal *Arthritis Research and Therapy* said, "Orthobiologics (Regenerative Orthopedics) is a relatively newer science that involves application of naturally found materials from biological sources (blood platelets) and offers exciting new possibilities to promote and accelerate bone and soft tissue healing. Platelet-rich plasma is an orthobiologic that has recently gained popularity as an adjuvant treatment for musculoskeletal injuries.

The relative ease of preparation, applicability in the clinical setting, favorable safety profile, and possible beneficial outcome make PRP a promising therapeutic approach for future regenerative treatments."[2]

Since then, hundreds of research papers worldwide have described the benefits of PRP treatments.

Studies Showing the Effectiveness of PRP

PRP is a great treatment option for orthopedic and sports medicine. But do studies back up its use? Here is what some of them say: "There are numerous basic science and clinical studies demonstrating the positive effects that PRP has on cartilage degeneration or injury (especially when combined with stem cells), plus the adverse risks are very low."[1] Studies show that PRP provides an abundance of growth factors in addition to other components that aid in joint health.[3]

Growth factor therapies and regenerative medicine strategies are emerging as promising alternatives to palliative care because these treatments bring significant potential to control chronic inflammation, enhance cartilage repair, and restore other joint tissues to a healthy state. As mentioned earlier, the growth and healing factors available through PRP are what make PRP effective for joint and spine repair.

Doctors at the University of Florence[4] described the growth, healing, and repair of platelet rich plasma as follows:

- Initiation of connective tissue healing through the promotion of collagen…a building block of soft tissue
- Promotion of protein synthesis
- Promotion of new blood vessels to bring healing factors to the injury

Another researcher says, "Given its biocompatibility and healing properties, percutaneous injections of PRP are used in athletes to treat tendon and muscle injuries. Studies of varying levels of evidence have demonstrated the safety and beneficial effects of PRP in these applications…."[5]

Choose an Experienced Practitioner for Comprehensive PRP Treatment

Patients will receive the maximum benefit of PRP when it is offered as part of a comprehensive program of joint healing.

At OrthoRegen®, we do offer PRP as part of a comprehensive regenerative orthopedics program that treats all of the affected soft tissue of the joint, including the ligaments, tendons, meniscus, and labrum.

We not only treat the effect (torn meniscus/labrum/ligament/tendon) with PRP but all the weakened areas around it with dextrose prolotherapy. Combining PRP with prolotherapy allows for the greatest benefit for repair of the whole joint. Many clinics only treat the effect and not the cause of the problem.

Since PRP is gaining so much popularity, there are physicians who are jumping on the PRP bandwagon without having much injection experience. Regenerative orthopedics is a specialized medical technique. It not only involves being able to choose the right proliferant for the patient's particular condition, but it also involves making a proper diagnosis, and then fully (or comprehensively) treating the entire injury.

Platelet rich plasma is a great treatment option for orthopedic and sports medicine.

As with any medical procedure, the success of the procedure is determined by the experience, compassion, and technique of the practitioner providing the treatment. Platelet rich plasma used for joint repair is no different.

Remember that once surgery is done it can never be undone!

References

1. Mascarenhas R, Saltzman B, Fortier L, Cole B. Role of platelet-rich plasma in articular cartilage injury and Disease. *J Knee Surg*. 2014. 28:003-010.
2. Dhillon RS, Schwarz EM, Maloney MD. Platelet-rich plasma therapy – future or trend? *Arthritis Res Ther*. 2012 Aug 8;14(4):219.
3. Parrish, WR, Roides B. Platelet rich plasma in osteoarthritis: more than a growth factor therapy. *Musculoskeletal Regeneration*. 2017;3.
4. Civinini R, et al. Growth factors in the treatment of early osteoarthritis. *Clinical Cases in Mineral and Bone Metabolism*. 2013;10(1):26-29.
5. Mei-Dan, Omer, et al. Autologous platelet-rich plasma: a revolution in soft tissue sports injury management? *The Physician and Sportsmedicine* 2010;38.4: 127-135.

◆

Peter A. Fields, MD, DC, The Athletic Doc®, is a world-renowned expert in the field of regenerative orthopedics. Dr. Fields is both a medical physician and chiropractor and is only one of a handful of physicians in the world with both these degrees.

He is director of OrthoRegen in Santa Monica, California, which is one of the largest practices in the world dedicated solely to regenerative orthopedics. He treats patients from around the US and the world. Dr. Fields helps people avoid unnecessary orthopedic surgeries and is an expert in using PRP, prolotherapy and stem cell therapy treatments to help people avoid surgery.

Dr. Fields has completed 11 Ironman triathlons and has had his back and shoulder treated by these techniques. In other words, 'this doc walks the talk!'

Vitamin D and Covid-19: This Nutrient's Potentially Pivotal Role in Combating Coronavirus

by Jill Carnahan, MD

Since the emergence of the coronavirus at the tail end of 2019, Covid-19 has been at the forefront of healthcare for nearly three years now. This perplexing virus has dominated headlines and flipped our world upside down as researchers across the globe have worked to find answers.

Some people can contract the coronavirus and experience nothing more than a few sniffles while others can quickly find themselves battling a life-threatening infection. And yet others seem to develop a host of seemingly unrelated health concerns that remain for weeks, months, or even years after their initial infection.

As clinicians in the field of integrative and functional medicine, we're seeing an influx of these patients struggling with lingering symptoms that seem to persist long after this viral infection is supposedly cleared. And considering that we are still only scratching the surface of truly understanding the coronavirus and each of its variants, it's safe to assume that the number of post-covid patients we encounter will continue to grow.

Fortunately, we are making significant strides in understanding how this virus exerts its perplexing effects and how we can best treat patients facing health challenges related to Covid-19. When we dig deep and look at the root underlying issue, we're finding that the problem, at least in part, can be traced back to a deficiency and depletion of the critical immune-supporting compound vitamin D.

The Vitamin D Pathway

Vitamin D in the form of cholecalciferol or ergocalciferol can be obtained via either diet, supplementation, or direct skin exposure to UVB rays. Obtaining vitamin D is a crucial first step but these molecules are rendered useless until the body is able to transform this raw material. Once within the body – either ingested via food or supplements or synthesized by the skin in response to UVB exposure – the vitamin D pathway goes something like this:[1]

- *Step 1:* Cholecalciferol or ergocalciferol molecules are transported to the liver where they undergo hydroxylation – picking up extra oxygen and hydrogen molecules to become 25-hydroxyvitamin D, or 25(OH)D – also known as *calcifediol*.
- *Step 2:* From there calcifediol is bound to either vitamin D binding protein or albumin to be shuttled to the next step. This next conversion takes place primarily in the kidneys, although other tissues such as epithelial cells, immune cells, and the parathyroid gland do contain small amounts of the enzyme needed to complete this conversion.
- *Step 3:* Once calcifediol travels to the kidneys it acquires another pair of oxygen and hydrogen molecules to become 1,25 dihydroxy vitamin D or 1,25(OH)2D – also known as *calcitriol,* the hormonal form of vitamin D.
- *Step 4:* Once converted to calcitriol, these metabolites are able to bind to vitamin D receptor sites on the outer membrane of most cells.

The complex interplay between vitamin D, vitamin D metabolites, and human cells has major implications for immune system function.

Vitamin D's Role in Immune System Regulation

Vitamin D is a potent regulator of immune system function. Just a handful of the ways vitamin D influences and modulates immune function include the following:[2-4]

- Activation of the transcription of antimicrobial peptides (AMPs): When vitamin D metabolites bind to vitamin D receptors on innate immune cells, it modulates gene expression – triggering an increase in the transcription and production of antimicrobial peptides such as defensin β2 (DEFB) and cathelicidin antimicrobial peptide (hCAP18).
- Enhancement of chemotaxis and phagocytic capabilities: Vitamin D can evoke and promote autophagy in innate immune cells – ramping up the encapsulation and neutralization of invading threats.

- *T cell regulation:* Vitamin D induces a more tolerogenic, immature state in dendritic cells. It also inhibits T cell cytokines such as *IL2* and *IL17* as well as toll-like receptors on monocytes leading to a significant reduction of the proinflammatory cytokine *IL6*. This combination of effects results in the modulation of T cells, which are crucial for controlling immune responses.
- *Inhibition of B cell differentiation and proliferation:* Vitamin D plays a crucial role in maintaining B cell homeostasis and mitigating the underlying pathophysiology seen in autoimmunity.
- *Enhancement of the integrity of mucosal barriers:* Epithelial and mucosal cells are the first line of defense against potentially invading pathogens. Vitamin D plays an important role in maintaining and strengthening the integrity of mucosal barriers by inducing and promoting the production of specific enzymes and proteins that form tight junctions that seal the spaces between mucosal and epithelial cells.

Understanding the role of vitamin D and its metabolites in immune system regulation is crucial when it comes to understanding the impact of Covid-19 on the human body.

How Covid Dysregulates the Immune System and Depletes Vitamin D

The coronavirus is a complex and rather tricky virus. SARS-CoV-2 is introduced into the human body predominantly via the route of respiratory, oral, or ocular mucosa. Once the virus is contracted, it throws the entire immune system off kilter and disrupts vitamin D levels in a couple of distinct ways.

An Overflow of Proinflammatory Cytokines. SARS-CoV-2 is a master at camouflage – swiftly sneaking its way into human cells and then disguising itself so the initial infection goes undetected by the immune system. Once inside, it hijacks human cells and manipulates them to enhance its survival while jamming up any cellular exit channels – thus preventing the cell from releasing any signaling proteins that may sound the alarm and activate an immune response.

As the virus renovates the inside of human cells and replicates, it eventually releases newly formed virions to infect new cells. Once these new virions exit the cell, the immune system catches on and launches an immune response. But by the time the immune system realizes there is a threat, the virus has replicated to a point that it triggers an exaggerated immune response – flooding the bloodstream with a massive influx of pro-inflammatory mediators in what's known as a *cytokine storm*.[5,6]

Downregulation of Vitamin D Receptors. In addition to triggering an overflow of cytokines and a massive spike in uncontrolled inflammation, SARS-CoV-2 can downregulate vitamin D receptors on human cells.[7] By blocking the activation of gene expression of vitamin D receptors, SARS-CoV-2 inhibits cells' ability to bind to and utilize vitamin D even if adequate levels of calcitriol are available.

This out-of-control inflammation, dysregulation of the immune system, and depletion of cellular vitamin D also creates the perfect storm for another serious concern – the reactivation of dormant viral infections.

Covid-19: A Potent Reactivator of Latent Viral Infections. Once infected with SARS-CoV-2, the immune system is preoccupied with trying to neutralize the imminent threat of the invading virus and there is a massive spike in ongoing inflammation. This creates an ideal scenario for latent viral infections that have been lying dormant within human cells to reactivate. Studies have found that Covid-19 infection can be a potent activator of common latent viral infections, namely herpes simplex virus type 1 (HSV-1), cytomegalovirus (CMV), Parvovirus B19, and Epstein-Barr virus (EBV).[8]

While reactivation of each of these latent viruses can present its own set of unique impacts on the human body, the Epstein-Barr virus (EBV) in particular has been identified as a primary culprit in symptoms associated with covid. This is in part due to EBV's potent ability to further deplete already dwindling vitamin D levels in covid patients.[9,10]

When paired together, the coronavirus and the reactivation of latent EBV can dramatically deplete vitamin D levels.

How Epstein-Barr Virus Cripples Vitamin D Pathways. The Epstein-Barr virus is a crucial piece of the puzzle when it comes to treating covid not only because roughly 95% of the population carries a latent form of this virus, but also because reactivation of EBV cripples vitamin D pathways. The EBV contains proteins known as *Epstein-Barr nuclear antigens* or *EBNA*. Three of these EBV proteins directly impede vitamin D signaling pathways as follows:[11]

- EBNA1: Impedes calcitriol biosynthesis
- EBNA2: Binds to a cofactor that inhibits binding of Vitamin D to Vitamin D receptor sites
- EBNA3: Binds to Vitamin D receptors rendering them inactive.

This trio works in unison to shut down vitamin D pathways and impair cells' antiviral defense programs. To further complicate matters, when EBV is reactivated, it is able to continue evolving based on each individual's immune system. Meaning as covid progresses and reactivates more latent Epstein-Barr viruses, new variants of EBV will develop and be spread throughout human populations.[12]

As you can see, when paired together, the coronavirus and the reactivation of latent EBV can dramatically deplete vitamin D levels. It's speculated that symptoms of the condition known as *long COVID* may be stemming from an ongoing calcitriol crisis (lack of calcitriol) due to the potent vitamin D blocking and depleting properties of both SARS-CoV-2 and EBV.

➤

➤

The Link Between Long Covid and Vitamin D Deficiency

While many patients recover from a Covid-19 infection within a few weeks, others exhibit persistent or new symptoms more than four weeks after initial infection and diagnosis. It's estimated that up to one-third of covid patients continue to struggle with ongoing symptoms six months or more after contracting SARS-CoV-2. This subset of patients experiencing lingering, ongoing symptoms post-covid are considered to have *long covid*, also referred to as *long-haul covid* or *post-acute sequelae of Covid-19* (PASC).

Using dexamethasone with calcifediol is a more potent way to increase bioavailable vitamin D.

According to studies, the top 15 most common post-viremic symptoms seen in long covid patients include:[13]

- Pain
- Breathing difficulties
- Hyperlipidemia
- Malaise and fatigue
- Hypertension
- Anxiety
- Intestinal issues
- Skin issues
- High levels (glucose, cholesterol, BP)
- Abnormal heart results
- Migraine and/or headache
- GERD
- Sleep disorders
- Depression
- Abnormal organ tests

Interestingly, all of these symptoms can be related to a vitamin D deficiency. While the underlying etiology of these persistent symptoms is likely more complex than *just* a simple deficiency in vitamin D, studies indicate that there is a clear and direct correlation between vitamin D levels and the severity of Covid-19 infection.

Understanding the role vitamin D plays in immune function as well as all of the factors that contribute to vitamin D depletion in a Covid-19 infection is an important piece of the puzzle when we begin looking at treatment options.

Therapeutic Strategies in the Treatment of SARS-CoV-2

Combatting and healing a SARS-CoV-2 infection requires a multi-pronged approach that must encompass aspects such as:

- Enhancing nasal mucosal immunity: The mucosal immune system is the largest component of the entire immune system. It is also the initial and primary site of SARS-CoV-2 infection, with initial interaction with the virus almost always taking place on respiratory, oral, or ocular mucosal surfaces.
- Boosting AMPs (antimicrobial peptides): AMPs play a critical role in blocking SARS-CoV-2 from entering cells and suppressing viral replication.
- Increasing autophagy: If the immune system is overwhelmed and dysregulated, it cannot adequately lower viral levels enough to reach the tipping point necessary to neutralize the infection and begin moving back towards immune homeostasis. Autophagy is a critical component of neutralizing and eliminating a viral infection.
- Suppressing dormant virus reactivation: The reactivation of latent viral infections can significantly complicate Covid-19 infections and contribute significantly to immune system overwhelm and dysregulation. Preventing or at the very least suppressing the reactivation of dormant viruses like EBV can allow the immune system to focus on addressing SARS-CoV-2 infection and aid in circumventing at least some symptoms associated with long covid.

Enhancing levels of vitamin D can accomplish all of these. Let's explore the best way to integrate vitamin supplementation as a treatment strategy.

Utilizing Vitamin D in the Treatment of Covid-19

Vitamin D supplementation can certainly be helpful in increasing vitamin D levels, but due to SARS-CoV-2's ability to downregulate vitamin D receptors, upping intake of vitamin D is often not enough. When addressing Covid-19 infections, a more potent way to dramatically increase bioavailable vitamin D levels and support immune system function is the pairing of *dexamethasone* and *calcifediol*. Utilizing both dexamethasone and calcifediol as a post-covid therapeutic duo works as follows:[14-18]

- Dexamethasone works to not only slow the pro-inflammatory cascade but also induces vitamin D receptor expression on immune cells – thus allowing for more sites for vitamin D metabolites to bind to.
- Adequate levels of calcifediol are a precursor to maintaining adequate levels of calcitriol – the form of vitamin D that binds to these vitamin D receptors.
- Once bound to vitamin D receptors, calcitriol activates genes that encode antimicrobial peptides.
- This increase in AMPs blocks viral entry into cells while suppressing viral replication – supporting the immune system in neutralizing active SARS-CoV-2 virions while inhibiting latent viral reactivation.
- An increase in vitamin D also stimulates autophagy – allowing immune cells to encapsulate and degrade viral particles and virus-damaged cells.
- As vitamin D levels rise, immune cells are better able to regulate and attenuate pro-inflammatory cytokines – mitigating uncontrolled inflammation and related tissue destruction seen in Covid-19.

Alone, dexamethasone can actually deplete vitamin D levels by upregulating 24 hydroxylase which inactivates calcitriol and calcifediol – shunting them into inactive forms. But pairing dexamethasone with supplementary

calcifediol induces the expression of vitamin D receptors on cells while restoring a missing metabolite needed for the biosynthesis of the active form of vitamin D, calcitriol.

Co-applying these two compounds can rectify the underlying calcitriol crisis seen in Covid-19 infections. Addressing this underlying calcitriol crisis can significantly reduce morbidity and severity in acute infections as well as aid in healing the root dysfunction triggering the symptoms seen in lingering long covid symptoms.

