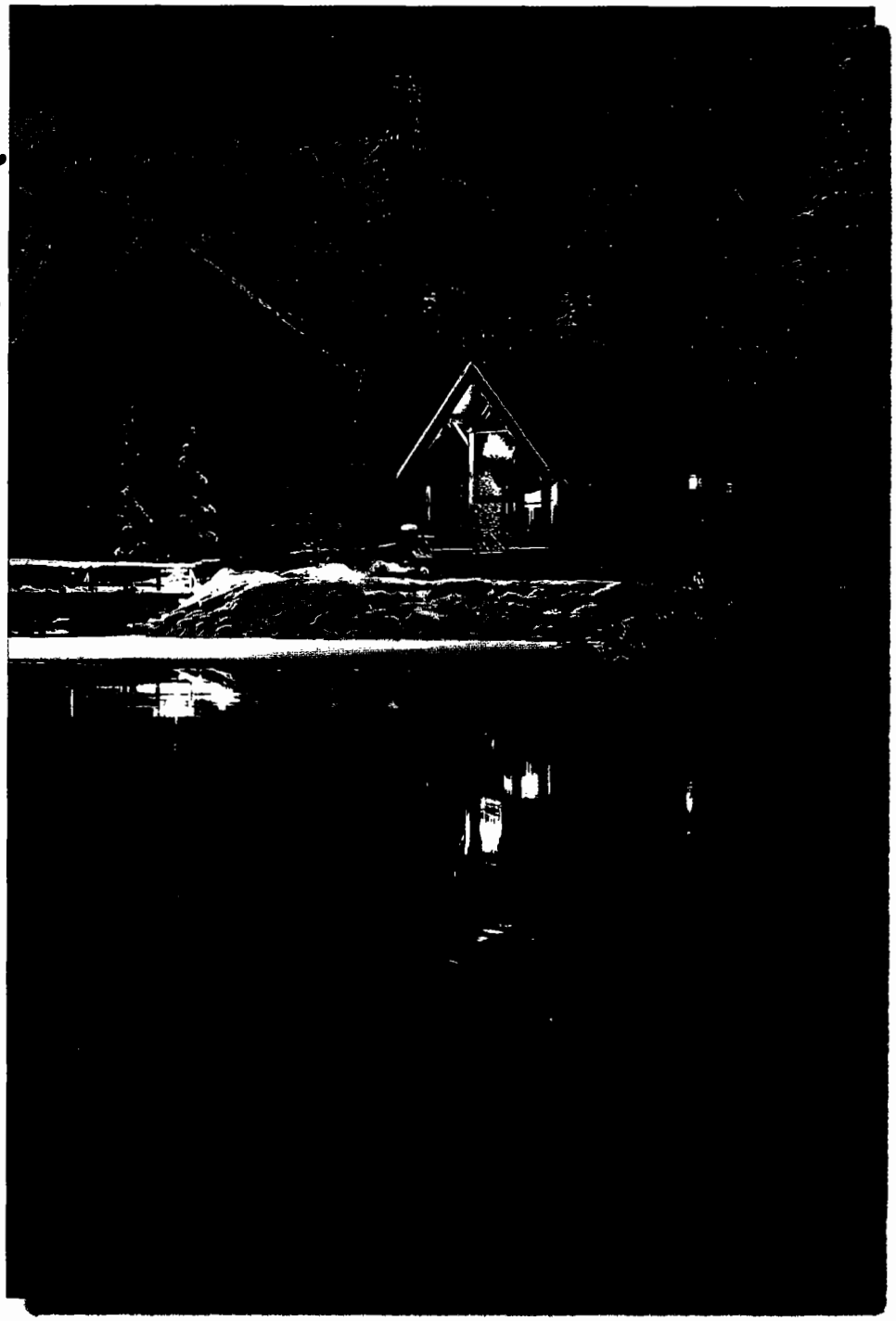
LAB TESTING IN ALTERNATIVE MEDICINE

TOWNSENDLETTER.COM

Townsend Letter

The Examiner of Alternative Medicine

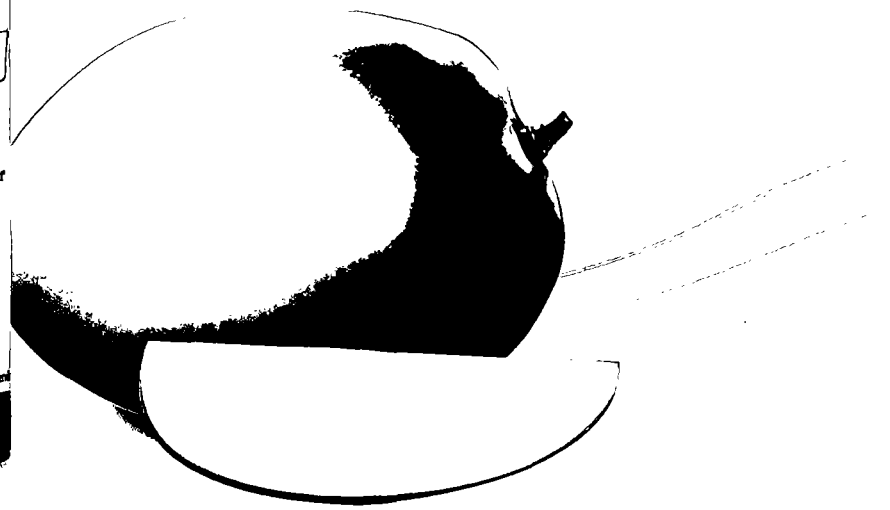


JANUARY 2014
ISSUE #366
$7.50

Delicious Taste. Better Compliance. Better Results.

New!

- Creamy mango flavor the whole family will love
- Exceptional taste supports patient compliance
- 525 mg omega-3s per serving
- Fast absorption for a tasty boost of omega-3s
- Supports heart, brain, and immune health*



Nordic Naturals tropical mango Omega Boost™ is a creamy, delicious formulation of omega-3s that supports optimal health and wellness. Like all Nordic Naturals products, Omega Boost is in the triglyceride form for better absorption.* Each velvety teaspoon contains 525 mg of omega-3s in a creamy mango flavor the whole family will love.

For heart, brain, and immune support, recommend Omega Boost to your clients.* Delicious taste and increased bioavailability means better compliance and results.

Committed to Delivering the World's Safest, Most Effective Omega Oils™

800.662.2544 x1 | nordicnaturals.com

NORDIC® NATURALS

* 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.

One probiotic won't fit them all either.

At Klaire Labs®, we understand different patients have different needs. And, those needs change over the course of their lives. So we developed the industry's most comprehensive line of probiotic formulations.

For 40 years, we've led in the development of pure, viable, hypoallergenic supplements guaranteed through independent testing. Klaire Labs® has everything you need for your patient's probiotic needs and a team ready to guide you in finding the right formula.

Klaire Labs® probiotics – because one formula does not fit all.

KLAIRE LABS®
A division of ProThera®, Inc.

The original hypoallergenic probiotic.™
klaire.com | 888-488-2488

Available only through health practitioners. Private labeling and custom manufacturing offered.
ProThera® operates a GMP 9000 registered facility certified by NSF® International.

Our passion for research started early. *Very early.*

Research isn't just part of our name, *it's our foundation.*

As a result of that commitment to research, we've created hundreds of superior supplements, including Bio-CardioSirt BP©. Bio-CardioSirt BP© supplies a unique, patent-pending combination of seven key micronutrients that have been clinically proven to support normal, healthy blood pressure levels.

Supplement Your Success™

Visit www.SupplementYourSuccess.com to download the peer-reviewed study, conducted by Mark Houston, MD at Vanderbilt Medical School, and help your patients achieve healthy blood pressure.

BIOTICS RESEARCH CORPORATION

Utilizing "The Best of Science and Nature" to Create Superior Nutritional Supplements

GLUTEN FREE GUARANTEE

800-231-5777
www.bioticsresearch.com

A4M AMERICAN ACADEMY OF ANTI-AGING MEDICINE

THE FUTURE OF MEDICINE TODAY

YOUR 2014 A4M EDUCATIONAL PLANNING SCHEDULE

The Most Powerful Medicine .... Your Experience AND Advancing Your Education

SAN FRANCISCO, CA
MARCH 13-16, 2014

BOARD CERTIFICATION EXAMS •
FELLOWSHIP MODULES •
BHRT SYMPOSIUM •

PHOENIX, AZ
SEPTEMBER 10-13, 2014

- BOARD CERTIFICATION EXAMS
- FELLOWSHIP MODULES
- BHRT SYMPOSIUM

DENVER, CO
APRIL 4-6, 2014

FELLOWSHIP MODULES •
IV SYMPOSIUM •

NEW ORLEANS, LA
OCTOBER 16-18, 2014

- FELLOWSHIP MODULES
- IV SYMPOSIUM

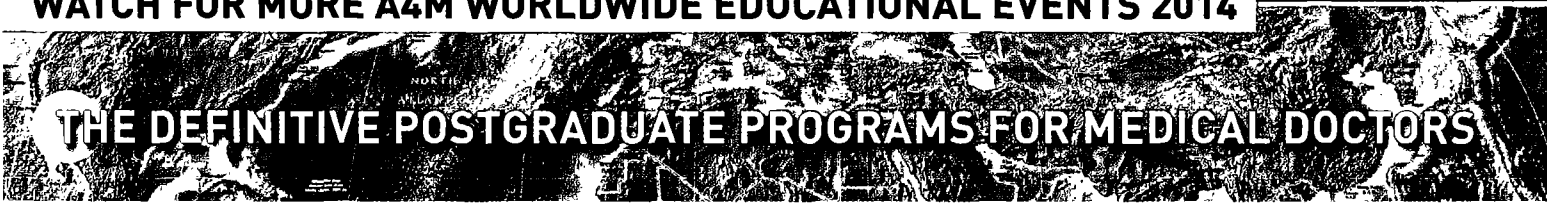
ORLANDO, FL
MAY 14-17, 2014

ANNUAL WORLD CONGRESS •
BOARD CERTIFICATION EXAMS •
FELLOWSHIP MODULES •

LAS VEGAS, NV
DECEMBER 10-13, 2014

- ANNUAL WORLD CONGRESS
- BOARD CERTIFICATION EXAMS
- FELLOWSHIP MODULES

WATCH FOR MORE A4M WORLDWIDE EDUCATIONAL EVENTS 2014



WWW.A4M.COM or 1.888.997.0112 FOR MORE INFORMATION

PRESCRIPT-ASSIST™

broad spectrum probiotic & prebiotic

The clinically proven
(in a double-blind, placebo-controlled trial)

broad-spectrum
(providing 29 strains of beneficial microorganisms)

shelf-stable
(retaining 95% viability 2 years after date of manufacture)

acid-resistant
(encased in hard spores that protect against stomach acid)

prebiotic-enhanced
(providing a reliable food source)

next-generation probiotic supplement.
(reliably delivering results for your patients)

For product literature, study manuscripts, free product samples — or to order Prescript-Assist today — call 888-919-8943 or visit www.prescript-assist.com

Most probiotic supplements are plagued with problems. For starters, they've never been tested in human clinical trials. They typically feature just a few strains of lactic acid based microflora, limiting their efficacy. They're easily destroyed by heat, pressure, light, and stomach acid. And they lack prebiotics — the food probiotics need to proliferate.

Prescript-Assist is different. The subject of multiple human clinical studies, Prescript-Assist solves all these problems. Which is why it has been shown to consistently provide positive patient outcomes.*

Available through healthcare professionals.

**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.*

Distributed by LL Magnetic Clay, Inc. • Livermore, CA 94550

NT FACTOR®

NOURISH YOUR MITOCHONDRIA!*

NT Factor® – Scientifically selected blend of phosphatidylcholine, glycolipids, and other phosphatidyl nutrients – The perfect mitochondrial food!*

NT Factor® Advanced Physicians Formula

Proprietary Membrane Phospholipids B Vitamins Plus

- Subjects took 5/day of Advanced Physicians Formula for one week: 36.8% reduction in fatigue.*[4]

76680 NT Factor® Advanced Physicians Formula

NT Factor® Healthy Curb®

Phospholipid Membrane Food* & White Kidney Bean

- Over 60% of subjects on Healthy Curb® lost 6 pounds avg.; 2.5 inch waist reduction, 1.5 inch hip.*
- Hunger reduced 44%, with less cravings for sweets, and 23% less fatigue.*[3]

76690 NT Factor® Healthy Curb®

NT Factor® Healthy Aging

NT Factor® with Mitochondrial Fuel*

- NT Factor, B vitamins, α-ketoglutarate, L-carnitine, and creatine pyruvate.
- Variously supports cellular and mitochondrial membrane function, cellular energy transport, and ATP production.*

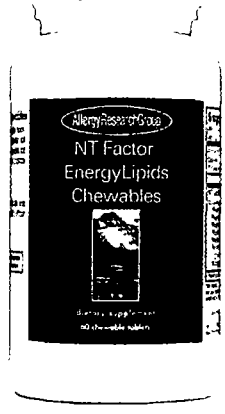
76700 NT Factor® Healthy Aging

NT Factor® EnergyLipids – Powder or Chewable Tablets

Pure Membrane Phospholipids - NO sugar, stimulants or herbs

- Reduced overall fatigue by 39.6% within 3 hours – most within 1 hour.*[1]
- In animals, increased mitochondrial function by 34% and helped prevent hearing loss.*[2]

76760 NT Factor® EnergyLipids Chewables



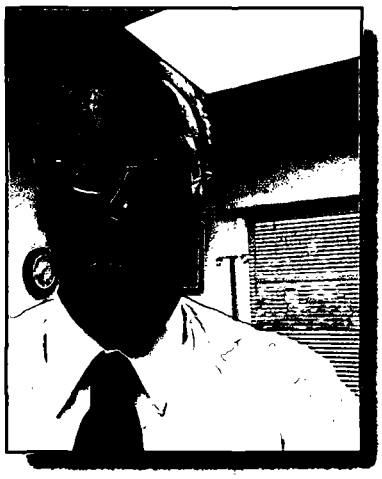
76710 NT Factor® EnergyLipids Powder

AllergyResearchGroup®

Innovative Nutrition

1. Ellithorpe RR, Settineri R, et al. Functional Foods in Health and Disease 2011; 8:245-254.
2. Seidman M, Khan MJ, et al. Otolaryngol Head Neck Surg 2002; 127: 138-144.
3. Nicolson GL, Ellithorpe R, Settiner R. Journal of IiME 2009; 3(1): 39-48.
4. Nicolson GL, Ellithorpe R, et al. J Am Nutraceut Assoc. 2010;13(1):10-14.

Allergy Research Group® Phone: 800-545-9960/510-263-2000
Fax: 800-688-7426/510-263-2100 www.allergyresearchgroup.com



From the Publisher

Probiotics Symposium

I had the pleasure to attend the October 2013 Probiotics Symposium in San Antonio, sponsored by Klaire Labs/ ProThera. Like most integrative physicians, I had the notion that probiotic supplementation is an important part of the clinical prescription; all I needed to know was that every patient needs to be using a probiotic supplement. After all, we know that most folks eat too much sugary, fatty fast food and that GI dysbiosis is a given for nearly everyone. From a nutritional viewpoint, the use of probiotics makes good sense – but what is the evidence base for its application in clinical medicine?

Michael Cabana, MD, MPH

Michael Cabana, MD, MPH, professor of pediatrics at UC San Francisco, is a principal investigator for the NIH/NCCAM study on Probiotic Outcomes on Enteric Microflora (POEM) and for the NIH Trial of Infant Probiotic

continued on page 8 ➤

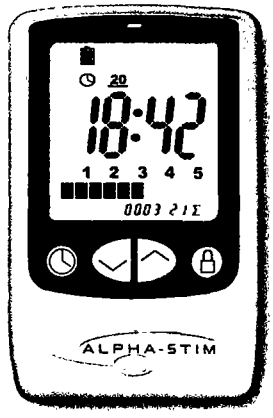
ALPHA-STIM®

It Melts Away Anxiety, Lifts Depression And Helps You Sleep Longer

And It Does All That Simultaneously And Safely

What is the Alpha-Stim® AID?

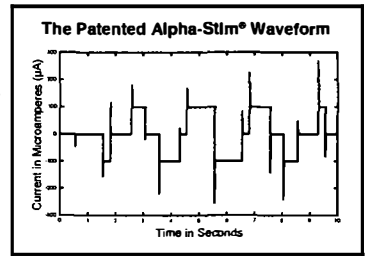
The Alpha-Stim® AID is a medical device used for the management of anxiety, insomnia and depression (AID). Alpha-Stim® AID provides a safe, effective and proven alternative to drugs. Use it while working at your desk, or at home watching TV or meditating. After treatment, there are no physical limitations imposed so you can immediately resume your normal activities. The treatment is simple and easily administered at any time.



What Makes Alpha-Stim® Unique?

It's the waveform. Alpha-Stim® generates a unique and proprietary waveform that no other device can replicate. The waveform in a therapeutic device is analogous to the precise chemical compound that differentiates one drug from another.

Alpha-Stim's® waveform is distinctive in its proven safety and effectiveness. It uses such a low current that some people can't even feel it. It is never turned up to where it is uncomfortable.



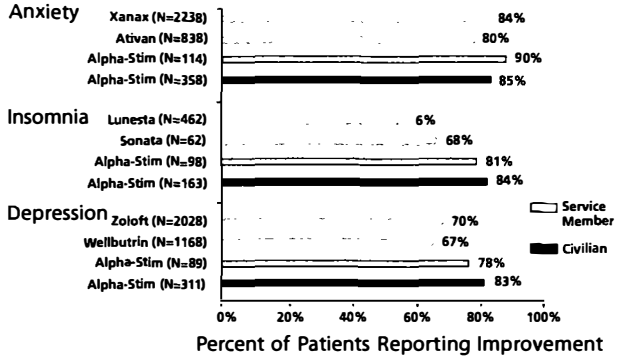
Try it Yourself.

You Will Be Amazed How Good You Can Feel.

Most People Experience a Significantly Better Mood, and Sleep Longer and Deeper.

- ✓ Simultaneously Treats Anxiety, Insomnia and Depression
- ✓ Proven Effective in Many Double-Blind Studies
- ✓ Most Research of Any Therapeutic Device
- ✓ Research Being Funded by DOD, VA, NIH, NCI
- ✓ Veterans Chose Alpha-Stim® 73% of the Time When Given a Choice of 5 Non Drug Therapies
- ✓ Results are Long Lasting and Cumulative

Patient Self Reports: Alpha-Stim® vs. Drugs



Patients who reported a positive response according to WebMD Drug Surveys, and Alpha-Stim Service Member and civilian surveys. Alpha-Stim Data from 2011 Military Service Member Survey (N=152) and Alpha-Stim Patient Survey (N=1,745). Conducted by Larry Price, PhD, Associate Dean of Research and Professor of Psychometrics and Statistics, Texas State University. Pharmaceutical Survey Data from www.WebMD.com/drugs. Accessed on October 28, 2011.

Special Offer
for Townsend Letter Readers

Want to try an Alpha-Stim®?

We have a **FREE** 60 day Practitioner Loan Program.
We offer **FREE** live webinars covering theory and practice by an M.D. for every new Alpha-Stim® practitioner.

Not a practitioner? First ask your physician or psychologist if Alpha-Stim® is right for you. We have a money back satisfaction guarantee. If Alpha-Stim® doesn't work for you return it and all you will pay is a restocking fee. Call for details.

Call us at 800.FOR.PAIN (800.367.7246) and speak with an Alpha-Stim® support representative to receive your **FREE** Overview of Alpha-Stim® Technology brochure or email us at info@epii.com

Visit our website at Alpha-Stim.com

The American Institute of Stress
2012
Award for Distinction and Innovation

Scan to take the Alpha-Stim® AID for a test drive

epi
ELECTROMEDICAL Products International, Inc.

2201 Garrett Morris Parkway
Mineral Wells, TX 76067 USA
800.FOR PAIN in USA and Canada
(940) 328-0788 • info@epii.com

In the USA the FDA restricts this device to sale by, or on the order of a licensed practitioner. It is sold over-the-counter throughout the rest of the world. Side effects occur in less than 1% of people and they are mild and self-limiting consisting mainly of headaches and skin irritation on the ear lobe electrode site.

Letter from the Publisher
continued from page 6

Supplementation to Prevent Asthma. Cabana reviewed that the method of delivery plays a major role in the infant gut's colonization: an infant delivered by C-section has gut flora that resembles the mother's skin colonization; for example, *Staphylococcus sp.* In contrast, the infant delivered vaginally has a greater diversity of microbiota that more closely resembles the maternal vaginal and intestinal flora. Animal trials reveal that there is a "window of time" in perinatal development that plays an important role in the development of allergic disease. Epidemiologic data suggest that infants exposed to a rural, farm environment and to a broad range of organisms develop a more robust immune system compared with infants growing up in a more sterile, urban environment. The thinking then is that the administration of probiotics to infants may prevent development of allergic disease. A large number of diverse studies having varying populations and differing probiotic formulations have had either positive or negative outcomes in demonstrating probiotics' prevention of allergic disorders. While there is insufficient evidence that prophylactic probiotic administration plays a role in the development of allergy, further studies are under way.

Maria Oliva-Hemker, MD

Studies undertaken by neonatologists of the role of probiotics in preventing necrotizing enterocolitis (NEC) in preterm low-birth-weight infants have more compelling evidence. Maria Oliva-Hemker, MD, chief of the Division of Pediatric Gastroenterology at Johns Hopkins University, reviewed trials supporting the use of probiotics in premature infants. Animal studies suggest that probiotic supplementation can protect against NEC. Human studies have demonstrated the role of breast-feeding in establishing diverse infant gut colonization as compared with formula feeding. The hypothesis is that probiotic supplementation in the neonate may play a role in preventing NEC. Clinical trials have demonstrated a consistent benefit in reducing NEC when the premature infant is supplemented with probiotics. There remain some concerns that there may be some adverse outcomes in the preterm infant population with probiotic supplementation.

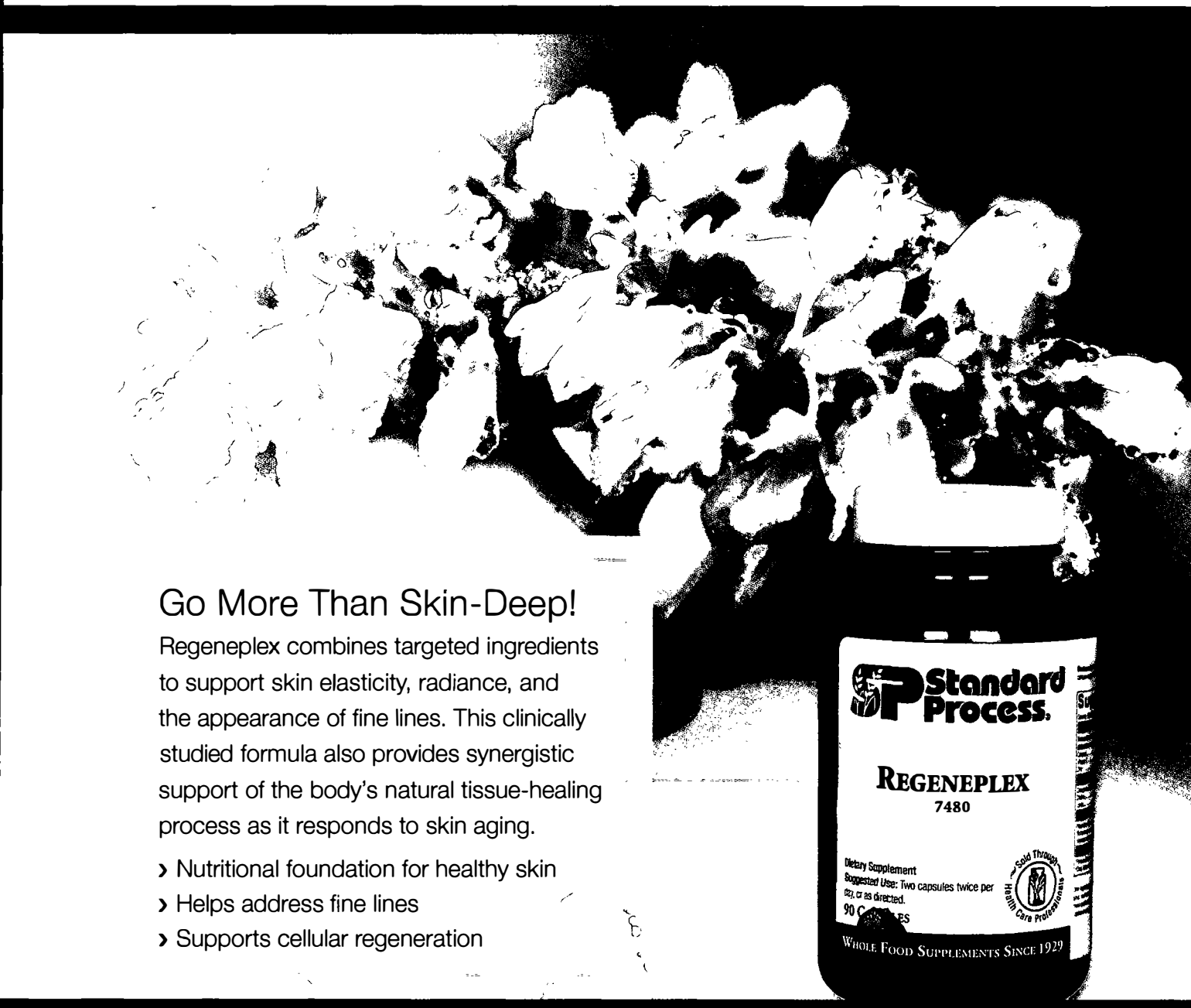
Charalabos Pothoulakis, MD

The moderator of the event, Charalabos Pothoulakis, MD, officiated the Q&A, offering insightful scientific discourse, flavored with his Greek accent, from his 25 years of research of *Saccharomyces boulardii.* Pothoulakis is professor of medicine and director of the UCLA Inflammatory Bowel Disease Center. Pothoulakis's lecture on the physiologic mechanisms by which *S. boulardii*

continued on page 15 ➤

Regeneplex

ESSENTIAL SKIN NUTRIENTS



Go More Than Skin-Deep!

Regeneplex combines targeted ingredients to support skin elasticity, radiance, and the appearance of fine lines. This clinically studied formula also provides synergistic support of the body's natural tissue-healing process as it responds to skin aging.

- Nutritional foundation for healthy skin
- Helps address fine lines
- Supports cellular regeneration

Place your order today. Visit standardprocess.com or call 800-558-8740.

Sold Through Health Care Professionals

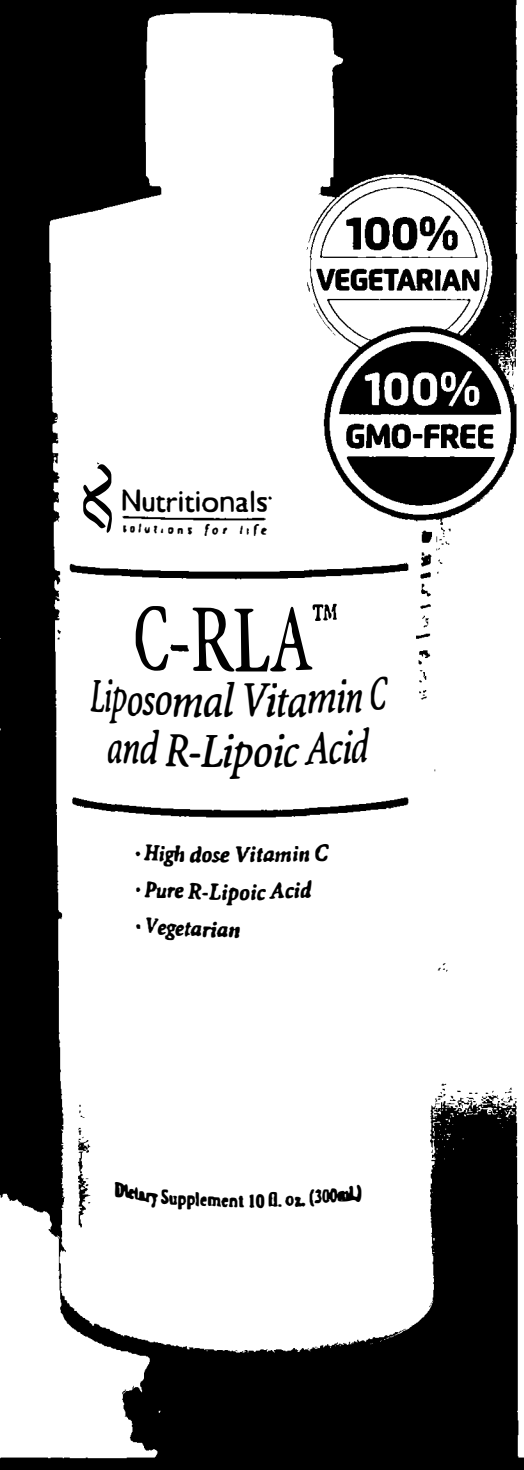
Whole Food Supplements Since 1929

Standard Process

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.

C-RLA™

High-dose Vitamin C & R-Lipoic Acid



LIPOSOMAL DELIVERY SYSTEM

C-RLA™ offers doctors and their patients a safe, efficacious delivery system of High Dose Vitamin C and R-Lipoic Acid in one formulation. Each serving contains 1500mg of Vitamin C and 70mg of R-Lipoic Acid in a natural (GMO-free) liposomal preparation.

OPTIMIZED VITAMIN C ABSORPTION

As most oral Vitamin C doses above 250mg are very poorly absorbed, the most effective high dose oral delivery system is via liposomes from natural phosphatidyl choline.* Many doctors may choose to supplement in-office Vitamin C drips with C-RLA™ so the patients continue to receive the benefit of high-dose Vitamin C without stomach distress.*

R-LIPOIC ACID—ENERGY & ANTIOXIDANT SUPPORT

Lipoic acid helps protect against oxidative stress.* The "R" form is the biologically active component (native to the body) and is the preferred form for optimal nutritional support and absorption.* The "S" form is produced from a chemical manufacturing process and is not as biologically active. Typical alpha-lipoic acid supplements consist of the "R" and "S" form in a 50/50 ratio, offering the patient only 50% of the active "R" form. R-Lipoic Acid's mitochondrial (energy) support is based on its role as an essential cofactor for several mitochondrial enzyme complexes that catalyze critical reactions related to cellular energy production.*

R-Lipoic Acid's antioxidant role is related to its ability to promote healthy glutathione levels, regeneration of other antioxidants (including C, E & glutathione) and support the body's goal of managing reactive oxygen species (ROS).*

SOY-FREE , GMO-FREE & VEGETARIAN

Our liposomes are derived from GMO-free sunflower oil so it is a natural product for patients with soy sensitivities. This product is 100% vegetarian.

JOSEPH BURRASCANO JR., MD

"R-lipoic acid is a valuable supplement for many of my patients. Including it with high-dose Vitamin C and putting it in a liposomal delivery system promotes efficacious delivery of the nutrients. Now that this is available from Researched Nutritionals, I can be confident in recommending a superior quality product."

Researched Nutritionals
solutions for life

CALL 800.755.3402

Tel: 805.693.1802 • Fax: 805.693.1806 • CustomerService@ResearchedNutritionals.com
www.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 January 2014 | #366

Correction

Regarding his review of the book *Enteroimmunology: A Guide to Prevention and Treatment of Chronic Disease*, by Charles A. Lewis, MD (December 2013), Dr. Schor writes: "I was mistaken when I wrote that ' ... raw kidney beans are remarkably poisonous: eating five of them can kill you.' I was misinterpreting what Dr. Lewis had written in his book; I implied that the kidney beans would be lethal. They are only toxic, according to Lewis, ' ... enough for a great gastroenteritis, and perhaps denuding of enterocytes.'"

ON THE COVER: Identifying Trigger Foods (62); New Hope for Glaucoma (77); Which Hormone Test? (53); Topical Progesterone (58); Treating Low Back Pain (106); Gluten-Induced Symptoms (81)

Townsend Letter

ISSN 1940-5434

Subscriptions • Editorial • Advertising – 360/385-6021
24 Hr. Fax – 360/385-0699
911 Tyler Street • Pt. Townsend, Washington 98368-6541 USA
www.townsendletter.com
info@townsendletter.com

Editor-in-Chief	**Jonathan Collin, MD**
Publisher	**Jonathan Collin, MD**
Editor	**Lauren Brown**
Contributing Medical Editor	**Alan Gaby, MD**
Managing Editor	**Barbara Smith**
Contributing Editor	**Jule Klotter**
Editor Emeritus	**Irene Alleger**
Circulation Manager	**Joy Reuther-Costa**
Managing Assistants	**Julie Reuther; Jill Tomasi**
Marketing Projects	**Affinity Collin**
Advertising Projects & Accounts	**Barbara Smith; Joy Reuther-Costa Jonathan Collin; Samuel Collin**

Columnists & Writers

Majid Ali, MD	Ronald Klatz, MD, DO
Robert A. Anderson, MD	Ingrid Kohlstadt, MD, MPH, FACN
Jason Barker, ND	Marianne Marchese, ND
Eleonore Blaurock-Busch, PhD	Ralph W. Moss, PhD
Julie Chen, MD	Judyth Reichenberg-Ullman, ND
Marcus A. Cohen	Jacob Teitelbaum, MD
Tami Duncan	Jade Teta, ND
Nancy Faass, MSW, MPH	Keoni Teta, ND
Peter A. Fields, MD, DC	Robert Ullman, ND
Alan R. Gaby, MD	Rose Marie Williams, MA
Michael Gerber, MD, HMD	Paul Yanick, PhD
Robert Goldman, MD, PhD, DO, FAASP	Elaine Zablocki
Tori Hudson, ND	

Contributing Writers
Beatrice Trum Hunter • Gary Null, PhD • Katherine Duff

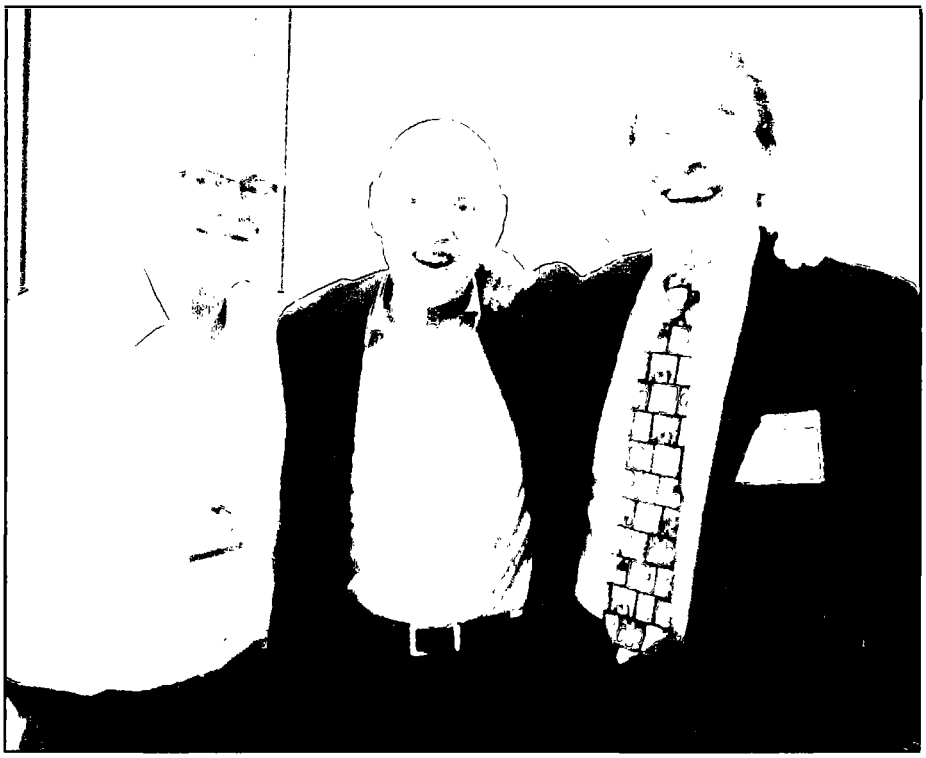
Editorial Advisory Board
Dharma S. Khalsa, MD • Tom Klaber • Robert A. Ronzio, PhD • Kerry Bone, FNIMH
Adrianne Harun • Melvyn Werbach, MD

Layout & Design	Sign Me Up! Inc.
Design Team	Barbara Smith; Joy Reuther-Costa; Jonathan Collin
Cover Photo Credit	Gerad Coles
Printing	Dartmouth Printing Company
Website Design & Maintenance	Sandy Hershelman Designs
Director of Logistics	John Hewitt

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

controls *Clostridium difficile* infection was deserving of an honorarium. *C. difficile* is the primary cause of infectious–disease associated diarrhea in the US. In its most extreme form it is capable of causing colitis, toxic megacolon, and death. *Clostridia* act by releasing toxins A and B. *S. boulardii*, originally discovered in 1920 and licensed in 1953, has been subject to more than 50 clinical trials and reported in more than 300 publications. The studies have established that *S. boulardii* effectively prevents and treats *Clostridia*-caused diarrhea. *S. boulardii* is very effectively colonized in the intestine while it is being administered therapeutically. It reduces cytokine formation by *Clostridia* and inhibits intestinal fluid secretions induced by the toxins. More importantly, *S. boulardii* prevents the histopathologic damage to the intestinal cells. Intestinal cell barrier functions disrupted by *Clostridia* are preserved by *S. boulardii*.

S. boulardii acts as a trophic factor for the intestinal mucosa, preserving its integrity. Pothoulakis leaves little doubt that *S. boulardii* is vitally important in controlling *C. difficile*. Moreover, *S. boulardii* is an important probiotic yeast for the control of many other infections.



Bob Waters, MD (Wisconsin); Stig Bengmark, MD, PhD (Sweden); and Jonathan Collin, MD, at San Antonio Probiotics Symposium.

Stig Bengmark, MD, PhD

I was also delighted to hear and meet Stig Bengmark, MD, PhD, former chief of surgery at Lund University Hospital in Sweden and visiting professor at University College London. Bengmark is the author of more than 1000 scientific publications, of which 500 have been included on PubMed. He has pioneered the use of probiotics for chronic liver disease and for preoperative management and control of infections in patients undergoing abdominal surgery. His current work focuses on nutritional education for the pubic and health professionals: he teaches how to increase prebiotics and probiotics in a healthful diet. At 87 years of age, Bengmark and his wife live what he preaches. Bengmark reminds us that the gut microbiota based on the genome of 100 trillion bacteria is 150 times larger than the human genome. Hence a dysbiotic gut replete with bacteria and yeast that are pathologic will induce inflammation and disrupt our DNA processes. A diet high in sugar, processed foods, allergenic foods, chemicals, and preservatives will favor dysbiotic organisms. Such organisms will increase intestinal permeability and absorption of lipopolysaccharide endotoxins. Bengmark reminds us that high consumption of cooked meats and processed grains results in absorption of advanced glycated end products (AGEs), which favors dysbiosis. The only means to reverse this process is to emphasize a diet of greens, fruits, spices, and nuts, with occasional meat, fish, and eggs. Even without allergy testing, individuals should avoid gluten, dairy, and sugar. Bengmark cites compelling literature to support the use of probiotics to treat abdominal inflammatory disease. He offers great patient education at his website: www.bengmark.com.

Russell Jaffe, MD, PhD

I was pleased to also meet Russell Jaffe, MD, PhD, at the symposium. Jaffe's talk on predictive biomarkers is also the title of his and Jayashree Mani's article in this issue of the *Townsend Letter*. I have had the pleasure of knowing Jaffe for years, as he has been a presenter at many conferences, including ACAM, ICIM, AAEM, and A4M. Jaffe is an internist, molecular biochemist, and clinical pathologist. Currently he is the lab director of ELISA/ACT Biotechnologies in Virginia. At the

➤

Letter from the Publisher

continued from page 15

probiotics symposium, Jaffe reviewed laboratory biomarkers that enable one to assess the state of the human microbiome. Jaffe argues, along with his coauthor, Mani, that these same biomarkers may be used to assess our overall health status and predict the relative risk for maintaining health or developing degenerative disease. The first three biomarkers, hemoglobin A1c (HgbA1c), high-sensitivity C-reactive protein (hs-CRP), and homocysteine, are well known to the conventional and integrative medical communities. Jaffe postulates that a very low HgbA1c, hs-CRP, and homocysteine would predict a greater than 99% likelihood that a person would be alive in 10 years; conversely, he conjectures that high scores of these biomarkers would offer less than a 20% chance that a person would be alive in 10 years. Jaffe thinks that there is "power" in observing each of these biomarkers at the same time: if one biomarker is high and the others are low, then the risk is not nearly as bad as if one had only measured the high biomarker.

Jaffe and Mani state that elevated levels of HgbA1c, hs-CRP, and homocysteine are responsive to lifestyle changes including optimization of diet, nutritional supplementation, exercise, and stress reduction. Optimization of the diet requires more than a reduction of junk foods high in sugar and fat; additionally, there needs to be a careful elimination of allergenic and sensitizing foods, through an "immunotolerant" diet. Further, the diet needs to focus on "super" foods having high levels of antioxidants, primarily by emphasizing more vegetables and fruits than starches and animal proteins. Getting the patient to implement these dietary changes requires considerable education and nutritional counseling (and medical coercion) as well as documentation of food allergies and sensitivities. Jaffe and Mani require that food allergies be tested; they propose that such testing include a measurement of reactive antibodies including IgA, IgM, and IgG as well as measurement of immune complexes and direct T-cell studies.

The idea that HgbA1c, hs-CRP, and homocysteine levels can be easily modified by adherence to a allergy-free "super food" diet is academically satisfying but may prove to be as unattainable as lowering an elevated cholesterol score without the use of a "statin." Jaffe and Mani think that an ideal HgbA1c would be 5.0; I think that this would require not only a vigilantly policed low-glycemic diet but megadose nutrient supplementation to optimize pancreatic and liver functioning. Likewise, achieving a homocysteine score of 6.0 may require more than optimization of the methyl and sulfur pathways. While nutrient therapy with methylfolate, hydrocobolamin, and other nutritional sulfur factors is thought to optimize homocysteine, it has been my observation that lowering homocysteine levels poses a challenging therapeutic challenge. The reduction of an elevated CRP with an immunotolerant diet and nutritional anti-inflammatories would seem more readily achievable; however, patients having marked elevations of CRP and sedimentation rate who suffer with highly inflamed autoimmune disease may not be so fortunate as to have reduction in their CRP scores by diet and supplementation alone.

Jaffe and Mani report on five other predictive biomarkers. They argue that the eight biomarkers taken as a whole offer a comprehensive means to quantify the patient's health status and ability to predict the risk for developing disease or maintaining health. The physical exam offered by primary doctors and internists typically includes a basic lab screening – the complete metabolic panel and a lipid panel. Although the lipid testing offers some insight into a patient's health, the metabolic panel is generally normal. Thus patients are given "clean bills of health" at their physicals, but there are little laboratory data to support this diagnosis. The biomarkers discussed by Jaffe and Mani offer a much broader level of information capable of evaluating metabolic functioning, inflammation, glycemic control, food allergy reactivity, and antioxidant status. A patient tested for these biomarkers would truly be given a "clean bill of health."

Jonathan Collin, MD

In Memoriam:
Dr. Richard Linchitz
of Glen Cove, New York

Dr. Richard Linchitz

Dr. Linchitz passed away on May 13, 2013.

The Best Answer for Cancer Foundation honored its "Physician of the Year" with the following tribute:

> In 2012, the Foundation and the International Organization of Integrative Cancer Physicians made a decision to honor one of our physician members who has gone above and beyond the call of duty, one who has made a true and lasting difference to integrative medicine.
>
> Moved by the personal stories of those living with chronic pain, Dr. Linchitz founded the first and only outpatient nationally accredited multispecialty pain program in New York. Over the next 22 years he managed the Pain Alleviation Center. He developed an integrated program of pain intervention based on lifestyle changes, rather than pharmaceutical-based solutions.
>
> Dr. Linchitz has always lived by his own advice. An accomplished athlete, he lived what he thought was a healthful lifestyle until a diagnosis of lung cancer in 1998 – despite never having smoked. It forever changed his life and overall perspective on medicine. After receiving a bleak prognosis for survival, he sought to understand his disease from the inside out and to design his own path towards balanced wellness.
>
> Determined to share the lessons learned from his own recovery, Dr. Linchitz became an expert in integrating conventional and alternative approaches to treat disease. Consequently, he created a unique program of health based on prevention and natural remedies.

- graduated with honors from Cornell University Medical College; completed his residency at the University of California, San Francisco, Moffit Hospital.
- board certified by the American Board of Psychiatry and Neurology, the American Board of Pain Medicine, the American Board of Anti-aging Medicine, and the American Board of Integrative Holistic Medicine
- successfully passed board exams from the American Board of Clinical Metal Toxicology and the International Board of Oxidative Medicine
- trained and certified in Medical Acupuncture and Insulin Potentiation Therapy

Dr. Linchitz dedicated his life to medical health and patient care. He was also actively involved in the medical community:

- board examiner, American Board of Anti-Aging Medicine (A4M)
- board of directors, American College for Advancement in Medicine (ACAM)
- board of directors, Best Answer for Cancer Foundation (BAFC)
- program cochair, Chelation Examination Committee
- board of directors, International College of Integrative Medicine (ICIM)
- International Oxidative Medicine Association (IOMA)
- Society for Integrative Oncology (SIO)
- medical advisory board, International Organization of Integrative Cancer Physicians (IOICP)

His wife, Rita Linchitz, said, "We are heartbroken and at a loss as to how so wonderful a man could be taken so soon. He was a loving son and brother, a beloved husband, devoted father and grandfather, and the most dedicated and caring physician. We cannot imagine life without him. Please keep him in your prayers."

We miss his steady guidance, his energy for education, his passion for better patient outcomes, and his unique friendship. ◆

The Revolution in Modern Women's Health Care Takes a Bold New Turn at Sold-Out Lifestyle Medicine Summit

The health issues facing today's woman are clear, but how to effectively address them is not. That concern is what drew the more than 750 forward-thinking health-care practitioners who attended the sold-out second annual Lifestyle Medicine Summit sponsored by Metagenics, held October 4–6, 2013, in Chicago. Practitioners from around the country learned that "lifestyle medicine" represents a shift in the conventional health-care model to one that empowers women to be active participants in caring for their health – especially when empowered with the latest information available to weigh health-care options and associated risks and benefits.

The summit is the premier forum for advancing lifestyle medicine. This past year's theme, "Women's Health: What Women Really Want," brought together 18 world-class physicians, research clinicians, and other practitioners across a variety of fields to lead discussions on some of today's top concerns and underlying risk factors that negatively affect a woman's quality of life. The goal of this year's summit was to inform and inspire practitioners with innovative nutritional and lifestyle medicine strategies that give their female patients the tools that they need to be healthier. The summit was once again sponsored by Metagenics Inc., a nutrigenomics and lifestyle medicine company focused on improving health.

Jeffrey Bland, PhD, a keynote speaker at the Metagenics Lifestyle Summit, presents to more than 750 health-care practitioners on lifestyle medicine.

Presenter Christiane Northrup, MD, signs a copy of her *New York Times* best-selling book at the Metagenics Lifestyle Summit.

"We are proud to host the Lifestyle Medicine Summit to provide a collaborative forum for health-

care practitioners to not only learn new and exciting approaches, but also to connect with other caring, like-minded professionals who are helping to change the modern health-care experience," said Willy Pardinas, senior vice president and general manager of the Americas for Metagenics. "There has never been a more opportune time for practitioners to embrace innovative strategies that help patients make meaningful, lasting changes in their health and the way they feel."

Women of today may be living longer, but they're not necessarily healthier. In fact, modern-living behaviors are contributing factors to the rising tide of many common chronic diseases and conditions – including heart disease, type 2 diabetes, obesity, mood disorders, back pain, fatigue, autoimmune disorders, and hormone-related conditions. Breakout sessions at the summit provided insights into recent scientific advancements and clinical discoveries in preventing and managing common women's health issues and bothersome symptoms.

Noteworthy sessions and speakers from the summit included:

- Mark Hyman, MD, six-time *New York Times* best-selling author, and an internationally recognized leader in his field, spoke to health-care practitioners about the five major triggers of autoimmune disease, stating that "less than one-third of those with an autoimmune disease are diagnosed." Hyman also revealed that 80% of those affected are women. "The primary causes of disease are toxins, allergens, microbes, stress, and poor diet. Nutrients like omega-3, zinc, vitamin D, magnesium, and vitamin A may help to treat some causes, along with stress management."
- Christiane Northrup, MD, internationally known for her empowering approach to women's health and wellness, closed the summit with an earnest discussion of what female patients desire in modern health care. Northrup revealed that probiotics play an important role in training the immune system. "There has been a large increase in autoimmune and allergic diseases in societies that are considered to have very good hygiene," said Northrup. "These increases may have occurred because our immune systems are not being challenged by pathogenic organisms. Introducing good bacteria like probiotics can support the immune system in a healthy way and help build it up."

Attendees listen to speakers talk about women's health issues at the Metagenics Lifestyle Summit.

"What I learned at this conference is beyond standard of care and looks more closely at the biology and science of human wellness," said summit attendee Dan Harper, MD, integrative medicine family practitioner from Solana Beach, California. "Medicine is traditionally focused on treatment, and this conference focuses on prevention at the molecular level."

The theme of the 2014 Lifestyle Medicine Summit is "Transformational Patient Care: Powering the Paradigm Shift," and it will build on previous events to encompass a broader range of conditions and challenges that may be effectively managed with personalized lifestyle medicine strategies. Another stellar line-up of world-class speakers will participate. The 2014 Lifestyle Medicine Summit will be held September 26–28 in Nashville, Tennessee, at the newly built Omni Hotel. Early registration is encouraged, as previous events have sold out months in advance. ◆

Vitamin C Prevents Radiation Damage: Nutritional Medicine in Japan

Orthomolecular Medicine News Service

Workers with severe radiation exposure at the Fukushima nuclear plant had major reduction in cancer risk when supplemented with vitamin C and other antioxidative nutrients. Sixteen men aged between 32 and 59 years worked 5 to 6 weeks in a radiation-contaminated area, collecting contaminated water, measuring radiation levels, operating heavy machinery, and removing debris. Blood samples were obtained to measure whole blood counts and blood chemistry, plasma levels of free DNA, and 47 cancer-related gene expressions.

Four workers who took intravenous vitamin C (25,000 mg) therapy before they went in, and continuously took antioxidative supplements during the working period, had no significant change in both free DNA and overall cancer risk.

Three workers who did not have preventive intravenous vitamin C had an increase in calculated cancer risk. After the 2 months' intervention with intravenous vitamin C and oral antioxidative nutritional supplements, free DNA returned to normal level and cancer risk score was significantly decreased.[1]

This important clinical demonstration confirms research done nearly 20 years ago showing that pretreatment of vitamin C, by oral intake or injection, increased sperm head survival after the injection of radioactive iodine-131 in mice.[2]

Oral intake of alpha-lipoic acid and vitamin E reduced urinary radioactivity and oxidative stress in irradiated children in Chernobyl.[3] Furthermore, there have been numerous scientific studies about the radioprotective effects of other vitamins, minerals, and antioxidative nutrients.

Notes

1. Yanagisawa A. Effect of Vitamin C and antioxidative nutrition on radiation-induced gene expression in Fukushima nuclear plant workers. Free download of full presentation at http://www.doctoryourself.com/Radiation_VitC.pptx.pdf.
2. Narra VR, Howell RW, Sastry KSR, Rao DV. *J Nucl Med*.1993;34(4):637–640. http://jnm.snmjournals.org/content/34/4/637.long.
3. Korkina L et al. Antioxidant therapy in children affected by irradiation from the Chernobyl nuclear accident. *Biochem Soc Trans*.1993;21:314S. PMID: 8224459.

Nutritional Medicine is Orthomolecular Medicine

Orthomolecular medicine uses safe, effective nutritional therapy to fight illness. For more information: http://www.orthomolecular.org.

The peer-reviewed Orthomolecular Medicine News Service is a nonprofit and noncommercial informational resource.

This article is reprinted courtesy of Orthomolecular Medicine News Service. To subscribe at no charge: http://www.orthomolecular.org/subscribe.html.

◆

Green Teas Vary in Strength and Amount of Lead Contamination

If you drink green tea for your health, be aware that the catechin and caffeine levels can vary by more than 240% across products. Some also contain significant amounts of lead in their tea leaves. This is according to recent tests by ConsumerLab.com, which reports on the quality of health and nutrition products. Brands of green tea reviewed were Bigelow, Celestial Seasonings, Lipton, Salada, and Teavana.[1] The products were tea bags, a loose tea, and a K-Cup (for brewing in a Keurig machine).

Studies of large populations have found that drinking at least 2 to 3 cups of green tea daily is associated with a reduced risk of cardiovascular disease, certain cancers, and type 2 diabetes. In addition, supplements containing green tea compounds may assist in weight loss and reduce the risk of prostate cancer.

ConsumerLab.com found the amount of tea leaf in a suggested serving of each product to range from 1.38 grams to 3.14 grams, with some larger tea bags actually containing less tea than some smaller bags. In terms of chemical strength, servings yielded from 25 mg to 86 mg of EGCG, one of the key "catechin" compounds in green tea and a natural phenol in the flavanol family. The amount of caffeine per serving ranged from 22.7 mg (less than in a can of cola) to 85.8 mg (similar to that in a cup of regular coffee), with decaffeinated teas containing just 5 mg.

ConsumerLab.com found the cost to get 200 mg of EGCG from the brewed teas ranged from 27 cents to $2.50. The cost to obtain the same amount of EGCG from green tea dietary supplements tested earlier by ConsumerLab.com ranged from 10 cents to $3.41, and from bottled green teas the cost was $4.45 to $71.72.

ConsumerLab.com also measured the amount of lead, a toxic heavy metal, in each product. Lead is known to be taken up into tea leaves from the environment and can occur in high amounts in tea plants grown near industrial areas and active roadways, such as in certain areas of China. Although the liquid portions of the brewed teas did not contain measurable amounts of lead (i.e., no more than 1.25 mcg per serving), when including the brewed leaves in the analysis, 2 to 5 mcg of lead was detected per serving in four different products, including an "organic" green tea. Interestingly, measurable lead was not found in decaffeinated green teas or in a Japanese green tea. Most of the teas reviewed likely originated in China.