Next Steps In Treating Patients Exposed to SARS-CoV-2

We still have much to learn when it comes to understanding the complexities of SARS-CoV-2 and each new variant that emerges. But there is a clear and direct correlation between cellular vitamin D levels and morbidity and mortality related to this perplexing virus.

As integrative and functional medicine practitioners at the forefront of root-cause medicine, we've made great strides in our understanding of the "upstream" issues causing the "downstream" symptoms seen in both acute covid infections as well as the growing number of persistent long covid cases. The need for practitioners well-versed in caring for patients suffering from the effects of this complex virus will only grow as the coronavirus and our understanding of it continues to evolve.

With all of the brilliant minds and countless hours of research being dedicated to understanding Covid-19, there is hope on the horizon. I am confident that together, we can continue to piece together the puzzle of Covid-19 and continually improve our treatment guidelines to best serve these patients.

For more articles and information by Dr. Jill Carnahan, visit https://www.jillcarnahan.com and Subscribe to Dr. Jill LIVE on Dr. Jill Carnahan's YouTube Channel where there are over 100 interviews with experts on topics like this. She co-authored the *Personalized and Precision Integrative Cardiovascular Medicine Textbook*, 2nd edition in 2022. Her prescriptive memoir, *UNEXPECTED*, will be released through Forefront Publishing in February 2023.

References

1. Vitamin D: Production, Metabolism and Mechanisms of Action – Endotext – NCBI Bookshelf (nih.gov)
2. Vitamin D and Immune Function - PMC (nih.gov)
3. Frontiers | Impact of vitamin D on immune function: lessons learned from genome-wide analysis (frontiersin.org)
4. Vitamin D, vitamin D receptor and tissue barriers - PMC (nih.gov)
5. How the coronavirus infects cells – and why Delta is so dangerous (nature.com)
6. COVID-19 infection: an overview on cytokine storm and related interventions | Virology Journal | Full Text (biomedcentral.com)
7. Vitamin D: A Role Also in Long COVID-19? - PMC (nih.gov)
8. Frontiers | Emergent Virus Reactivation in SARS-CoV-2-Negative Community Acquired Pneumonia Patients During the COVID-19 Pandemic (frontiersin.org)
9. Positive Epstein–Barr virus detection in coronavirus disease 2019 (COVID-19) patients | Scientific Reports (nature.com)
10. A Detailed Study of Patients with Long-Haul COVID – An Analysis of Private Healthcare Claims – A FAIR Health White Paper.pdf
11. EBNA1, EBNA2, and EBNA3 link Epstein-Barr virus and hypovitaminosis D in multiple sclerosis pathogenesis –ScienceDirect
12. The influence of human genetic variation on Epstein–Barr virus sequence diversity | Scientific Reports (nature.com)
13. COVID-19 associated EBV reactivation and effects of ganciclovir treatment - Meng - 2022 - Immunity, Inflammation and Disease - Wiley Online Library
14. Glucocorticoid Regulation of the Vitamin D Receptor - PMC (nih.gov)
15. IJERPH | Free Full-Text | The Interaction of Vitamin D and Corticosteroids: A Mortality Analysis of 26,508 Veterans Who Tested Positive for SARS-CoV-2 (mdpi.com)
16. RETRACTED ARTICLE: Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease | Scientific Reports (nature.com)
17. Immunological Aspects of SARS-CoV-2 Infection and the Putative Beneficial Role of Vitamin-D - PMC (nih.gov)
18. The Interaction of Vitamin D and Corticosteroids: A Mortality Analysis of 26,508 Veterans Who Tested Positive for SARS-CoV-2 - PubMed (nih.gov)

◆

Known as 'Your Functional Medicine Expert®', Jill Carnahan, MD, has been featured in *People* magazine, *Shape, Parade, Forbes, MindBodyGreen, First for Women, Townsend Letter*, and *The Huffington Post* as well as seen on NBC News and Health segments with Joan Lunden. She is a prominent global keynote speaker and a prolific writer sharing her knowledge on stage and podcasts.

She is Medical Director of Flatiron Functional Medicine, a widely sought-after practice with a broad range of clinical services including functional medicine protocols, nutritional consultations, chiropractic therapy, naturopathic medicine, acupuncture, and massage therapy that attracts A-list celebrities and athletes. A survivor of breast cancer, Crohn's disease, and mold toxicity, she routinely treats patients who come to her for solutions to their medical mysteries that haven't been solved.

Genetics, Hypertension, and Cardiovascular Disease

by Mark Houston, MD

Editor Note: This article is Chapter 11 in the book *Controlling High Blood Pressure Through Nutrition, Supplements, Lifestyle, and Drugs* by Mark Houston, MD, and Lee Bell (CRC Press, Taylor & Francis, LLC; 2021). Dr. Houston also published a new book, *The Truth About Heart Disease* (CRC Press, Taylor & Francis, LLC), in 2022. Both books are available at Amazon, and bulk orders may be obtained from the publisher.

If one of your parents had high blood pressure, you have a 25% chance of developing high blood pressure yourself. If both parents had high blood pressure, then the risk is about 50% that you will have high blood pressure. If your parents or a sibling developed high blood pressure before the age of 50 years then your risk is even higher to develop high blood pressure, but it will also occur at an earlier age. Numerous genes that cause hypertension can be specific for treatment with a drug, a supplement, an electrolyte, and with a diet or nutrition. There are numerous genes for hypertension that have now been discovered that help us to understand the previous unknown details and causes underlying the concept of "family history of hypertension." This genetic testing will allow your doctor to measure many of the genes that cause hypertension and provide a more direct, personalized, and precision treatment program without any of the guess work. This means that your blood pressure will be controlled sooner, better, with fewer drugs, less cost, and better cardiovascular outcomes. The Cardia X genetic profile from Vibrant Labs America in San Francisco measures 25 genes related to cardiovascular disease and hypertension. The "family history" is your primary risk factor to develop high blood pressure and now you can find out what the specific genes are in many cases.[1-65]

Genetics and nutrigenomics (the effect of nutrition and supplements on genes) provide us with an expanded perspective on the prevention and treatment of hypertension and cardiovascular disease. In cardiovascular management, nutrigenomics encompasses genetic testing and the identification of single nucleotide polymorphisms (SNPs), nutrient-genetic interactions, and how the genes express themselves. The genes may be "turned on" or "turned off" by nutrition, supplements, drugs, and other environmental factors. This is referred to as gene expression.[1-65]

Most genetic expression is driven by inflammation, and the majority of the genes, once turned on, promote an inflammatory response. Most of the active areas on genes associated with hypertension, heart attack, heart failure, and coronary heart disease are expressed through inflammation, oxidative stress, and immune-vascular dysfunction. A similar dynamic is evident in the vascular system. Regardless of the type of insult, blood vessels respond to insults via these same three mechanisms: inflammation, oxidative stress, and immune-vascular dysfunction.[1-65]

Consequently, the inflammatory pathways have become the primary focus in the management of genetic expression and of genetic risk for hypertension and cardiovascular disease. The prevention and the reduction of cardiovascular disease hypertension are not likely to improve without using genetic testing. Let us look at some of these influences on your genes such as nutrients, diet and nutrition, electrolytes, supplements, and drugs.[1-65]

Nutrients. Nutritional factors provide information that determines whether our genes are turned on or turned off, with a corresponding beneficial or detrimental outcome. One change in a single nutrient such as magnesium may cause 300 different changes in downstream mediators related to cardiovascular function and health. This is just one example of environmental influences and the importance of genetic expression. When there is interference with a metabolic pathway, a single area of abnormality can result in a myriad of defects and a spoke-like effect, resulting in a ripple of downstream changes in many metabolic pathways.

Epigenetics. There are several issues we want to define in patients. One is their genetic profile, the genes they were dealt. There are also epigenetic influences that are not genetic that alter the function of DNA that are termed methylation, histone modification, and non-coded messenger RNA function. These influences are not in the genetic code but can be passed on from mother to fetus and from generation to generation. For example, a mother that is malnourished during pregnancy is more likely to have a child that develops hypertension later in life. This risk for hypertension can then be passed on "epigenetically" to future generations. The final aspect is gene expression, as genes express themselves in response to nourishment or insults from different types of information coming in from the environment. Genetics have become

important in determining not only dietary intake but also medication use in many patients, based on their genetic profile.

Diet

Mediterranean diet. We know the Mediterranean diet (MedDiet) turns on numerous beneficial genetic pathways that can reduce the risk for hypertension, cardiovascular disease, as well as the risk for type II diabetes. If you consume a Western diet, it will result in totally different outcomes in terms of gene expression, since most of the foods included in a Western dietary pattern have been shown to express 30–40 different inflammatory and immune pathways.

The MedDiet has an advantageous effect on many genes. In a clinical trial of this diet, other prevalent beneficial effects were related to atherosclerosis and hypertension. The MedDiet, in combination with CoEnyme Q 10 (CoQ10), has been shown to be the most beneficial intervention for healthy aging, preventing processes and diseases related to chronic oxidative stress, hypertension, and coronary heart disease. Changes in genetic expression toward a protective mode were often associated with improvement in systemic markers for inflammation, immune function, oxidative stress, hypertension, and coronary heart disease.

Pritikin and DASH diets. The Pritikin diet is one of the most effective ways to turn off the gene expression that increases the risk for hypertension and cardiovascular disease. The Pritikin diet can reduce risk of cardiovascular disease by as much as 30–35%. That benefit is directly correlated with the diet itself but is also enhanced when supplementing with nutrients such as CoQ10. The DASH-1 and DASH-2 diets have also been found beneficial in relation to changes in inflammatory genes, reducing the blood pressure, and improving the response to the types of medications prescribed for hypertension.

Specific Nutrients

Electrolytes. The electrolytes, particularly sodium, potassium, and magnesium, can change genetic expression, salt sensitivity, intravascular volume, blood pressure, risk for coronary heart disease, heart attack, cardiac arrhythmias, and congestive heart failure. In terms of salt sensitivity, one of the most important is cytochrome P4A11 (expressed as CYP4A11), which relates to sodium and water diuresis and the role of the epithelial sodium channel (ENaC) function in the kidney tubules. Patients who have resistant hypertension due to CYP4A11 and are treated with the drug amiloride have dramatic reductions in blood pressure and often can discontinue or reduce the dose of other antihypertensive drugs.

Omega 3 fatty acids. Omega 3 fatty acids affect a large number of genes that reverse changes in our metabolic profile and in our genes that can improve mitochondrial health. As a result, adenosine tri-phosphate (ATP) production goes up, cells are healthier, and patients live longer. ATP is the energy produced by the mitochondria in our cells from metabolism of our food. The mitochondria are like small "nuclear power plants". We know that omega 3 fatty acids by themselves have dramatic effects on many receptors that can have enormous influences, reversing inflammation, oxidative stress, blood pressure, and risk for heart disease. In specific studies, omega 3 fats changed expression of 610 genes in men and 250 genes in women.

Monounsaturated fats. Olive oil and nuts contain monounsaturated fat that will have a positive impact on different SNPs and receptors, improving hypertension, coronary heart disease, and diabetes mellitus. Even without the MedDiet, olive oil and nuts given as a supplement can have dramatic and highly beneficial influences on genetic expression related to the three finite vascular responses for reducing blood pressure and cardiovascular disease.

Genes Relevant to Cardiovascular Risk

Every patient should have their cardiovascular genetics tested by their physician (Tables 11.1 and 11.2). The recommended lab is Vibrant America Labs. The genes are as follows:

Gene 9p21. One of the primary genes we are now measuring is the 9p21 gene that increases the risk of atherosclerosis, coronary heart disease, and heart attack. Patients who have a heterozygote SNP (1/2 of the gene) for 9p21 have a risk for heart attack that is increased by 50%. When a patient has a homozygote SNP (both halves of the gene), the risk goes up to approximately 100%. However, there are many other genes that should also be evaluated, not just for coronary heart disease but also for hypertension and dyslipidemia (abnormal cholesterol).

Genes may be "turned on" or "turned off" by nutrition, supplements, drugs, and other environmental factors.

GLU 1q25 increases the risk of heart disease and heart attack in diabetes mellitus.

Apo E4 genotype. The Apo E4 genotype increases risk for coronary heart disease and heart attack. Management of risk factors for patients with the APO E4 allele, especially with the homozygote E4/E4 type, addresses issues such as:

- Increased cholesterol absorption and delayed clearance, resulting in higher serum LDL cholesterol (the bad form of cholesterol).
- Increased coronary heart disease risk with smoking and alcohol intake and overall increased incidence of heart attack, Alzheimer's disease, and dementia.
- Inability to repair the vascular endothelium to produce nitric oxide, which may increase blood pressure.
- Less response to statins to lower cholesterol.
- Best reduction of LDL occurs through dietary restriction of carbohydrates, with low fat diets, and omega 3 fatty acids.

COMT polymorphisms. One of the newest genes that we're looking at is COMT (catechol-*O*-methyltransferase), which provides instructions for the breakdown of norepinephrine and epinephrine (adrenalin from the adrenal glands). If this genetic SNP is present, the patient will have higher levels of norepinephrine and epinephrine in the blood and urine and an increased risk

➤

➤

of hypertension, coronary heart disease, and heart attack. There is a variation in response depending on which of the specific COMT SNPs the patient carries; for example, aspirin or vitamin E may be beneficial for patients with one type of COMT SNP but detrimental if one of the other SNPs is present.

Glutathione-related SNPs. The risk of myocardial infarction can be increased by 71% if a SNP affecting glutathione metabolism (GSH-Px, glutathione peroxidase) is present. This selenium-dependent enzyme expresses different capacities to neutralize oxidative molecules related to increases in oxidative stress and cardiovascular disease. For these patients, glutathione peroxidase and selenium levels would be key measurements to track for the risk of heart attack:

- Low GSH-Px is a major coronary heart disease risk factor.
- Higher levels of glutathione peroxidase support more rapid recycling of glutathione, resulting in higher availability of glutathione that is one of the most important antioxidants inside the cell.
- Increased glutathione peroxidase (GSH-Px) decreases blood pressure and heart attack.

Genes Relevant to Hypertension

There is a whole host of genetic influences on blood pressure, probably over 30 different genes that we have recognized to date, all of which are helpful in determining both risk for hypertension and risk for cardiovascular target organ damage (Tables 11.1 and 11.2)

These genes are also helpful to determine the response to diet and nutrition, various nutrients, supplements, electrolytes, caffeine, and medications.

P-450-1A2. We know, for example, that someone who consumes caffeine in the form of caffeinated coffee and tea, and has the SNP, cytochrome P-450-1A2 and is a slow metabolizer of caffeine, will increase their risk of tachycardia, hypertension, aortic stiffness, and myocardial infarction. Of course, one could have the right type of SNP for caffeine detoxification and that will reduce their risk. The risk of having this gene is about 50% of the population. The 50% of the population with this gene are slow metabolizers of caffeine, and their risk for hypertension and heart attack actually go up directly based on the amount of caffeine consumption and their age. Before you drink caffeine (coffee, tea), you need to check the gene for cytochrome P-450 function.

TABLE 11.1 Recommended Genetic Testing (Vibrant America Labs)

1. 9p21 (GG/CC) (inflammation, plaque rupture, thrombosis, aortic aneurysms atherosclerosis, coronary heart disease, heart attack, and diabetes mellitus)
2. 6p24.1 (coronary heart disease)
3. 4q25 (atrial fibrillation)
4. ACE I/D (DD allele) (hypertension, left ventricular hypertrophy, renal failure, coronary heart disease, heart attack, carotid disease, kidney failure, and microalbuminuria)
5. COMT: Val/Val or Met/Met allele (coronary heart disease, heart attack hypertension)
6. 1q25 (GLUL) (coronary heart disease in diabetes)
7. APO E (E4/E4) (coronary heart disease, lipids, dietary response to fats)
8. MTHFR (A1298C and C677T) for methylation (endothelial dysfunction, hypertension, thrombosis, coronary heart disease, heart attack, stroke, and hyper-homocysteinemia).
9. CYP 1A2 (IF/IF) and caffeine (hypertension, heart attack)
10. Corin (hypertension, volume and sodium, heart failure, and preeclampsia and eclampsia)
11. CYP 11 B2 (TT allele) (hypertension and aldosterone)
12. GSH-Px (glutathione peroxidase) (ALA-6 alleles, selenium) (CHD and MI)
13. NOS 3 (nitric oxide, HBP, and CHD)
14. ADR B2 (AA allele vs GG allele) (HBP and DASH diet and drugs)
15. APO A1 and A2 (lipids)
16. CYP4AII and CYP4F2 (HBP, sodium and volume overload, and ENac) (amiloride)
17. MMP-2, MMP-9, and TIMP-1 (cardiovascular remodeling, DD, LVH, CHF, and hypertension)
18. AGTR1, NR3C2, HSD11B1, and B2 (HBP, potassium) and AGTR1 (AA/AC) and ARB response
19. AT1R-AA (AT1R autoantibodies); hypertension (ARB vs ACEI)
20. Blood group type A, B, and AB (vWF and thrombosis)

CYP 11 B2. The CYP 11 B2 is related to resistant hypertension, salt and water retention, increased blood volume, high aldosterone levels, and low blood potassium that can be treated with the drugs spironolactone or eplerenone. These patients may be on four or more drugs for hypertension, and it is still not controlled. This may be a cause of hypertension in 20% of the population that is resistant to other drugs. Once the correct blood pressure medication (spironolactone or eplerenone) and dose is started, in about 6–8 weeks, the blood pressure will decrease often to normal and the previous medications can be stopped. We will review these blood pressure-lowering drugs later in this book.