"The bad news from our tests is that there can be significant amounts of lead contamination in some green tea sold in the US," said Tod Cooperman, MD, president of ConsumerLab.com. He continued, "The good news is that most of this lead stays within the leaves and doesn't get into the tea." His advice: Be sure to use a tea bag or other filter for your tea and don't eat the tea leaves unless you know they are not contaminated."

Test results and comparisons of all the products are found in ConsumerLab.com's report "Green Tea Supplements, Drinks, and Brewable Teas Review," which can be accessed online.

ConsumerLab.com is a leading provider of consumer information and independent evaluations of products that affect health and nutrition. Membership to ConsumerLab.com is available online, providing immediate access to reviews of more than 1000 products from over 400 brands (https://www.consumerlab.com/NewSubscriber.asp). The company is privately held and based in Westchester, New York. It has no ownership from, or interest in, companies that manufacture, distribute, or sell consumer products. ConsumerLab.com is affiliated with PharmacyChecker.com, which helps consumers evaluate online pharmacies and drug prices, and MedicareDrugPlans.com, which reviews and rates Medicare Part D plans.

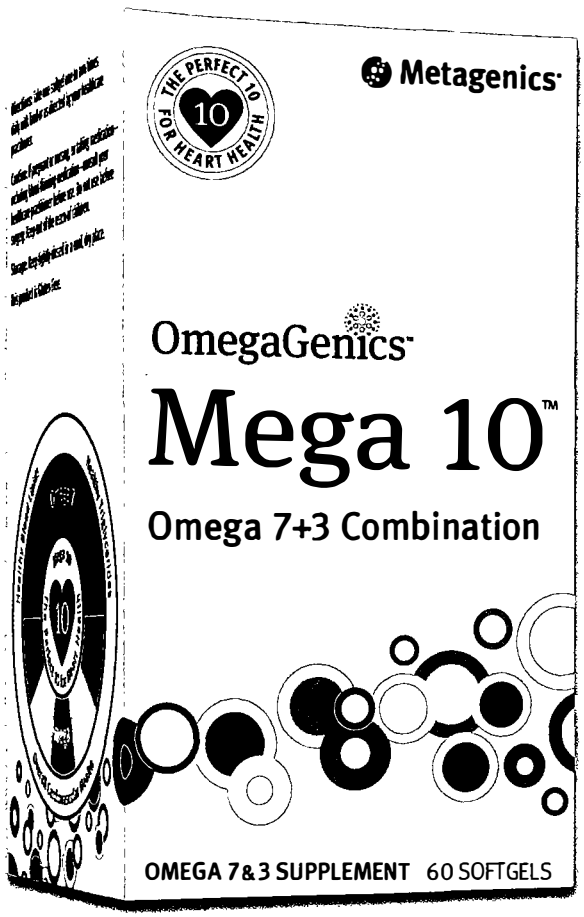
Notes

1. Green tea supplements, drinks, and brewable teas review [Web page]. ConsumerLab.com. https://www.consumerlab.com/reviews/Green_Tea_Review_Supplements_and_Bottled/Green_Tea.

◆

A Quantum Leap in Omegas

Breakthrough Omega 7+3 Combination



Mega 10—the Perfect 10 for Heart Health*

- Mega 10 is the more complete omega formula, delivering a powerful combination of purified omega-7 and omega-3 fatty acids*
- The unique levels and ratios of omega-7 and omega-3 fatty acids in Mega 10 are designed to support healthy triglycerides and blood lipids*
- 6.6 times more EPA-DHA than the leading krill oil (500 mg vs. 74 mg per softgel)
- Provides targeted, enhanced support for overall cardiovascular health*

THE PERFECT 10 FOR HEART HEALTH

Mega 10 provides a unique combination of purified omega-7s and a concentrated dose of omega-3s. And each batch is purity guaranteed and tested by a third-party lab for quality you can trust.

For enhanced patient compliance, Mega 10 enteric softgels are easy to swallow and feature a natural lemon flavor. Try Mega 10 today!

Order Today!
Call: 800 692 9400

Open an Account
metagenics.com/newaccount

Learn More
KnowMega10.com

Metagenics

* 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.

Breakthrough Science + Nutrigenomic Based Products + FirstLine Therapy + Unsurpassed Quality = The Metagenics Difference

IMAGINE WHAT YOU CAN DO
WITH A REMEDY LIKE THIS.

Now Available in Tablet Form!

DON'T TRAVEL WITHOUT IT!

PLEO OKU TABLETS

Our BEST from SANUM-Kehlbeck

Pleo Oku Tablets Are Effective For:

- Prevention of or for acute traveler's diarrhea
- Food poisoning and gastrointestinal infections
- Food intolerances and over indulgence in food or alcohol
- Parasites
- Elimination of metabolic waste
- Pancreas insufficiencies
- Shown to reduce acute dietary allergic reactions

The NEW Pleo Oku tablets are great for travelling. Acute diarrhea and food poisoning can stop travelers in their tracks while on vacation. Pleo Oku, derived from an African tree bark, is a quick acting and healing remedy for infectious conditions of the GI tract. *Also available in drops.*

Swiss doctor, Dr. Thomas Rau, M.D., has been known to say: *"It is the law to have Pleo Oku in the pocket always."*

Call now for your
Pleo Oku Tablets
FREE SAMPLES

Item #800-400-SA001. 10 tablets per sample.

1-800-665-8308

See what *YOU* can do with Pleo Sanum in your practice.

While quantities last!

Patient Sample kit offer in effect until April 30, 2014.
Call today! For licensed practitioners.
Limit 10 samples per customer account.

✓ No side effects ✓ Effective ✓ Non-toxic

The BEST support for acute diarrhea and food poisoning.

14EP04 • TL01-2014

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.

innovation you can trust

1-888-415-0535

www.terra-medica.com

TERRA MEDICA

Finally, a Probiotic Supplement That's Worth Recommending to Your Patients

"It's worth taking the time to find supplements that demonstrate proven results."

Dr. Natalie Engelbart
Specializing in Functional Neurology and Clinical Nutrition

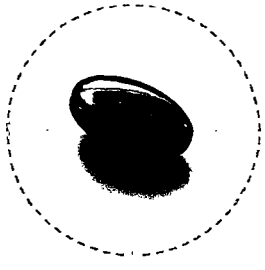
I only recommend products that are backed by clinical research and contain superior ingredients—so my patients experience consistent results. That means I don't limit myself to a single nutritional company; I find individual nutritional products that are the best of their kind.

That "best product" philosophy is key when it comes to probiotics. Years of research have confirmed that healthy probiotic balance has a trickle down effect on immune response, energy level, mood, and the overall wellness of every body system. But not just any probiotic will achieve positive patient outcomes.*

A colleague who understood my high standards recommended Dr. Ohhira's Probiotics®. After much research, I discovered they had received rave reviews in not only scientific circles but also from people using the product.

I recommend Dr. Ohhira's Probiotics® Professional Formula to my patients, my family, and I take the product myself—because it is the very best probiotic formula on the market today, period!

"Dr. Ohhira's Probiotics® Professional Formula exceeds my strict criteria for probiotics, and consistently provides excellent patient outcomes."



- Backed by 25 years of research
- Fermented with mulitple probiotic strains for 5 years to concentrate health-supporting organic acids, vitamins and other biogenic components*
- Contains the probiotics' food supply to ensure coherence*
- Supports health of the individual's own unique probiotic strains*
- No refrigeration needed – fermented at seasonal temperatures

ESSENTIAL FORMULAS®
PROFESSIONAL

Essential Formulas Incorporated ◦ (972) 255-3918 (phone) ◦ www.EssentialFormulas.com ◦ Become a friend of Dr. Ohhira on Facebook.

*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.

HEALTHY BLOOD SUGAR = HEALTHY AGING

MAKE SX-FRACTION® A PART OF YOUR HEALTHY LIFESTYLE!

A unique patented extract from the Maitake mushroom, SX-Fraction®, in recent independent studies has been shown to:

- Promote healthy lipid glucose metabolism*
- Promote healthy glucose metabolism*
- Promote healthy insulin function*
- Promote healthy weight management*
- Promote healthy cardiovascular function*

For more information:
and 20% Discount!
Call: 800-747-7418
or online:
www.mushroomwisdom.com
use code: TL12

Gluten-Free No Sugar, Wheat or Dairy

MUSHROOM WISDOM®

THE POWER OF KNOWLEDGE

* 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.

Pathways to Healing

by Elaine Zablocki

Accurate Diagnosis: The Foundation of Quality Care

In recent years, US health-care organizations have taken significant steps toward improving quality and increasing patient safety. Hospitals are monitoring medication errors, falls, bedsores, preventable infections, and hundreds of other problems; and they are taking active steps to reduce them.

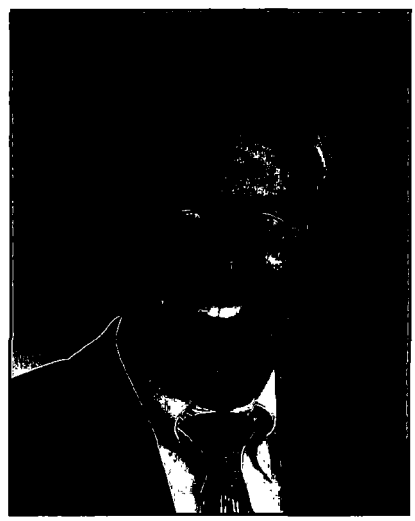
However, there's a notable gap. Cases of delayed, missed, and incorrect diagnosis are common, occurring in 10% to 20% of cases. Diagnostic error may be responsible for billions of health-care dollars for inappropriate care, and is the leading cause of medical malpractice claims. However, current efforts to improve health-care quality have overlooked the subject of diagnostic error.

"Diagnostic errors can happen to anyone," says Mark L. Graber, MD, a senior fellow in health care quality and outcomes at RTI International. "There is a great deal of harm that is preventable. According to the best estimates, there are 40,000 to 80,000 deaths every year that are the result of diagnostic errors. We believe many of those could have been prevented."

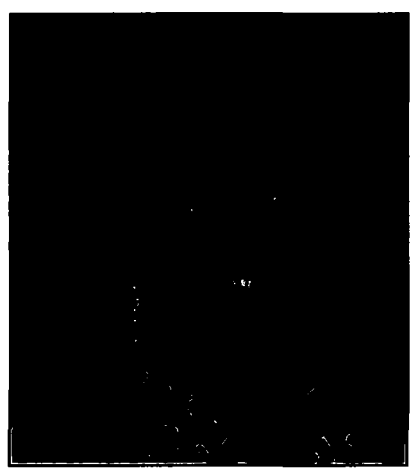
There are several different reasons for diagnostic error. One is the lack of continuity and coordination in the health-care system. For example, if someone has a test done at one doctor's office and then goes to see another physician, most likely the second physician won't know the results of the initial tests. In some cases, lab results can sit in a doctor's inbox and not be looked at for weeks. "There are many opportunities for information to fall between the cracks," Graber observes. "Given the inherent uncertainty involved in making a diagnosis, given the fact that there are over 10,000 different diseases, I think we do remarkably well. At the same time, many errors are preventable, so we need to look more closely at steps we could take to prevent them."

In 2008, Graber founded and chaired the Diagnostic Error in Medicine conference series. He is founder and president of the Society to Improve Diagnosis in Medicine (SIDM), which holds this major conference every year. "We're trying to build a community of people interested in diagnostic error, to promote dialogue and get the word out on this important issue," he says. "We also promote research on diagnostic error, and we are working actively to promote education on this topic in both medical school and residency training." A new journal, *Diagnosis,* will launch this month.

SIDM believes that we need a comprehensive report from the Institute of Medicine (IOM) on diagnostic errors. The proposal has been approved by the IOM National Research Council Governing Board's executive committee, and enthusiastically endorsed by IOM President Harvey Feinberg. This forward movement is significant, because previous IOM reports, on topics such as health-care quality, patient safety, and the future of nursing, have been extremely influential in shaping policy and the future of US health care. (To read and



Mark L. Graber, MD



Ilene Corina

➤

➤

download previous IOM reports, go to the IOM website.)

Cautious Patient Communities

The Cautious Patient Foundation has provided substantial grant support to SIDM to raise awareness of diagnostic error as a significant issue, and create training and tools to empower patients to avoid these errors. In addition, the foundation has developed the concept of Cautious Patient Communities (CPC).

These communities are local groups wherein patients and families learn how to be informed and involved in their own health care. This can lead to better outcomes, as well as a sense of "no longer being an outsider in your own care." Participants are invited to exchange stories with peers at local meetings; they can learn from each other by sharing their own experiences about what has worked well for them.

Supportive materials have been developed by the Cautious Patient Foundation, and assistance is available to help people set up groups in their local communities. "We have only been doing this for a year, and our website offers tools to help people get started," says Ilene Corina, CPC director. "Typically we recommend having three sessions, lasting one hour to 90 minutes. What is said during these meetings is never shared outside the doors of the meeting. We hope participants will take away important information from the written materials and from other people's experiences to help ensure their own best outcomes. We all get strength from each other."

Steps that Patients and Practitioners Can Take

There are a number of steps that patients and practitioners can take to increase the chances of an accurate diagnosis. "It's important for patients to keep full records of all the things that are bothering them, and all the medications they are taking," Corina says. "If the doctor doesn't know that we are on a medication, they have no way to consider potential side effects of that medication. They need to hear a full history that includes past surgeries and problems because it's all interrelated."

A 2013 article published by *BMJ Quality and Safety* offers a valuable discussion of ways to improve communications between patients and care providers, including detailed checklists. The full text of the article is available online, and it is well worth reading (see below). For example, it includes a list of sample questions that patients might want to ask during a visit with their health-care practitioner:

- What are my primary concerns and symptoms?
- How confident are you about the diagnosis?
- What further tests might be helpful to improve your confidence?
- Will the tests you are proposing change the treatment plan?
- Are there findings/symptoms that do not fit your diagnosis?
- What else could it be?
- Can you facilitate a second opinion by providing me with my medical records?
- When should I expect to see my test results?
- What resources can you recommend for me to learn more about diagnosis?

McDonald KM, Bryce CL, Graber ML. The patient is in: patient involvement strategies for diagnostic error mitigation. *BMJ Qual Saf*. 2013 Aug 7. Available at http://qualitysafety.bmj.com/content/early/2013/08/07/bmjqs-2012-001623.full.pdf.

Health-care practitioners are short of time these days, and when the doctor gives someone lots of new information, it may be difficult for the patient to absorb it. "While you're seeing the doctor you may be on overload, so be sure to ask them whether you can call back later, and who you should contact. Ask for written information you can take with you," Corina says. "If you don't understand what they are saying, then ask for someone who can help you understand. It only takes a few minutes for a nurse to take the time for a fuller explanation, but it makes a really big difference for the patient."

It is very important for patients to understand that most diagnoses are not final, Graber emphasizes. "The initial diagnosis is an educated 'best guess,'" he says. "It is what seems most likely at the present time. The diagnosis might change if symptoms change, and patients need to understand this. They need to know how to get back in touch with the physician if their symptoms don't resolve, or if they don't respond to treatment. This is extremely important in preventing diagnostic errors."

The key to being a good diagnostician is taking the time to get a good history and gather all prior consults and records. "There is so much pressure of time these days, but it is still essential to do a thorough analysis," Graber says. "Diagnosis requires devoting time to gathering all the relevant facts; it requires *taking time to think*. It is extremely important not to rush to judgment but to consider what other possibilities there may be."

Resources

Society to Improve Diagnosis in Medicine: http://www.improvediagnosis.org.

SIDM 2014 Conference: Diagnostic Error in Medicine 7th International Conference, September 13–17, 2014; Atlanta, GA.

For more information about the journal *Diagnosis*, go to www.degruyter.com/view/j/dx.

Cautious Patient Communities

Website: http://www.cautiouspatientcommunities.org. Contact Corina at iCorinaCPC@gmail.com.

To see previous Institute of Medicine reports, go to http://www.iom.edu/Reports.

Elaine Zablocki has been a freelance health-care journalist for more than 20 years. She was the editor of *Alternative Medicine Business News* and *CHRF News Files*. She writes regularly for many health-care publications.

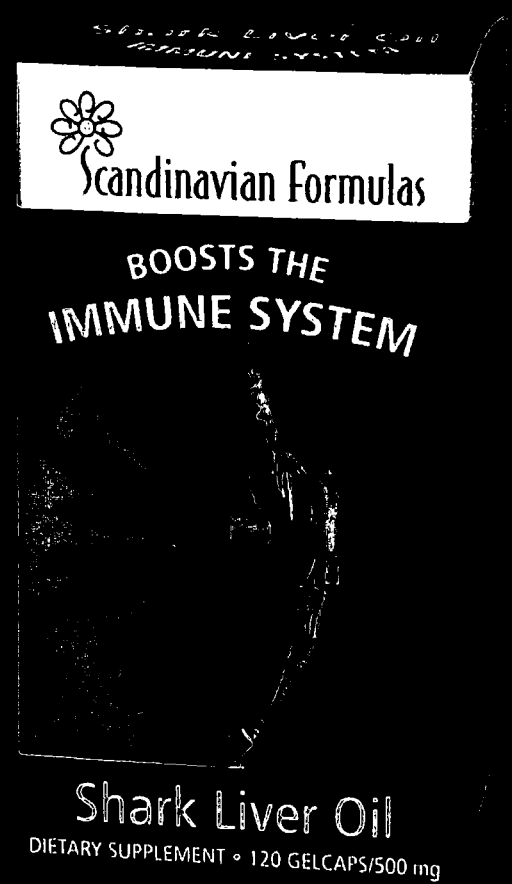
◆

Scandinavian Formulas

Put the Power of Alkylglycerols Behind Your Immune System With...

Shark Liver Oil
GELCAPS

Scandinavian Formulas is an environmentally concerned corporation and only uses shark livers that are a byproduct of the fisheries industry.



Alkylglycerols are found naturally in bone marrow, liver, spleen, and human breast milk. Alkylglycerols from sharks' livers are highly concentrated and have been thoroughly tested since the late 1950's as immune system enhancers. People rely on Alkylglycerols to fight colds, the flu and also to keep their white blood cells strong.

- The only oil containing Alkyglycerols
- From the deep-sea Greenland sharks' livers which contain the highest level of alkylglycerols found in nature
- Standardized and carefully controlled, containing no toxic impurities

Another Fine Product from Scandinavian Formulas

To order, please call 215-453-2507 or visit us at www.scandinavianformulas.com

Shorts

briefed by Jule Klotter
jule@townsendletter.com

Theranos Laboratory Testing

Theranos Inc. has unveiled a new automated model of laboratory testing that promises to be less invasive, more accurate, less expensive, and faster than conventional laboratory services. The 10-year-old company joined forces with Walgreens pharmacies, the largest retail chain in the US, to set up its first Theranos Wellness Center in a Walgreens in Palo Alto, California, in September 2013. The CLIA-certified system can run multiple tests from a single "microsample" of blood, often provided via finger stick instead of taking a vial of blood for each test. In addition to basics such as a CBC (complete blood count), the tests include metabolic tests for glucose tolerance and thyroid activity, measurements of biomarkers such as C-reactive protein, antibody levels for Epstein-Barr and borrelia, serum vitamin levels for B12 and D3, and many more. Each test costs 50% or less of Medicare reimbursement rates and is listed online (www.theranos.com). Patients must pay up front for testing; major insurers, Medicare, and Medicaid will reimburse them for doctor-ordered tests. Theranos also posts margins-of-error variations for each test online and on the test report itself. Results are e-mailed to patients' physicians within hours instead of days.

Elizabeth Holmes, Theranos's 29-year-old founder, envisions Theranos Wellness Centers in Walgreens stores throughout the US, giving patients easy access to automated testing. Patients with chronic problems could get doctor-recommended tests before their appointments. Results would then be available during the consult, allowing practitioners to make more informed decisions. If the Theranos-Walgreens venture succeeds, laboratory testing will be revolutionized.

Rago J. Elizabeth Holmes: the breakthrough of instant diagnosis. *Wall Street Journal*. September 8, 2013. Available at http://online.wsj.com. Accessed October 12, 2013.

Theranos selects Walgreens as a long-term partner through which to offer its new clinical laboratory service [press release]. September 9, 2013. news.walgreens.com/article_display.cfm?article_id=5794.

Pharmaceuticals and Epigenetic Side Effects

Numerous factors, including basic nutrients, tobacco smoke, heavy metals, pesticides, and the social environment, can bring about epigenetic changes, affecting gene expression via methylation or histone acetylation. These epigenetic modifications pass from one generation of cells to the next until some change in the environment tweaks gene expression yet again. Antonei B. Csoka at University of Pittsburgh Medical Center and Moshe Szyf at McGill University (Montreal, Quebec, Canada) maintain, in their 2009 paper "Epigenetic Side-Effects of Common Pharmaceuticals: A Potential New Field in Medicine and Pharmacology," that some pharmaceutical drugs cause persistent epigenetic changes. Csoka and Szyf say, "Epigenetic processes are natural and essential to the function of organisms, but if they occur improperly, there can be major adverse health and behavioral effects."

Possible adverse epigenetic effects, according to the authors, include obesity, infertility, cognitive disorders, heart disease, cancer, and autoimmune disease. Hydralazine, a vasodilator for hypertension, and procainamide, an antiarrhythmic sodium channel blocker, inhibit DNA methylation and thereby affect the epigenome. Both drugs, in some people, trigger a lupuslike autoimmune disease with anti-DNA antibodies. Csoka and Szyf propose that other drugs that cause persistent effects may actually be affecting the epigenome; researchers have simply not yet investigated the drugs' affects on DNA methylation or histone acetylation. Csoka and Szyf believe that drugs' effects on the epigenome needs to become a standard aspect of research: "A systems biology approach employing microarray analyses of gene expression and methylation patterns can lead to a better understanding of long-term side-effects of drugs ... in the future, epigenetic assays should be incorporated into the safety assessment of all pharmaceutical drugs."

Csoka AB, Szyf M. Epigenetic side-effects of common pharmaceuticals: A potential new field in medicine and pharmacology. *Med Hypotheses*. 2009;73:770–780. Available at www.medicinabiomolecular.com/br/biblioteca/pdfs/Nutrigenomica/nutrig-0043.pdf. Accessed October 16, 2013.

Food Additives and Conflict of Interest

The Food Additives Amendment of 1958, which is still in effect, gives manufacturers the authority to decide whether an additive is "generally recognized as safe" (GRAS) without notifying the FDA. About 1000 of an estimated 4300 GRAS additives have not been reported to the FDA, according to a 2013 investigation led by Thomas G. Neltner, JD, with the Pew Charitable Trusts. GRAS food additives range from the ordinary, such as salt, to controversial additives such as nanoparticles, microscopic particles with unknown effects that are being added to food and food packaging. The US FDA maintains little oversight of the process, according to Neltner and colleagues. Between 1997 and 2012, they found only one instance in which the FDA questioned manufacturers' GRAS determination: the addition of caffeine to alcoholic beverages that produced injuries and deaths among consumers.

How does an additive gain GRAS status? Either individual employees or expert panels, hired by manufacturers or their consultants, perform the evaluation. Neltner and colleagues reviewed the 451 GRAS notifications that manufacturers had submitted to FDA between 1997 and 2012: "22.4% of the safety assessments were made by an employee of an additive manufacturer, 13.3% by an employee of a consulting firm selected by the manufacturer, and 64.3% by an expert panel selected by either a consulting firm or the manufacturer. A standing expert panel selected by a third party made none of these safety assessments." A panel, even one consisting of three people, has access to more perspectives than a single employee. Neltner et al. found that 216 people served on 290 GRAS panels between 1997 and 2012. A small number of these experts were hired repeatedly: "At least 1 of the 10 individuals with the most frequent service was a member of 225 panels (77.6%)." Relying so heavily on a small group of people when the Institute of Food Technologists has certified 1200 food scientists "... would limit the range of knowledge and experience on the panels," say the authors. It also raises questions about financial conflict of interest. Experts' financial ties to manufacturers do not necessarily sway their opinions about an additive's safety. On the other hand, manufacturers are unlikely to rehire experts who make it difficult to pursue their business.

A 2010 Government Accountability Office report recommended that the FDA increase its supervision of the GRAS system and "'minimize the potential for conflicts of interest in companies' GRAS determinations.'" In her commentary about the Neltner conflict-of-interest study, Marion Nestle, PhD, MPH, said that the FDA responded to the GAO report by reopening the comment period for rules proposed in 1997, but never finalized the process. In October 2013, the agency was still working on its GRAS regulations.

Neltner TG, Alger HM, O'Reilly JT, Krimsky S, Bero LA, Maffini MV. Conflicts of interest in approvals of additives to food determine to be generally recognized as safe out of balance. *JAMA Intern Med.* Epub August 7, 2013. doi:10.1001/jamainternmed.2013.10559. Available at http://archinte.jamanetwork.com. Accessed August 11, 2013.

Nestle M. Conflicts of interest in the regulation of food safety: a threat to scientific integrity. *JAMA Intern Med.* Epub August 7, 2013. Available at http://archinte.jamanetwork.com. Accessed August 11, 2013.

Journal Impact

The journal impact factor (JIF), a measurement originally used to help university librarians pick journals for their libraries, is an easy way to evaluate a journal's impact on research and, therefore, its demand; but two recent articles claim that the JIF is being misused. The JIF is calculated by dividing the number of journal articles cited by other researchers in a given year by the total number of citable articles published in the previous two years. The higher the number, the greater the journal's prestige. JIF refers to a journal as a whole, not to the quality of individual articles. The quality and import of an article does not necessarily correspond to the impact factor of the journal in which it appears. Nonetheless, journal impact factors are being used to assess researchers' work and their articles' scientific value when making decisions about hiring, promotions, and grants, "particularly in Europe," according to Lutz Bornmann and colleagues.

The number of citations of a journal's articles in a single year does not reflect clinical importance, as Americans Joseph Bernstein and Chancellor F. Gray point out in their 2012 article. As an example, they use *CA: A Cancer Journal for Clinicians*, the scientific journal with the highest impact factor in 2010 (JIF = 94.33): "This number is calculated by noting that 19 source items were published in 2008 and 23 items in 2009 and in turn the journal's 2008 and 2009 material was cited a total of 3,962 times in 2010 (3,962/42 = 94.33)." The majority of the citations refer to just two articles: "Cancer Statistics 2008" and "Cancer Statistics 2009." If those two frequently cited articles had not been published, the JIF for *CA: A Cancer Journal for Clinicians* would have been 8.07. Statistics citing incidence and types of cancers usually appear in the background or introduction of an article. They are not the foundation for research that involves diagnosis or treatment.

Articles that offer new clinical approaches often do not gain widespread attention in the first two years after publication – the time span used to calculate JIF. Bernstein and Gray point to the 1983 paper in which J. R. Warren identified *H. pylori* as a cause of peptic ulcer disease. "By 1985 – the last year this paper could be counted toward *The Lancet's* Impact Factor – it was cited 37 times," say the authors. "In the years that followed, the paper was cited more than 2,000 additional times, with profound impact on both the author (who won the 2005 Nobel Prize) and the practice of medicine."

Practitioners usually know which journals give them useful information and which do not; they do not need the JIF to make their decisions. They do, however, need to understand that a low JIF does not indicate a journal's or an article's quality. The impact factor is simply based on the number of citations that a journal receives over a year. Fewer citations may result from researchers' unfamiliarity with the journal's topics or with the journal itself.

Berstein J, Gray CF. Content factor: a measure of a journal's contribution to knowledge. *PLOS ONE.* July 2012; 7(7):e41554. Available at www.plosone.org. Accessed October 16, 2013.

Bornmann L, Marx W, Gasparyan AY, Kitas GD. Diversity, value and limitations of the journal impact factor and alternative metrics. *Rheumatol Int.* Epub December 23, 2011. doi:10.1007/s00296-011-2276-1. Available at www.ease.org.uk. Accessed October 16, 2013.

Shorts

➤

Lymphocyte Transformation Test for Lyme/Borrelia

Lymphocyte transformation testing (LTT) is useful for diagnosing active Lyme infection caused by borrelia bacteria, according to recent studies. Presently, diagnosis is made using an enzyme-linked immunosorbent assay (ELISA) followed by a western blot test, if ELISA results are positive or borderline. Both tests detect antibodies to Lyme antigens. Antibodies indicate that the body has been exposed to and fought a pathogen. They are not a good indicator of active infection because antibodies can remain in circulation long after resolution of symptoms. In addition, these tests are often negative in early Lyme disease, when the body is just beginning to respond to the infection. If a patient is among the 40% without erythema migrans (bull's-eye rash), which marks a tick's bite, diagnosing an active Lyme infection can be very difficult because symptoms are so diverse.

Elizabeth Valentine-Thon and German colleagues were the first team to investigate the use of MELISA (memory lymphocyte immunostimulation assay), an LTT format that uses a higher cell concentration (1×10^6 lymphocyte cells per test) to test for borrelia infection. LTT-MELISA was developed in the 1980s, to detect metal sensitivities. In a 2007 study, Valentine-Thon et al. reported a specificity of 96.7% for the test; that is, one of 30 seronegative healthy controls was false positive for borrelia infection. The researchers did not have appropriate samples to authenticate infection for most of the 68 patients in the study, so they could not determine the test's sensitivity (false negatives). They did, however, observe a correlation between clinical improvement and LTT-MELISA in 54 patients who were tested before and after antibiotic therapy: "After therapy, most patients (90.7%) showed negative or markedly reduced lymphocyte reactivity correlating with clinical improvement."

A second German research team, led by Volker von Baehr, used LTT with 2×10^5 cells per well to evaluate 1480 patients suspected to have Lyme. The test's specificity (ability to avoid false positives) was 98.7%, and its sensitivity (ability to avoid false negatives) was 89.4%. In addition, the team compared patients' LTT results with their serology (ELISA/western blot). Results from the serologic tests and LTT matched in 79.8 cases. In 18% of the patients, the serologic tests were positive and LTT was negative; most of these patients had received antibiotic therapy. The remaining 2.2% had a positive LTT result and negative serological result; half of these patients had a bull's-eye rash indicating an early stage of infection. Like Valentine-Thon et al., von Baehr's team also found changes in LTT test results after patients completed antibiotic treatment: "Following antibiotic treatment, the LTT became negative or borderline in patients with early manifestations of borreliosis, whereas in patients with late symptoms, it showed a regression while still remaining positive.

LTT accuracy depends upon the laboratory. Valentine-Thon et al. say, "Because of the complexity of lymphocyte proliferation assays and the controversy surrounding their use for diagnosing [Lyme borreliosis], we strongly recommend that the LTT-MELISA® described here, or comparable tests, be applied only in accredited laboratories with proven cell culture expertise."

Valentine-Thon E, Ilsemann K, Sandkamp M. A novel lymphocyte transformation test (LTT-MELISA®) for Lyme borreliosis. *Diagn Microbiol Infect Dis.* 2007;57;27–34. Available at www.onesong.com/uploads/pathologies/lymphocite-transformation-test.pdf. Accessed October 16, 2013

Von Baehr V, Doebis C, Volk HD, von Baehr R. The lymphocyte transformation test for borrelia detects active Lyme borreliosis and verifies effective antibiotic treatment. *Open Neurol J.* 2012;6 (Suppl 1-M5);10–112. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3474945. Accessed October 16, 2013.

Probiotic Supplementation and Upper Respiratory Infections

Probiotic supplements can reduce the number of upper respiratory tract infections (URTI) in athletes, according to recent studies. The stress of intense exercise and competition is known to depress immune function. In a 2013 randomized controlled trial, 30 rugby players were given either 1 probiotic capsule per day or a placebo during training for 4 weeks. After a 4-week washout period, the players received the opposite treatment. This study was the first to look at team athletes, who have a greater opportunity to spread illness to one another, study coauthor Katherine E. Black told Kirk Hamilton in an October 2013 interview. The capsules contained *Lactobacillus gasseri*: 2.6 billion CFU; *Bifidobacterium bifidum*: 0.2 billion CFU; *Bifidobacterium longum*: 0.2 billion CFU. While taking the probiotic, 14 of 30 athletes remained healthy, whereas only 6 of them stayed healthy when taking the placebo. Players who became ill while taking the probiotic recovered more quickly: "The mean $\pm$ standard deviation for the number of days of illness tended to be higher for the placebo, (5.8 ± 6.6 days) than probiotic (3.4 ± 4.6 days), ($p=0.054$)." No difference in severity of illness was apparent.

Michael Gleeson at Loughborough University (Loughborough, UK) and colleagues have tested other probiotic supplements on endurance athletes. A 2011 double-blind study followed 84 people who participated in at least three training sessions, totaling a minimum of 3 hours, each week for 4 months during winter. Half of the athletes received a placebo supplement, and the others took a commercially available product containing *Lactobacillus casei* Shirota. (Manufacturer Yakult Honsha Co. Ltd. Japan sponsored this study.) Ninety percent of the placebo group compared with 66% of the probiotic group reported upper respiratory tract symptoms for 1 or more weeks during the study. Symptom severity and duration did not significantly differ between the two groups, but more athletes in the placebo group reported difficulty training when URTI symptoms were present compared with the probiotic group (.54 and .81, respectively; $p = 0.036$).

A 2012 study, also led by Gleeson, looked at a *Lactobacillus salivarius* preparation using the same study design with 66 participants during 4 months of spring training. (Manufacturer GlaxoSmithKline Ltd. sponsored the

study.) This study found no effect on URTI incidence. The authors report several confounding factors: a 10% difference in activity levels between the groups, predominance of female subjects, fewer colds in spring, and possibly too few subjects. They also state that *L. salivarius* may simply have no effect on URTI. "No two probiotics are exactly alike," say the authors, "so we should not expect reproducible results from studies that employ different species or strains, variable formulations, and diverse dosing schedules."

Consumers wishing to reduce and avoid respiratory infections need to understand that probiotic supplements differ in strain and quality. Seek products whose effects have been verified by research.

Gleeson M, Bishop NC, Oliveira M, McCauley T, Tauler P, Lawrence C. Effects of a *Lactobacillus salivarius* probiotic intervention on infection, cold symptom duration and severity, and mucosal immunity in endurance athletes. *Int J Sport Nutr Exerc Metab.* 2012;22:235–242. Available at https://dspace.lboro.ac.uk. Accessed October 16, 2013.

Gleeson M, Bishop NC, Oliveira M, Tauler P. Daily probiotic's (*Lactobacillus casei* Shirota) reduction of infection incidence in athletes. *Int J Sport Nutr Exerc Metab.* 2011;21:55–64. Available at https://dspace.lboro.ac.uk. Accessed October 16, 2013.

Haywood BA, Black KE. Baker D, et al. Probiotic supplementation reduces the duration and incidence of infections but not severity in elite rugby union players [abstract]. *J Sci Med Sport.* (in press) Available at www.jsams.org/article/S1440-2440(13)00190-4/abstract. Accessed October 15, 2013.

Transgenerational Environmental Effects

Exposure to chemicals such as bisphenol A, DEET, dioxin, nicotine, and others can producing observable transgenerational effects in animals, according to an *Environmental Health Perspectives* article by Charles W. Schmidt. He says, "Chemicals given to pregnant females (the F_0 generation) interact not only with the fetal offspring (the F_1 generation) but also the germ cells developing within those offspring which mature into the sperm and eggs that give rise to the F_2 generation." Multiple animal studies show that the F3 generation, which had no exposure, also exhibits effects. Andrea Cupp first noticed transgenerational effects while studying descendents of pregnant rats exposed to the insecticide methoxyclor. She observed decreased sperm counts and higher infertility rates in succeeding generations of male rats, including the F3 generation, the great-grandchildren of the pregnant rat.

Since then, other researchers have discovered that specific chemicals have diverse transgenerational effects. Virender Rehan at Harbor UCLA Medical Center found "that prenatal exposure to nicotine in rats starting at embryonic day 6 was associated with asthma-like symptoms among F3 males and females," writes Schmidt. R. Chamorro-Garcia et al. observed a nonalcoholic fatty liver condition in F3-generation mice descended from females "exposed to *extremely low levels* of the biocide tributyltin (TBT)" during pregnancy (my emphasis). At this time, the only multigenerational human study to track the effects of a chemical is the DES Third Generation Cohort Study, which is studying the now adult grandchildren of women who took diethylstilbestrol (DES) to prevent a miscarriage. Daughters of the exposed women have a higher risk of reproductive cancers and other problems, and sons have a higher incidence of urogenital defects. Preliminary evidence indicates that female grandchildren may have an increased risk of ovarian cancer.

Shorts

The National Institute of Environment Health Sciences has begun funding research on chemicals' transgenerational effects on mammals. We may learn a new reason to keep the welfare of the seventh generation in mind when making decisions.

Schmidt CW. Transgenerational effects of environmental exposures. *Environ Health Perspect.* October 2013;121(10):A298–A303.

Test for Respiratory Infections

Duke University researchers have developed a quick new blood test that determines when a virus is the cause of an upper respiratory infection. The test measures the body's genetic response to viral infection using a reverse transcription polymerase chain reaction (RT-PCR) TaqMan low-density array (TLDA) platform. "Improved ways to diagnose acute respiratory viral infections could decrease inappropriate antibacterial use and serve as a vital triage mechanism in the event of a potential viral pandemic," say Aimee K. Zaas and colleagues.

To develop the test, the researchers exposed healthy volunteers to influenza A H3N2/Wisconsin or influenza A H1N1/Brisbane and took blood RNA samples. Then they tested the assay in 41 healthy volunteers and 102 adults who arrived at an emergency unit with a fever and "microbiologically proven viral respiratory infection or systemic bacterial infection." The test correctly identified viral infection and avoided false negatives in 89% of the patients with viral infection (sensitivity). The test's specificity (the ability to avoid false positives) was 94%. Researchers aim to reduce the turnaround time to just one hour by reducing the number of genes analyzed.

By quickly identifying viral infections, the RT-PCR test could reduce inappropriate antibiotic use. Every time an antibiotic is used, bacteria have an opportunity to mutate and gain resistance to the drug. In addition to slowing antibiotic overuse, this new test will permit early recognition of emerging virus epidemics.

Heitz D. Is your illness viral or bacterial? A New rapid blood test can tell [online article]. Healthline. September 18, 2013. Available at www.healthline.com. Accessed October 9, 2013.

Zaas AK, Burke T, Chen M et al. A host-based RT-PCR gene expression signature to identify acute respiratory viral infection [abstract]. *Sci Transl Med.* September 18, 2013;5(203):203ra126. Available at http://stm.sciencemag.org/content/5/203/203ra126. Accessed October 9, 2013.

◆

War on Cancer

by Ralph Moss, PhD
www.cancerdecisions.com

In November 2013, I gave a keynote address at the 32nd annual conference of the International Clinical Hyperthermia Society (ICHS), hosted by Clifford Pang, MD, in Guangzhou, China. My topic was "Hyperthermia and the Crisis in the War on Cancer." I also visited several hospitals in China that are using complementary and alternative medicine (CAM) in interesting and important ways.

I am also proud to announce that I have been appointed a standing director of the World Federation of Chinese Medicine Societies (WFCMS).

In October, a paper that I coauthored with Tibor Bakacs, MD, PhD, DSc, of the Hungarian Academy of Science, and Prof. Shimon Slavin, MD, of Tel Aviv, was accepted by a peer-reviewed medical journal. I will give details once it appears in print.

Progress in Targeted Chemotherapy: Colorectal Cancer

Hardly a week goes by that one does not read of some new breakthrough in the treatment of cancer of the colon and rectum (colorectal cancer). Since I published "Questioning Chemotherapy" in 1996, there have been thousands of such articles. A Google search of progress in colorectal cancer returns 2.2 million hits.

In considering the question of progress, I propose that we avoid secondary sources and go directly to the clinical trial data. Here, substantial progress is more difficult to detect, especially if we look for increased overall survival when new drugs are added to standard chemotherapy regimens (such as the FOLFOX and FOLFIRI). But any reports of progress are more dependable than articles intended for laypeople.

I will focus on the treatment of metastatic stage IV colorectal cancer, or mCRC, as it is abbreviated. Some people may say that it is unfair of me to focus on mCRC, since it is extremely difficult to treat. But that is precisely the point. When we speak of a "cure for cancer," we certainly must include people with advanced disease. Anything short of successfully treating this stage of cancer will never qualify as a genuine "cure."

Some Facts About Colorectal Cancer

Colorectal cancer is the second most common cancer in women and the third most common in men in the world. There is an estimated worldwide incidence of 1.2 million and mortality of 600,000 (2008 figures).[1] In the US, colon cancer afflicts ~100,000 people per year while rectal cancer affects ~40,000. CRC killed 50,830 Americans in 2013, or 9% of all cancer deaths.

The age-adjusted death rate of colon cancer has thankfully declined since 1996: it was ~30 per 100,000 in the male population and is now ~20 per 100,000. This represents excellent progress which has come about mainly through the use of colonoscopy as a mass screening tool, which enables doctors to find polyps or early-stage colon cancer. I urge all of my readers to have colonoscopies on a regular schedule (usually once every 5 years).

However, the question at issue is not progress in early detection but the treatment of late-stage disease. Here the picture is less promising. Few very effective new drugs or drug regimens have emerged over the past 20 or so years. Leonard Saltz, MD, a leading colorectal cancer expert at Memorial Sloan-Kettering Cancer Center, New York, has stated that chemotherapeutic regimens still basically rely on 5-fluorouracil (5-FU), a drug developed in the early 1960s. Meanwhile, the cost of treating mCRC has risen exponentially.

The American Cancer Society (ACS), as is its habit, paints an optimistic picture: "Several targeted therapies are approved by the FDA to treat metastatic colorectal cancer: bevacizumab (Avastin) and ziv-aflibercept (Zaltrap) block the growth of blood vessels to the tumor, and cetuximab (Erbitux) and panitumumab (Vectibix) block the effects of hormone-like factors that promote cancer growth."

But how effective are these new "targeted" agents?

Panitumumab (Vectibix)

The so-called PICCOLO randomized controlled trial published in *Lancet Oncology* this year compared the new drug panitumumab (Vectibix) + irinotecan vs. irinotecan alone in the treatment of mCRC. Panitumumab is the first fully human monoclonal antibody to epidermal growth factor receptor (EGFR) to enter clinical trials for the treatment of solid tumors.[2]

Those in the combined-treatment group experienced more frequent side effects (diarrhea, skin toxicity, lethargy, and infection). There were also five treatment-related deaths. Developers of the drug say that patients who receive it have better progression-free survival (PFS) and a greater number of responses than those who receive irinotecan alone. But PFS is not the most important parameter of benefit. Most important is overall survival, and the bottom line of this study was that "there was no difference in overall survival between the [two] groups."[3]

Meanwhile, the cost of panitumumab is $4000 for an infusion every two weeks, or around $100,000 per year.

Bevacizumab (Avastin)

There are a number of clinical trials of bevacizumab (Avastin) in mCRC; in fact, too many to consider here. However, one classic paper showed an increase in median PFS from 8.0 months in the placebo group to 9.4 months in the bevacizumab-added group. Median overall survival was 19.9 months in the placebo group vs. 21.3 months in the bevacizumab-added group. However, this 1.4-month improvement was *not* statistically significant.

Ziv-Aflibercept (Zaltrap)

Another targeted drug for mCRC is ziv-aflibercept (Zaltrap). In a Belgian clinical trial, this was compared with the standard FOLFIRI regimen (5-FU, leucovorin, and irinotecan). The paper claimed that the addition of ziv-aflibercept "improves survival in patients with metastatic colorectal cancer."

The median survival time with FOLFIRI alone was 12 months, but when ziv-aflibercept was added, median survival went to 13.5 months. Thus, the addition of the new drug added 1½ months, or 6 weeks, to overall survival.[4]

Meanwhile, the cost of ziv-aflibercept was set at USD $11,000 per month, or $132,000 per year.

This 1½ month extra survival happened to be the same benefit as bevacizumab (Avastin). But Avastin costs half as much.

When doctors at Memorial Sloan-Kettering Cancer Center (including Saltz) announced in the *New York Times* that they would not buy ziv-aflibercept at that price, Sanofi announced that it was giving hospitals a 50% discount on the price, effective immediately.[5,6] Sometimes it pays to complain.

Regorafenib (Stivarga)

Much was made at the 2012 American Society for Clinical Oncology (ASCO) meeting about the so-called CORRECT trial. This was a clinical trial of a new oral multikinase inhibitor, regorafenib, for colorectal cancer. But regorafenib only outperformed best supportive care (BSC) by 1 week of progression-free survival and 1.4 months of median overall survival. The overall response rate was 1.6%. Yet it is said that the manufacturer, Bayer, expects to make more than $1 billion per year on this drug.

Bottom Line

Despite much positive publicity, the actual benefit of targeted agents over standard chemotherapy appears to be small, about 1½ months' increase in median overall survival.

Does Beer Prevent Barrett's Esophagus?

Beer is one of the most popular drinks in the world. Consumption ranges from 2 liters (or quarts) per person per year in India to a whopping 132 liters in the Czech Republic (home of the original Pilsner and Budweiser beers). Asia as a whole consumes 1/3 of the world production, Europe takes about 30%, and North and South America combined consume another 30%. Consumption is very low in the Middle East, mainly because of Islamic strictures against alcohol.

What is the impact of beer drinking on cancer, particularly cancer of the esophagus? This is the eighth most common cancer worldwide and the sixth leading cause of cancer deaths. A precursor condition to esophageal cancer is Barrett's esophagus, which is a chronic erosion of the lining of the esophagus.

The reason for concern is that alcohol is a known carcinogen.[7] Alcohol is also a known cause of esophageal squamous cell carcinoma, and "may increase the risk of Barrett's esophagus (BE) through direct contact with esophageal mucosa."[8] There is also "strong evidence of a causal link between alcohol and the risk of cancers of the oral cavity, pharynx, liver, colon, rectum, and, in women, breast." Many doctors understandably caution patients not to drink alcohol, especially when they are at risk of Barrett's esophagus or esophageal cancer.

However, there is a difference between pure alcohol and some of the drinks in which it occurs. This is well known for red wine, but may also be true of beer.

In October 2013, Aaron P. Thrift of Brisbane, Australia, published a very interesting paper in the *American Journal of Gastroenterology* with extraordinary findings on beer and Barrett's esophagus. According to Thrift, alcohol consumption (which in Australia primarily means beer) was not associated with any increased risk of Barrett's esophagus. In fact, a moderate intake (defined as between 14 and 28 glasses per week) led to an odds ratio (OR) of Barrett's of just 0.39.[9] That means that there was a 61%

➤

➤

reduction in Barrett's among people who averaged 2 glasses of beer per day.

This follows a 2011 study by the same group showing that (1) alcohol consumption in general did not increase the risk of Barrett's esophagus, and (2) there was in fact a "significant inverse association" of Barrett's with beer consumption. In the 2011 study, the OR of drinking 7 to 21 glasses of beer per week was 0.53, while the OR of drinking 21 to 41 drinks per week was 0.37. In other words, a glass or 2 of beer per day reduced the risk of Barrett's esophagus in half, while 3 to 5 glasses per day reduces the risk by $^2/_3$!

Being a naturally suspicious sort, I looked for but found no mention of any financial support of this study by Australia's beer companies.

The Reinheitsgebot

Beer is a fascinatingly complex beverage. In Germany, according to the Beer Purity Law (*Reinheitsgebot*) of 1516, it can only be made from four ingredients: water, yeast, malted barley, and hops. The infinite variety of beers worldwide mainly comes from the varieties of these four ingredients and the manner in which they are brewed. The final product contains hundreds of constituents, so figuring out which is doing what, biologically speaking, can be daunting.

Beer contains carbohydrates, amino acids, minerals, vitamins, and many antioxidants, especially phenols. The antioxidants in hops alone include phenols, cinnamic acid derivatives, coumarins, catechins, proanthocyanidins, and flavonoids, according to Clarissa Gerhäuser of Heidelberg, who has counted and classified 78 in toto.[10]

Hops (*Humulus lupulus*) are a form of "herbal medicine" that the average person is unlikely to encounter except in beer. The dried hop cones of this vine contain 4% to 14% polyphenols by weight. Hop plant or its constituents have been used as a sleep aid, tranquilizer (anxiolytic), and general relaxant. Hops even increased "sexual motivation in hormone-primed female rats."[11]

There is also experimental evidence for the anticancer effect of beer. Rats given a chemical that induces colorectal cancer were coadministered tap water, 5% pure ethanol (alcohol), or beer to drink. Water and pure ethanol had no effect on colon cancer formation. But beer significantly reduced tumor formation by 33% and diminished the number of tumors per rat by more than half![12]

Bitter Is Better

Because fresh beer tends to get cloudy in storage, America's massive commercial breweries treat their product with chemicals that remove most of the antioxidants. You might as well be drinking carbonated water with alcohol added. From a health point of view, the purity and the integrity of the beer are extremely important. Since hops are the main source of antioxidants, in general, the "hoppier" the better (although individual preference is a major consideration). You might say, all things being equal, bitter is better.

The ideal beer should be served soon after brewing, without preservatives or other chemicals, such as you would find at your local microbrewery. In the late 1970s, the total number of US breweries had shrunk to just 89. Then came the microbrewery revolution. As of June there were 2483 craft breweries in the US (and 24 large noncraft breweries, such as Miller and Budweiser). There are now more breweries in the US than there were in Mark Twain's day. You may be fortunate to live in a "brewtopia," such as Portland, Oregon, with its 52 in-town breweries. But if not, odds are good that there is a local microbrewery within driving distance.

Of course, not only is beer physically complex, but so is its sociology. I live in a college town notorious for excess drinking, and so I get to see the negative effects of alcohol close up. These college kids generally drink "beer" that is more like soda than true beer. For some, it is just a fast way to get drunk. Excessive consumption of alcohol is truly a danger, and can harm bystanders as well as those who partake.

But moderate consumption of beer by people with self-control might have unexpected benefits. Scientists describe a U-shaped curve in relation to beer consumption and cancer. This means that zero consumption is not necessarily the best course, nor is heavy consumption. The most reasonable intake, if you enjoy beer, might include one or two glasses of microbrewed beer per day.

Notes

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127:2893–2917.
2. Berardi R, Onofri A, Pistelli M, et al. Panitumumab: the evidence for its use in *the treatment* of metastatic colorectal cancer. *Core Evid*. 2010;5:61–76.
3. Seymour MT, Brown SR, Middleton G, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. *Lancet Oncol*. 2013;14(8):749–759. doi:10.1016/S1470-2045(13)70163-3.
4. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*. 2012;30(28):3499–3506. doi:10.1200/JCO.2012.42.8201.
5. Bach PB, Saltz LB, Wittes RE. In cancer care, cost matters. *New York Times*. October 14, 2012:A25.
6. Goldberg B. Zaltrap price cut in half effective immediately. *Cancer Lett*. 2012;38:1–4.
7. Thrift AP, Pandeya N, Smith KJ, et al. Lifetime alcohol consumption and risk of Barrett's esophagus. *Am J Gastroenterol*. 2011;106(7):1220–1230.
8. Ibid.
9. Thrift AP, Kramer JR, Richardson PA, El-Serag HB. No significant effects of smoking or alcohol consumption on risk of Barrett's esophagus. *Dig Dis Sci*. 2013. doi:10.1007/s10620-013-2892-6.
10. Gerhäuser C. Beer constituents as potential cancer chemopreventive agents. *Eur J Cancer*. 2005;41(13):1941–1954. doi:10.1016/j.ejca.2005.04.012.
11. Di Viesti V, Carnevale G, Zavatti M, Benelli A, Zanoli P. Increased sexual motivation in female rats treated with Humulus lupulus L. extract. *J Ethnopharmacol*. 2011;134(2):514–517. doi:10.1016/j.jep.2010.12.040.
12. Nelson RL, Samelson SL. Neither dietary ethanol nor beer augments experimental colon carcinogenesis in rats. *Dis Colon Rectum*. 1985;28(6):460–462.

Ralph W. Moss, PhD, is the author of 12 books on cancer-related topics. The former science writer at Memorial Sloan-Kettering Cancer Center, for 35 years Moss has investigated the validity of many cancer treatments. He currently directs the *Moss Reports*, a library of reports for patients on over 200 different cancer diagnoses. ◆

Literature Review & Commentary

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

Licorice Extract for *Helicobacter Pylori* Infection

One hundred seven patients with *Helicobacter pylori* infection were randomly assigned to receive, in double-blind fashion, 150 mg of a licorice extract (GutGard; Natural Remedies, Bangalore, India) or placebo once a day for 60 days. Each capsule of GutGard contained 150 mg of active components of licorice root (*Glycyrrhiza glabra*): glabridin (at least 3.5%), glabrol (at least 0.5%), eicosanyl caffeate (at least 0.1%), docosyl caffeate (at least 0.1%), and glycyrrhizin (not more than 0.5%; licorice root typically contains 4% glycyrrhizin). *H. pylori* infection was assessed at days 0, 30, and 60 with a urea breath test and a stool antigen test. At day 60, the proportion of patients who were *H. pylori*-negative according to the urea breath test (48% vs. 2%) and according to the stool antigen test (56% vs. 4%) was significantly higher in the active-treatment group than in the placebo group. Side effects did not differ between groups.

Comment: Licorice extracts have previously been shown to be effective for treating both gastric and duodenal ulcers and for preventing their recurrence. Deglycyrrhizinated licorice (DGL; licorice from which most of the glycyrrhizin has been removed) has been used in most studies, because glycyrrhizin can cause hypertension and hypokalemia, and because it does not appear to an important contributor to the antiulcer effect of licorice. It has been assumed that the protective effect of DGL is due mainly to its capacity to increase the number of cells in the gastrointestinal lining that produce protective mucus. However, the results of the present study suggest that an additional mechanism of action may be the eradication or suppression of *H. pylori*. The amount of glycyrrhizin contained in a daily dose of GutGard is less than that present in a typical therapeutic dose of DLG.