CYP4A11. Also, in terms of salt sensitivity and resistant hypertension, one of the most important is cytochrome P4A11 (expressed as CYP4A11), which relates to sodium and water diuresis and the role of the ENaC function in the kidney. These patients have an avid reabsorption of sodium in the kidney tubules from the ENaC, which increases the blood volume and blood pressure. Most of these patients have resistant hypertension and are taking three or four drugs, and their blood pressure remains elevated. Patients who have resistant hypertension due to CYP4A11 and treated with the drug amiloride have dramatic reductions in blood pressure and often can discontinue or reduce the dose of other antihypertensive drugs within 2 months. We will review these blood pressure-lowering drugs later in this book.

ACE I/D. The ACE I/D (DD allele) is associated with hypertension, left ventricular hypertrophy (enlargement of the heart), coronary heart disease, heart attack, carotid disease, kidney failure, and microalbuminuria (loss of the protein, albumin, in the urine due to damage of the kidney) These patients respond well to the blood pressure-lowering class called ACEI, or angiotensin-converting enzyme inhibitors. We will review these blood pressure-lowering drugs later in this book.

COMT (Val/Val or Met/Met allele) is causative of hypertension due to high levels of norepinephrine and epinephrine (adrenalin). These hormones cause the

arteries to constrict, become inflamed with an increase in blood pressure.

MTHFR gene is related to methylation and folic acid and other B vitamins and if defective will cause hypertension

GSH-Px (glutathione peroxidase), if abnormal, increases oxidative stress in the artery and causes hypertension.

NOS 3 is an important enzyme in the production of nitric oxide that improves vascular health and lowers blood pressure. If the NOS 3 is defective, then blood pressure increases as does cardiovascular disease. Treatment with high a nitrate/nitrite diet with dark green leafy vegetables, like kale and spinach and with beets or some beet root extracts like NEO 40 will improve nitric oxide levels. We will discuss these treatments in the nutrition section of this book later.

ADR B2 gene is related to how effective the DASH diet will be in lowering blood pressure. If you have a defect in this gene then the DASH 2 diet results in a reflex increase in the enzyme, renin, with increases the formation of the potent vasoconstrictor angiotensin II that increases blood pressure. If this happens, giving an ACEI or ARB (angiotensin receptor blocker) will lower the blood pressure effectively with the DASH diet. We will review these blood pressure-lowering drugs later in this book.

AGTR1 (AT1R-AA) is related to autoantibodies and hypertension. An autoantibody is an abnormal antibody (part of your immune system that attacks your own organs, i.e., attacks "the self"). This autoantibody attaches to and stimulates a receptor called AT1R (angiotensin receptor I) that causes hypertension. ARBs are the most effective treatment to lower blood pressure in patients with this defective gene. We will review these blood pressure-lowering drugs later in this book.

TABLE 11.2
Additional Hypertension Genes

ADD 1,2,3: Adducin
ADM: Adrenomedullin
ADORA2A: Adenosine
NEDD4L
PPARG
STK39
CALCA
GNA 12 and S1: G protein
GNB3: G Protein
GRK 4: G protein coupled receptor kinase type 4
M235T: Angiotensinogen gene

As you can see, there are numerous genes for hypertension that have now been discovered that help us to understand the previous unknown details and causes with the idea of "family history of hypertension." This will allow your doctor to measure many of the genes that cause hypertension and provide a more direct, personalized, and precision treatment program without the guess work. This means that your blood pressure will be controlled sooner, better, with fewer drugs, less cost, and better cardiovascular outcomes.

Cardiovascular SNPs. Obviously, there are large numbers of cardiovascular SNPs that we could check. At this point, I recommend testing for those that have the best validation, the highest correlation with risk prediction, and those that are easily attainable and have implications for a specific treatment. The genetic tests listed in Table 11.1 define risk for coronary heart disease, arrhythmias, heart failure, and hypertension; these are the genetic factors I recommend that you evaluate. From these tests, you will be able to determine the nutritional programs, medications, and other interventions that are the best.

Response to Specific Blood Pressure-Lowering Drug Classes

- Beta Blockers: rs1801253, GNA S1, ADR B1 GRK4
- Diuretics: ADD 1, GNB3, NOS 3, ACE, ADRBK1, CYP4A11 (amiloride) CYP11B2 (spironolactone and eplerenone), or GRK2
- ACEI: ACE I/D, ADR B1, and M235T
- ARB: ACE I/D, ADR B, AGTR1, and M235T
- Clonidine: GNB3
- CCB (calcium channel blockers) : ACE I/D
- Salt sensitivity: GRK4, M235T

Summary and Key Takeaway Points

1. If one of your parents had high blood pressure, you have a 25% chance of developing high blood pressure yourself. If both parents had high blood pressure, then the risk is 50% that you will have high blood pressure. If your parents or a sibling developed high blood pressure before the age of 50 years then your risk is even higher to develop high blood pressure, but also at an earlier age.
2. Numerous genes that cause hypertension are specific for treatment with a drug, a supplement, an electrolyte, or with a diet and nutrition. There are numerous genes for hypertension that have now been discovered that help us to understand the previous unknown details and causes underlying the concept of "family history of hypertension." This will allow your doctor to measure many of the genes that cause hypertension and provide a more direct, personalized and precision treatment program without any guess work. This means that your blood pressure will be controlled sooner, better, with fewer drugs and less cost.
3. Evaluate specific genetic SNP's, for cardiovascular disease and hypertension, The Cardia X genetic profile from Vibrant Labs in San Francisco measures 25 genes related to cardiovascular disease and hypertension.
4. Traditional MedDiet with five tablespoons EVOO/day (50 g) and nuts and CoQ10 lowers blood pressure, cardiovascular disease, and diabetes mellitus.
5. Modified low-glycemic DASH 2 for hypertension is recommended. These patients especially respond related to the B2-AR AA/GG alleles.
6. Omega 3 fatty acids should be given to all patients, dose dependent (1–5 g/day to lower blood pressure and reduce cardiovascular disease.
7. Recommended intake of electrolytes is 2 g sodium, 5–10 g of potassium, and 1000 mg of magnesium per day.
8. Avoid caffeine in CYP 1A2 SNP (IF/IF and IF/IA alleles).
9. Selective use of ASA, vitamin E depending on COMT phenotype.
10. 20.5 methylfolate and B vitamins depending on MTHFR genotype for methylation.
11. Selenium should be given with GSH-Px gene if defective
12. Specific antihypertensive drug selection based on genotypes such as ACE I/D, CYPII B2, CYP 4A11, ADRB2, AGTR1, and AGTAA. ◆

References are available online at www.townsendletter.com.

Botanical Approach to Hydrogen-Positive SIBO: A Case Report

by Samantha Davison and Bradford Case, ND, DC

Abstract

Small intestinal bacterial overgrowth (SIBO) is one of the leading causes of irritable bowel syndrome (IBS) and presents with a range of intestinal and extraintestinal symptoms that impair quality of life.[1] Prescription standards of care, which include oral antibiotics such as rifaximin or metronidazole, have shown variable success and have proven to be economically unfavorable. This case report involves the successful treatment of hydrogen-positive SIBO with a broad-spectrum antimicrobial approach incorporating the use of berberine, oregano, neem,[2,3] and a specific carbohydrate low FODMAP diet with marked reduction of gastrointestinal symptoms, improved Bristol stool chart, and improved integumentary symptomatology.

Introduction

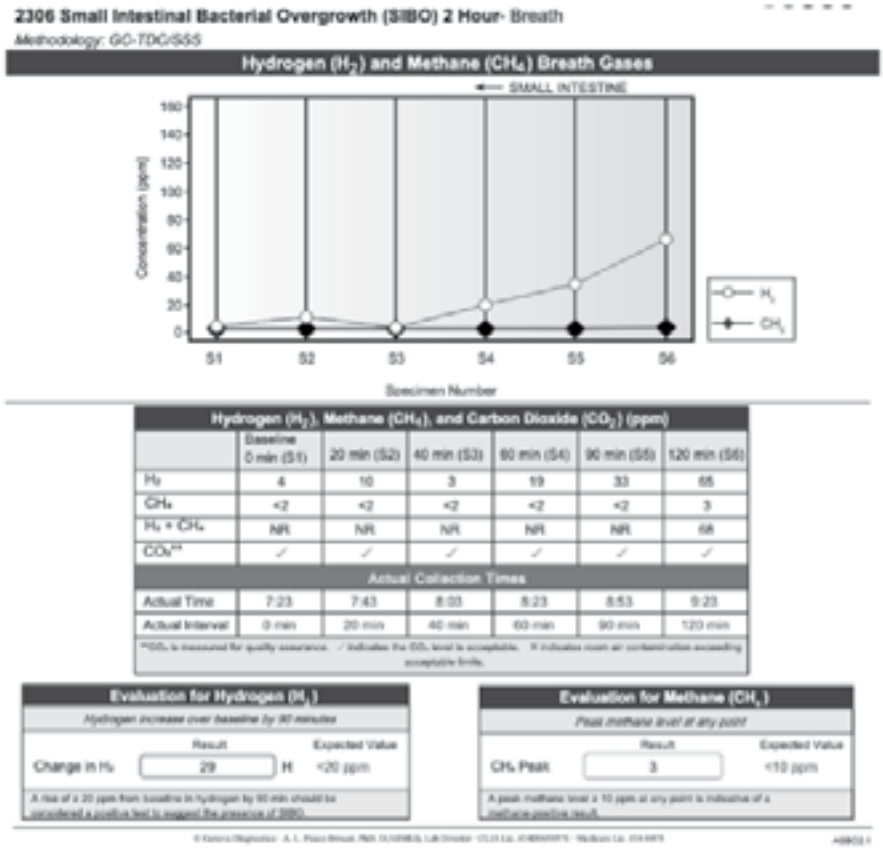
Small intestinal bacterial overgrowth (SIBO) is an excessive amount of abnormal bacteria in the small intestine.[4] Symptoms associated include abdominal discomfort, distention, bloating, dyspepsia, flatulence, belching, fatigue, nausea, diarrhea and/or constipation, sensation of incomplete evacuation, and urgency.[4,5] Less frequent but more serious manifestations of SIBO include malabsorption, weight loss, anemia, iron deficiency, and vitamin deficiency.[4]

Risk factors may include anatomical abnormalities (i.e., small intestinal diverticulosis), postsurgical structural changes (i.e., ileocecal valve resection, gastric bypass, Roux-en-Y), iatrogenic causes of slow gut motility (i.e., narcotics, anticholinergics, anti-diarrheals), hypo- or achlorhydria due to surgery, autoimmune gastritis, or proton pump inhibitors, and small bowel dysmotility regardless of cause (i.e., inflammatory bowel disease, celiac disease, radiation enteritis, small bowel adhesions, and systemic diseases associated with dysmotility, which include diabetes, amyloidosis, and scleroderma) and trauma (i.e., traumatic brain injury).[4]

The most common diagnostic tests for SIBO include glucose or lactulose breath tests, small intestinal aspiration and culture, and assessment of clinical symptom profiles.[4] Breath testing has proven to be the most economic, non-invasive, and reliable approach. This involves enumerating hydrogen and methane gas via breath samples over an indicated period of time, generally two or three hours. Gas production is dependent

continued on page 54 ➤

Image 1. Genova Diagnostics 2-Hour Lactulose Breath Test



Relax Far Infrared Saunas & Lamps

FULFILLING THE DREAM OF HIPPOCRATES!

"FIND ME A WAY TO CREATE SWEAT OR FEVER, AND I WILL CURE DISEASE." - HIPPOCRATES

The Relax Sauna can increase body temperature 3° in 25 minutes. Significantly more than any other sauna

Increasing core temperature will:

- Mobilize Lymphatic System (Detox)
- Increase Circulation & Microcirculation
- Activate Parasympathetic Nervous System
- Help Mitochondria to create ATP + nitric oxide

Detoxifying from heavy metals, glyphosate, dioxins, plastics, metabolic waste. Lowering blood pressure, reducing inflammation & pain (arthritis, fibromyalgia, sports injuries), helping repair ulcers & scar tissue, assimilating nutrients, ending neuropathy. Reducing stress, giving deep profound relaxation, helping sleep disorders, & Creating Vitality and Rejuvenation.

Silver Tent Sauna

Professional Sauna

Medical Grade Lamp

Lie Down Sauna

Patented semiconductor chip

Sauna carrying case

Rebecca Harder: author of "Gastra Girl: *Saving America One Colon at a Time,"*

Rebecca Harder has been promoting high quality wood infrared saunas for 10 years in her clinic. After trying the Relax Sauna at a conference, she could feel the difference in only 3 minutes. She excitingly related this in 8 glowing pages about the Relax Sauna in her book "Gastra Girl", saying it was the BEST sauna. Rebecca has since sold many Relax Saunas to her clients.

See two reviews comparing the Relax Sauna to Wooden Saunas & to other Portable Saunas:
relaxsaunas.com/superior

Preferred by hundreds of medical professionals

Dr. Thomas Lucky - M.D.
Author "Unleashing the Healing Miracle Within"

"The radiant energy going through my body feels like instant magic. I really must have one of these."

Dr. Bill Akpinar (M.D., D.S., O.M.D.)

Author "No Sweat?, Know Sweat!" Definitive Guide to Reclaiming your Health"

Every time I use the Relax Sauna, I cannot for the life of me see how people can live without it! "We recommend it to many of our patients, as this technology is unique.

See over 800 True Testimonials: youtube.com/relaxsaunas

phil@relaxsaunas.com **CALL 626.200.8454** **relaxsaunas.com/townsend**

Go to: relaxsaunas.com and use code **town12** to get **$125 OFF** the cost of a Relax Sauna until DEC 31, 2022

➤ *continued from page 52*

on the concentration and strains of bacteria colonized in the small intestine, availability of carbohydrate residue, and small intestinal absorptive capacity. The presence of these gasses in human breath signifies metabolism of carbohydrate residues by the gut, absorption across the gastrointestinal mucosal barrier, and sequentially, expiration through the lungs. These findings yield significance due to the inability of human cells to produce hydrogen or methane gases.[6] When lactulose or glucose solution is given to a patient with suspected SIBO, changes in hydrogen and methane concentration in breath samples indicates the presence of SIBO.

The generalized treatment strategy for SIBO is induction of remission through eradication; maintaining remission and addressing etiology; restoring mucosal function; and balancing the microbiome. Conventional treatment remains empirical, using broad spectrum antibiotics for two weeks. Oral antibiotics such as rifaximin or metronidazole have shown variable success. Rifaximin is the safer and more efficacious drug of choice; however it has proven to be economically unfavorable for the patient and its long-term safety profile is unclear. Potential side effects of rifaximin include flatulence, headache, incomplete bowel emptying, urgency, abdominal pain, nausea, vomiting, constipation, fever, bloating, dizziness, fatigue and swelling.[7]

Alterative treatment strategies provide a least invasive approach to SIBO eradication, which generate restoration of the mucosal lining and mechanical function. The elemental diet provides essential nutrients administered in