Puram S et al. Effect of GutGard in the management of Helicobacter pylori: a randomized double blind placebo controlled study. *Evid Based Complement Alternat Med.* 2013;2013:263805.

Nutrients Promote Wound Healing

Twenty trauma patients (mean age, 45 years) with wounds that were not healing were randomly assigned to receive, in double-blind fashion, in addition to their hospital diet, 40 g of glutamine, 1000 mg of vitamin C, 332 mg of alpha-tocopherol, 6.4 mg of beta-carotene, 200 µg of selenium, and 13.2 mg of zinc, in 2 divided doses per day, or placebo (an isocaloric amount of maltodextrin) for 14 days. The mean time until wound closure occurred was significantly less in the active-treatment group than in the placebo group (35 vs. 70 day days; $p = 0.01$).

Comment: The results of this study demonstrate that supplementation with glutamine plus various micronutrients accelerated wound healing in trauma patients with impaired wound healing. Previous research suggests that the beneficial effect of these nutrients would be enhanced by increasing the dosage of zinc and by adding copper and B vitamins.

Blass SC et al. Time to wound closure in trauma patients with disorders in wound healing is shortened by supplements containing antioxidant micronutrients and glutamine: a PRCT. *Clin Nutr.* 2012;31:469–475.

Intravenous Magnesium for Neuropathic Back Pain

Eighty patients (mean age, 56 years) with chronic low back pain with a neuropathic component, who had had an inadequate response to anticonvulsants, antidepressants, analgesics, and interferential current therapy, were studied. While continuing those treatments, they were randomly assigned to receive, in double-blind fashion, magnesium or placebo. Magnesium therapy consisted of 1 g of magnesium sulfate intravenously in 250 ml of 0.9% saline given over 4 hours every day for 2 weeks, followed by oral magnesium (245 mg twice) a day for 4 weeks. The placebo group received 0.9% saline intravenously followed by oral placebo. All patients reported a significant

➤

improvement in pain after 2 weeks, with no significant difference between groups. At 6 months, compared with baseline, a significant reduction in pain intensity was seen in the magnesium group (4.7 vs. 7.5 on a 10-point scale; $p = 0.034$). In contrast, mean pain intensity improved nonsignificantly in the placebo group, from 7.4 at baseline to 7.2 ($p < 0.03$ for the difference in the change between groups). The improvement in pain was also significantly greater in the magnesium group than in the placebo group at 6 weeks and 3 months. The reduction in pain intensity in the magnesium group was accompanied by significant improvement in lumbar spine range of motion during the follow-up period.

Comment: Persistent mechanical irritation of the nerve root (as seen with degenerated or herniated discs) sets up a series of events that lead to chronic pain, mediated by sensitization of the dorsal roots and dorsal horns in the spinal cord. Magnesium blocks sensitization in the central nervous system through its effect on N-methyl-D-aspartate receptors. The present study demonstrated that treatment with intravenous magnesium followed by oral magnesium over a 6-week period improved pain intensity and lumbar spine mobility during a 6-month period in patients with refractory chronic low back pain with a neuropathic component.

Yousef AA, Al-deeb AE. A double-blinded randomised controlled study of the value of sequential intravenous and oral magnesium therapy in patients with chronic low back pain with a neuropathic component. *Anaesthesia*. 2013;68:260–266.

L-Carnitine Improves Narcolepsy

Thirty patients (mean age, 41.2 years) with narcolepsy were randomly assigned to receive, in double-blind fashion, 510 mg per day of L-carnitine (340 mg in the morning and 170 mg in the evening) or placebo for 8 weeks and then the alternate treatment for an additional 8 weeks. The total amount of time per day spent dozing off during the daytime (as measured by sleep logs) was significantly less during the L-carnitine period than during the placebo period (49 vs. 58 minutes; $p < 0.05$).

Comment: Narcolepsy is characterized by excessive daytime sleepiness. The cause is not known, but it appears to be an autoimmune disease and is associated with various neurotransmitter abnormalities. Carnitine enhances energy production by facilitating the transport of fatty acids into mitochondria. Levels of acylcarnitine (a metabolite of carnitine) have been found to be low in narcolepsy patients. That finding suggests that these individuals may have suboptimal carnitine status, which might exacerbate daytime sleepiness. The results of the present study indicate that L-carnitine supplementation can reduce daytime sleepiness in narcolepsy patients. The beneficial effect was only modest, but the dosage used in the study was relatively low in comparison with the amounts used to treat conditions such as congestive heart failure and angina (1.5 to 2.0 g per day in most studies). It is possible that those larger doses would be more effective than 510 mg per day.

Miyagawa T et al. Effects of oral L-carnitine administration in narcolepsy patients: a randomized, double-blind, cross-over and placebo-controlled trial. *PLoS One*. 2013;8(1):e53707.

Selenium and Diabetes

Sixty patients (mean age, 55 years) with type 2 diabetes who were being treated with oral hypoglycemic agents were randomly assigned to receive, in double-blind fashion, 200 μg per day of selenium (as sodium selenite) or placebo for 3 months. At baseline, the mean serum selenium concentration in the selenium group was 42.7 μg/L, as compared with a mean of 101 μg/L in healthy individuals living in the same region. The mean fasting plasma glucose concentration increased in the selenium group from 132 mg/dl at baseline to 148 mg/dl, whereas it decreased in the placebo group from 150 mg/dl to 130 mg/dl ($p < 0.01$ for the difference in the change between groups). The mean HbA1c level decreased in the selenium group from 7.21% at baseline to 6.83%, and in the placebo group it decreased from 7.80% to 6.54% ($p < 0.01$ for the difference in the change between groups). The mean HDL cholesterol level increased in the selenium group from 42.5 mg/dl at baseline to 46.2 mg/dl, and in the placebo group it decreased slightly ($p = 0.04$ for the difference in the change between groups).

Comment: While the increase in HDL-cholesterol levels in the selenium group might predict lower cardiovascular disease risk, the adverse changes in glycemic control compared with placebo is cause for concern. However, it would be premature to recommend that patients with diabetes avoid selenium supplements. Selenium levels tend to be low in people with type 2 diabetes, and selenium deficiency is a known cause of cardiomyopathy. It is therefore possible that selenium could help prevent the cardiomyopathy that is associated with diabetes.

It is difficult to understand how the selenium group could have shown both an increase in fasting plasma glucose levels (suggesting worse diabetic control) and a decrease in HbA1c levels (suggesting better diabetic control). One possible explanation is that selenium supplementation actually exerted an antidiabetic (glucose-lowering) effect or enhanced the effect of the oral hypoglycemic drugs, which led to nocturnal hypoglycemia followed by rebound hyperglycemia in the morning. This phenomenon has been described previously, and is known as the Somogyi effect. When worsening morning hyperglycemia is caused by nocturnal hypoglycemia, it can be improved by lowering, not increasing, the dosage of antidiabetes medication. This explanation for the worsening morning glucose levels in the selenium group is supported by the results of animal studies, in which selenium supplementation improved glucose metabolism. Longer-term studies are needed to determine what effect selenium supplementation has on outcomes such as cardiovascular disease and mortality in people with diabetes.

Faghihi T et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. *Am J Ther*. Epub 2013 Apr 9.

N-Acetylcysteine for COPD

One hundred twenty Chinese patients (mean age, 70.8 years) with stable chronic obstructive pulmonary disease (COPD) were randomly assigned to receive, in double-blind fashion, 600 mg of N-acetylcysteine (NAC) twice a day or placebo for 1 year. Compared with placebo, NAC significantly improved forced expiratory flow 25% to 75% ($p < 0.04$) and significantly decreased the mean number of exacerbations per person (0.96 vs. 1.71; 44% decrease; $p < 0.02$). No major adverse effects were reported.

Comment: Oral administration of NAC at a dose of 600 mg per day has been shown to enhance the clearance of mucus by the pulmonary cilia, presumably by exerting a mucolytic effect. In addition, NAC is a precursor to glutathione, one of the major antioxidants in lung tissue. Numerous studies have demonstrated that NAC (usually in doses of 400–600 mg per day) is beneficial for patients with chronic bronchitis. COPD is characterized by the combination of chronic bronchitis and emphysema. The results of the present study demonstrate that high-dose NAC given for 1 year improved small airways function and decreased the exacerbation rate in patients with stable COPD.

Tse HN et al. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest*. 2013;144:106–118.

Vitamin E Effective Against Peyronie's Disease

Seventy patients (mean age, 54 years; range, 26–69 years) with Peyronie's disease (mean disease duration, 13.5 months) were treated with verapamil (injection and iontophoresis) and topical diclofenac, with or without (control group) 900 IU per day of vitamin E for 6 months. After 6 months, the mean reduction in plaque size (−50.2% vs. −35.8%; $p < 0.03$), the mean curvature decrease (−12.25 degrees vs. −6.73 degrees; $p = 0.01$), and the proportion of patients who showed an improvement in penile curvature (96.6% vs. 48.4%; $p = 0.0001$) were significantly greater in the vitamin E group than in the control group.

Comment: Vitamin E has been investigated previously as a treatment for Peyronie's disease because it appears to have an antifibrotic effect. Although vitamin E was effective in several uncontrolled trials, 2 previous double-blind trials failed to demonstrate any benefit. The results of the present study suggest that vitamin E is of value when used as an adjunct to other therapies.

Paulis G et al. Efficacy of vitamin E in the conservative treatment of Peyronie's disease: legend or reality? A controlled study of 70 cases. *Andrology*. 2013;1:120–128.

Is Silicon Beneficial for Alzheimer's Patients?

Fifteen patients with Alzheimer's disease and 14 of their caregivers (controls) consumed up to 1 liter per day of silicon-rich mineral water (35 mg per L of silicon) for 12 weeks. Mean urinary excretion of aluminum increased significantly in both patients and controls, whereas urinary excretion of iron and copper did not increase. During the treatment period, 3 of 15 patients showed clinically relevant improvements in cognitive performance.

Gaby's Literature Review

Comment: There is evidence, though conflicting, that aluminum exposure plays a role in the pathogenesis of Alzheimer's disease. Silicon has been reported to decrease the body's aluminum burden, both by decreasing gastrointestinal absorption and increasing renal excretion of aluminum. Consequently, increasing dietary silicon intake has the potential to prevent Alzheimer's disease. The results of this preliminary study suggest that silicon supplementation may also improve cognitive function in people with established Alzheimer's disease. However, the observed improvement could have been due to a placebo effect or to a "learning effect" (the improvement that is sometimes seen with repeat testing). Placebo-controlled trials are therefore needed to confirm these promising findings. The amount of silicon used in this study (up to 35 mg per day) is generally considered safe, but very large doses of silicon have the potential to cause kidney stones.

Davenward S et al. Silicon-rich mineral water as a non-invasive test of the 'aluminum hypothesis' in Alzheimer's disease. *J Alzheimers Dis*. 2013;33:423–430.

◆

Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

Five Ways to Improve Your Microbiome Alongside Drugs and Bugs

Introduction

At my medical school commencement, the dean said, "Doctors, keep observing. Keep learning. By the time you are at my stage of your career, half of what you learned during the past four years will be disproven. Your job is to figure out which half." Twenty years later, my dean's prediction appears to be on track.

Several of the tautologies of the 1990s were built around great expectations for the human genome project. Emerging science reveals that some unmet expectations of the human genome are conferred by microbial genetic material. Now treatments include a burgeoning array of probiotics and antibiotics. Presented here are simple evidence-based steps to cultivating a more healthful microbiome alongside or *sans* drug and bug therapies.

A Daily Dose of Polyols

"If you chew it, they will come." This could be the subtitle of Scandinavian-led research on how chewing gum sweetened with the sugar alcohol xylitol favorably changes the human microbiome. Thinking of xylitol as a sugar substitute is accurate but not the primary reason to chew it. Xylitol gum's association with reduction in otitis media, dental caries, and various newborn conditions links to a direct effect on oral flora. For newborn health, the chewing gum is given to the mother during pregnancy and lactation.

Sugar alcohols, also called polyols, are among the components of fruit that make it sweet. Polyols tend to be removed from plant-derived foods during processing and represent a smaller component of sweetness in the modern diet than in diets past. Polyols are not usually part of the sweetness blend of foods for several reasons. In concentrated amounts, they cause bloating and diarrhea. Polyols break down with heat and lose their sweetness. But added to one stick of chewing gum a day, xylitol is tolerated by the gastrointestinal tract and the taste is enjoyable to most palates, young and old. A number of companies purvey xylitol gum. At NutriBee, we use a brand called XyliChew.

Up Close on Short-Chain Fatty Acids

Get a whiff of butyrate without being forewarned of its odor, and the container is sure to land in the trash. That's because butyrate is a short-chain saturated fatty acid that is produced by anaerobic bacteria during fermentation and it is produced in the human gut. In other words, putrid is how it smells because putrid is what it *is*. Putrid doesn't mean it is unhealthful. Butyrate is one of many important bacterial byproducts on which human health depends.

Here's the challenge. Modern diets and diseases interfere with butyrate-synthesizing bacteria in the colon. Raising butyrate levels is being studied as a treatment for colon cancer and inflammatory bowel disease, among other conditions. Butyrate is available in capsule form as a dietary supplement, if you can get it past your nose. The prescription medication is Buphenyl, which is sodium phenylbutyrate.

It's also possible to increase butyrate levels in the colon through daily diet. Dietary fiber and other prebiotics promote colonization (note the word *colon* in *colonization*) of butyrate-producing bacteria. Eating foods containing butyrate also raises butyrate levels. Clarified butter, known as ghee in South Asia, is a concentrated dietary source of butyrate. Unrefined saturated fats from plants such as coconut, macadamia, and red palm can be metabolized into butyrate. All of these fats are intended to be consumed in small proportions as part of the daily diet.

Cultivating Benevolent Skin Microbes

"Find victory in d'feet," I advise my patients with fungal nails, athlete's foot, psoriatic or scaly skin, or lingering wounds. These are outside evidence of an imbalance of microbes that can be corrected. In addition to the usual recommendations, I suggest that patients soak feet in Epsom salts baths and regularly apply essential oils. Oils that are fragrant and contribute to microbial management are lemongrass, neroli, cardamom, tamanu, frankincense, lavender, and juniper.

Incorporating Stool Softeners and Motility Agents into the Daily Diet

Long before the Internet age, studies of the country mouse and the city mouse showed that the country mouse had bigger and more frequent bowel movements. Then the same study was conducted on people, comparing bowel habits in a traditionally rural plant-based diet with a Western diet. The findings aren't surprising. Bowel movements less than daily are less than sufficient for good health. An infrequently moving bowel could be compared to the river stone that is not rolling and therefore gathers moss. Here moss is a colony of unwanted microbes.

Improving bowel habits is easier than commonly portrayed and doesn't need to involve discomfort. My dietary recommendations usually include vitamin C + magnesium + cutting all artificial sweeteners and trans fats + adding a few extra vegetables and/or kelp.

Making Waves

Ambient energy wavelengths select some microbes over others. There are two immediately relevant considerations for clinical practice. First are the effects of ultraviolet light on skin microbes, and second are the unknown effects of electromagnetic waves on the human microbiome. Studies in these areas would influence my clinical practice. Until there are answers, I reason that direct UV light confers more than vitamin D synthesis, possibly regulation of some microbes. I also reason that EMFs may alter microbes and stress them into releasing toxins.

In Summary

In the course of our daily lives, we can indeed change the DNA that is a part of us – inside and out.

I introduced this topic with a story about the evolving nature of medical science and would like to conclude with another such story. I took an 8-week intensive course on tropical medicine. On the last day of lectures, a senior professor told the class that the microscopy, biochemistry, medical treatment, and parasite life cycles could all be summarized in one slide. The slide looked something like this:

Don't get bit;
Don't breathe spit;
Don't get lit; and
Don't eat ****.

Today's research has turned the last truism on its head. Hand washing and bottled water are still recommended while traveling abroad. However, the most detrimental tropical gastrointestinal infections are being successfully treated with fecal implants or microbial denizens of the human colon.

Ingrid Kohlstadt, MD, MPH, FACN, FACPM, is the founder of INGRIDients Inc., where she has edited *Advancing Medicine with Food and Nutrients*, 2nd edition (CRC Press; 2012). On the faculty of Johns Hopkins Bloomberg School of Public Health, Dr. Kohlstadt is researching an approach to leverage nutrition more fully in disease prevention.

◆

Society for Integrative Oncology: 10th Annual Conference

by Jacob Schor, ND, FABNO

I attended my first Society for Integrative Oncology (SIO) conference last October and am writing to tell you about the experience. It might be worth it for some of you to attend this year's conference in Texas.

The SIO was founded in 2003 by a group of medical doctors interested in integrative medicine: David Rosenthal, MD (from Dana-Farber); Lorenzo Cohen, MD (M. D. Anderson); and Brian Drucker, MD (Oregon Health Sciences). Barrie Cassileth was the group's first president. They organized a conference in 2004 and have held one every year since.[1] While the group's membership is a mix of researchers and practicing oncologists working in integrative medical settings, the group is open to naturopathic physicians, exhibiting a level of professional inclusivity that stands out in a field known for its narrow views. As a result, the naturopathic profession is well represented both at this conference and in the organization.

SIO's NDs

In fact, the group's incoming president, Heather Greenlee, received her ND from Bastyr University in 2001, then went on to get a MPH from the University of Washington and a PhD in 2008 from Columbia University, where she now teaches. Greenlee is not the only ND active in SIO. Suzie Zick (NCNM 1996), ND, PhD, who now teaches at the University of Michigan, is on the SIO board of directors and serves as the group's secretary. Dugald Seeley, ND (CCNM 2003), who leads the clinical practice and cancer research programs at Ottawa Integrative Cancer Centre, is also a board member. Leanna Standish (Bastyr 1991) of course was there; links to a webinar of hers are front and center on the SIO's member website. Cancer Treatment Centers of America sent a contingent of 16 naturopathic physicians, who occupied a good portion of the second row in the main lecture room and an aisle of the poster hall.

The SIO conference is one of those rare events wherein NDs mingle freely with medical doctors, particularly medical oncologists. I found myself thinking of Venn diagrams, those overlapping circles that categorize various "sets" of things. The circle of SIO membership includes naturopathic doctors such as me who belong to the American Association of Naturopathic Physicians (AANP) and other doctors who belong to the American Society of Clinical Oncologists (ASCO). Thus at the SIO conference there were attendees who attended the 28th conference of the AANP in Keystone last July and others who were at the 50th annual ASCO meeting last March in Chicago. This is a rare confluence of individuals.

Our mutual interest in improving patient outcome is enough of a common cause that the normal barriers are lowered, at least for the duration of the conference, and hopefully over the long term opening the doorways to greater cooperation among a broad spectrum of practitioners.

Having helped plan conferences for both the AANP and the Oncology Association of Naturopathic Physicians (ONCANP), I took interest in how this conference both paralleled and differed from naturopathic conferences.

Research vs. Clinical Pearls

Where the conferences parallel each other is the focus on alternative and complementary therapies and how these might be integrated into or used in adjunctively with standard medical therapies. SIO's attendees are far more research oriented than almost all NDs, who by and large remain clinicians. As a result, SIO's lectures were also far more research oriented, dwelling on designing studies, finding adequate placebos, grant writing, the minutiae of interpreting data, and of course reporting findings of completed studies. One might say that their approach is more conservative, just now starting to talk about considering using therapies that we have used for years. I found myself impatient at moments, downright ADD impatient, wanting to know the bottom line: "Did it help? What's the dose?"

AANP and ONCANP conference lectures focus on clinical utility. The litmus test that our conference planners use when reviewing abstracts is whether attendees will acquire knowledge that will prove useful for their patients the day that they return. Tina Kaczor, ND, medical editor of the *Natural Medicine Journal*, summed it up: "Clinical relevance/ how-to is the most valuable aspect of our educational offerings. I love theory and academic musings, but the rubber hits the road in office. ..."

My guess is that SIO's committee members ask themselves how a presentation will change the way they design their next study. Once I let go of my expectations for clinical relevance and my desire to collect practice pearls, I found many of the presentations interesting.

Firsthand vs. Secondhand Information

Naturopathic conference lectures tend to summarize and translate other people's data. SIO speakers present their own data. It's one thing to read or hear about a paper, it's quite another to listen to the author of the study talk about her results.

Let me write about several of the presentations that remain prominent in memory:

Standout Speakers

Victoria Sweet gave the opening keynote presentation on Sunday and added a new word to my vocabulary, a word that our profession should contemplate with interest. It is the Latin term *viriditas*, which Sweet translates as "greening power" (but which Google translates as "weed"). The naturopathic profession has a history of adopting new ideas as they come along. This may be an idea that we should latch on to.

Kerry Courneya, from the University of Alberta in Edmonton, was one of these interesting speakers whose research is already familiar. Courneya is the driving force behind a series of studies on exercise and cancer, in particular breast cancer. If you tell patients that they should exercise during chemotherapy, you are likely referencing one or more of Courneya's studies. Courneya is study cochair for the Colon Health and Life-Long Exercise Change (CHALLENGE) Trial designed to determine the effects of exercise on disease-free survival. He also coleads the Alberta Moving Beyond Breast Cancer (AMBER) cohort study seeking associations between physical activity, health-related fitness, and disease outcomes in 1500 breast cancer survivors. The bottom line is that exercise increases disease-free survival significantly, on par with other standard cancer therapies.[2,3]

Susan Lutgendorf lectured about the benefits that a healthy mind has on cancer. She is a professor of psychology at the University of Iowa, and a core member of the National Cancer Institute Network on Biobehavioral Pathways in Cancer. Its mission is to accelerate the translation and communication of biobehavioral discoveries to advance clinical cancer care. Her review of how stress affects cancer ran parallel to what Lise Alschuler, ND, has been lecturing us naturopaths about for the past several years. The only difference, of course, is that Lutgendorf is the author of the studies. The titles of a few of these will give you an idea of her focus of study (with links to the texts):

- "Impact of Stress on Cancer Metastasis"[4]
- "Biobehavioral Influences on Cancer Progression"[5]
- "Biobehavioral Factors and Cancer Progression: Physiological Pathways and Mechanisms"[6]
- "Stress Influences on Anoikis"[7]
- "Neuroendocrine Modulation of Cancer Progression"[8]
- "Why Stress is BAD For Cancer Patients."[9]
- "β-Blockers: A New Role in Cancer Chemotherapy?"[10]

While she may have been preaching to the choir, her message is one that we need to keep hearing over and over and to communicate to our patients.

Moshe Frenkel is a name that I recognized right off, remembering his articles on homeopathy and cancer, not because he was writing about homeopathy but because he was working at M. D. Anderson while doing so.[11,12] Frenkel is currently practicing in Israel and came to SIO to speak about his current research on exceptional outcomes, the patients who defy the odds, shocking their caretakers, and inexplicably getting better. [13]

Lung Cancer Guidelines

A committee of SIO members has worked to create guidelines for alternative therapies to consider for lung cancer patients. After an exhaustive review, the SIO feels comfortable suggesting a few mind-body techniques and the advice to eat more fruits and vegetables and less meat to this patient group. This approach clearly differs from our routine naturopathic approach that quickly incorporates any possible hint of knowledge into a patient's protocol despite how weak the evidence is. We might be described as rapid translators, turning research into practice as fast as we can, even if the evidence is weak. Anne Fonfa (a.k.a. Annie Appleseed), the well-known patient advocate, who also spoke at the conference, summed up her criticism of the more conservative SIO approach well when asking her audience, "What is the evidence for saying no?"

October 26–28, 2014:
11th International Conference of the Society for Integrative Oncology
Personalized Integrative Oncology:
Targeted Approaches for Optimal Outcomes
Omni Houston Hotel, Houston, Texas

Pot

A panel presentation on cannabis use in cancer care was of interest to this doctor from Colorado, a state where the stuff becomes legal January 1, 2014. One patient advocate who spoke quoted an 1823 issue of *Lancet*: "When pure and administered carefully, [cannabis is] one of the of the most valuable medicines we possess."

I had the opportunity to listen to a lecture on medical marijuana that I first heard at a conference three years ago. While still a good lecture, it hadn't changed or been updated since. This is something of a complaint. Many of the presenters gave their standard "conference lecture," the

➤

same lecture that they always give and they may have given repeatedly over the years. This practice was new to me. I am accustomed to presenters who prepare a new lecture for a specific conference. In its way, repeating lectures is kind of like recycling and has advantages as some lecturers may improve with practice. Certain lectures may have been in use for a decade, or at least the newer references cited were that old.

This practice is unheard of at naturopathic conferences, wherein lectures rarely get more than one presentation, and references are expected to be updated and current. Naturopathic conferences usually feature lectures that are yearly updates on what is new in the literature from the last 12 months. That may be easier to do when you aren't actually doing the research yourself, but simply reading and citing the work of others.

The Biome

Monday morning consisted of a series of presentations on the human biome and how it might affect cancer. I wrote down a nice 1908 quote from Eli Metchinikoff, "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes."[14]

The actual material was interesting but not new; I recall hearing similar ideas in naturopathic school two decades ago. There was no mention of the recent papers reporting a possible link between cytomegalovirus and glioblastoma. One speaker who attempted to suggest how to use this data cynically put in a plug for a lab that was present as a vendor, something that we would consider a major faux pas at a naturopathic conference. Such corporate mentions were present in many of the talks, which I'm not accustomed to. If this occurs at AANP conferences, the organizers are forced to debate whether to withhold CE credit for the attendees.

Frank Meyskens and Why Research Fails

In hindsight, the lecturer who gave me the most material for rumination was Frank Meyskens Jr., director of the Chao Family Comprehensive Cancer Center, University of California at Irvine. In 2006, Meyskens received the American Society of Preventive Oncology's Distinguished Achievement Award for three decades of work. He also is a founding member of the International Society of Cancer Prevention, and an active member of many other professional organizations, including the American Society of Clinical Oncology and the American Association for Cancer Research. Much of Meyskens's research has been in chemoprevention of cancer, attempting to identify key chemicals that might lower the risk of getting cancer. His presentation was on several new ideas that may explain a problem that has particular relevance to him to us.

It seems as if Meysken's been wrong a lot more than he's been right when it comes to research. He was involved in the CARET trial, which reported that beta-carotene increased rather than lowered risk of lung cancer in smokers.[15–17] He also worked on SELECT, which found that vitamin E and selenium increase risk of getting prostate cancer rather than prevent it.[18,19] And he was involved in the recent trial which reported that increased omega-3 fats in the blood were associated with an increased risk for prostate cancer.[20] You'll find Frank Meyskens's name on all of these papers plus a whole lot more. (With his steady track record of failed RCTs, it's a surprise to see his name associated with the trial that suggested that curcumin lowers risk or colon polyp recurrence.[21])

For the SIO, Meyskens tried to explain why cancer clinical trials have such a poor track record in supporting the findings predicted by epidemiologic studies. He reviewed results from the May 2013 report by Moorthy et al. that compared meta-analyses of randomized controlled trials with the epidemiological data that the RCTs were meant to confirm. Meyskens's failures have clearly not been unique.