Table 1. Symptom Timeline

2006	Recalls experiencing dermatitis and eczema.
2011	Has a concussion which induces pain and vomiting.
Spring 2011	Develops food poisoning while eating hamburgers at a backyard barbeque. Patient reports overindulgence in undercooked hamburgers. Patient and his father report at least 4 episodes of food poisoning since initial episode.
January 2015	Presents to BUC Clinic with spontaneous, multiple episodes of nausea and vomiting. Patient has difficulty absorbing fats and has associated signs and symptoms of hand delusions, headaches with vomiting, floating stool, fatigue, leukonychia, indigestion, and a post-prandial heaviness in his stomach. He consumes a diet high in processed carbohydrates and suspects symptoms are caused by food intolerance and indigestion to fats. Lipid panel reveals low HDL (36 mg/dL), low chloride (96 mEq/L), and functionally low vitamin D (34.5 ng/mL).
March 2015	Dermatitis begins to worsen, presenting with dry, scaled, and cracked skin on the palmar surface of hands and digits bilaterally.
September 2017	Celiac disease ruled out via Prometheus Celiac Plus testing and IgG food allergen testing revealed sensitivity to pineapple, chicken, and eggs.
2018	Went vegetarian for 5-6 month due to dyspepsia when consuming meat.
April 2021	Presents to BUC Clinic with abdominal pain, distention, excessive, burning flatulence and belching, and widespread eczematous/psoriatic rash. We ordered a CBC, CMP, lipid panel, and lactulose breath test. Treatment recommendations included Bio-gest digestive enzymes (betaine HCL, L-glutamic acid hydrochloride, pancreatin, ox bile concentration, pepsin), 2 capsules before meals, increased exercise, adequate hydration, and hypoallergenic lotion after showers for dry skin.
June 2021	Lactulose breath test reveals H^2+ SIBO, CBC and CMP WNL, lipid panel reveals low HDL.
Early July 2021	At follow up appt., patient has improvement in hand dryness with use of lotion, minimal improvement in GI symptoms with digestive enzymes. Dietary recall reveals a diet high in processed carbohydrates, ½ C water daily and minimal exercise. Treatment recommendations at this time are highlighted in Table 2 and include a 6-week protocol of berberine, oregano oil, neem, digestive enzymes, low FODMAP SCD "legal" diet, lifestyle modification (hydration and exercise).
Mid July 2021	Incomplete adherence to SCD "legal" diet by consuming corn chips, corn tortillas, and oatmeal. No improvement in symptoms. Patient reports use of oregano peppermint oil (Solaray) 70 mg TID, Berberine HCL (Integrative Therapeutics) 500 mg TID, neem (Natural Factors) 300 mg TID.
Late July 2021	Patient has strongly adhered to diet and reports experiencing die-off reaction (very fatigued). He has been taking his digestive enzymes after meals rather than before. Overall, patient is connecting to his food, and last dietary recall revealed bone broth soups, several servings of whole food forms of vegetables, fruit, and organic protein.
August 2021	At 4-week follow up patient reports improved skin lesions along palmar surfaces of hands bilaterally and rash no longer present along his shin. Patient advised to continue with protocol and follow up in 4 weeks to assess status of symptomatology and reintroduce SCD "legal" high FODMAP foods.
September 2021	Patient placed on biofilm agent Interphase Plus (Klaire Labs) 2 capsules TID between meals for 6 weeks. After 2 weeks, patient reports increased flatulence, worsening of skin symptomatology. Biofilm agent changed to Biofilm Phase-2 Advanced (Priority One) 2 capsules QD taken away from food. Biofilm agent changed due to suspected reaction to lysozyme ingredient derived from egg white. Patient additionally placed on SIBO-MMC prokinetic (Priority One) 3 capsules in the morning and evening away from food. After 1 week, patient reports improved flatulence and skin symptoms. After 1 month, patient discontinued berberine, neem, and oregano, and was retested for SIBO via Genova 3-hour lactulose breath test. He continued with legal "high" FODMAP, allowing 4 hours between meals, Thorne Bio-Gest digestive enzymes 2 capsules before meals, SIBO MMC 3 capsules in the morning and evening away from food.
December 2021	Genova, 3-hour lactulose breath test revealed hydrogen 2 ppm and methane <2 ppm indicating negative results. Patient is no longer experiencing stomach pain, excessive flatulence, eructation, or fatigue. He is passing bowel movements regularly (Bristol Stool Chart 3-4) and is experiencing continued improvement of skin with minimal lesions on palmar surface of first digits bilaterally. Patient was recommended probiotic TherBiotic Complete (Klaire Labs) 1 capsule QD with food and continued adherence to SIBO-MMC and digestive enzymes. Patient recommended to transition to SCD high FODMAP foods for 2 weeks, then begin introducing all non-triggering foods into the diet.

Abbreviations: TID, three times daily; QD, daily; PRN, as needed.

liquid form for several weeks and is a safe, exceptional option for patients with allergies or aversion to antibiotics. Herbal antibiotics in combination with a low FODMAP diet are the treatments of choice for most naturopathic or other naturally oriented physicians. In a non-randomized, open label trial, herbal antibiotics compared to rifaximin yielded comparative results indicating herbal treatment is as effective as rifaximin in patients with lactulose-positive SIBO breath tests.[8]

Case Study

A 23-year-old Caucasian male presented to Bastyr University California (BUC) Clinic in April 2021, with complaints of abdominal discomfort and dry skin. His abdominal pain had been ongoing for the past three years and was increasing in intensity. Pain was worse after eating, lasting around thirty minutes to one hour and was primarily in the epigastric region of his abdomen. The patient described his pain as dull with cramping and minor pains throughout the day that strengthened in severity after each meal. He also complained of cramping and burning flatulence, and belching, both of which were foul in odor. He noticed that his symptoms were particularly worse after eating high fat containing foods such as peanut butter, pork, fish, or fish oils, and further reported that he'd had issues digesting fats since he was 13 years old.

The patient also had an eczematous rash on the tips of his fingers, palms of his hands, calves, knees, abdomen, and back, which was previously and unsuccessfully treated with coal tar and salicylic acid. The rash was scaled, dry, pruritic, and occasionally presented with hemorrhagic fissures. Additional signs and symptoms included leukonychia and cold intolerance. His 24-hour dietary recall consisted of eggs, gluten-free toast, ramen, slices of ham, vegan sausage, potatoes, and a peanut butter and jelly sandwich. He passed 1-2 bowel movements per day, which were well-formed, type 2-3 on the Bristol stool chart, but hard to pass and malodorous. He denied noticeable blood, mucus, or undigested food in his stool.

Clinical Findings

Physical exam revealed a scaled rash with dry, flaking skin along his back, sides of abdomen, extensor surfaces of arms, lower limbs, and a scaled, white plaque over his right patella. Fissures were visualized along his fingers bilaterally with leukonychia on the nail bed of his left fourth digit. Capillary refill was less than two seconds. Abdomen appeared flat. Bowel sounds were heard in all four quadrants with scattered dullness on percussion. The abdomen was soft with no hepatomegaly, but tenderness was noted in the right lower quadrant on palpation.

Laboratory analysis consisted of CBC with differential and comprehensive metabolic panel that were within normal limits, and a lipid panel showing low HDL. The lactulose breath test revealed a hydrogen level of 29 ppm at 90 minutes from baseline indicating hydrogen positive SIBO. Methane was negative, with a level of 3 ppm at 90 minutes and 120 minutes from baseline *(*Image 1).

Timeline

Upon taking a thorough history (Table 1), we discovered the patient began experiencing dermatitis and eczema

➤

➤

around 2006. In 2011, he endured a concussion. In that same year, he also contracted gastroenteritis after eating undercooked beef. In 2015, the patient presented to Bastyr University Clinic with episodes of nausea and vomiting, which occurred sporadically a few times each year. At this visit, the patient and his father noticed a pattern of malabsorption when consuming foods high in fat. He further experienced signs and symptoms of hand delusions, headaches with vomiting, steatorrhea, fatigue, leukonychia, indigestion, and a post-prandial heaviness in his stomach. He consumed a diet high in processed carbohydrates and suspected symptoms were caused by food intolerance and indigestion of fats. Lipid panel revealed low HDL (36 mg/dL), low chloride (96 mEq/L), and functionally low vitamin D (34.5 ng/mL). Shortly after, in March 2015, his dermatitis began to worsen and presented with dry, scaled, and fissured skin on the palmar surfaces of his hands and digits bilaterally. In September 2017, another provider established celiac disease as unlikely via Prometheus Celiac Plus testing and IgG food allergen testing revealed sensitivity to pineapple, chicken, and eggs. As the patient's dyspepsia with meat consumption worsened, he voluntarily began following a vegetarian diet for six months. The patient's symptoms continued to worsen until seeking naturopathic care in April 2021.

Diagnostic Assessment

Results of the patient's lactulose breath test are highlighted in Image 1. Given the results were conclusive for hydrogen positive bacterial overgrowth, we were able to confirm a positive

Table 2. Prescribed Intervention

ANTIMICROBIAL MEDICATION

Intervention: Integrative Therapeutics Berberine Complex: *Berberis vulgaris* (barberry), 400 mg, *Mahonia aquifolium* (Oregon grape), 400 mg, and *Hydrastis canadensis* (goldenseal), 100 mg. Other ingredients: Hydroxypropyl methylcellulose (vegetable capsule), cellulose, magnesium stearate, silicon dioxide.
Instructions: 2 capsules, PO, TID, with meals, x 6 weeks
Rationale: This complex contains the alkaloid compound of berberine shown to have broad spectrum antimicrobial and antifungal effects.[12]

Intervention: *Origanum vulgare* (Oregano) oil, 50 mg. Other ingredients: cellulose, modified cellulose gum, potassium sorbate, stearic acid (vegetable source), silica, water and gum Arabic.
Instructions: 50 mg, PO, TID, with meals, x 6 weeks
Rationale: Phenolic constituents carvacrol and thymol have broad spectrum antimicrobial effects and act by accumulating in the lipid bilayer of the bacterial cell membrane causing structural disruption.[9,13]

Intervention: Banyan Botanicals *Azadirachta indica* (Neem): Other ingredients: *Maltodextrin, *gum Arabic, *rice flour.
Instructions: 500 mg, PO, TID, with meals, x 6 weeks
Rationale: Used to promote elimination and removal of toxins and harmful bacteria while protecting the gastrointestinal lining. One small clinical trial showed that oral supplementation in addition to sun exposure and topical application of Vaseline and salicylic acid reduced psoriasis by 50% compared to placeco.[14]

DIGESTIVE SUPPORT

Intervention: Thorne Bio-Gest Digestive Enzymes: betaine hydrochloride, 480 mg, L-glutamic acid hydrochloride, 480 mg, pancreatin (porcine), 140 mg, ox bile concentrate, 80 mg, pepsin (porcine), 70 mg. Other ingredients: Hypromellose (cellulose) capsule, leucine, silicon dioxide.
Instructions: 2 capsules, PO, QD, AC
Rationale: This product contains HCL, pepsin, pancreatin, and ox bile to aid in fat, protein, and carbohydrate digestion.

Intervention: Priority One SIBO-MMC: Vitamin B6, 15 mg, L-5-Hydroxytryptophan, 75 mg, *Zingiber officinale* (Ginger), 200 mg, *Zanthoxylum clava-herculis* bark (Southern Prickly Ash), 200 mg, *Ziziphus jujuba* seed (Jujube), 200 mg, *Linum usitatissimum* (Flax), 50 mg.
Instructions: 3 capsules PO AM and PM, away from food
Rationale: This product contains botanicals and nutrients to maximize the healthy functioning of migrating motor complex nerves to stimulate the natural forward movement of the gastrointestinal tract and eliminate reintroduction of undesirable compounds.

Abbreviations: PO, by mouth; TID, three times per day; QD, daily; AC, before meals; BID, twice per day; PRN, as needed; *organic.

Intervention: Klaire Labs Ther-Biotic Complete: 25 billion CFU
Instructions: 1 capsule PO, QD
Rationale: Broad-spectrum hypoallergenic blend of 12 probiotic species in a base of inulin. Probiotic support intended to colonize transient strains of commensal microbial species to protect against undesirable microorganisms, strengthen intestinal epithelial barrier integrity, nourish enterocytes through short chain fatty acid production, reduce inflammation, and support innate and acquired immunity.

BIOFILM DISRUPTING AGENT

Intervention: Priority One Biofilm Phase-2 Advanced: Bismuth Subnitrate, 200 mg, Alpha Lipoic Acid, 300 mg, *Nigella sativa* seed (black cumin), 100 mg. Other Ingredients: L-leucine, rice chelate, silicon dioxide, vegetarian capsule.
Instructions: 2 capsules, PO, QD
Rationale: This product is used for the disruption of advanced biofilms typically present amongst SIBO cases.

DETOXIFICATION SUPPORT

Intervention: Natural Factors Activated charcoal, 500 mg. Ingredients: activated charcoal powder from activated purified carbon coconut shells, gelatin, purified water, coconut oil, sunflower lecithin, yellow beeswax.
Instructions: 2 capsules PO, PRN
Rationale: Charcoal acts as a binding agent to mitigate Herxheimer reaction

DIETARY MODIFICATION

Intervention: Specific Carbohydrate (SCD) Low FODMAP diet
Instructions: Progression of diet was dependent on patient improvement. Patient began with SCD "Legal" Low FODMAP and was transitioned SCD "Legal" Moderate FODMAP; SCD "Legal" High FODMAP; and lastly, SCD "Illegal".
Rationale: 'FODMAP' stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which are short chain fatty carbohydrates and poorly absorbed sugars. High FODMAP foods are problematic for SIBO patients because they draw water into the intestines, causing bloating, and are fermented by intestinal bacteria for energy. This fermentation produces gas as a byproduct and causes the intestine to stretch, causing pain.[15]

LIFESTYLE

Intervention: Exercise
Instructions: 30-45 minutes three to five times per week
Rationale: Increase exercise in the form of strength or cardiovascular training.

Intervention: Hydration
Instructions: ½ body weight in ounces of water QD
Rationale: This is the standard recommendation for ensuring adequate hydration for individual needs with 3.7 L being the average recommended intake for adult males.[16]

diagnosis of hydrogen dominant SIBO. Treatment may range from six to twelve months and prognosis is individualistically dependent upon the patient's adherence and physiological response. While herbal antibiotics have been shown clinically and statistically analogous to Rifaximin in SIBO eradication, herbal antibiotics induce worse Herxheimer reactions, i.e., flu-like symptoms including headache, joint and muscle pain, sore throat, malaise, sweating, chills, and nausea, compared to antibiotics. While this is largely understudied, the primary theory is that many patients have concomitant small intestinal fungal overgrowth (SIFO), likely caused from candida and their consequential biofilms. Herxheimer reactions may persist while targeted treatment disrupts biofilm integrity.[9] Herxheimer reactions to SIBO eradication are successfully mitigated with activated charcoal as needed.[10]

Therapeutic Intervention

This patient had 10 visits in six months and received therapeutic interventions – antibacterial medication, dietary supplementation, nutritional and lifestyle recommendations – guided by laboratory testing (Image 1 and Table 2*).* Obstacles to cure at the time of initial treatment included dietary compliance, inadequate hydration, and inadequate physical exercise. Our treatment goals were to increase stomach acid, thereby improving digestion and absorption, and to eradicate small intestinal bacteria with use of the herbal antibiotics, highlighted in Table 2. Herbal therapy has been shown to be equivalent to Rifaximin in the treatment of SIBO.[11] The following six-week supplementation protocol was originally developed by herbalist Steven Harrod Buhner and modified by Dr. Lela Altman. Our patient was initially placed on a six-week eradication protocol, including Integrative Therapeutics Berberine Complex, 500 mg three times daily; ADP Oregano Oil, 50 mg three times daily; Banyan Botanicals Neem, 500 mg three times daily; Thorne Bio-Gest Digestive Enzymes 2 capsules before meals; and a specific carbohydrate diet (SCD) in the "legal" low FODMAP category, developed by Dr. Allison Siebecker, reference Table 2 for detailed rationale. Additional determinants of health warranted recommendations to increase exercise 30-45 minutes three to five times per week in the form of strength or cardiovascular training and to ensure adequate hydration by consuming one-half of his body weight in ounces of water daily (Table 2).

As the patient's gastrointestinal and integumentary symptoms lessened in severity, he was transitioned to the SCD "legal" moderate FODMAP diet for 4 weeks, then SCD "legal" high FODMAP diet for another four weeks.

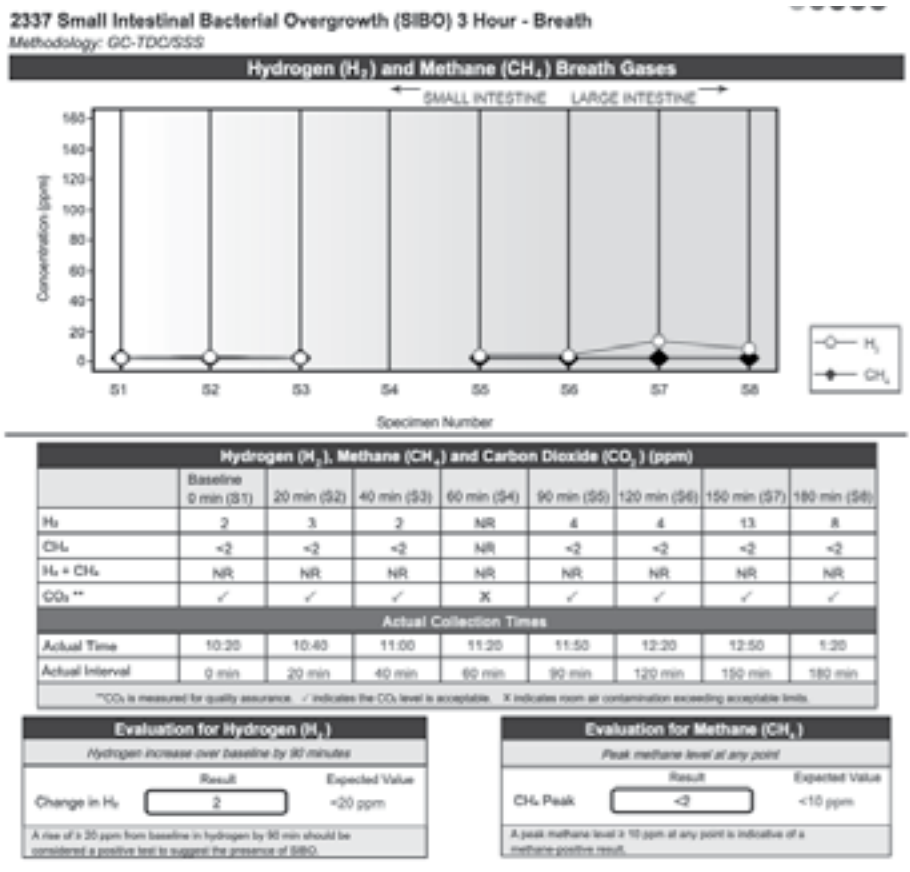
Follow-up and Outcomes

At the patient's three-week follow up, low FODMAP dietary adherence was incomplete due to daily consumption of high FODMAP foods including corn tortillas, corn chips, and oatmeal. The patient further reported that he was taking 70 mg of Solaray oregano with peppermint oil three times daily, 500 mg of berberine HCL three times daily, instead of the recommended berberine complex, and 300 mg of neem three times daily, instead of the recommended dose of 500 mg three times daily. Patient reported no improvement in symptoms at this time and was advised to follow the previously recommended therapeutic dosages. Through dietary counseling and patient education, complete adherence to the recommended protocol was achieved at the patient's 4-week follow up. He had strongly adhered to the SDC legal low FODMAP diet and reported the Herxheimer reaction of increased fatigue.

At the patient's six-week follow up, he reported significant improvement in symptoms with no abdominal pain, mild flatulence with distention after eating, and his skin symptoms had resolved along his legs, knees, arm, and elbows bilaterally. Mild dry and flaky skin was still noted along his first and second digits bilaterally and one 0.5 cm fissure was located along the palmar surface of his left thumb. The patient had experienced reconnection with his diet with increased consumption of clean protein sources and vegetables and reported no new onset of symptoms.

While there was an overall improvement in the patient's presentation, symptoms of flatulence and distention indicated the persistence of SIBO, therefore, the patient was instructed to continue the herbal antimicrobial ➤

Image 2. Genova Diagnostics 3-Hour Lactulose Breath Test.



➤

protocol, was transitioned to a SCD "legal'' moderate FODMAP diet and instructed to incorporate more variety of fruits and vegetables. Patient was additionally placed on a biofilm disrupting agent, Klaire Labs Interphase Plus, 2 capsules three times daily, to reduce incidence of recurrence and potentiate effect of the herbal antibiotics.[17]

At nine-week follow up, the patient was advised to discontinue Interphase Plus and initiate Priority One Biofilm Phase-2 Advanced, 2 capsules daily away from food, due to suspected reaction to lysozyme, an enzyme ingredient derived from egg white. Patient was advanced to the SCD "legal" high FODMAP diet for four-weeks duration. Treatment was further advanced to incorporate a prokinetic, SIBO-MMC, 3 capsules in the morning and evening away from food, to support the nerves of his migrating motor complex to stimulate the natural forward movement of the gastrointestinal tract and eliminate reintroduction of undesirable compounds.

At 13-week follow up, the patient reported complete resolution of symptoms. He was advised to discontinue berberine, neem, and oregano supplementation for a minimum of two weeks prior to three-hour Genova lactulose breath testing. Patient continued to adhere to the SCD "legal" high FODMAP diet in addition to eating his meals 3-5 hours apart to support his migrating motor complex. He continued to take digestive enzyme support and SIBO-MMC supplementation.

At the patient's last follow up appointment, approximately 22 weeks after treatment initiation, Genova three-hour lactulose breath test (Image 2) revealed negative hydrogen (2 ppm) and methane (<2 ppm) results. Patient was no longer experiencing stomach pain, excessive flatulence, eructation, or fatigue. Skin symptoms reduced to one lesion along the palmar surface of thumb bilaterally. Patient was instructed to advance to SCD "illegal" foods for two weeks, continue taking digestive enzymes, 2 capsules before meals, SIBO-MMC, 3 capsules in the morning and evening. Patient was introduced to Klaire Lab's Ther-Biotic Complete probiotic, 1 capsule daily with food, to support reinoculation of commensal bacteria and support gastrointestinal integrity. After two weeks, the patient was advised to begin challenging foods consumed prior to treatment protocol.

Table 3. Patient Outcomes.

Date of Visit: 4/20/21
Bristol Stool Chart: 2-3
Abdominal pain: TTP in RLQ
Rash/Sxs: Present. Dry, cracked, scaled, pruritic

Date of Visit: 7/01/21
Bristol Stool Chart: 3-4, difficult to pass, BM occasionally burn
Abdominal pain: TTP in RLQ
Rash/Sxs: Improved after digestive enzyme support.

Date of Visit: 7/21/21 (1st F/U after Tx)
Bristol Stool Chart: 3-4, difficult to pass
Abdominal pain: TTP in RLQ
Rash/Sxs: Dermatitis worsened on hands while remaining body lesions improved.

Date of Visit: 7/28/21 (2nd F/U after Tx)
Bristol Stool Chart: 4-5; easier to pass; full elimination of BM
Abdominal pain: TTP in RLQ
Rash/Sxs: Improved. Hands consistent with previous presentation. Reports increased fatigue (die-off reaction).

Date of Visit: 8/12/21 (3rd F/U after Tx)
Bristol Stool Chart: 5-6; easier to pass; looser stools for 2 days.
Abdominal pain: No TTP or abdominal pain
Rash/Sxs: Significantly improved. Rash no longer visualized on legs and arms bilaterally. Mild dry skin along palmar surfaces of hands bilaterally, with one 0.5 cm fissure along left thumb.

Date of Visit: 9/2/21 (4th F/U after Tx) Telemedicine Consult.
Improved flatulence and skin symptoms.

Date of Visit: 9/27/21 (5th F/U after tx) Telemedicine Consult.
1-week following 4th F/U visit, patient reports regression in flatulence and skin symptoms due to Interphase Plus biofilm disrupting agent. One week after changing biofilm disrupting agent to Biofilm Phase-2 Advanced, patient reports continued improvement in flatulence and skin symptoms.

Date of Visit: 12/6/22 (6th F/U after Tx)
Bristol Stool Chart: 3-4; easy to pass and passing regular BM
Abdominal pain: No TTP or abdominal pain.
Rash/Sxs: All symptoms improved. Patient no longer experiencing stomach pain, flatulence, eructation, fatigue. Significantly improved skin symptomatology, reduced to palmar surfaces of first digit bilaterally.

Legend: Bristol stool chart: Type 2: Sausage-shaped, but lumpy; Type 3: Like a sausage but with cracks on its surface; Type 4: Like a sausage or snake, smooth and soft (average stool); Type 5: Soft blobs with clear cut edges; Type 6: Fluffy pieces with ragged edges, a mushy stool (diarrhea). TTP (tenderness to palpation). RLQ (right lower quadrant).

Discussion

This case reports on the approach of utilizing botanical medicine to optimally manage and successfully treat hydrogen positive, methane negative SIBO. It further addresses the obligation of extrapolating a patient's determinants of health in a clinical care setting while incorporating motivational interviewing to support patient adherence to individualized medicine.

We suspect the pathogenesis of the patient's hydrogen positive SIBO is multifactorial but was likely set in motion from multiple cases of infectious gastroenteritis. Food borne illness is commonly due to bacterial agents such as *Campylobacter, Shigella, E. coli,* and *Salmonella*. These bacteria generate cytolethal distending toxin-B (Cdt-B), a toxin that is structurally similar to vinculin, an intestinal protein responsible for small intestinal motility.[18,19] After infection, antibodies develop to Cdt-B, but also attack vinculin due to molecular mimicry. The subsequent loss of vinculin from the enteric nervous system causes decreased motility and loss of migrating motor complex (MMC) function.[18,19] The MMC normally creates a wave of motility during the fasting state that cleans the small intestine by pushing food and bacteria distally into the large intestine at a rate of approximately one foot every 5 minutes, which is faster than bacterial replication time. Compare this to the large intestine, in which food moves approximately 1 foot every five hours.[9] When the MMC is impaired and food, especially fermentable food, becomes static, this allows bacterial proliferation and colonization, generating

small intestinal bacterial and/or fungal overgrowth. Long after recovery from gastroenteritis, anti-vinculin antibodies remain in the body, attacking this important protein. The destruction of vinculin can lead to permanent loss of the MMC, which is presumably why so many patients with SIBO suffer from recurrence, even after a successful kill protocol.[18,19]

The patient's concussion may have also contributed to or caused impaired gastric acidity through loss of vagal tone. When there is even minimal damage to the CNS, the ANS and enteric nervous system activate and signal inflammatory hormonal release, which negatively impacts vagal tone.[13] Impaired vagal motor activity may cause SIBO due to reduced intestinal contractility; impaired motility, defecation, and valve control, which leads to bacterial translocation; and lack of HCl production.[13] When a patient is deficient in HCl, the chyme entering the duodenum may not be acidic enough to cause sufficient cholecystokinin release, thus causing less bile and pancreatic enzyme release, including lipase. This causes lack of digestion, especially of fats, and malabsorption occurs. Fats are responsible for energy production and vitamin/mineral repletion; and though it is likely multifactorial, we suspect that fat malabsorption is strongly contributing to the patient's dry skin condition. Besides fat malabsorption, his skin rash may also have a hereditary component as well as dehydration and inadequate nutrition.[11] Other potential etiological factors in this patient's presentation of SIBO may include ileocecal valve dysfunction and pancreatic insufficiency.

This case was concluded in December 2021 after reversal of symptoms and negative three-hour lactulose breath test. We can conclude through this case study that a naturopathic botanical approach to treating hydrogen-positive SIBO with herbal antibiotics, digestive enzymes, herbal prokinetics, and biofilm-disrupting agents demonstrates overall improvement in symptomatology and quality of life, while restoring gastrointestinal function. We can also conclude that more research is warranted regarding herbal medicine and its effective mechanism of action in targeting and eradicating methane and hydrogen positive small intestinal bacterial overgrowth and other dysbiotic conditions.

Conclusion

This case report presents a cost-effective, successful treatment of a patient with hydrogen-positive, methane negative SIBO and subsequent dermatitis. SIBO is becoming more prevalent in naturopathic primary care due to enhanced understanding of symptomatology, etiology, and pathogenesis. Through utilizing the Genova Diagnostics lactulose breath test, we were able to gain clarity in the patient's symptomatology and construct an appropriate treatment plan. Our approach encompassed the use of herbal antimicrobials, berberine, oregano and neem, in conjunction with specific carbohydrate low FODMAP dietary modification. This approach has shown equivalent efficacy to conventional pharmaceuticals in research and from a clinical perspective, as showcased in this case study.

Acknowledgements: This case report was prepared according to the CARE guidelines.[20]

Author Disclosure Statement: Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review. The authors sincerely thank the patient for his trust in our care, compliance, and willingness to participate in this case report.

References

1. Shah A, Talley NJ, Jones M, et al. Small Intestinal Bacterial Overgrowth in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Case-Control Studies. *Am J Gastroenterol*. 2020;115(2):190-201.
2. Pandey, S., Jha, A., and Kaur, V. Aqueous extract of neem leaves in treatment of psoriasis vulgaris. Indian Journal of Dermatol Venereol Leprol 1994;60(2):63-67.
3. Irkin, R. and Korukluoglu, M. Growth inhibition of pathogenic bacteria and some yeasts by selected essential oils and survival of L. monocytogenes and C. albicans in apple-carrot juice. *Foodborne Pathog Dis*. 2009;6(3):387-394.
4. Rezaie, A., Pimentel, M., & Rao, S. S. (2016). How to test and treat small intestinal bacterial overgrowth: an evidence-based approach. *Current gastroenterology reports*, *18*(2), 8.
5. Barros, L. L., Farias, A. Q., & Rezaie, A. (2019). Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment. *World journal of gastroenterology*, *25*(31), 4414–4426. https://doi.org/10.3748/wjg.v25.i31.4414
6. Levitt, M. D., & Bond Jr, J. H. (1970). Volume, composition, and source of intestinal gas. *Gastroenterology*, *59*(6), 921-929.
7. Pimentel, M. (2009). Review of rifaximin as treatment for SIBO and IBS. *Expert opinion on investigational drugs*, *18*(3), 349-358.
8. Chedid V. et al (2014). Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth. *Global Advances in Health and Medicine*, *3*(3), 16-24.
9. Siebecker A. Clinical Experience, SIBO specialty private practice. SIBO Center for Digestive Health at NCNM Clinic, Portland,Or. 2010-present. www.siboinfo.com.
10. Pound MW, May DB. Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions. *J Clin Pharm Ther*. 2005;30(3):291-295.
11. Drago, F., Ciccarese, G., Indemini, E., Savarino, V., & Parodi, A. (2018). Psoriasis and small intestine bacterial overgrowth. *International journal of dermatology*, *57*(1), 112-113.
12. Ling, Y., et al. (2018). Novel berberine derivatives: Design, synthesis, antimicrobial effects, and molecular docking studies. *Chinese journal of natural medicines*, *16*(10), 774-781.
13. Sandberg-Lewis, K. (2021, January 12). *Brain injuries and sibo*. National University of Natural Medicine. https://nunm.edu/2019/10/brain-injuries-and-sibo/.
14. De Martino, L., De, Feo, V, Formisano, C., Mignola, E., and Senatore, F. Chemical composition and antimicrobial activity of the essential oils from three chemotypes of Origanum vulgare L. ssp. hirtum (Link) Ietswaart growing wild in Campania (Southern Italy). Molecules. 2009;14(8):2735-2746.
15. Salem, A., & Roland, B. C. (2014). Small intestinal bacterial overgrowth (SIBO). *J Gastroint Dig Syst*, *4*(225), 2.
16. Sawka, M. N., Cheuvront, S. N., & Carter, R. (2005). Human water needs. *Nutrition reviews*, *63*(suppl_1), S30-S39.
17. Ruscio M. Biofilms- Presentation. 2017 SIBO Symposium, National University of Natural Medicine, June 3, 2016.
18. Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterol Hepatol (N Y). 2007;3(2):112-22.
19. Altman L.. Natural Approaches to Small Intestinal Bacterial *Overgrowth Introduction to SIBO, Diagnosis, Treatment Lecture*. 2020.
20. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol*. 2017;89:218-235.

◆

Samantha Davison is completing her Doctorate of Naturopathic Medicine at Bastyr University-California and has further completed her studies with the Institute of Functional Medicine. In 2015 she received her BSc in biology and pre-health sciences at the University of North Dakota, graduating *Magna Cum Laude*, in addition to playing NCAA Division I women's soccer. Samantha's core clinical interests include gastroenterology, women's health, fertility, oncology and environmental toxicity. She is passionate about root cause medicine while incorporating modern technology with nature cure. Samantha is dedicated to intentionally educating and empowering her patients throughout their health journey to optimum wellness."

Brad Case, DC, ND, received his Doctor of Chiropractic from the National College of Chiropractic (now NUHS) in 1993, He ran a holistic chiropractic practice in Monterey County, California for eighteen years. In 2007, he was published in the book *101 Great Ways to Improve Your Health*. In 2010, he published his own award-winning book, *Thugs, Drugs and the War on Bugs*. He then retired from practice and began his teaching career. He had his own radio show for a year and then taught anatomy and physiology at the undergrad level before entering into a three-year family practice residency at National University of Health Sciences. While completing his residency, he also acquired his ND degree, graduating *Summa Cum Laude* and valedictorian of his class.

He taught in the clinical sciences department at NUHS-Florida for two years as part of their Doctor of Chiropractic program. He now teaches naturopathic medicine at Bastyr University-California and is a clinical supervisor at Bastyr University Clinic in San Diego. While he claims no true specialty, GI health, physical medicine, AK/muscle testing, and whole food concentrates are mainstays of his practice life. He's also a veteran, serving in the Army National Guard for six years, retiring as a staff sergeant.

Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

Allergies, Asthma, and the Air We Breathe

Introduction

Most health care providers involved with direct patient care will report that the number of patients with allergies and asthma is increasing. Patients who have had these conditions for years report that their symptoms are getting worse. There seems to be a direct correlation with air that patients breathe and the development of allergies and asthma and the worsening of symptoms. It is important for physicians to understand the connection to chemicals in our air and allergies and asthma to help provide the best comprehensive and integrative treatment approach.

Allergies and Asthma

According to the American Academy of Allergy, Asthma and Immunology, https://www.aaaai.org, allergies and asthma can be due to a reaction to a drug, pet, food, pollen, trees, and grasses. The immune system responds to allergen by releasing histamine and chemical mediators that cause symptoms, an IgE mediated event.

Seasonal allergic rhinitis is most often caused by pollen as well as triggered by smoke and air pollution. Classic rhinitis symptoms include nasal congestion, rhinorrhea, sneezing and itching. Nonallergic rhinitis causes year-round symptoms, and this condition differs from allergic rhinitis because the immune system is not involved – not an IgE mediated event but can also be linked to air pollution, dust.[1]

Asthma presents as wheezing, shortness of breath, chest tightness or pain, and coughing. Asthma involves airway inflammation, intermittent airflow obstruction, and bronchial changes. Asthma can be triggered by allergies such as pet dander, dust mites, pollen, or mold. Non-allergic triggers include cold air or changes in the weather, dust, smoke, and air pollution. Asthma, like allergies, is an immune mediated condition. A trigger or antigen exposure leads to lymphocyte and cytokine response creating airway inflammation and asthma symptoms.[1]

Environmental toxicants can alter immune response and function in the body and are linked to immune-mediated diseases such as asthma and allergies. The pro-inflammatory immune response induced by exposure to some toxicants contributes to cellular changes involved in allergies and asthma. The immune system is composed of multiple organs and cells and an appropriate immune response involves the interaction of multiple cell types, immunoglobulin, and cytokines. These responses are altered by exposure to certain chemicals and/or toxicants creating immunotoxicity.[2]

Air Pollution

Outdoor air pollution is caused by solid and liquid particles and certain gases that are suspended in the air. These come from car and truck exhaust, factories, dust, pollen, mold spores, volcanoes, and wildfires. They are from fossil fuels – coal, petroleum and wood, car exhaust, factories, and wildfires – and form through chemical reactions in the air.[3] Outdoor air pollution consists of particulate matter (PM), ozone (O3), nitrogen dioxide (NO2), sulfur dioxide (SO2). arsenic, cadmium, lead and mercury, pesticides, and volatile organic compounds (VOCs).[3] Climate change is expected to create more outdoor air pollution. Warmer temperatures, change in precipitation patterns, higher ocean acidity, and reduced sea-ice cover will have effects on concentrations of toxicants in the environment. Higher temperatures mean more ozone air pollution, increase in pests and subsequent increase in pesticide use in agriculture.[4,5]

Indoor air is just as bad if not worse than outdoor air in some homes. Common chemicals and toxicants found include carbon monoxide (CO), formaldehyde from pressed wood products, lead, nitrogen dioxide (NO2) pesticides, radon, indoor particulate matter, tobacco smoke, toxic metals, solvents, and volatile organic compounds (solvents, PAHs). These come from the following:

- Fuel-burning combustion appliances
- Smoking indoors
- Fireplaces
- Building materials and furnishings
- Deteriorated asbestos-containing insulation
- Newly installed flooring, upholstery or carpet
- Cabinetry or furniture made of certain pressed wood products
- Products for household cleaning and maintenance, personal care, or hobbies
- Central heating and cooling systems and humidification devices.[6]

Outdoor sources such as radon, pesticides, and outdoor air pollution also pollute indoor air.