In only 23 out of 34 associations, the findings from meta-analyses of epidemiological studies and of RCTs were in the same direction. Yet in only 6 of those 23 associations were the findings statistically significant. In the remaining 11 out of 34 associations, meta-analyses of epidemiological studies and of RCTs had summaries pointing in opposite directions. The association between epidemiological observations and RCTs were statistically significant in only 12 of 34 associations: 6 were in the same direction and 6 in the opposite direction of what was predicted by the epidemiologic observations.[22] In other words, there is poor correlation of what we think will help prevent cancer based on epidemiology and what is eventually actually proved to work.

Meyskens presented the SIO attendees with several possible explanations for these recurrent failures. His bottom line is that the biology of living systems is more complex than we had hoped and that rarely if ever will single agents prove to be silver bullets, but rather we will need to think in terms of multiple variables and complex interventions – an idea sounding rather naturopathic to my ear.[23] (The full text of this paper

is available free online: http://cebp.aacrjournals.org/content/14/6/1366.full.pdf+html.)

Yet Meyskens seems to be a perpetual optimist and admitted that he recently mortgaged his house to fund a start-up company that will market a chemical which had shown promising results in early trials.

Eager-Beavers

As I've said, our tendency as naturopathic doctors is to practice what might be described as "eager-beaver translational medicine." We rush to translate newly published research into clinical practice as quickly as we can. Think of the rush we were in to have everyone take selenium when Clark's 1996 paper first hinted that selenium might cut cancer risk by half.[24] All too often we mistake epidemiologic data as evidence of causality. Meyskens reminds us to slow down, that we may be in too much of a hurry; when it comes to cancer, it is rare for early results to hold through later clinical trials. This is a message that we should perhaps pay more attention to.

Naturopathic physicians, in particular OncANP members, may be more interested in the implications of research on integrative oncology than in knowing the details; we want only the bottom line. Yet when constantly looking at new research, the way we tend to, the bottom line is not so clear. In fact, it can often be downright blurry, wavering from day to day with each new published study. Thus paying more attention to the details of a study may help us guess more accurately which information to believe and what to discard. This is something that we can learn from having a closer association with SIO. Having study authors present and respond to questions is an advantage. SIO brings an entirely different level of scientific focus to bear on the big questions, the ones to which we need accurate answers.

Naturopathic physicians can be a great resource to SIO, as we possess a wealth of clinical experience doing and using the things that SIO members are only thinking or reading about. Our clinical impulsivity can be an asset if we can figure out and communicate what we know. SIO is a place where diverse ends of the medical spectrum meet together for mutual benefit.

Next Year

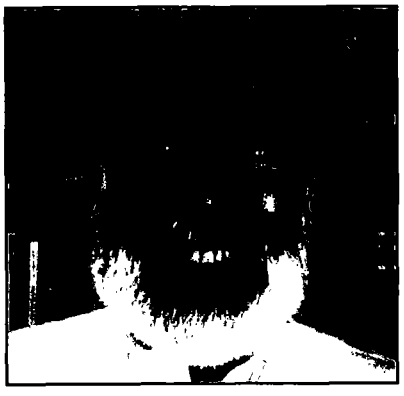
I've already put next year's SIO conference on my calendar. For more information: www.integrativeonc.org.

Notes

1. Geffen JR. Integrative oncology for the whole person: a multidimensional approach to cancer care. *Integr Cancer Ther.* Feb. 11, 2010;9(1):105–121.
2. Courneya KS, Vallance JK, Culos-Reed SN, et al. The Alberta moving beyond breast cancer (AMBER) cohort study: a prospective study of physical activity and health-related fitness in breast cancer survivors. *BMC Cancer.* 2012 Nov 16;12:525. PMID: 23153358. Free PMC article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3534483.
3. Courneya KS, McKenzie DC, Mackey JR, et al. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst.* 2013 Oct 22. PMID: 24151326.
4. Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. *Future Oncol.* 2010 Dec;6(12):1863-81. PMID: 21142861 Free PMC article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3037818.
5. Costanzo ES, Sood AK, Lutgendorf SK. Biobehavioral influences on cancer progression. *Immunol Allergy Clin North Am.* 2011 Feb;31(1):109–132. PMID: 21094927. Free PMC article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3011980.
6. Lutgendorf SK, Sood AK. Biobehavioral factors and cancer progression: physiological pathways and mechanisms. *Psychosom Med.* 2011 Nov–Dec;73(9):724–30. doi:10.1097/PSY.0b013e318235be76. PMID: 22021459. Free PMC article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3319047.
7. Sood AK, Lutgendorf SK. Stress influences on anoikis. *Cancer Prev Res (Phila).* 2011 Apr;4(4):481–5. PMID: 21464029. Free PMC article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3074235.
8. Armaiz-Pena GN, Lutgendorf SK, Cole SW, Sood AK. Neuroendocrine modulation of cancer progression. *Brain Behav Immun.* 2009 Jan;23(1):10–15. Free PMC article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2630522.
9. Nagaraja AS, Armaiz-Pena GN, Lutgendorf SK, Sood AK. Why stress is BAD for cancer patients. *J Clin Invest.* 2013 Feb 1;123(2):558–560. doi:10.1172/JCI67887. Epub 2013 Jan 25.
10. Nagaraja AS, Sadaoui NC, Lutgendorf SK, Ramondetta LM, Sood AK. β-blockers: a new role in cancer chemotherapy? *Expert Opin Investig Drugs.* 2013. Nov;22(11):1359–63. doi:10.1517/13543784.2013.825250. Epub 2013 Aug 7.
11. Frenkel M, Mishra BM, Sen S, et al. Cytotoxic effects of ultra-diluted remedies on breast cancer cells. *Int J Oncol.* 2010 Feb;36(2):395–403.
12. Frenkel M. Homeopathy in cancer care. *Altern Ther Health Med.* 2010 May–Jun;16(3):12–16. Review.
13. Engebretson JC, Peterson NE, Frenkel M. Exceptional patients: Narratives of connections. *Palliat Support Care.* Epub 2013 Jul 4:1–8.
14. Metchnikoff E. *Optimistic Studies.* New York: Putman's Sons; 1908:161–183.
15. Goodman GE, Thornquist MD, Balmes J, et al. The Beta-Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. *J Natl Cancer Inst.* 2004 Dec 1;96(23):1743–1750.
16. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med.* 1996 May 2;334(18):1150–1155. Free article: http://www.nejm.org/doi/full/10.1056/NEJM199605023341802.
17. Omenn GS, Goodman G, Thornquist M, et al. Chemoprevention of lung cancer: the beta-Carotene and Retinol Efficacy Trial (CARET) in high-risk smokers and asbestos-exposed workers. *IARC Sci Publ.* 1996;(136):67–85.
18. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA.* 2009 Jan 7;301(1):39–51.
19. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA.* 2011 Oct 12;306(14):1549–1556.
20. Brasky TM, Darke AK, Song X, et al. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst.* 2013 Aug 7;105(15):1132–1141.
21. Carroll RE, Benya RV, Turgeon DK, et al. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. *Cancer Prev Res (Phila).* 2011 Mar;4(3):354–364.
22. Moorthy D, Chung M, Lee J, Yu WW, Lau J, Trikalinos TA. Concordance between the findings of epidemiological studies and randomized trials in nutrition: an empirical evaluation and citation analysis: Nutritional Research Series, Vol. 6. *AHRQ Tech Rev.* 17.6.
23. Meyskens FL Jr, Szabo E. Diet and cancer: the disconnect between epidemiology and randomized clinical trials. *Cancer Epidemiol Biomarkers Prev.* 2005 Jun;14(6):1366–1369. Free full text: http://cebp.aacrjournals.org/content/14/6/1366.long.
24. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA.* 1996 Dec 25;276(24):1957–1963.

◆

Jacob Schor, ND, FABNO, has practiced as a naturopathic physician in Denver, Colorado, with his wife, Rena Bloom, ND, since they graduated from National College of Naturopathic Medicine in 1991. He was humbled in 2008 when presented with the Vis Award by the American Association of Naturopathic Physicians (AANP). He has had the honor of serving the members of the Oncology Association of Naturopathic Physicians as a board member and currently as president. Dr. Schor began a term on the AANP's board of directors in January 2012. He is a frequent contributor to, and associate editor of, the *Natural Medicine Journal*.



Warburg Revisited: Maverick Cancer Researcher Questions the Origin of Cancer

An interview with Thomas Seyfried, PhD

by Michael Uzick, ND

According to Boston College professor and cancer research scientist Thomas Seyfried, the very origin of cancer is in dispute. His recently published book *Cancer as a Metabolic Disease* is having a dramatic impact on the field of integrative oncology.

To quote Ralph Moss, "Once in a long while, a book comes along that revolutionizes our understanding of the cancer problem. ... You need to buy, read, and assimilate this book in its entirety if you expect to thoroughly understand the debate over cancer."

The war on cancer has not been won. In his book, Seyfried meticulously explains why it is not a genetic disease and says that we will not likely make any substantial progress until we recognize and direct our therapies toward the true cause of cancer.

Seyfried will be a keynote speaker at the Oncology Association of Naturopathic Physicians (OncANP) 3rd annual conference this coming February 14 in Scottsdale, Arizona (www.oncanp.org).

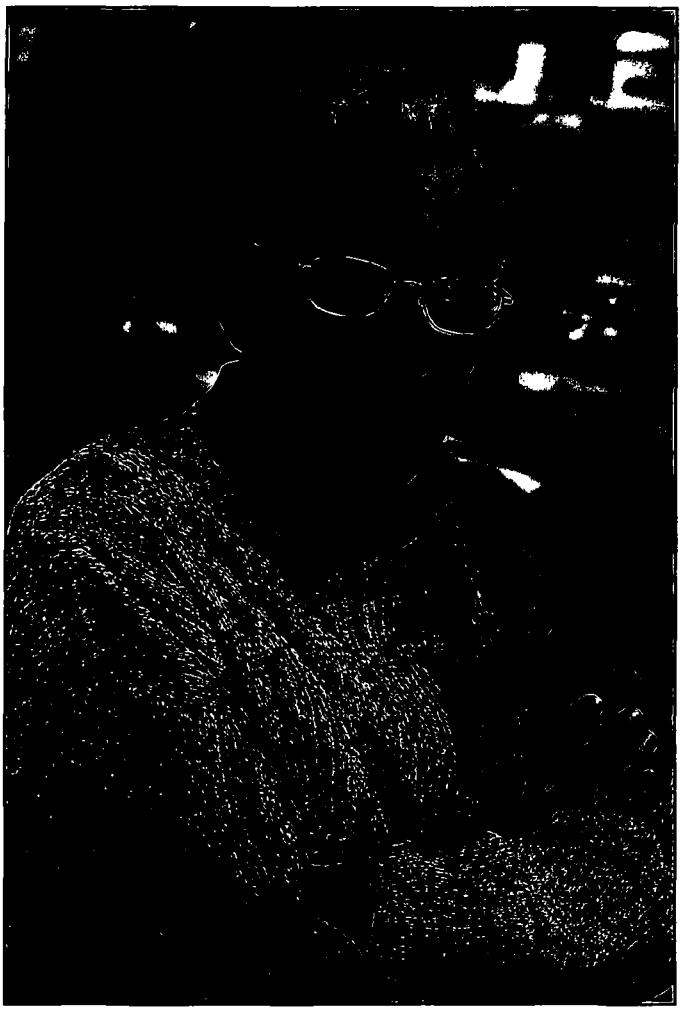
As I am a member of the conference speaker committee, the *Townsend Letter* very graciously gave me the opportunity to interview Seyfried to highlight his work and appearance at our conference.

Michael Uzick: How did you become involved in researching the effects of ketogenic diets in cancer?

Thomas Seyfried: We had been doing research on the biochemistry of tumors for decades, particularly lipid metabolism. We knew there were certain kinds of lipids expressed in tumor cells and we were mainly interested in figuring out what kind of function the lipids might have. At the same time, we had a parallel study on the genetics of epilepsy and one of my students talked to me about the ketogenic diet as a therapy for epilepsy. We took the natural models that we had developed and evaluated ketogenic diets for epilepsy and we became very involved in the mechanisms by which ketogenic diets affect epileptic seizures. We found that the majority of the therapeutic benefit of the ketogenic diet came from calorie restriction. One of my other colleagues knew that calorie restriction could be effective against tumors, so we tried this and we saw how powerful it was in blocking tumors. This has been known for a hundred years. Then we just put them together and found out that if you restrict calories on the ketogenic diet you can actually get better therapeutic benefit than either alone. So, it was a fortuitous combination of research activities that were taking place in the lab at the same time.

MU: Your book, *Cancer as a Metabolic Disease*, challenges the current scientific paradigm on the origin of cancer. Can you describe the current paradigm and how you came to question it?

TS: The current view now, without any question, is that cancer is a genetic disease. If you go on the National Cancer Institute website or you read any of the major articles published in *Nature* and *Science*, often the articles will start with, "Cancer is a genetic disease." I think that this has become dogma. It became clear to us as we did our research that the therapeutic benefits we were seeing from calorie restriction had their origin with Otto Warburg. But if he was correct, why are we talking about genes? The gene theory became predominant following Watson and Crick's evidence that DNA is the genetic material and finding all the mutations in cancer cells. One thing led to another and, among the powers that be, the gene theory won out. The gene theory seemed to be more consistent, and there were mutations that seemed to be either provoking the growth of the tumor or failing to suppress the tumor. The entire field was built on this foundation, that genes are regulating this entire process. But if one goes back in the literature, one can see clear disconnects in the linkage between nuclear genetic problems and the



Thomas Seyfried, PhD

origin of the disease. For example, Darlington had clearly shown that there were carcinogens that did not damage the nuclear DNA, but did cause cancer. He concluded that cancer could not be a nuclear genetic disease. It had to be something in the cytoplasm and he alluded to factors that were related to the mitochondria. That's exactly what Warburg had said, but Warburg's theory had been discredited because it was observed that you could see normal respiration in cancer cells. Of course the genetic argument is that the metabolic issues are due to oncogenes and that's where the big controversy is and I looked at that very carefully and was able to parse it out. It turns out that the oncogenes are responding to the abnormal metabolism of the cell and we were able to show this. It is actually the abnormal metabolism of the cell that's dictating the genetic mutations. This is where my book challenges the field. It provides credible scientific evidence that seriously questions the notion that cancer is a genetic disease. And I think you are not going to make major advances in the field of cancer until this becomes more widely recognized.

MU: You mentioned that Warburg was discredited because some cancer cells were found to have normal respiration. Can you explain how this is possible?

TS: Most of the work that challenged Warburg's theory was done in culture. When you grow mammalian cells in culture, they take on characteristics that they don't generally have when growing in vivo. For example, if you take normal cells and grow them in culture, invariably they produce lactic acid. This doesn't happen in vivo. Muscle will produce lactic acid when it's under incredible physiologic stress, until there's enough oxygen returning to the system to suppress the formation of lactic acid. So there are a number of artifacts of the in vitro system that compromised the view of cancer as a disease of respiration. Now, when you look in vivo at cancer cells, invariably most cancers will have structural aberrations in their mitochondria. In breast cancer the majority of aggressive breast tumors have no mitochondria. So there's no way that these cells could have normal oxidative phosphorylation. So none of this is discussed in the literature. They just ignore it. I went back and looked at it and I said, "You can't say respiration in cancer cells is normal when there's so much evidence to say it isn't."

Michael Uzick, ND

MU: Let's assume that everyone agrees all cancer cells have damaged respiration. But then the question becomes, which came first – damage to the genes or the abnormal respiration?

TS: If you go into the literature, the studies reveal the answer. If oncogenes are the drivers of this disease, why is it that when you take the nucleus from a tumor cell and put it into a normal cytoplasm, the nucleus is no longer capable of producing the disease? And now within the last year people have been able to transplant mitochondria. So if you transplant normal mitochondria into a tumor cell's

➤

➤

cytoplasm, you suppress the tumorgenic phenotype. And if you transplant abnormal mitochondria into a normal cytoplasm, you can produce developmental abnormal cells or dead cells. You can actually stimulate oncogene upregulation. So it tells me that the mitochondria are calling the shots.

Thomas Seyfried will be one of three keynote speakers at the third annual conference of the Oncology Association of Naturopathic Physicians, February 14–16 in Phoenix, Arizona. Other speakers include Jeanne Drisko, MD, and Valter Longo, PhD. For more information: oncanp.org

MU: Your research has shown that a CRKD [calorie-restricted ketogenic diet] significantly inhibits brain cancers and in your book you have suggested that this dietary intervention should be effective in every kind of cancer. Can you explain how a CRKD impacts cancer?

TS: So why are tumor cells producing lactate if they have normal respiration? We have blood cancers that have plenty of oxygen in the environment, yet they still produce lactic acid. Cancer cells are producing lactic acid because they can't get sufficient energy through normal respiration, and must therefore use fermentation instead. Fermentation usually occurs in the absence of oxygen, not in the presence of oxygen. So what's going on here? The simplest explanation and the one supported by a variety of different studies, is that their respiration is damaged or insufficient in some way. Now ketones are an alternative fuel, which evolved to substitute for glucose when our food intake was suspended. Our bodies will transition to stored fat for energy, which is broken down to ketone bodies which can then be burned by all of the tissues, especially the brain. But you need good mitochondria to metabolize ketones. These have been shown to be abnormal in many different kinds of cancers. So the tumor cells can't transition to the alternative fuel that normal cells evolved to use. This seems like a very simple way to put pressure on cancer cells without toxicity.

MU: I understand how ketones are involved. But where does the caloric restriction come in? Why does that become important?

TS: We gave animals unrestricted ketogenic diets and the tumor cells grew just as fast, or even faster sometimes, than a standard high-carbohydrate diet. So we said, what's going on here? There's a diet with zero carbohydrate and the animals are eating as much as they want and when we looked at their blood, their blood sugars were very high. So it turns out if you eat large amounts of fat in a ketogenic diet you get insulin insensitivity, which then increases the level of sugar, and the cancer cells are fat and happy using this. So you have to restrict the diet. Because the glucose is now low and the ketones must be retained to be used for energy.

MU: So if caloric restriction is required, how can one maintain this approach in order to target cancer?

TS: You know the issue is, how long should you do this? I have to admit in some of my earlier publications, we were pretty hyped on the calorie restriction aspect of it. We were probably going a little overboard on how many calories you need to restrict. Only after we saw rather substantial regression of tumors or stabilization in people who cut down to maybe 1500 calories a day, which is not anywhere near a heavily restricted diet, did we begin to see that each individual is a unique metabolic entity. Some people require minimal restriction and other people require more restriction. If you look in the literature, a lot of people are using ketogenic diets to remain in a healthy state at low weight. And people can maintain this for years and they seem to be very healthy. Now I'm not saying all cancer patients need to maintain for the rest of their lives a state of low glucose and elevated ketones. I suggest they do it until there is clear evidence that the disease has been arrested or stabilized. And then there's a likelihood one could transition off of this, as they would for any kind of therapy.

MU: Valter Longo, PhD, will also be speaking at the OncANP conference about his research looking at the benefit caloric restriction during the administration of chemotherapy. Do you have any thoughts on Longo's research and any parallels between your own?

TS: You know I agree, I think what he's seeing is real and I think it's important. I have heard of and spoken to people, physicians who have done therapeutic fasting on some of their patients for as much as 30 days and have seen cancer regression in some patients. Water only, you know without any chemo. So if you fast with only water like the Longo group does, the body goes into defense mode. And what I think is happening is a lot of these tumor cells become very compromised under these stressed conditions. Here's where the mutations play an important role in allowing these therapies to work. Many of these cancer cells are loaded with all kind of mutations. And what those mutations do is prevent those cells from making the correct adaptations to the new stressful environment, so they now

become in a much more compromised state. So if you give chemo under this therapeutic fasting condition, those cells are going to be less able to deal with the chemo and die faster than the normal cells, which are able to make these adjustments to this new metabolic state. I think it's another view of the same kind of approach. There are metabolic approaches to managing cancer that people need to recognize.

MU: Your book opened my mind to the idea of ketones as anticancer agents. I specialize in enhancing the effectiveness of conventional therapies while reducing their toxicity. I was surprised by the number of studies showing that ketones, at least in vitro, enhance the effectiveness of several chemotherapeutic agents.

TS: The question is, are they toxic in vivo? We have a paper that's under review now with my colleague Dominic D'Agostino and his graduate student Angela Poff at the University of South Florida. He has evidence that elevated ketones can in fact be toxic to the tumor cells. In my earlier writings, we were considering the ketones to be largely protective of normal cells and basically tumor cells just can't use them. But now we have evidence that they may in fact be toxic to the tumor cells. So it's a one-two hammering of the tumor cells. You're pulling away their glucose, forcing an alternative fuel they can't use, and potentially an alternative fuel that will actually kill them.

MU: I see a general fear among cancer patients about losing weight. Medical oncologists for the most part recommend that patients eat ice cream and high carbohydrate foods so as to not lose weight. When you have a patient who is already starting off thin, is there reason to be concerned?

TS: For those patients, we know that the ketogenic diet will cause some initial weight loss, but it also maintains muscle mass. Tisdale showed this years ago in England. So, there's a certain way to do this and the patient's weight can be stabilized. Cachexia is a very dangerous situation but you can institute a ketogenic diet, and yes, initially there will be some weight loss, but the weight will stabilize.

MU: Currently the NIH (National Institutes of Health) lists eight clinical trials under way or completed examining the effects of ketogenic diets in patients with cancers. Have you been involved with any of studies and do you think your research has played a role in the interest in this topic?

➤

TS: Our studies were motivated by Linda Nebeling's 1995 case report on the therapeutic efficacy of the KD in two children with malignant brain cancer. Our research has certainly established the evidence for the current interest and I am excited that some members of the medical community find our approach to cancer management interesting and worthy of patient application. I have helped with protocols for some studies, but not for others. I am not presently participating in any of the studies. I can only hope that the PIs of these studies know what to do, and how to collect and interpret the data.

These studies are all in combination with either radiation or chemotherapy. My preference is to start metabolic therapy with GBM (glioblastoma multiforme). This is a devastating type of brain cancer. Metabolic therapy with a restricted KD could be done with a few tumors where you know the conventional standard of care doesn't work at all. You would choose those kinds of patients and do a clinical trial based on historical controls and see what the outcome would be and see if you could get some level of survival that would match or be better than the conventional standard of care.

MU: Since the publication of your book, have you become aware of more successful cancer cases using your approach?

TS: We are hearing about more cases for sure. I know only of a few, that I've participated in directly, where people are really collecting the key biomarkers to establish the therapeutic efficacy. So the people whom I do know that are responding fairly well are showing me very careful and comprehensive daily blood glucose and ketone values. We have documented blood work from some individuals that go over years. I think up to about 2 years for the most part and sometimes longer.

I have data on a dog, if you can believe; you know dogs respond really well to this therapy, I never saw such responses in some. We have a good case-controlled report we are working on now out of Greece where the person had non-small cell lung cancer metastasized to the brain. He's been on the metabolic therapy now for 4 years and he seems to be doing well. But these are all anecdotal reports. Nevertheless, if you do the case studies correctly, like we did for the Italian woman, that we published in *Nutrition & Metabolism*, there's a very comprehensive case report that served as a basis for others.

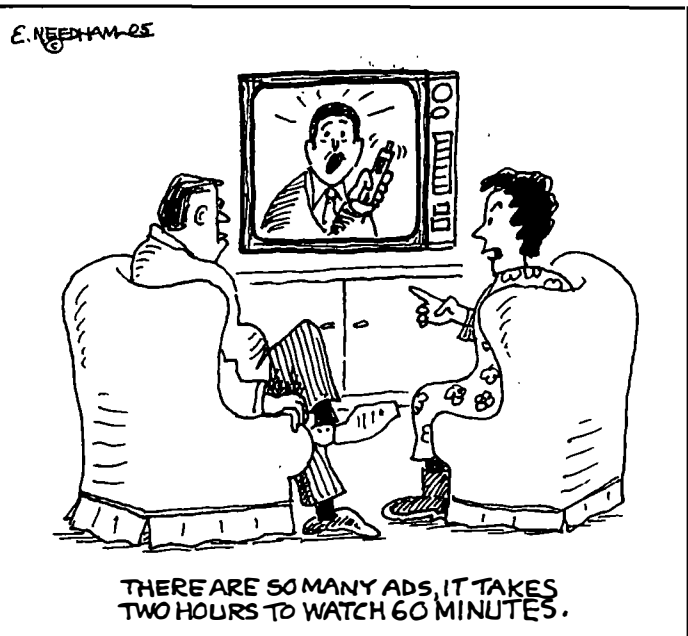
There are some people out there, like any media thing, they'll say, "Oh, the ketogenic diet cures cancer." We know there's no evidence for that. We haven't used it long enough to know if anybody is going to be cured from cancer using a ketogenic diet. All we can say is that the ketogenic diet has the potential to arrest the growth of the tumor. Now whether it's cured in the long run, who knows? It's going to take a long time to figure out whether these people are cured or not.

MU: In your book you mention 2-deoxyglucose as an adjunctive treatment to the CRKD. Many integrative oncology specialists are using DCA (dichloroacetate) in a similar way. Are there any new or exciting metabolic therapies to go along with a CRKD?

TS: Well, I think this is going to be the future. I mean the ketogenic diet by itself is just like step number one. As I said, you bring the patient into a new metabolic homeostasis where ketones become the predominant metabolic fuel and glucose is reduced. At that point now your tumor cells are under metabolic stress to a much greater extent than the normal cells. Now you can have add-ons, you have DCA, you can have 3-bromopyruvate, phenylbutyrate, there are approaches that are attempting to control the glutamine issue with respect to cancer. I think hyperbaric oxygen from the work I've seen with Dominic D'Agostino has tremendous potential, and the mechanism of action become clear once you recognize that cancer is a metabolic disease. The important thing is that in most cases the patient does not need to be harmed by these approaches. So many patients are harmed today from the current standard of care. Some drugs have very little effect when used alone, can have tremendous affect when matched together with CRKD. So there's a lot to be hopeful about I think in the future.

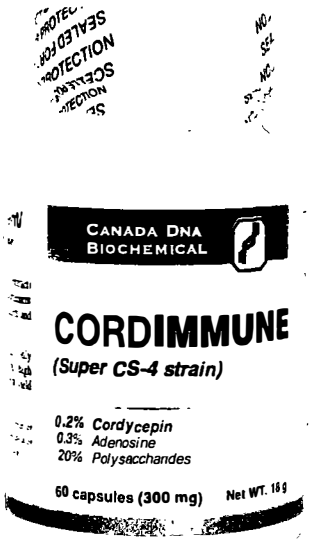
MU: You have written about glutamine being a specific fuel for cancer cells. Several clinical trials have shown that high doses of glutamine significantly reduce chemo- and radiation-related side effects, without interference in outcomes. This has become a controversial issue among naturopathic oncologists. Can you address this concern about glutamine?

continued on page 52 ➤



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 hematopoiesis
- 0.2% Cordycepin (worth over $100 per bottle)
- 0.3% Adenosine • 22% Polysaccharides

Immune Support Beyond Just Polysaccharides!

CORIO PSP ™

The most clinically researched mushroom in Japan and China

- Unmatched 38% polysaccharides
- Lessens the side effects of toxic treatments
- Raises the quality of life
- Raises the activities of NK cells and macrophages
- Increases thymus weight

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

Warburg Revisited

➤ *continued from page 50*

TS: The glutamine issue is a really important one. If you go into the basic scientific literature, you see numerous papers in top scientific journals. It's pretty well recognized among the individuals who do basic research that glutamine together with glucose act as a powerful synergistic metabolic stimulus to tumor cells.

So let's talk a little about glutamine. OK, well first of all we know that glutamine is the most abundant amino acid in the body. And it's used extensively by cells of the immune system, like macrophages and lymphocytes, as a prime fuel. In burn patients they give glutamine infusions. You have to jack up the immune system to fight the bacteria. Certainly glutamine is going to be a good metabolite to restore some level of immune function.

On the other hand we have to recognize that many of the metastatic cancer cells are part of the immune system. There's a number of articles from John Pollack at Yale, Melisa Wong at Oregon, and a number of others showing that the cancer metastatic cell is a fusion hybrid between an immune cell like a macrophage and some cancer stem cell. So you have this hybrid cell that has the characteristics of both a stem cell and an immune cell. So what's going to happen to that cell when it gets the glutamine? Of course the cell is going to be rescued. So you're enhancing one aspect of the immune system. Well, on the other hand you could potentially be rescuing cells for eventual reoccurrence sometime down the road. So again you have to make your treatments in line with what we understand about the metabolism of the tumor cell. And the evidence in the literature is huge that glutamine for many different cancers is a primary fuel that is used by tumor cells, especially those tumor cells that have some level of mitochondrial function.

We have a model of metastatic cancer we developed here at Boston College. It's one of the best models for systemic metastasis; it's brutal. It just rips through the mouse's body from the tip of his nose to the tip of his tail. This tumor doesn't respond to anything. We gave them DON (6-diazo-5-oxo-L-norleucine), which is a toxic drug, it's a glutamine analog (cannot be metabolized). We were able to really knock out metastatic cancer throughout the body of the mouse, except the spleen. It turns out the spleen is kind of like a sanctuary for cells like macrophages and these kinds of cells.

We just wanted to use it to get some concept of the role of glutamine. Because we couldn't stop this tumor using calorie restriction alone. The glutamine issue has to be carefully dealt with, I think. We recommended phenylbutyrate (Buphenyl) that's metabolized to phenyl acetate, which binds to glutamine and you excrete it. This will lower some levels of glutamine. And there has to be more cross-talk between the basic scientists and the clinicians about this glutamine issue.

MU: I'm not aware of any treatment which cancer cells cannot ultimately resist. Why can't cancer cells develop the ability to use ketones as a fuel source?

TS: You know, burning ketones requires normal mitochondria. Ketones are even more efficient than fatty acids, which uncouple, and they are more efficient than pyruvate. So ketones are a wonderful, highly sophisticated fuel that reduces oxygen free radicals, but in order to do that your mitochondria must be in good shape. And as I've mentioned and I've shown over and over again, the mitochondria of tumor cells are compromised in one way or another, making them less able to use ketone bodies for energy. That's the reason they ferment. They are fermenting because their mitochondria are insufficient. So, how are they going to adapt, unless they grow new mitochondria? And if they generate new mitochondria, they will be able to burn ketones, but they will no longer be cancer cells. So it's very hard to get around this.

If cancer is viewed as a metabolic disease, then these kinds of ideas and these kinds of understandings become more apparent. Why are all these other cancer cells adapting to the drugs and other therapies? Because you're not targeting their metabolic fuels. If you target their metabolic fuels that they absolutely require, they are not going to do very well. If you're not targeting their glucose or glutamine issues, they look like they're adapting. You're just making them more likely to ferment than respire. Then you get cancer cells that have no mitochondria. All right, well, those cells should be remarkably sensitive to the CRKD. So it's going to take time for this to sink into the minds of people that work in this area.

We have so many ways to manipulate this metabolic therapy. Not only with the diet as the main platform, but then the add-on drugs and hyperbaric oxygen. And I am hopeful we will be able to come up with an approach that is effective for the management of cancer without toxicity for the majority of people who suffer with this disease. It's just a matter of time. I think this is what's going to happen, but how long that time will be I don't know; I'm hopeful that it won't take too long.

Thomas N. Seyfried, PhD, has taught and conducted research in the fields of neurogenetics, neurochemistry, and cancer for more than 25 years at Yale University and Boston College. He has published more than 150 scientific articles and book chapters and is on the editorial boards of *Nutrition & Metabolism*, *Journal of Lipid Research*, *Neurochemical Research*, and *ASN Neuro*.

Michael Uzick, ND, FABNO, is a graduate of Bastyr University. He is a Fellow American Board of Naturopathic Oncology (FABNO) and a past vice president of the Oncology Association of Naturopathic Physicians (OncANP). He is a cofounder and the medical director of Genesis Natural Medicine Center in Tucson, Arizona.

◆

Hormone Testing: When to Use Serum, Saliva, and Urine

by Pushpa Larsen, ND; Michael Kaplan, ND; Leah Alvarado, ND; and Mi-Jung Lee, ND, LAc

Picture this: A 52-year-old woman comes in to your office for her initial visit. On the phone, she told you that she wanted to come in "for hormones." In her intake, you find out that she is still having menstrual cycles, although they are somewhat irregular and sometimes quite heavy. She has occasional hot flashes, but they are not bothersome. She feels tired and burned out most of the time, although she tends to be optimistic and tries to make the best of things. She has noticed that her hair is thinning and she has put on a few pounds around her middle. She had an aunt who died of breast cancer and her mother has osteoporosis, as did her maternal grandmother. She has a very busy life, with two daughters, 13 and 15, who are active in sports and multiple other activities. She has her own business as a graphic designer. Her husband is an attorney. She stays up late to get work done for clients after her daughters have gone to bed. She tends to be a bit of a night owl anyway. Her libido has been diminishing over the past couple of years, although she and her husband have a great partnership and a loving relationship. A friend of hers said she got her life back after starting on hormones, and your patient would like to see if hormones could make that kind of difference for her, too. You think that she is probably a good candidate for hormones, but you like to know where you are starting, and it seems possible that your patient may have multiple endocrine issues. What is the best way to assess her current hormonal status and monitor any hormone replacement for safety and effectiveness?

Traditionally, all hormone testing was done via serum, but these days, it is possible to use serum, saliva, and urine to assess a wide array of hormones. Each of these methodologies has advantages and limitations, and each has a best use. Sometimes a combination of tests will be necessary to provide you with the most complete information.

Serum

Serum testing of hormones has long been accepted by the conventional medical community as the standard for measuring hormones. It has the advantage of being a relatively simple collection, requiring little patient involvement, and has very well-established reference ranges. Serum is ideal for testing peptide hormones such as FSH, LH, prolactin, fasting insulin, and thyroid hormones, including reverse T3, as well as thyroid antibodies. It is also used to measure sex hormone binding globulin (SHBG) and, less commonly, cortisol binding globulin (CBG). For sex hormones, serum testing has a more limited utility. There are several reasons for this. For most sex hormones, no distinction is made in serum between bound and free hormone. Estradiol, estrone, estriol, and progesterone are reported as total hormone and free hormones assays are not commonly available. This may lead to misleading results in which hormone levels appear to be normal or even high normal because of an abundance of bound hormone. However, if the free hormone level is low, the patient can be functionally deficient even with a normal total hormone level. Serum testosterone is an exception in that it is commonly available as both total and free, and therefore can be useful in assessing hormone balance.

Another limitation of serum hormones testing is the "snapshot" nature of single-point testing. Because hormones are secreted in a pulsatile manner over the course of the day (and night), it is difficult to know whether the levels in serum represent a peak, a valley, or something in between.[1,2] This also presents a difficulty in monitoring treatment, as it is not possible to know whether today's test was drawn at a similar point of hormone secretion as a previous test.

Estradiol (E2) is the female hormone most commonly measured in serum, although estrone (E1) is also available from many labs. Serum estriol (E3) testing, however, is not routinely performed. E3 is an important estrogen, generally considered protective because it binds to estrogen receptor beta (ERb), which is understood to increase differentiation and decrease proliferation of cells.[3–5]

Monitoring progesterone supplementation in serum also poses a problem. Transdermal progesterone does raise serum progesterone levels in a statistically significant manner, but the magnitude of change is quite small, which can lead to excessive dosing of progesterone as practitioners strive to achieve therapeutic levels.[6]

Finally, serum hormone testing does not typically allow for the measurement of estrogen, androgen, and adrenal metabolites, which can provide a wealth of information to assist practitioners in understanding their

➤

patient's condition and help to guide and fine-tune treatment options.

Saliva

In the past decade and a half, saliva testing has gained in popularity among practitioners of functional medicine. Saliva has the advantage of being noninvasive as well as being accessible to practitioners such as naturopathic physicians, chiropractors, and acupuncturists who may be practicing in states where they are not licensed to order blood tests or draw blood. Saliva collection also allows for multiple collections over a period of a day or month, which can help elucidate abnormal hormonal patterns, such as a shortened luteal phase. While this can theoretically be done with a serum test, it would be logistically cumbersome.

Saliva is best used to evaluate the balance and flow of the estrogens and progesterone in women who are still having menstrual cycles. It can also be used to evaluate cortisol secretion patterns by taking multiple samples over the course of a day and evening. A saliva test measures free hormone and its multipoint versatility makes it a better measure than serum for evaluating unsupplemented hormone status. Another novel use of saliva hormone testing is in pregnancy: salivary estriol spikes about two weeks before the onset of labor and can be used to identify women who are at risk for preterm labor.[7-9]

Saliva production is difficult for some patients, and there are multiple restrictions regarding eating, drinking, gum-chewing, makeup use, topical application, and toothbrushing that must be observed to get a usable specimen. Microdamage from toothbrushing can result in elevated salivary testosterone levels for up to an hour after brushing, even in the absence of visible signs of bleeding, such as "pink toothbrush."[10] Saliva can only be used to evaluate steroid hormones. Peptide hormones, such as growth hormone and thyroid, are not available. While estradiol, estrone, and estriol, progesterone, testosterone, DHEA, and cortisol are all available, depending on the lab, steroid hormone metabolites are not measured in saliva, limiting its utility in assessing metabolism of hormones.

Saliva measurements are greatly affected by the use of exogenous hormones.[11,12] Transdermal progesterone and testosterone, in particular, can result in supra-physiological levels in saliva testing, but all exogenous hormone use seems to distort results to some extent. Because of this, patients are instructed to discontinue hormone use for between 12 and 36 hours prior to collection, depending on the hormone preparation. This can pose problems for practitioners who want to monitor hormone therapy. Estrogen, for example, washes out of the system almost entirely in 20 hours and drops significantly within 12 hours.[13]

Saliva collection, like blood, is a single-point collection. Although cortisol can be collected at multiple points, sex hormones are measured from a single morning collection. Just as with serum tests, a single point of collection does not account for individual variation and may catch a peak or a valley in hormonal secretion – or perhaps a peak for one hormone and a valley for another.

Urine

Measuring hormones in urine is less common in clinical practice than either serum or saliva, yet it is quite common in research. A 24-hour urine collection is the preferred method for testing hormones that are secreted at night and during deep sleep, such as growth hormone and melatonin, and is the most economical and reliable way to evaluate steroid hormone metabolites.[14,15] This method has been gaining in popularity among integrative practitioners since it was brought into clinical practice by Dr. Jonathan Wright in the early 1980s.

Not all urine hormone testing methods are equal. Serial single-point

urine collection does not account for individual differences in hormone secretion, especially for patients with nontraditional schedules, such as shift workers. Twenty-four hour urine collection accounts for the full day and night of hormonal secretion. This eliminates the possibility of falsely elevated or depressed levels that may be obtained when a single point collection occurs at a peak or valley of an individual's secretory cycle.

Just as single-point and 24-hour collection are different, not all technical methods of urine assay are equally accurate. Highly sophisticated gas chromatography (GC) run in tandem with mass spectrometry (MS) is emerging as the method against which all other methods are measured.[16]

Urine assays measure unbound hormone, reflecting that which is bioavailable. The use of 24-hour urine hormone profiles in clinical practice has found these profiles to correlate well with symptoms reported by patients on hormone symptom questionnaires. Similarly, supplementation with exogenous hormones or other treatments and improvement in symptoms is reflected in values seen on follow-up tests.

An important advantage of a 24-hour urine hormone collection is the ability to measure hormone metabolites. This is most important when evaluating the adequacy and safety of exogenous estrogen supplementation and in assessing adrenal function. It is well established that certain estrogen metabolites are "good" estrogens, having a protective effect on estrogen-sensitive tissues. Other metabolites are known to have more carcinogenic effects.[17,18]

The utility of measuring estrogen metabolites has been the focus of much recent attention. Studies from 2012 and 2013 (a prospective case-control study and a retrospective case-control study) uncover new data that find a statistically significant association between 2-hydroxylation pathway estrogen metabolites and lower breast cancer risk.[19,20] These studies focused on postmenopausal women not taking hormone replacement. While there are no studies to date that examine estrogen metabolite ratios in postmenopausal women while concurrently taking hormone replacement, it stands to reason that supplemented levels of parent estrogens will make estrogen metabolite analyses an important test in this population group.

Estrogen metabolism is also malleable, being easily altered with supplements such as diindolylmethane (DIM), indol-3-carbinol (I3C), methylated B vitamins, and magnesium.[21–23] Being able to evaluate the relative balance of protective estrogens to potentially harmful estrogens and see the effects of treatment interventions is invaluable to the clinician working to maximize quality of life while also protecting against harmful effects. Because 24-hour urine hormone profiles measure both phase 1 and phase 2 liver metabolites of estrogen, these profiles also offer a peek into liver function and may suggest further avenues for treatment.

Twenty-four hour urine hormone panels are excellent for evaluating adrenal health and function. In addition to measuring DHEA and cortisol, a complete panel also measures cortisone (the storage form of cortisol) and several important cortisol and cortisone metabolites, as well as aldosterone and other mineralocorticoids. The importance of measuring these metabolites can be seen in the stressed patient with normal or high-normal cortisol. Cortisol and cortisone metabolites can point to decreasing daily cortisol production that signals adrenal deficiency. The ➤

52-year old Female, irregular cycles and other sx

DDX: perimenopause, hypothyroidism, hypoadrenalism, anemia
Consider: Insulin resistance Evaluate for: breast cancer and osteoporosis risk

	Serum	Saliva	24-Hour Urine
Female Hormones	Estrone Estradiol Estriol Progesterone FSH LH	Estrone Estradiol Estriol Progesterone	Estrone Estradiol Estriol Estrogen quotient 2-hydroxyestrone 16α-hydroxyestrone 2/16α ratio 4-hydroxyestrone 2-methoxyestrone 2-methoxyestradiol Pregnanediol
	Commentary: Any of these three methods would be acceptable for baseline measurements. FSH and LH can be used to confirm reproductive decline. Saliva has an advantage over serum in that it is measuring free hormone. 24-hour urine also measures bioavailable hormone and has the advantage of the 24-hour perspective. The 24-hour urine profile also measures metabolites that can give insight into estrogen metabolism, risk for breast cancer and risk for osteopenia.[26]		
Androgens	Total Testosterone Free Testosterone DHEA or DHEA-S	Testosterone (free) DHEA-S	Testosterone DHEA & DHEA-S 5α-androstenediol 5β-androstenediol Androsterone Etiocholanolone
	Commentary: Any of these three methods would be acceptable for baseline measurements. All three measure free hormone. Saliva requires careful attention to collection procedures to avoid falsely elevated testosterone levels. 24-hour urine has the advantage of the 24-hour perspective and includes metabolites that allow assessment of 5α-reductase activity. This may point to risk for insulin-resistance.[27]		
Adrenal Hormones	Cortisol Cortisone	Cortisol, 4-point	Cortisol Cortisone Tetrahydrocortisone (THE) Allo-tetrahydrocortisol Tetrahydrocortisol (THF) 11β-hydroxyandrosterone 11β-hydroxyetiocholanolone Aldosterone Allo-tetrahydrocorticosterone Tetrahydrocorticosterone 11-dehydro tetrahydrocorticosterone
	Commentary: 4-point saliva collection allows assessment of diurnal pattern of cortisol secretion. 24-hour urine includes glucocorticoid metabolites that give comprehensive information about adrenal reserves and health. Aldosterone and mineralocorticoid metabolites give further information about the extent of adrenal depletion (or lack thereof).		
Thyroid	TSH T4 (Total and/or free) T3 (Total and/or free) rT3 Thyroid antibodies	Not available	FreeT3 Free T4 THE/THF ratio
	Commentary: Serum panels are standard for thyroid evaluation and have the most comprehensive panels. It is important to evaluate reverse T3 (rT3) as elevated levels can be indicative of underlying heavy metal toxicity, which may be contributing to thyroid dysfunction and symptoms. 24-hour urine Free T3 has excellent correlation with clinical symptoms of hypothyroidism.[28] The ratio of adrenal metabolites THE and THF is also highly correlated with thyroid function.[29-30]		

Table 1. This table outlines the testing options in all three methods for the hormones of interest. The commentary in each section provides the rationale for choosing a particular option.

ratio of cortisol and cortisone is another important indicator of adrenal function, as are the mineralocorticoids: low mineralocorticoids are a clear indicator of chronic adrenal fatigue and are an excellent marker to monitor adrenal recovery with treatment.[24,25]

Twenty-four hour urine hormone results may be altered in patients with significant liver or kidney disease. Dehydration or excessive fluid intake can also affect the results. As with all other methods of testing, nonbioidentical hormone substances are not measured. The 24-hour urine collection does not allow elucidation of the diurnal cortisol pattern. However, it has been observed clinically that an elevated cortisol and cortisone in the 24-hour urine panel may be related to nighttime cortisol spikes. Some practitioners have expressed a concern about the convenience of a 24-hour urine collection; however, all methods have their challenges. 24-hour urine hormone panels contain a wealth of information and may appear overwhelming. A good laboratory will have experts with clinical experience available to help you get the most from your results.

So back our theoretical patient. What is the best way to work her up? Let's start with a review of her symptoms and a DDx. She is 52, with irregular, sometimes heavy menstrual periods, mild hot flashes, thinning hair, and some central weight gain. She feels tired and burned out, has a busy and stressful life, probably doesn't get enough sleep, and is losing her sex drive. She has a family history which suggests some increased risk for breast cancer and a stronger risk for osteoporosis. She hasn't seen a doctor in several years, as she has felt well and been busy raising her daughters. Because of the central weight gain, it would be worth determining if she has some early insulin resistance. Table 1 (p. 55) outlines a rationale for choosing appropriate laboratory investigations.

For the most complete assessment of hormone function, the ideal combination of tests would be an in-depth 24-hour urine hormone profile, a 4-point salivary cortisol, a serum thyroid panel, and serum FSH and LH. FSH and LH are not absolutely necessary. Additional work-up appropriate to DDx would be CBC, serum Fe, TIBC, ferritin, comprehensive metabolic panel, Hgb1C, fasting insulin, and a baseline DEXA.

Serum, saliva, and urine testing can offer important insight into a patient's hormonal status. Each has a set of clinical strengths and limitations, such that a combination of testing methodologies may occasionally be appropriate. Multiple testing methods may not always be practical given financial or insurance constraints. However, a well-chosen series of laboratory evaluations can play a critical role in prioritizing and choosing among treatment options.

Notes

1. Brambilla DJ et al. Intraind vidual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. *Clin Endocrinol (Oxf).* 2007;67:853–862.
2. Plymate SR et al. Circadian variation in testosterone, sex hormone binding globulin, and calculated non-sex hormone binding globulin bound testosterone in healthy young and elderly men. *J Androl.* 1989;10:366–371.

Pushpa Larsen, ND, graduated from Bastyr University in naturopathic medicine, naturopathic midwifery, and spirituality, health and medicine. She is a regular contributor to naturopathic and integrative-medicine publications and a sought-after speaker for continuing-education seminars. Dr. Larsen has written and presented webinars on many topics in laboratory medicine. She consults with hundreds of doctors every year on the use and interpretation of hormone profiles, blood viscosity, and other tests offered by Meridian Valley Lab. plarsen@meridianvalleylab.com.

Michael Kaplan, ND, is a naturopathic physician specializing in men's health. He divides his time between his private practice at the Tahoma Clinic North Seattle and Meridian Valley Lab, where he trains physicians on the safe and effective use of bioidentical hormone replacement.

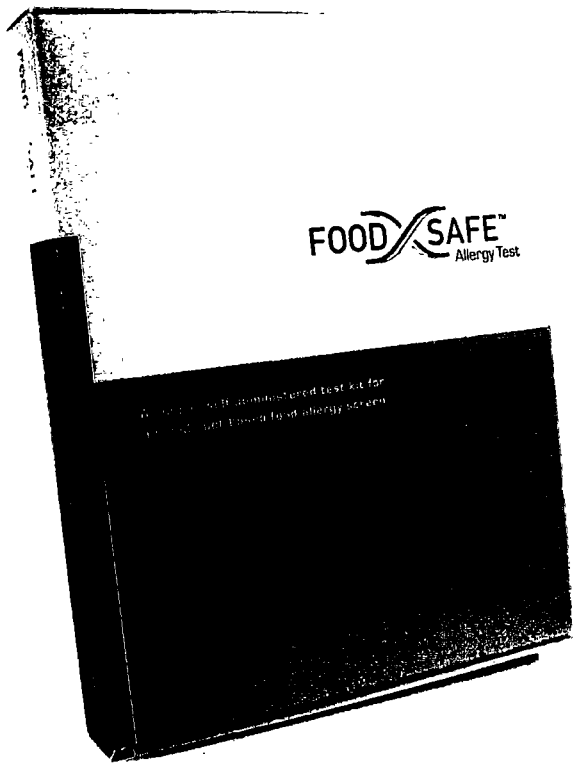
Leah Alvarado, ND, completed her undergrad degree in molecular and cellular biology at Texas A&M University and received her doctorate in naturopathic medicine from Bastyr University. She is a senior consulting physician for Meridian Valley Lab, teaching other doctors to interpret labs and prescribe hormones. She has coauthored three publications on hormone replacement therapy and food allergies.

Mi-Jung Lee, ND, LAc, has a doctorate in naturopathic medicine and degree in Chinese medicine and acupuncture. She is a consulting physician at Meridian Valley Lab and has trained extensively in the use and monitoring of bioidentical hormone replacement therapy. Dr. Lee is also skilled in mesotherapy, a minimally invasive anti-aging therapy from Europe. She practices at the Tahoma Clinic in Redmond, Washington.

3. Mishra RG et al. Metabolite ligands of estrogen receptor-beta reduce primate hyperreactivity. *Am J physiol.* 2006;290(1):H295–H303.
4. Maehle BO et al. Estrogen receptor beta – an independent prognostic marker in estrogen receptor alpha and progesterone receptor-positive breast cancer? *APMIS.* 2009 Sep;117(9):644–650.
5. Imanov O et al. Estrogen receptor in health and disease. *Biol Reproduct.* 2005;73(5):866–871.
6. Elshafie M et al. Transdermal natural progesterone cream for postmenopausal women: inconsistent data and complex pharmacokinetics. *J Obstet Gynecol.* 2007. 27(7)655–659.
7. McGregor JA. et al. Salivary estriol as risk assessment for preterm labor: A prospective trial. *Am J Obstet Gynecol.* 1995;Oct;173(4):1337–1342.
8. McGregor JA. et al. Diurnal variation in saliva estriol level during pregnancy: A pilot study. *Am J Obstet Gynecol.* 1999 Jan;180(1 pt3):S223–S225.
9. Heine RP et al. Serial salivary estriol to detect an increased risk of preterm birth. *Obstet Gynecol.* 2000. Oct;96(4):490–497.
10. Granger DA et al. The "trouble" with salivary testosterone. *Psychoneuroendocrinology.* 2004 Nov;29(10):1229–1240.
11. O'Leary P et al. Salivary, but not serum or urinary levels of progesterone are elevated after topical application of progesterone cream to pre- and postmenopausal women. *Clin Endocrinol.* 2000;53(5):615–620.
12. Lewis JG et al. Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women. *Maturitas.* 2002;41(1):1–6.
13. Ginsberg ES. et al. Half-life of estradiol in postmenopausal women. *Gynecol Obstet Invest.* 1998;45(1):45–48.
14. Hirohata T et al. Urinary growth hormone level and insulin-like growth factor-1 standard deviation score (IGF-SDS) can discriminate adult patients with severe growth hormone deficiency. *Endocrine J.* 2013;60(3):369–373.
15. Kovacs J et al. Measurement of urinary melatonin: a useful tool for monitoring serum melatonin after its oral administration. *J Clin Endocrinol Metab.* 2000;85(2):666–670.
16. Stanczyk FZ et al. Standardization of steroid hormone assays: Why, how and when? *Cancer Epidemiol Biomarkers Prev.* 2007 Sep;16(9):1713–1719.
17. Bradlow HL et al. 2-hydroxyestrone: the 'good' estrogen. *J Endocrinol.* 1996 Sep;150 Suppl:S259–S265.
18. Saeed M et al. Formation of depurinating N3Adenine and N7Guanine adducts by MCF-10F cells cultured in the presence of 4-hydroxyestradiol. *Int J Cancer.* 2007 Apr 15;120(8):1821–1824.
19. Fuhrman BJ et al. Estrogen metabolism and the risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* 2012 Feb 22;104(4):326–339.
20. Falk RT et al. Relationship of serum estrogens and estrogen metabolites to postmenopausal breast cancer: a nested case-control study. *Breast Cancer Res.* 2013 Apr 22;15(2):R34.
21. Dalessandri KM. et al. Pilot study: Effect of 3,3'-diindolymethane supplements on urinary hormone metabolites in postmenopausal women with a history of early-stage breast cancer. *Nutr Cancer.* 2004;50(2):161–167.
22. Anderson et al. Nutrition and epigenetics: an interplay of dietary methyl donors, one-carbon metabolism and DNA methylation. *J Nutr Biochem.* 2012 Aug;23(8):853–859.
23. Catechol-O-methyltransferase [Web page]. GeneCards. http://www.genecards.org/cgi-bin/carddisp.pl?gene=COMT&search=COMT.
24. Tomlinson J et al. 11β-hydroxysteroid dehydrogenase type 1: A tissue specific regulator of glucocorticoid response. *Endocr Rev.* 2004;25(5);831–866.
25. Jerjes WK, Taylor NF, Peters TJ, Wessely S, Cleare AJ. Urinary cortisol and cortisol metabolite excretion in chronic fatigue syndrome. *Psychosom Med.* 2006;68(4):578–582.
26. Lotinun S et al. Tissue selective effects of continuous release of 2-hydroxyestrone and 16alpha-hydroxyestrone on bone, uterus and mammary gland in ovariectomized growing rats. *J Endocrinol.* 2001;170(1):165–174.
27. Vassiliadi D et al. Increased 5 alpha-reductase activity and adrenocortical drive in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2009;94(9):3558–3566.
28. Baisier WV et al. Thyroid insufficiency. Is TSH measurement the only diagnostic tool? *J Nutr Environ Med.* 2000;10:105–113.
29. Hoshiro M et al. Comprehensive study of urinary cortisol metabolites in hyperthyroid and hypothyroid patients. *Clin Endocrinol.* 2006;64(1):37–45.
30. Taniyama M et al. Urinary cortisol metabolites in the assessment of peripheral thyroid hormone action: application for diagnosis of resistance to thyroid hormone. *Thyroid.* 1993;3(3):229–233.