The Connection

To help emphasize the link between toxicants present in air pollution and asthma and allergies, a few examples are outlined here.

Polyaromatic hydrocarbons (PAHs) are created when organic materials are burning in high temperatures. PAHs can react with ultraviolet light and other pollutants (e.g., ozone, nitrogen oxides and nitrate radicals). They enter the lungs causing inflammation and affecting respiratory health. There is an association between exposure to PAHs, concentrations of air pollutants, and allergic and non-allergic asthma, including increased symptoms of asthma, risk of asthma exacerbations, and decreased lung function.[7]

The use of insecticides and pesticides around the home is linked to allergies and asthma. A large Canadian cohort study found an association between exposure to organophosphates and reduced lung function in the adult general population and pyrethroids and reduced lung function in children and adolescents.[7]

Mercury from coal burning powerplants can travel long distances in the air and end up in both children and adults. Blood concentrations of mercury from air pollution in children are associated with allergies, asthma and elevated IgE.[7]

Cadmium is present in cigarette smoke and is also released from natural sources such as volcanos and forest fires. Studies show that urinary elevations of cadmium is linked with asthma. The blood level of cadmium had an association with self-reported asthma and allergies.[7] Chronic exposures to arsenic and lead is also associated with asthma and allergies.[7]

Volatile organic compounds (e.g., solvents, formaldehyde) are present in outdoor and indoor air. Exposure is linked to allergies, asthma, airway inflammation, respiratory symptoms, oxidative stress, and decreased lung function.[8]

Avoidance

A discussion of avoiding toxicants present in air pollution is challenging since it is difficult to control outdoor air. Many chemicals in outdoor air are determined by the size of the city where someone lives, number of cars in the road, air traffic, nearby industry, and agriculture, and is dependent on temperature, precipitation, and many other factors. So, we do the best we can with avoidance and improving our air quality. According to the Environmental Protection Agency and the American Lung Association, there are ways to help improve air quality both outdoors and indoors.

Some ways to help improve outdoor air include the following:

- Commit to one day a week to carpool or public transportation
- Refill your gas after dark.
- Instead of idling at a drive-through, park your car, and go inside.
- Join your company's travel reduction program, ride-share system, or light rail pass.
- On No Burn Days, choose not to burn a fire in your fireplace or backyard.
- Don't use pesticides around the yard
- Stop smoking anything and vaping
- Don't grill meat and fish at high temperatures

Some ways to help improve indoor air include:

- HEPA air filtration in the bedroom
- Stop smoking anything or vaping
- Change cleaning and personal care products to eliminate VOCs
- Don't use non-stick pans to eliminate PFOS
- No solvent based or fragranced products in the home
- Use non-toxic mattresses, furniture, carpeting and paint
- Test your home for radon

Summary

The evidence is clear that toxicants from air pollution play a role in allergies and asthma symptoms. Physicians should always be aware of the air quality where they practice and screen patients for chemical exposure. This type of approach to health addresses the root cause of allergies and asthma. Educating patients on avoidance and ways to improve air quality is key to prevention and management of asthma and allergies.

References

1. AAAAI | American Academy of Allergy, Asthma & Immunology. Accessed 8/15/2022
2. Duramad P, Holland NT. Biomarkers of immunotoxicity for environmental and public health research. *Int J Environ Res Public Health.* 2011 May;8(5):1388-401.
3. World Health organization. Ambient Outdoor air pollution. Sept 2021. https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health. Accessed 8/13/2022
4. Balbus JM, et al. Implications of global climate change for the assessment and management of human health risks of chemicals in the natural environment. *Environ. Toxicol. Chem.* 2013;32:62–78.
5. Moe SJ, et al. Combined and interactive effects of global climate change and toxicants on populations and communities. *Environ Toxicol Chem.* 2013 Jan;32(1):49-61.
6. Environmental protection agency. Introduction to air quality. Dec 16, 2021. https://www.epa.gov/indoor-air-quality-iaq/introduction-indoor-air-quality. Accessed 8/12/2022
7. Mattila T, et al. Scoping Review-The Association between Asthma and Environmental Chemicals. *Int J Environ Res Public Health.* 2021 Feb 1;18(3):1323.
8. Kwon JW, Park HW, Kim WJ, Kim MG, Lee SJ. Exposure to volatile organic compounds and airway inflammation. *Environ Health.* 2018 Aug 7;17(1):65

Dr. Marianne Marchese is the author of the bestselling book *8 Weeks to Women's Wellness* about the environmental links to women's health and how to mitigate the effects from toxicants. She maintains private practice in Phoenix, Arizona, and is adjunct faculty at SCNM, teaching both environmental medicine and gynecology. She lectures throughout the US and Canada on integrative medicine topics. Dr. Marchese recently helped develop three supplements for Priority One Vitamins. She runs an annual women's health seminar for physicians in Scottsdale, Arizona. www.drmarchese.com

◆

Pediatric Pearls

by Michelle Perro, MD

A Painless Approach to Pain in Children

Teething. Otitis media. Bumps and bruises. A fall from a skate board. These are just a few of the many types of events that may befall our children and can cause significant discomfort. Any parent who's been up with a child all night with a raging ear infection knows how uncomfortable that experience may be for both the child and the parent! Adults presenting to an emergency department with otitis media often request morphine, so there is no doubt to the level of pain one might experience with common childhood conditions such as otitis.

The "Pediatric Pearls" reader may now recognize from past publications that children are not mini-adults, and their physiology, biology, and how they experience the world can vastly differ from that of grown-ups. For the non-verbal child, pain experiences may be more heightened due to their inability to express their discomfort (not because they are not having pain). Managing pain in children is an important topic, and I will provide some of my favorite insights and tools in helping practitioners navigate the array of childhood pain complaints.

A Pain Scale

Of interest, pain scales for children have been around for decades and were developed in 1983.[1] The goal was to develop a method on how child could effectively communicate about their pain. Children respond well to facial expressions as well as play. (Hopefully, several years of masking will not have permanently altered our children's ability to communicate via facial expressions!)

Studies have shown that these methods show a strong correlation and validation from children self-reporting and can be easily learned and utilized in clinical settings.[2] When faced with a child who is non-verbal or reticent to talk, the pain scale can help them communicate their degree of discomfort.

Homeopathy to the Rescue

Painful conditions respond extremely well to homeopathic remedies. When conditions are acute, they are more easily "repertorized" and the correct homeopathic prescription can be selected. (A homeopathic repertory is a comprehensive compilation of the symptoms for each remedy; this is an index for the Materia Medica. A free online homeopathic repertory can be found here: www.oorep.com.) Some of the more difficult aspects of homeopathic prescribing may include which remedy to choose, how often they should be taken, how long they are administered, and what to do if the remedy doesn't seem to be working.

Every provider that works with children can purchase an affordable copy of *Homeopathic Medicine for Children and Infants,* by Dana Ullman.[3] Now in print for over three decades,

this guide enables clinicians and parents alike to choose the best remedy for the condition being treated. If after several doses no response is noted, I will often relook at the child's case to see if some important features were missed and try another remedy. If a partial response is noted, I may increase the potency of the remedy or dose more frequently. Occasionally, when a partial response is elicited, you might be close in the selection of the correct remedy, but not spot on.

Acute conditions often require more frequent dosing, every hour for example, and then tapering down to 2 to 3 times a day as the child's condition improves. When the child is approximately 75% better, I begin to taper off and stop the remedy.

The beauty of the remedies is that they are made with sugar (often lactose or sucrose), which can easily reduce the stress of administration. (Wear an apron when trying to get a child to take a yucky tasting medicine!) They can be sucked on or chewed or dissolved in a little filtered water for infants. I try to administer remedies away from food for at least 15 minutes, when possible, in order to maximize their efficacy.

The following are some of my typical cases demonstrating the ease and effectiveness of administration in painful situations.

Susie and Teething

Susie is a 6-month-old infant teething all four central incisors simultaneously. She has been inconsolable, screaming for hours on end. The parents administered acetaminophen without success and her icy teething ring helped somewhat. Her stools were loose and greenish.

Chamomilla is the first medicine to try and was confirmed by her symptoms. I usually start with the 30c potency since they are easily obtained in health food stores and that potency is often indicated for physical complaints. After the first dose, Susie stopped crying for the first time in days and by 24 hours later, she no longer required the remedy. Other considered choices were C*alcarea carbonicum*, *Belladonna,* and a combination teething remedy (a blend of several remedies in low potencies such as 6X, 12X or 30X) called "teething tabs," which can be purchased in any health food store.[4]

Of note, in 2010, the FDA issued a warning to consumers to stop taking these teething tablets because it contained belladonna. This advisory was reissued in 2016 and the FDA has taken a strong stance against homeopathy.[5] It is important to note that remedies are highly diluted and are only energetic in nature. Their potential to cause harm is minuscule, especially in comparison to the extensive list of side-effects from drugs. The basic principle of homeopathy is "like cures like" and providers try and match the vibrational energy of the patient's complaints with the energy of the remedy. In 30 years of homeopathic practice, I've never seen a negative outcome from a remedy. The same cannot be said for allopathic pharmaceuticals.

Jarod and a Skateboarding Injury

Jarod is a 16-year-old teen who received a new skateboard for his birthday. His first attempt at an "airwalk"[6] landed him with a sprained ankle, road rashes on both lower legs, and a crushed ego. The following remedies were given for his painful ankle and for his abraded skin: ➤

➤

- *Arnica* 200c – The best remedy for injury, particularly after the initial shock and trauma. It can also assist in the repair of damaged blood vessels and clear bruising. The 200c potency was chosen since Jarod was in serious denial about his injury, stating he "was just fine." The higher potencies can help both the physical and mental state, and *Arnica* is an excellent choice from the "shock" of trauma, aiding in clearing his mental state.
- *Calendula* 30c – Jarod was given both the pellets and the topical ointment. This remedy can work as an antiseptic, astringent, and can control bleeding. It is important to avoid use of the products made with gels (alcohols) which can burn abraded skin. I usually recommend creams since ointments can lead to increased moisture and infection with deep wounds. Since these wounds were superficial but extensive, I opted for the ointment, steering clear from ointments derived from petroleum products.
- Curcumin – One of my favorite go-tos for its antimicrobial, anti-inflammatory and wound healing ability.[7.] Of note, curcumin can stimulate the production of growth factors involved in the wound healing process.

Jarod was back on his board after several days and his ankle and abrasions were healing nicely. I advised him to hold off on the airwalk for now and just go for the 180. (Smile)

Monique and Needle Phobia

Ten-year-old Monique needed a venipuncture for routine lab work. She was severely needle phobic due to a past trauma when she was a toddler. Despite every type of psychology (and bribes) by her parents, the phlebotomists refused to draw her blood after being bitten and hit. (Yes, welcome to the world of the pediatric blood draw!) A hypnotist was being considered to help resolve her past experience.

This situation required a bit more finesse but is still doable even for the homeopathic novice. The following plan was devised which seemed to do the trick:

- *Gelsemium* 200c – I have found that this remedy is extremely useful in children who have anxiety from a possible painful procedure, performance anxiety, or competition. While this is not the exact prescribing of this remedy, it can help reduce the anxiety of a blood draw.
- Topical EMLA or lidocaine anesthetic – A topical approach to ease the pain of a draw, applied 1/2 hour prior to the venipuncture. In the wary and precocious 10 y/o, I have them try this medication and then pinch themselves in the area prior. This assures the child that indeed there is a numbing effect. Lidocaine patches can be purchased over-the-counter in any drug store. I recommend cutting a portion of the patch depending on the size of the child and placing it in several areas where there are accessible veins before the procedure, such as the antecubital fossae.[8]
- *Bach's Rescue Remedy* – Homeopathic flower remedies (Rock Rose, Impatiens, Clematis, Star of Bethlehem, and Cherry Plum) were developed by Dr. Edward Bach more than 80 years ago. They are gentle, effective remedies for stress-related events.[9] (They are also available for the family pet!)

What About Acetaminophen and Ibuprofen?

Acetaminophen in its present form has been around since 1909. However, the McNeil corporation launched the children's formulation in 1955. For nearly seven decades, acetaminophen has been an over-the-counter analgesic and anti-pyretic, touting efficacy and safety for our kids. It's also routinely given in many pediatric clinics prior to a vaccination to prevent pain/fever. However, this dogma began to be questioned when a 2019 study reported that exposure to acetaminophen during pregnancy could increase the child's risk for ADHD and ASD.[10] Additional concerns were previously brought to light in 2005, where a study reported that asthma morbidity was exacerbated by acetaminophen via a reduction in intracellular glutathione.[11] Acetaminophen is of questionable safety for children and should be avoided.

In my clinical experience, ibuprofen provides superior pain relief as compared to other analgesics. In a meta-analysis of over 1,000 patients, a study recently published in 2021 showed that ibuprofen had a lowered incidence of adverse effects as compared to other analgesics.[12] However, for musculoskeletal injuries, ibuprofen alone may not be adequate, but the addition of codeine, codeine/acetaminophen or oxycodone did not improve the analgesia and led to more adverse events. This is an excellent opportunity to offer homeopathic remedies alongside ibuprofen when more pain management is required.

Despite the safety profile of this non-steroidal anti-inflammatory for short-term usage, the excipient list in the children's ibuprofen liquid suspension is a who's who of toxic ingredients, including acetic acid, artificial flavor, butylated hydroxytoluene, carboxymethylcellulose sodium, citric acid monohydrate, edetate disodium, FD&C blue no.1, FD&C red no. 40, glycerin, microcrystalline cellulose, polysorbate 80, propylene glycol, purified water, sodium benzoate, sorbitol solution, sucrose, and xanthan gum. A dye-free preparation is now available, eliminating some of the toxic ingredients.

Pain management in kids is a priority, and every practitioner should be savvy on how to manage and resolve discomfort in children. How we approach their "owies" can be done compassionately, age-appropriately, and without toxicity! The use of homeopathic remedies for pain in kids can be a game changer. Emotional pain will be addressed in a future *Pearls!*

References

1. www.wongbakerfaces.org
2. Tsze, D, et al. Validation of self-report pain scales in children. Multicenter Study; *Pediatrics*. 2013 Oct;132(4):e971-9.
3. Ullman, D. Homeopathic Medicine for Children and Infants; *Tarcher Perigee*; Sept. 8, 1992.
4. https://hylands.com/products/hylands-baby-oral-pain-relief
5. https://www.fda.gov/consumers/consumer-updates/hylands-homeopathic-teething-tablets-questions-and-answers
6. https://www.surfertoday.com/skateboarding/the-glossary-of-skateboarding-terms-and-slang
7. Tejada, S., et al. Wound Healing Effects of Curcumin: A Short Review; *Pharm Biotechnol;*.2016;17(11):1002-7
8. https://www.drugs.com/pro/lidocaine-patch.html
9. https://www.rescueremedy.com/en-us/range/all-products/rescue-remedy-dropper/
10. Ji, Y, et al. Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA* Psychiatry; 2020 Feb 1;77(2):180-189.
11. Dimova, S., et al. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro; *Int J Biochem Cell Biol*; 2005 Aug;37(8):1727-37.
12. Jin, J., et al. Efficacy and safety of ibuprofen in children with musculoskeletal injuries: *Medicine*; July 02, 2021; vol 100; Issue 26; p 326516.

◆

The Lobay Viewpoint

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

Zinc, Antiviral Effects, and the Common Cold

Zinc is vitally important in human health. Most nutritionally oriented health care professionals would probably recommend zinc in the treatment of the common cold. Some important questions regarding what dose, how often, and what formulation should be addressed to ensure a standard of care and practice is met. A review of the literature gives some insight into what practitioners can effectively, scientifically, and safely recommend to patients.

Zinc is a silvery, white metal that has an atomic number of 30 and an atomic mass of 65. It is a major constituent of the American penny, and it is also a minor constituent of the alloy brass. The great Swiss physician Paracelsus integrated the necessity of micronutrient chemistry into human health in the 16th century. He referred to the mineral by the German word "zinke" to reflect its jagged or pointed appearance of its crystals.[1]

Zinc is the second most abundant trace mineral in the human body after iron. The adult human body contains between 2000 to 3000 milligrams of elemental zinc. Ninety percent is stored in muscles and bones. Zinc in the serum is primarily protein bound to albumin, globulin, and transferrin. Thirty to 40% of zinc is concentrated within the cell nucleus, 50% in the cytosol, and 10% is in the cell membrane.[2]

One of the main intracellular proteins to sequester zinc is the cysteine-rich metallothionein. There are four different isoforms of metallothionein. There are at least seven different cysteine binding sites per molecule. Methallothionein releases zinc in response to oxidative stress or viral infection. The increased release of free zinc is mediated by cellular cytokines and other cell signaling chemicals. The free zinc interacts with various aspects of the immune system and the pathogen. Increased zinc decreases NF-KB (nuclear factor kappa beta), which helps to decrease inflammation.[2,3]

Zinc is estimated to be involved in 10% of all protein synthesis reactions in the human body. It is believed to be involved in 750 different transcription factors that code for various proteins. It is involved in different aspects of DNA synthesis and RNA transcription and translation. Zinc is also estimated to be involved in 2000 different enzymatic reactions. It is involved in multiple aspects of growth and development. It is also involved in multiple aspects of innate and acquired immune function.[3]

It is estimated that 17% to 20% of the world's population or 1.6 billion people have some degree of zinc deficiency. Zinc deficiency can impact proper growth and development. Zinc deficiency is also associated with mild to severe immune deficits.[3]

The RDA for zinc was established in 1974 and set at 15 milligrams per day. The revised RDA for zinc is currently 8 milligrams for adult females and 11 milligrams for adult men. The highest food source of zinc by a large margin is oysters.[4]

Zinc has demonstrated to have multiple effects on both innate and acquired immunity. It affects both production and activity of B and T lymphocytes, NK (natural killer cells), neutrophils, monocytes, macrophages, cytokine production, chemotaxis, phagocytosis, and intracellular destruction of pathogens. Zinc has shown to stabilize membrane structure and help prevent pathogen invasion. Zinc also reduces cellular oxidative stress and functions as an antioxidant. It should be emphasized that the effects of zinc on the immune system are exceedingly complex and still relatively poorly understood.[4,5]

Zinc has demonstrated direct antiviral effects. Zinc has demonstrated varying degrees of antiviral activity against herpes, picorna, influenza, corona, metapneumo, flavidae, toga, roto, HIV, and papilloma viruses. Two primary antiviral mechanisms have been demonstrated. The first is protease inhibition. Proteases are a group of enzymes that function to cleave larger nascent viral proteins into smaller active proteins. This step is necessary for viral reproduction. The discovery of

➤

➤

modern pharmaceutical antiviral medicine frequently targets viral protease inhibition. Zinc functions as a natural viral protease inhibitor via direction inhibition of the protease active site.

The second mechanism of antiviral activity is through inhibition of polymerase activity. Polymerase is an enzyme that synthesizes copies of viral DNA or RNA. The process of creating new copies is called transcription. The DNA is transcribed to RNA, which is ultimately translated to viral protein. Zinc directly inhibits viral polymerase from creating new copies of either genetic material. As mentioned earlier, another possible third mechanism of antiviral activity is at the cell membrane level, where zinc might help prevent viral uptake.[3,4,5]

One meta-analysis compared zinc acetate lozenges to zinc gluconate lozenges in the treatment of the common cold and to examine dose dependent effects. Seven randomized placebo-controlled studies involving 575 participants were included. Three trials with zinc acetate showed a 40% decrease in the duration of cold in treated patients. Four trials with zinc gluconate showed a 28% decrease in the duration of cold in treated patients. Five trials involved an elemental zinc dose between 80 to 92 milligrams per day and showed a 33% decrease in the duration of cold in treated patients. Two trials involved an elemental dose between 192 and 207 milligrams per day and showed a 35% decrease in the duration of colds in treated patients. The difference between the high and lower doses of zinc in alleviating cold duration was not statistically significant. Additionally, lozenge composition and dosage schedule were deemed important.[6]

Another randomized placebo-controlled trial involving 100 Cleveland Clinic employees with colds showed an improvement in the zinc-treated group. Half the sick employees took a zinc lozenge supplying 13.3 milligrams of elemental zinc every two hours as long as they had symptoms. The other half took placebo. Cold symptoms lasted an average of 4.4 days in the zinc-treated group compared to 7.6 days in the placebo group.[7]

Zinc supplementation potentially reduced cold duration by an average of 2.25 days in a review of 10 studies.[8]

A Cochrane review of zinc supplementation for both therapeutic and preventive outcomes was performed in 2011. A meta-analysis of 13 randomized placebo-controlled trials helped to shed light on the benefits of zinc in the common cold. Pooled data revealed that the elemental zinc dosage ranged from 10 to 24 milligrams per lozenge, taken every one to four hours for a duration of three to seven days. In 11 of 13 studies, zinc supplementation was initiated within 24 hours after the onset of symptoms. In two of 13 studies, zinc was initiated within 48 hours after the first onset of symptoms. In six of 13 studies, the average cold was improved by 0.97 days compared to placebo. The severity of symptoms with zinc supplementation was 0.39 when compared to placebo. Side effects of bad taste and nausea were noticed at an odds ratio of 2.64 and 2.15 with zinc supplementation respectively. An additional two studies on the use of zinc to prevent the occurrence and severity of common cold was reviewed. There was some evidence the preventive use of zinc for five months helped to reduce absenteeism and prescriptions in school aged children.[9,10]

The ingestion of large doses of zinc for prolonged periods of time suppresses the immune system in much the same way as zinc deficiency. Decreased NK activity, decreased neutrophilic phagocytosis, decreased monocyte function, and increased B cell apoptosis were observed. Additionally, an increase in pro-inflammatory cytokines like IL1, IL6, and interferon were noted with large zinc doses. In one study of 11 healthy adult subjects who took 150 milligrams of elemental zinc twice per day for six weeks showed a decrease in lymphocyte stimulation to phytohemagglutinin and a decrease in chemotaxis and phagocytosis by polymorphonuclear leukocytes. Another study involved fifteen participants (70 years and older), who took 220 milligrams of zinc sulphate twice per day for one month. An increase in T-lymphocyte activity, delayed hypersensitivity reaction, and increased IgG antibody response was noted. Other studies show that the use of elemental zinc in doses that exceeds 40 milligrams per day does not have deleterious effects on the immune system when used for less than two weeks. Large doses of zinc cause transient nausea in many people. Elemental doses of zinc between 225 and 450 milligrams can cause vomiting in many individuals.[11,12]

There are several important factors to consider beside the elemental zinc dosage when directed at the treatment and prevention of the common cold. First is the solubility of the zinc molecule used. Second is the degree of ionization of the zinc compound. The better the solubility, the higher the degree of ionization of the zinc compound, producing a larger concentration of cationic positive 2 charged elemental free

zinc ions. This appears to better produce a local effect at the site of viral infection and inhibit pathogenic inflammation created there. It is plausible that the local effects of zinc are primarily directly antiviral via one of the two and possible three mechanisms mentioned earlier. An upregulation of the immune system and white blood cells can also occur but is realistically a little slower to develop than the immediate antiviral effects. Taken together, direct antiviral activity and the immune enhancement effects both contribute to the use of zinc in the treatment of the common cold. It is further worth mentioning that the types of zinc compounds with the highest degree of solubility and ionization are indeed the type of zinc compounds that reveal the best effects in treatment of the common cold. Zinc acetate, zinc gluconate, and zinc sulphate are among these compounds. Zinc citrate, zinc oxide and other chelated forms of zinc are less soluble.[1-5]

Zinc may be effective in the prevention and treatment of the common cold. Highly soluble and ionizable forms of zinc in the forms of lozenges and liquids are probably the best compounds to use. The earlier zinc supplementation is started the better. Within 48 hours, but probably within 24 hours of the first onset of cold symptoms is best. An elemental dose between 5 and 25 milligrams of zinc can be recommended. Repeated dosing every one to four waking hours is best. Taken for a minimum of three days and up to 7 to 14 days or when symptoms disappear is reasonable. Side effects of nausea and upset stomach are common and can occur. Reducing the dose and following the intake of food may help. Larger daily doses beyond 75 to 150 milligrams of elemental zinc are not recommended for most people. Taking high doses beyond two weeks of the first onset of cold symptoms is not recommended. Of course, it is advised to consult a licensed health care professional for specific dosing and treatment instructions. Also, if pregnant, nursing, or under the age of 12, consult a licensed health care practitioner for specific guidelines.

References

1. Krezel M and Maret W. The biological inorganic chemistry of zinc ions. *Archives of Biochemistry and Biophysics*. 2016 December 1; vol 611:3-19.
2. Plum LM et al. The Essential Toxin: Impact of Zinc on Human Health. *Int J Environ Res Public Health*. 2010 Apr; 7(4):1342–1365.
3. Read SA et al. The Role of Zinc in Antiviral Immunity. *Adv Nutr*. 2019 Jul; 10(4):696-710.
4. Prasad AS. Zinc in Human Health: Effect of Zinc on Immune Cells. *Mol Med.* 2008 May-Jun; 14(5-6): 53-357.
5. Ibs KH and Rink L. Zinc-Altered Immune function. *Journal of Nutrition*. May 2003; volume 133 issue 5:1452S-1456S.
6. Hemila H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. *JRSM Open*. 2017 May; 8(5): 2054270417694291.
7. Mossad SB et al. Zinc gluconate lozenges for treating the common cold. A randomized, double-blind, placebo-controlled study. *Ann Intern Med*. 1996 Jul 15; 125(2):81-88.
8. Wang MX et al. Zinc Supplementation Reduces Common Cold Duration among Healthy Adults: A Systematic Review of Randomized Controlled Trials with Micronutrients Supplementation. *Am J Trop Med Hyg.* 2020 Jul; 103(1):86-99.
9. Rao G and Rowland K. Zinc for the common cold—not if, but when. *J Fam Pract*. 2011 Nov; 60(11):669-671.
10. Singh M and Das RR. Zinc for the Common Cold. *Cochrane Database Syst Rev*. 2011 Feb 16;(2):CD001364.
11. Chandra RK. Excessive Intake of Zinc Impairs Immune Responses. *JAMA*. 1984; 252(11):1443-1446.
12. Duchateau J et al. Beneficial effects of oral zinc supplementation on the immune response of old people. *Am J Med. Clinical Trial*. 1981 May; 70(5):1001-4.

◆

CALENDAR

OCTOBER 1: LDN 2022 VIRTUAL ON-DEMAND CONFERENCE BEGINS online. Available for 12 months. CONTACT: https://ldnresearchtrust.org/ldn-2022-conference

DECEMBER 9-10: INTERNATIONAL CONFERENCE ON PREVENTIVE AND INTEGRATIVE MEDICINE in New York City, New York. CONTACT: https://waset.org/preventive-medicine-and-integrative-medicine-conference-in-december-2022-in-new-york

DECEMBER 9-11: A4M presents LONGEVITY FEST 2022 in Las Vegas, Nevada. CONTACT: https://www.a4m.com/longevity-fest-2022.html

DECEMBER 9-11: A4M/MMI PEPTIDE THERAPY CERTIFICATION in Las Vegas, Nevada. CONTACT: https://www.a4m.com/peptides-ii-a4m-december-2022.html

DECEMBER 9-11: A4M/MMI ADVANCED ENDOCRINOLOGY: THE HORMONAL SYMPHONY (Module 1) in Las Vegas, Nevada. CONTACT: https://www.a4m.com/module-i-a4m-december-2022.html

DECEMBER 9-11: A4M/MMI TRIADS: A SYSTEMS BIOLOGY APPROACH (Module V) in Las Vegas, Nevada. CONTACT: https://www.a4m.com/module-i-a4m-december-2022.html

DECEMBER 10: PSYCHIATRY REDEFINED presents EFFECTIVE SUPPLEMENT PROTOCOLS IN CLINICAL PRACTICE IN FUNCTIONAL PSYCHIATRY with James Greenblatt, MD. Online. CONTACT: https://www.psychiatryredefined.org/supplement-protocols-for-clinical-practice-seminar/

JANUARY 28-29, 2023: INTERNATIONAL CONFERENCE ON TRADITIONAL MEDICINE AND HERBS in New York City, New York. CONTACT: https://waset.org/traditional-medicine-and-herbs-conference-in-january-2023-in-new-york

FEBRUARY 15-19: 16th ANNUAL INTERNATIONAL INSULIN POTENTIATION THERAPY CONFERENCE in Mexico. CONTACT: https://www.eventbrite.com/e/16th-international-ipt-conference-tickets-404946615227

FEBRUARY 23-25: INTEGRATIVE HEALTHCARE SYMPOSIUM in New York City, New York. CONTACT: https://www.ihsymposium.com/

FEBRUARY 27-MARCH 3: INTEGRATIVE MEDICINE AND HEALTH SYMPOSIUM in Chicago, Illinois. CONTACT: https://www.consortiummeeting.org/#home

MARCH 3-5: EXPLORING COMPLEX, CHRONIC ILLNESS THROUGH THE LENS OF TRUE HEALING online. CONTACT: https://forumforintegrativemedicine.org/

MARCH 24-26: JOINT AMERICAN HOMEOPATHY CONFERENCE in San Antonio, Texas. CONTACT: https://www.jahc.info/

APRIL 24-25: INTERNATIONAL CONFERENCE ON INTEGRATIVE MEDICINE AND NUTRITION in New York City, New York. CONTACT: https://waset.org/integrative-medicine-and-nutrition-conference-in-april-2023-in-new-york

APRIL 27-30: ACUPUNCTURE MERIDIAN ASSESSMENT FOR DOCTORS, DENTISTS, AND HEALTH PROFESSIONALS in St. Louis, Missouri. Detecting parasites, dental & fungal problems with Simon Yu, MD. CONTACT: https://preventionandhealing.com/training/

MAY 18-20: A4M 31st ANNUAL SPRING CONGRESS - INFLAMMATION: THE COMMON PATHWAY TO DISEASE in Orlando, Florida. CONTACT: https://www.a4m.com/the-fire-inside-2023.html

JUNE 1-3: INSTITUTE FOR FUNCTIONAL MEDICINE ANNUAL INTERNATIONAL CONGRESS in Orlando, Florida. CONTACT: https://discover.ifm.org/aic-2023

JUNE 2-4: SASKATCHEWAN ASSOCIATION OF NATUROPATHIC DOCTORS HEALING SKIES CONFERENCE in Saskatoon, Saskatchewan, Canada. CONTACT: http://www.sasknds.com/healing-skies-conference.html

JUNE 16-18: 5th INTERNATIONAL HOMEOPATHY RESEARCH in London, United Kingdom. CONTACT: https://www.hri-research.org/2022/07/hri-london-2023-save-the-date/

JULY 20-22: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS CONVENTION in Phoenix, Arizona. CONTACT: https://naturopathic.org/

AUGUST 24-27: ACUPUNCTURE MERIDIAN ASSESSMENT FOR DOCTORS, DENTISTS, AND HEALTH PROFESSIONALS in St. Louis, Missouri. Detecting parasites, dental & fungal problems with Simon Yu, MD. CONTACT: https://preventionandhealing.com/training/

◆

Classified Advertising

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
drjacobschor1@msn.com

Does Exercise Intensity Matter?

My dog Ruby and I went for an excellent walk this morning. Starting at the road junction we came back toward the cabin through what we call the black forest, across the creek, almost up to the clearing, but we then veered east onto the old logging road and followed it along until it petered out. We had to muddle about a bit until I could find the trail that veers north to what I call Alex's corner. Snow and deadfall have so camouflaged this trail that there were moments of uncertainty along the way. What was an obvious path last summer is far less clear now beneath snow. When I chanced across a rock 'duck' at a sharp turn I promised myself to never make fun of my wife again for leaving these trail markers when she walks in the woods. From the corner, the dog and I bushwhacked uphill to what is locally known as Moser's Summit, a hilltop clearing with a bit of a view. From there, we followed the ridge down to the town boundary line and then back home. All in all, a most excellent walk through the woods. I confess it was a bit of a challenge making it uphill to the summit; I had to pause a few times to catch my breath least I start to sweat. Sweating is tolerable in the summer but not in the winter when the temperature is low.

I describe this activity in the hope that you can sense the pleasure I experienced going for this morning tramp in the woods. I am trying to understand the current enthusiasm some people have about what is called high intensity interval training (HIIT). An article by Gretchen Reynolds has been posted on the *New York Times* website for several weeks that suggests "Including high-intensity training in your workouts provided better protection against premature death than moderate workouts alone."[1]

It surprises me that the *Times*, which prides itself on accurate reporting, has left her opinions in place for so long. It's not true. The article describes a prospective trial by Dorthe Stensvold et al published in October 2020, which compared several exercise regimes and their impact on mortality in older adults. The researchers began this ambitious trial in Trondheim, Norway, in 2012 by inviting all of the city's older inhabitants (aged 70 to 77) to participate. Although about 5,000 declined their invitation, 1,567 did sign up. These volunteers were randomized into three groups and were assigned to three different exercise protocols. The control group (n=780) were instructed to follow the Norwegian National Guidelines for Physical Activity, which prescribe 30 minutes of moderate level physical activity almost every day. The other 800 participants were split into two groups of 400. They also followed the national guidelines but were asked to substitute two of their five weekly exercise sessions with one of two experimental regimes. One group (n=400) added two sessions of moderate intensity continuous training (MICT) while the other experimental group (n=400) performed high intensity interval training (HIIT).

The HIIT sessions consisted of a 10-minute warm-up followed by four 4-minute intervals at about 90% of peak heart rate, while the MICT sessions consisted of 50 minutes of continuous work at about 70% of peak heart rate. All-cause mortality was the primary outcome assessed; the researchers compared how many people in each exercise group died.

The mortality rate for all three groups together was 4.6% (n=72). The control group following national guidelines had a slightly higher than average mortality at 4.7% (n=37). The combined MICT and HIIT groups had a slightly lower mortality at 4.5% (n=35). However, the MICT group alone had the seeming highest mortality at 5.9% (n=23) and the HIIT group the lowest at 3.0% (n=12).[2]

I write "seeming" because these differences between groups did not reach statistical significance. Perhaps we should pause a moment to review a few things I may have forgotten over the years.

A hazard ratio (HR) is a measure of an effect on an outcome of interest over time. Hazard ratio is often used for reporting in time-to-event analysis or survival analysis. Hazard Ratio = Hazard in the intervention group ÷ Hazard in the control group. In these exercise studies, HR represents the probability that an individual would die at a particular given point in time after the intervention.

A confidence interval (CI) is the range of values that is likely to include the true population value and is used to measure the precision of the study's estimate. The narrower the confidence interval, the more precise the estimate. If the confidence interval

➤

➤

includes 1.0, then the hazard ratio is not considered statistically significant.[3]

This is why we include all those tedious numbers in these articles that define confidence intervals in the data; it's because this communicates whether the numbers are meaningful or not.

Remember, confidence intervals for hazard ratios that cross the 1.0 line lack statistical significance. HRs less than 1.0 mean a lower risk of something happening – in these studies, dying. HR greater than 1.0 means a greater risk of something happening. HRs that include values above and below 1.0 are not statistically significant and are not considered meaningful; we don't count them as real. Sometimes when they narrowly miss significance, researchers will report them as trends, but that expression is a euphemism, a way to not mention the lack of significance.

When Stensvold et al examined the MICT and HIIT groups separately, comparing them with the control group, HIIT was associated with a 1.7% risk reduction (hazard ratio 0.63, 95% confidence interval 0.33 to 1.20) while the MICT group had a 1.2% (1.24, 0.73 to 2.10) increase in risk. But being scholarly people, let's look at the confidence intervals; they all include 1.0. Thus, these changes were trends but not statistically significant differences.

The study authors accurately describe their findings: "No differences were observed in cardiovascular disease, cancer, or related events between the control group and the combined MICT and HIIT group, or any effect of exercise intensity."

That statistical non-significance did not stop Reynolds and other news outlets from reporting the results as if they were significant. Reynolds in her *Times* article interpreted these null findings to mean "The men and women in the high-intensity-intervals group were about 2 percent less likely to have died than those in the control group, and 3 percent less likely to die than anyone in the longer, moderate-exercise group."[1] Except that we know that these slight differences don't count.

A number of factors may account for Stensvold not finding significant differences between groups. The purpose of the experiment was hard to hide and some of the study participants not in the HIIT group opted to mimic the HIIT routine that the researchers expected to be most beneficial. In fact, about 20% of those in the control group and 13% of the MICT group added HIIT workouts to their regimes. On the other hand, HIIT is not easy-to-follow long term and about half of the HIIT group gave up trying to keep up with their assigned routine. This muddied the data for sure.

Probably as a result of the nature of the invitation to participate in the study, all of the study participants exercised more than average Norwegians do. Those who didn't want to exercise didn't volunteer. Only about a third of older adults in Norway meet the national guideline.[4] All three study groups did better than this, with 35-45% meeting the guidelines at the study start. (In comparison, less than 5% of American adults exercise 30 minutes or more daily.[5]) Seeking volunteers for this study may have created a cohort of such highly active and fit people that slight variations in exercise had little effect.

At baseline, 80% of the participants were already exercising regularly. There may just be no difference in the long-term effects of these workouts. That's the simplest interpretation of the data. We should note that the predicted death rate for adults in Norway of the same ages as this study's participants was 10%, more than twice of what was seen for the individuals in this study.[6] The most likely explanation for not finding a significant difference between exercise groups may simply be that the type of exercise regime one follows doesn't matter that much.

There is another method to measure exercise's impact on health, that is worth considering because we do not need to wait until study participants die in order to assess outcome. We can look at abdominal adiposity, or in simpler words, excess belly fat. This measurement is clearly associated with mortality and is independent of basal metabolic index (BMI), whether someone is overweight or not.[7]

Two types of fat accumulate in the abdomen, subcutaneous or visceral. The latter, visceral fat, is what matters most in regard to health. Visceral fat is metabolically active, secreting adipokines that cause inflammation and increase disease risk.

HIIT does a good job at reducing abdominal fat. A 2018 meta-analysis by Maillard et al, which pooled 39 studies, concluded that HIIT was effective at reducing abdominal and visceral fat.[8] Thus, we can say that HIIT is probably helpful. Yet, HIIT has not been shown to reduce belly fat any better than moderate-intensity continuous exercise.[9,10] A 2019 meta-analysis pooled data from 22 studies that compared HIIT with moderate-intensity exercise and examined the impact on heart health.[11] Both types of exercise equally reduced weight, body fat, cholesterol, and improved fitness. The only difference was that the HIIT required about ten minutes less time a day to perform.

It's with this in mind that I am taking great pleasure in my morning walks. Sure, if the trail was more certain, and there weren't branches under the snow waiting to snare my feet, I could jog up the hill in spurts that duplicate a HIIT workout, but for what purpose really? If anything, I would like to take more time for my walks. Going slowly, I can pause and look around, enjoy the exuberant dog galloping though the woods, study animal tracks in the snow and just take pleasure in being alive. One of these days I'll carry my book on animal track identification along but so far, the need to wear mittens has made me hesitant.

Some people, of course, prefer shorter but more intense workouts. The world needs all types of people, I suppose. Just let's not fool ourselves into thinking one type of exercise is all that superior. If there is more benefit to HIIT, it is slight. The real challenge is that most people simply don't exercise.

References

1. https://www.nytimes.com/2020/12/23/well/move/high-intensity-exercise-workouts.html?searchResultPosition=2
2. Stensvold D, et al. Effect of exercise training for five years on all cause mortality in older adults-the Generation 100 study: randomised controlled trial. *BMJ*. 2020 Oct 7;371:m3485.
3. https://s4be.cochrane.org/blog/2016/04/05/tutorial-hazard-ratios/
4. Hansen BH, et al. Monitoring population levels of physical activity and sedentary time in Norway across the lifespan. *Scand J Med Sci Sports*. 2019 Jan;29(1):105-112.
5. https://www.hhs.gov/fitness/resource-center/facts-and-statistics/index.html
6. Statistics Norway https://www.ssb.no/befolkning/statistikker/dode/aar
7. Sahakyan KR, et al. Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality. *Ann Intern Med*. 2015 Dec 1;163(11):827-35.
8. Maillard F, Pereira B, Boisseau N. Effect of High-Intensity Interval Training on Total, Abdominal and Visceral Fat Mass: A Meta-Analysis. *Sports Med*. 2018 Feb;48(2):269-288.
9. Roy M, et al. High-Intensity Interval Training in the Real World: Outcomes from a 12-Month Intervention in Overweight Adults. *Med Sci Sports Exerc*. 2018 Sep;50(9):1818-1826.
10. Wewege M, et al. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. *Obes Rev*. 2017 Jun;18(6):635-646.
11. Su L, et al. Effects of HIIT and MICT on cardiovascular risk factors in adults with overweight and/or obesity: A meta-analysis. *PLoS One*. 2019 Jan 28;14(1):e0210644.

◆

➤ *continued from page 72*

Study). In the pooled analysis, after adjustment for potential confounding variables, for each one-egg-per-day increase there was a statistically significant 14% increase in the risk of developing type 2 diabetes. The review article did not mention that finding. The second part of the study was a meta-analysis of 16 prospective cohort studies (including a total of 589,559 participants). In the meta-analysis, for each one egg per day consumed, there was a 7% increase in the risk of developing type 2 diabetes, which was of borderline statistical significance. The association between egg consumption and diabetes differed significantly in different regions of the world. Among the studies conducted in the US, each 1 egg per day consumed was associated with a statistically significant 18% increase in risk of type 2 diabetes. None of this information was mentioned in the review article.

The abstract that accompanied the meta-analysis did state that there was "no overall association between moderate egg consumption and risk of [type 2 diabetes]." Even though that statement is of questionable validity (because the failure to demonstrate that a correlation is statistically significant is not the same as demonstrating the absence of a correlation), one might grant the author of the review article some leeway for simply quoting the other paper. However, the failure of the review article to mention the three large prospective cohort studies or the US portion of the data from the meta-analysis seems to indicate bias.

Another statement made in the review article was that "eggs reduce inflammatory markers including IL-6, CRP [C-reactive protein], serum amyloid alpha, TNF-alpha, and liver enzymes in patients with metabolic syndrome or those with diabetes." The review article cited three references to support that statement. One of these references presented data on lipoprotein profiles and insulin sensitivity but did not discuss inflammation.[7] The other 2 studies that were cited[8,9] presented a mixed picture. In one of these studies, consumption of eggs significantly decreased C-reactive protein levels, but in the other study the concentration of C-reactive protein was nonsignificantly higher in subjects assigned to consume eggs than in the control group. One of the studies found that another measure of inflammation (monocyte chemoattractant protein-1; MCP-1) fell substantially more in subjects consuming egg substitute than in those given whole eggs. One of the studies found that egg consumption decreased TNF-alpha levels, but the other study found that TNF-alpha levels fell slightly (nonsignificantly) more with egg substitute than with whole egg. Thus, it seems like a major stretch to imply that eating eggs is a good way to decrease inflammation.

Open-access journals and supplements to journals are not the only place one might find bias in medical writing. However, because of the financial incentives associated with these types of publications, the risk of bias is increased. Journals should improve their peer-review process, and we as readers should maintain a healthy degree of skepticism when evaluating educational materials that might be influenced by financial conflicts of interest.

Alan R. Gaby, MD

References

1. Kuzminski AM, et al. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood*. 1998;92:1191-1198.
2. Citrome L. Citability of original research and reviews in journals and their sponsored supplements. *PLoS One*. 2010 Mar 24;5(3):e9876.
3. Fernandez ML. The role of eggs in healthy diets. *J Fam Pract*. 2022;71(Suppl):S71-S75.
4. https://www.incredibleegg.org/about-us
5. https://www.incredibleegg.org/about-us/egg-nutrition-center
6. Drouin-Chartier JP, et al. Egg consumption and risk of type 2 diabetes: findings from 3 large US cohort studies of men and women and a systematic review and meta-analysis of prospective cohort studies. *Am J Clin Nutr*. 2020;112:619-630.
7. Blesso CN, et al. Whole egg consumption improves lipoprotein profiles and insulin sensitivity to a greater extent than yolk-free egg substitute in individuals with metabolic syndrome. *Metabolism*. 2013;62:400-410.
8. Ratliff JC, et al. Eggs modulate the inflammatory response to carbohydrate restricted diets in overweight men. *Nutr Metab*. 2008;5:6.
9. Ballesteros MN, et al. One egg per day improves inflammation when compared to an oatmeal-based breakfast without increasing other cardiometabolic risk factors in diabetic patients. *Nutrients*. 2015;7:3449-3463.

◆

Medical Education or Advertisement?

A number of years ago, I came across an article about vitamin B12 in the journal *Blood*, which is a specialty journal for hematologists. The following notation appeared in small print at the bottom of the first page: "The publication costs of this article were defrayed in part by page charge payments. This article must therefore be marked 'advertisement' in accordance with 18 U.S.C. section 1734 solely to indicate this fact."[1] The law to which this notation referred stated, "Whoever, being an editor or publisher, prints in a publication entered as second class mail, editorial or other reading matter for which he has been paid or promised a valuable consideration, without plainly marking the same 'advertisement' shall be fined under this title."

The US Postal Service no longer has a category of second class mail, so the regulation listed in 18 USC section 1734 no longer applies. However, the practice of researchers or their sponsors paying journals to publish their papers (typically in open-access journals or in supplements to journals) has become widespread. Which raises the question, to what extent should these papers be considered promotional pieces (i.e., advertisements), as opposed to educational or scientific articles?

Supplements to medical journals are typically paid for by organizations or companies that have a vested interest in promoting a specific point of view. The pharmaceutical industry and their affiliates are the most frequent sponsors, but other vested interests are also involved in some cases. Because of this apparent conflict of interest, the information in supplements to journals is perceived by many to be less credible than the information in the parent journal. Nevertheless, articles in supplements to journals are frequently cited by others, possibly even more often than articles in the parent journals,[2] and can be influential in guiding clinical practice.

I recently came across a review article titled, "The Role of Eggs in Healthy Diets," published in a supplement to the *Journal of Family Practice*.[3] The article was written by ML Fernandez, a researcher with impressive academic credentials, who has published a number of studies regarding the biochemical and physiological effects of eating eggs. The review article was "supported by funding from the American Egg Board," which I assume means that the American Egg Board paid Dr. Fernandez to write the article. The American Egg Board is a farmer-funded organization that is "dedicated to increasing demand for all US eggs and egg products."[4] Some of Fernandez's research has been funded by the Egg Nutrition Center, which is the "science and nutrition education division of the American Egg Board."[5]

As an academic exercise, I decided to undertake an analysis of this article, to determine whether there was evidence of bias. As a point of reference, I believe there is good evidence that eating eggs can have a number of health benefits, and that the evidence that egg consumption increases the risk for cardiovascular disease is weak. In addition to containing high-quality protein, eggs are a good source of lutein (which may help prevent age-related macular degeneration) and choline (which may enhance brain function).

In my review of the review article, most of the information presented appeared to be accurate, but I found two instances in which there appeared to be bias or misrepresentation of the data. One statement in the article was, "A recent epidemiological analysis conducted by Harvard investigators reported no correlation between egg intake and risk of diabetes." However, the study cited to support that statement[6] presented a different picture. The study actually had two parts. The first part was a pooled analysis of three large prospective cohort studies of US health professionals (the Nurses' Health Study [NHS], NHS II, and the Health Professionals Follow-up

continued on page 71 ➤

When working out isn't working enough.

Shark Liver Oil

The highest known concentration of Alkylglycerols that affect the body's natural defense mechanisms.

- Scandinavian Formulas' Shark Liver Oil is a trusted name and product recognized and sold world-wide.
- Harvested from cold water, deep-sea Greenland sharks.
- Clinically studied since 1962.
- All-natural and carefully controlled.
- Contains no unwanted fats or impurities.

Available from major distributors such as Threshold, Emerson Ecologics, and Super Natural.

The information presented is not intended to be prescriptive or to replace the care of a licensed health professional in the diagnosis and treatment of illness.

Scandinavian Formulas

Sellersville, PA 18960 • P: 215-453-2507 800-688-2276
F: 215-257-9781 • scandinavianformulas.com

Truly the Best CBD: Now Two Proven Formulas!

TruEase®: today's best-in-class CBD product, produced under the highest ethical and quality standards, now validated as the truly superior CBD product in a newly published **Clinical Trial Study: "A Novel Self-Emulsifying Drug Delivery System (SEDDS) Based on VESIsorb® Formulation Technology Improving the Oral Bioavailability of Cannabidiol in Healthy Subjects"†**.

TruEase® + Curcumin: a patented, synergistic formulation with unmatched therapeutic benefits of Curcumin, Cannabidiol (CBD), Beta-caryophyllene, & Vitamin D3 powered by the VESIsorb® delivery system for maximum absorption and bioavailability and validated by the recent TruEase® Clinical Trial Study†. The active constituents in Curcumin can act as effective antioxidants against excessive free radical damage, along with support for joints, brain, and overall good health*.

TruGen3® continues the Lioon family legacy of three generations and more than a half-century of nutraceutical experience, with products produced under the highest ethical standards, available exclusively through Health Professionals. Contact us to find out how you can put our highly innovative products to work for your patients, and your practice, today.

Contact us today for FREE SAMPLES and to find out how you can put our innovative, one-of-a-kind products to work for your patients, and your practice, today.

† For a complete copy of the TruEase® Clinical Trial Study, visit trugen3.com/truease.

Get More with TruGen3®

Direct access to **Chief Clinical Advisor Dr. Chris D. Meletis** for answers to all your CBD questions

- **VESIsorb® Technology for up to 440% more** bioavailability than ordinary CBD products†. Many Turmeric components' (including curcuminoids) fat-soluble nature can make gastronomical absorption a challenge. The VESIsorb® delivery system minimizes these challenges, better supporting the body's natural inflammatory response, as well as joint, brain and immune health.*
- **Proprietary Super Critical CO^2 extraction process** eliminates solvents and impurities with non-detectible THC content at < 10pm.†
- Cannabinoid profile confirmed by 3rd party Certificate of Analysis

TruGen3®

Three Generations of Truth in Nutrition

www.trugen3.com 1-844-387-8436