◆

TESTING FOR **FOOD ALLERGIES** JUST GOT A WHOLE LOT EASIER.



This is a bloodspot for delayed hypersensitivity Reactions (igG). These responses may cause delayed symptoms, such as joint or muscle pain, chronic headaches, fatigue, eczema, and psoriasis. Since IgG reactions often occur hours or days after particular foods are consumed, correlating symptoms can be difficult.

Foodsafe makes it easier!

FOOD SAFE™
Allergy Test

Great for kids too!

95 FOODS TESTED	NO BLOOD DRAW	CLINICALLY RELEVANT	ROTATION FOOD PLAN

Free Shipping | Fast Turnaround
MeridianValleyLab.com
855.405.TEST

Meridian Valley LAB

The Trouble with Topical Progesterone and Testing

by Dr. David Zava

Introduction

Historically, topical progesterone delivery has been much maligned because, regardless of dose, it fails to raise serum progesterone to the levels known to counter estrogen-activated cell proliferation. Oddly, the results of serum progesterone testing, suggesting poor progesterone absorption, have trumped multiple studies showing the clinical benefits of topical progesterone used at physiological doses. Nearly 10 years ago, I wrote an article in the *Townsend Letter* explaining why topical progesterone is more beneficial than the serum levels might suggest.[1] I based this on saliva progesterone testing and published clinical studies, which showed that progesterone applied to the skin results in a dramatic increase in salivary progesterone, as well as tissues, without showing much increase in serum. Since that time, studies have continued to show that topical progesterone does absorb through the skin extremely efficiently, contrary to low venipuncture serum levels, and distributes systemically to other tissues, where it has biological effects. With the advent of capillary blood spot testing for steroid hormones in 2007, we also discovered, serendipitously, that topically delivered progesterone can be found in much higher amounts in capillary blood than in venipuncture serum, adding further support to the concept that topically delivered progesterone enters tissues other than the salivary gland and increases in capillary blood to a level high enough to affect estrogen-activated cell proliferation. In this report I briefly review studies relevant to topical progesterone delivery and include a recent publication in *Menopause* reporting on the distribution of progesterone in different body fluids following topical progesterone treatment.[2]

Optimal Endogenous Progesterone Production in Premenopausal Women and Progesterone Measurement in Serum and Saliva

In premenopausal women, the ovaries optimally produce about 30 mg of progesterone daily during the peak of the luteal phase, which occurs around days 19 to 22 of the menstrual cycle. This peak production of progesterone results in steady state blood serum levels of about 10 to 25 ng/mL, rising from a baseline follicular level of <1 ng/mL. Under these conditions, luteal salivary progesterone ranges from about 100 to 300 pg/mL, or 1% to 2% of serum levels (ZRT Laboratory data), with follicular levels usually <25 pg/mL.

While most laboratories report that serum progesterone ranges from about 3 to 25 ng/mL during the luteal phase of the menstrual cycle, it is well appreciated that >10 ng/mL is required to inhibit estrogen-activated proliferation of estrogen target tissues such as the breasts and uterus.[3,4] This is particularly true when the serum estradiol levels are within the high range of normal (100–300 pg/mL). Estradiol within this physiological range seen during the luteal phase of the menstrual cycle requires at least 100 times more progesterone (10,000–30,000 pg/mL; i.e., 10–30 ng/mL, the optimal luteal level) to prevent estradiol from causing excessive tissue hypertrophy and proliferation, which can increase risk for uterine cancer if such proliferation persists for multiple menstrual cycles

Exogenous Topical Progesterone Therapy: Low Serum Progesterone Inconsistent with Clinical Efficacy

When progesterone is applied topically to the skin in physiological amounts (about 30 mg) in the form of a cream or gel, serum levels increase slightly to <1–3 ng/mL, which is considered inadequate to counter the actions of estradiol when it is present at optimal physiological concentrations and higher (>100 pg/mL).[5,6] Based on serum progesterone levels, it is assumed that only about 10% of topically applied progesterone is absorbed into the systemic circulation, which accounts for the low serum progesterone (1–3 ng/mL) with physiological (20–30 mg) topical progesterone dosing. Because topically delivered progesterone is assumed to have such poor absorption kinetics, little emphasis has been placed on its potential clinical efficacy, despite evidence to the contrary. This assumption has also led to much higher pharmacological dosing (common dosing with topical progesterone 100–300 mg) in an attempt to raise serum progesterone levels. However, even with pharmacological dosing optimal luteal serum progesterone levels (10–30 ng/mL) are never achieved.[5,6]

A large body of evidence has been accumulating over the past 30 years to suggest that topically delivered progesterone is indeed clinically effective even though it does not raise serum progesterone levels to optimal luteal levels (10–30 ng/mL). What clinical research studies have shown repeatedly is that topical progesterone at physiological dosing (20–30 mg) has many beneficial effects to reverse symptoms associated with excessive estrogen exposure. It also lowers estradiol-activated cell

proliferation in target tissues such as the breasts and uterus. Several pilot studies have explored what effect topically applied progesterone has on estrogen-activated breast cell proliferation.[3,7,8] The study by Chang and colleagues showed that when a physiological dose (25 mg) of progesterone gel was applied topically to the breasts for 10 to 13 days, progesterone increased 100-fold in breast tissue biopsies to supraphysiological levels (about 60 ng/g tissue).[7] Even though the study clearly showed breast tissue uptake and a biological response to progesterone, serum progesterone levels did not change significantly from placebo-treated patients. Very similar studies have been done by others showing that near-physiological (50 mg) topical progesterone increases breast tissue levels of progesterone and evokes a measurable bioresponse, but does not raise serum levels significantly.[8] Similarly, nasal progesterone spray at physiological dosing (11.2 mg 3 times daily) has been shown to lower estrogen-stimulated uterine hyperplasia without increasing serum levels of progesterone to optimal physiological levels (> 10–30 ng/ml).[9] Similar studies and outcomes have been reported looking at the effects of topical progesterone on estrogen-activated endometrium. Leonetti and colleagues have demonstrated that progesterone applied topically to the skin at physiological dosing (30 mg) inhibits cell proliferation caused by conjugated estrogens, which alone can cause excessive proliferation of the endometrium and increase risk for uterine cancer.[4,10] In one of these studies, topical progesterone was as effective as the synthetic progestin, medroxyprogesterone acetate, in inhibiting the stimulating effects of conjugated estrogens.[4]

Women's Health Initiative Study Shifts Emphasis from Synthetic Progestins to Natural Progesterone

The landmark series of reports on large clinical trials of postmenopausal hormone replacement therapy all concurred that synthetic progestins increase risk for breast cancer and are associated with more adverse side effects than natural progesterone.[11–13] This resulted in a trend toward replacement of the synthetic progestins with natural progesterone for treating women using estrogen replacement for menopausal symptoms.

Despite the demonstrable clinical efficacy of topical progesterone shown in the studies listed above, and the widespread and anecdotal successful use of topical progesterone as an OTC cream and as compounded creams and gels, this form of therapy is not FDA approved and therefore has not received widespread acceptance by most conventional allopathic physicians. Because topical progesterone does not raise venipuncture serum progesterone levels, it has been given little consideration as a treatment option for women endogenously producing estrogens without adequate luteal progesterone (mostly perimenopausal women) or postmenopausal women supplementing with exogenous estrogens.

Because oral progesterone is FDA approved in the form of a capsule containing 100 mg of progesterone in peanut oil, it is widely used as treatment of choice by most physicians. At 200 to 300 mg dosing, it has been shown to be clinically effective at suppressing estrogen-activated cell proliferation of the endometrium, and not to increase risk for developing breast cancer, as seen with synthetic progestins such as medroxyprogesterone acetate.[11–15]

The obvious question arises as to why topical progesterone is clinically effective, but cannot be found in significant amounts in serum. Testing of progesterone in different body fluids has helped shed some light on this apparent paradox.

Saliva and Capillary Blood Testing for Progesterone Show that Topical Progesterone Absorbs Well and is Systemically Available

As a saliva testing lab, ZRT Laboratory first noticed that women using topical progesterone, as well as other topical steroid hormones (estrogens, androgens, glucocorticoids), had unusually high levels of the topically delivered hormone in their saliva. In fact, physiological dosing of topical progesterone, which most physicians found to be clinically effective (i.e., improved symptoms and signs typical of estrogen excess such as fibrocystic breasts, and prevention of endometrial hyperplasia caused by estrogens) resulted in salivary progesterone levels that were about 10 times the physiological level seen in women at peak of the luteal phase (i.e., 300–3000 pg/mL vs. 100 –300 pg/mL luteal, respectively). Some saliva testing laboratories interpreted this to mean that treating women with a physiological dose of progesterone was an overdose. Serum testing laboratories, which were the majority, had the opposite interpretation. Based on the very low serum progesterone results, their interpretation was that topical progesterone is poorly absorbed and therefore could not be clinically effective. Both views were inconsistent with research studies showing that 10-30 mg of topical progesterone is neither an excessive nor an insufficient dose, since it is clinically effective in many tissues throughout the body.

Capillary Blood Testing Shows that Topical Progesterone is Effectively Transported to Tissues

The advent of capillary blood spot testing, using blood drops from a finger-prick, began to shed some light on this paradox. We developed sex-steroid testing in dried blood spot samples as an alternative to conventional serum testing because, like saliva, it allowed individuals to collect a sample at any time at their convenience.[16] Capillary blood spot testing was also a good alternative to saliva for those individuals who had trouble collecting enough saliva and those using hormones in the form of a troche or sublingual drops, which causes false-high hormone levels in saliva due to supersaturation of the oral mucosa.

➤

Topical Progesterone and Testing

Our early work with capillary blood spot testing, which was published in *Fertility and Sterility*, showed that dried blood spot estradiol and progesterone, as well as LH and FSH, levels were quantitatively comparable to conventional venipuncture serum levels in premenopausal cycling women.[16] Once we expanded the testing from endogenously produced hormones into the realm of exogenous hormone delivery by various routes of administration (topical, oral, vaginal, sublingual/troche, subcutaneous injections and pellets), we serendipitously discovered that capillary blood levels of progesterone, with physiological topical progesterone dosing (10–30 mg), rose to physiological luteal levels of progesterone (20–40 ng/mL). Venipuncture serum levels under the same conditions rose very little (< 3 ng/ml), as elaborated above. We also found that with topical progesterone the capillary blood, progesterone levels increased proportionally to dose, which more closely reflects what others have found with tissue uptake of progesterone, as well as clinical response.[3,4,7–10]

What we discovered with capillary blood testing of progesterone, following topical progesterone delivery, holds true also for topical delivery of estrogens (estradiol, estriol, estrone) and androgens (testosterone, DHEA) in that physiological dosing with these hormones results in little increase in venipuncture serum levels but a physiological level of hormone in capillary blood. Topical estradiol, even at doses as high as 5 mg (100 times the 25 to 50 μg of estradiol produced by the ovaries daily), does not increase serum estradiol beyond about 50 pg/mL, which would be low range for a premenopausal woman; serum and capillary blood levels of estradiol are about 80 to 150 pg/mL in the luteal phase of premenopausal women.[16] Commercially available, FDA-approved topical estrogen sprays and gels deliver estradiol at doses from about 1 to 5 mg but raise serum estradiol levels very little (usually < 50 pg/mL). In sharp contrast, this same dosing shows a significant and dose-dependent increase in capillary blood and salivary estradiol that is 50 to 100 times higher than serum levels.

The obvious question that arises is, how could levels of hormone in capillary blood, or blood-feeding tissues, be so much higher than levels in blood returning to the heart (venous blood)?

In a pilot clinical study published in *Menopause*, we addressed some of these pressing questions regarding topical progesterone supplementation and body fluid distribution.[2] In the study, women used 80 mg of topical progesterone gel or cream daily for several weeks to allow for tissue equilibration, and then levels were followed in venipuncture serum and whole blood, capillary blood from the fingertip, and saliva over a 24-hour time course after morning application. What we found is that, as expected from our clinical testing of tens of thousands of patients, very high levels of progesterone in saliva and capillary blood, but not in venous serum or venous whole blood. Whole venous blood, in addition to venous serum, was tested to exclude the possibility that progesterone was residing on erythrocytes and thereby excluded from analysis with serum testing. We found that venous whole blood contained even less progesterone per unit volume than venous serum, which suggests that nearly all of the progesterone in venous blood is present in the serum, and not on the surface of blood cells. This did not exclude the possibility, however, that arterial blood entering the capillaries might have a higher concentration of bioavailable progesterone that off-loads into capillary beds, where it enters and is retained by interstitial tissues and target cells.

As an alternative explanation to erythrocyte transport and delivery of progesterone, we also speculated that progesterone might be present in and around capillary beds

Dr. David Zava has devoted his 40-year professional career to exploring the role of hormones in aging and disease. After completing his PhD in biochemistry at the University of Tennessee in 1974, Dr. Zava spent much of his time researching hormones and breast cancer in Switzerland, Texas, California, and Oregon. In 1998, he established ZRT Laboratory, a CLIA-certified laboratory that is a front-runner in the innovative development of test methods to identify hormonal imbalances that can lead to debilitating symptoms, diminished quality of life, and increased risk for cancers and many of the diseases of aging, such as diabetes, cardiovascular disease, and senile dementia. ZRT Laboratory was one of the first laboratories to develop and commercialize noninvasive saliva and dried urine and semi-invasive dried blood spot methods for testing hormones as an alternative to conventional serum testing. Using these unique methods of body fluid collection, ZRT is actively engaged in hormone research studies with universities, government agencies such as the NIH and CDC, military agencies, private physicians, and professional sports teams.

In addition to his innovations in clinical laboratory testing and development, and numerous scientific publications, Dr. Zava coauthored a landmark book, *What Your Doctor May Not Tell You About Breast Cancer: How Hormone Balance Can Help Save Your Life*. In this book, Dr. Zava and coauthors describe how breast cancer can be caused by hormonal imbalances that occur naturally as we age, but can be prevented if the types of hormonal imbalances are identified with testing and restored to optimal healthy levels with bioidentical hormone replacement therapy and improved lifestyle.

due to its uptake, retention, and presence in lymphatics, which form a weblike structure with blood capillaries in all tissues except the brain. The lag from time of use to presence in saliva and capillary blood, about 4 to 6 hours, is not consistent with blood transport, which is rapid, but suggests instead that transport of topical progesterone and other topically delivered hormones could in fact be transported via lymphatics. Lymphatic flow is slow and depends on movement and muscle contractions, and therefore delivery to tissues from the lymphatics could depend on one's degree of physical activity.

What we have also discovered about topical hormone delivery is that very little of the hormone, or its downstream metabolites, is delivered into the urine as determined by GC-MS/MS testing. Therefore, urine testing, like serum testing, is not reflective of tissue uptake or bioresponse to topically delivered hormones. All other forms of hormone delivery that we have evaluated (oral, intramuscular/subcutaneous injections, subcutaneous pellets, sublingual/troche) result in dose-dependent increases in salivary, venipuncture serum, capillary blood, and urine levels of supplemented hormones. Topically delivered hormones are uniquely different in that saliva and capillary blood levels rise in proportion to dose, but venipuncture serum and urine levels increase very little and rarely reach optimal physiological levels with physiological dosing.

Conclusion

To summarize, topical delivery of sex-steroid hormones can be monitored effectively with saliva and capillary blood, but not venipuncture serum or urine. Endogenously produced hormones, and all other forms of delivery (exception topical) can be effectively monitored with all of the commonly used body fluids (saliva, venipuncture serum, capillary blood, urine). Use of venipuncture serum or urine hormone levels following topical hormone delivery may lead to underestimation of tissue hormone delivery and consequent overdosing in attempts to achieve physiological levels.

Notes

1. Zava DT. Saliva hormone testing. *Townsend Lett.* 2004 January:120–124.
2. Du JY, Sanchez P, Kim L, Azen CG, Zava DT, Stanczyk FZ. Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood. *Menopause.* Epub 2013 May 6.
3. Sitruk-Ware R, Seradour B, Lafeye C. Treatment of benign breast diseases by progesterone applied topically. In: Mauvais-Jarvis P, Vickers CF, Wepierre J, eds. *Percutaneous Absorption of Steroids.* Academic Press; 1980:219–229.
4. Leonetti HB, Landes J, Steinberg D, Anasti JN. Transdermal progesterone cream as an alternative progestin in hormone therapy. *Altern Ther Health Med.* 2005;11:36–38.
5. Burry KA, Patton PE, Hermsmeyer K. Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *Am J Obstet Gynecol.* 1999;180:1504–1511.
6. Wren BG, McFarland K, Edwards L, et al. Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women. *Climacteric.* 2000;3:155–160.
7. Chang KJ, Lee TT, Linares-Cruz G, Fournier S, de Lignieres B. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. *Fertil Steril.* 1995;63:785–791.
8. De Boever J, Verheugen C, Van Maele G, Vandekerckhove D. Steroid concentrations in serum, glandular breast tissue, and breast cyst fluid of control and progesterone-treated patients. In: Angeli A, ed. *Endocrinology of Cystic Breast Disease.* New York: Raven Press; 1983:93–99.
9. Cicinelli E, Cignarelli M, Resta L, Scorcia P, Petruzzi D, Santoro G. Effects of the repetitive administration of progesterone by nasal spray in postmenopausal women. *Fertil Steril.* 1993;60:1020–1024.
10. Leonetti HB, Wilson KJ, Anasti JN. Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium. *Fertil Steril.* 2003;79:221–222.
11. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321–333.
12. Beral V, Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet.* 2003;362:419–427. Erratum in *Lancet* 2003;362:1160.
13. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer.* 2005;114:448–454.
14. Hargrove JT, Maxson WS, Wentz AC, Burnett LS. Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. *Obstet Gynecol.* 1989;73:606–612.
15. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA.* 1996;275:370–375.
16. Edelman A, Stouffer R, Zava DT, Jensen JT. A comparison of blood spot vs. plasma analysis of gonadotropin and ovarian steroid hormone levels in reproductive-age women. *Fertil Steril.* 2007;88:1404–1407.

◆

The Patented Mediator Release Test (MRT): A Comprehensive Blood Test for Inflammation Caused by Food and Food-Chemical Sensitivities

by Mark J. Pasula, PhD

Introduction

There are a wide range of chronic inflammatory conditions wherein food and food-chemical sensitivities play either a primary or secondary role in generating inflammation and symptoms (Table 1). Fully addressing food sensitivities can have a major impact on the speed and completeness of clinical outcomes. It can also improve the effectiveness of other therapies, as a chronic source of inflammation has been eliminated.

Table 1. Medical Conditions Where Food Sensitivities Can Play a Primary or Secondary Role

Gastrointestinal
- Irritable Bowel Syndrome
- Functional Diarrhea
- GERD
- Crohn's Disease
- Ulcerative Colitis
- Microscopic Colitis
- Lymphocytic Colitis
- Cyclic Vomiting Syndrome

Gynecological
- Polycystic Ovary Syndrome

Musculoskeletal
- Fibromyalgia
- Inflammatory Arthritis
- Chronic Fatigue Syndrome

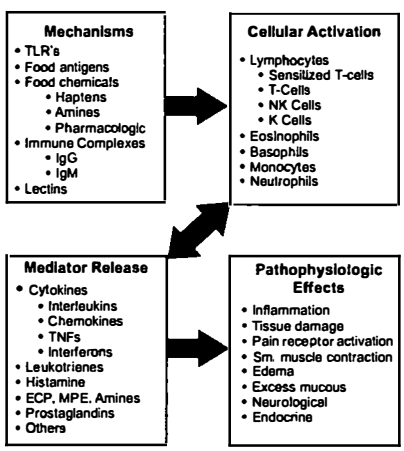
Urological
- Interstitial Cystitis

Neurological
- Migraine
- ADD/ADHD
- Autism Spectrum Disorders
- Epilepsy
- Depression
- Insomnia
- Restless Leg Syndrome

Endocrine
- Type II Diabetes
- Metabolic Syndrome
- Obesity

Dermatological
- Atopic Dermatitis
- Urticaria
- Psoriasis

Diagram 1: How Food Sensitivities Cause Inflammation



Food sensitivities are highly complex non-IgE non-celiac inflammatory reactions involving multiple triggering mechanisms, multiple white cells, and a vast number of proinflammatory and proalgesic mediators. Released mediators cause a variety of clinical or subclinical effects.

Definition of Food Sensitivity

Food sensitivities can be defined as any inflammation-generating reaction against a specific food or food component that does not involve type 1 IgE-mediated hypersensitivity or food-related autoimmunity. The inflammatory process associated with food sensitivities is significantly more complex than IgE-mediated food allergy. Multiple triggering mechanisms and pathways, multiple classes of reacting white cells, a vast number of pro-inflammatory mediators, and a wide array of symptoms and conditions make sensitivities a highly complex category of adverse food reaction (Diagram 1).

Innate Immunity Governs Reactions in Gluten Sensitivity

In 2011, Fasano et al. published a study documenting a new type of adverse reaction to gluten, *gluten sensitivity* (GS). It was established that GS was distinctly different than celiac disease in several important ways:

1. Expression of TLR-2 showed that gluten sensitivity is governed by innate immunity.
2. Gut permeability in GS was significantly less than in both controls and celiac patients.
3. Low to moderate levels of inflammation were detected but no tissue damage was visible.
4. There was less infiltration of intraepithelial lymphocytes.

The historic importance of this study cannot be overstated. Until it was done, the innate immune system had been fully ignored by allergy researchers as having any involvement in diet-induced inflammation. Estimates of the prevalence of GS are 6 to 8 times greater than celiac disease, affecting approximately 15 to 20 million Americans.

It is worth noting that the most commonly ordered blood test to help identify culprit food items – food-specific IgG – is a response of the adaptive immune system, as is type 4 delayed-type hypersensitivity governed by sensitized T cells (lymphocyte transformation).

It is also worth noting that the clinical presentations of the GS patients in this study (brain fog, joint and muscle pain, headaches, diarrhea, etc.) were consistent with the presentations of food sensitivity sufferers reported for decades. Further research has confirmed the findings of innate involvement in gluten sensitivity.[2-4]

Inflammation and Symptoms Depend on Mediator Release

All clinical and subclinical effects brought about by food-induced inflammation are the direct result of pro-inflammatory and proalgesic mediator release from various white blood cells. Without the release of histamine, cytokines, prostaglandins, leukotrienes, and so on, there is no tissue damage, no pain receptor activation, no smooth muscle contraction, nor any other negative effect associated with diet-induced inflammation. This is true for any form of food-induced inflammation; that is, food allergy, food-related autoimmunity, or food sensitivity, and whether potential mechanisms are elevated.

Identifying Trigger Foods and Food-Chemicals with Antibodies

Food sensitivity management starts with identification of trigger foods and food-chemicals. Therapy typically involves some form of elimination of offending substances; that is, rotation or avoidance diets. The more precisely practitioners can identify and remove inflammation-generating food items, the greater the clinical value of the method.

Most blood tests designed to identify sensitive foods and food-chemicals are typically limited to either a single mechanism or a specific part of the inflammatory process, which may or may not be involved in actual inflammation and consequently may or may not be clinically relevant. For example, food-specific antibodies other than IgE have not shown a strong correlation with inflammation or symptoms.

IgE, by its function as a trigger of mast cell degranulation in allergy, has an acceptable though not excellent correlation with both the degree of the inflammatory response and the severity of clinical effects. Other antibody tests (IgG, IgM, IgA) have not demonstrated an acceptable correlation with inflammation or clinical symptomatology in adverse food reactions.[5–8]

The Function of Non-IgE Antibodies

The function of non-IgE food-specific antibodies appears to be related more to the clearing of food antigens and macromolecules via immune complexes, rather than a direct inflammation-producing role. If any, the inflammatory effects of food-specific IgG, IgM, or IgA are more likely the result of factors related to the in vivo environment, such as the production of too many smaller immune complexes or complexes that deposit on tissue, eliciting an aggressive reaction by immune cells. But insight into the sizes of immune complexes or whether they deposit on tissue cannot be gleaned from quantifying how much food-specific IgG, IgA, or IgM is produced. In addition, in IgE-mediated inhalant allergy, elevated levels of allergen-specific IgG have shown anti-inflammatory properties.[9,10]

Other limitations of non-IgE antibody tests are that they don't offer testing for food-chemical reactions, an area that is often clinically significant. Thus, the information provided by most commercially available food sensitivity blood tests is of limited clinical value.

White Cells Are an Immunologic End Point

White cells play a critical role in food-induced inflammation. Neutrophils, monocytes, eosinophils, mast cells, and various lymphocytes, release mediators in pathogenic reactions. Neutrophils and monocytes/macrophages are first responders in innate pathways (Figure 1).[18–25] Other cells, such as tissue mast cells, eosinophils, and lymphocytes, are involved in reactions related to both adaptive and innate pathways. Whether reactions are governed by innate or adaptive pathways, mediator release from white cells are the immunologic "end point" of all food-induced inflammatory reactions.

Elevation of various inflammatory markers (HS-CRP, IL-15, PGE3, etc.), as well as white cell involvement, has been documented in many food–sensitivity related conditions. Neutrophils and eosinophils were confirmed active in ulcerative colitis and diarrhea-predominant IBS via measurement of myeloperoxidase and eosinophil cationic protein.[11] Eosinophils were shown to infiltrate the colon in some cases of chronic constipation.[27,28] Killer and natural ➤

Figure 1

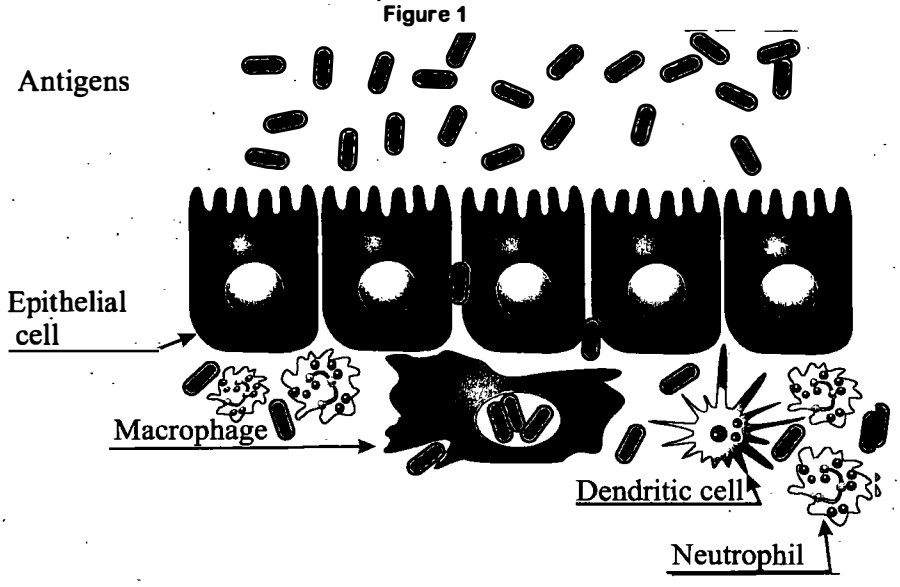


Figure 1 represents a simplified in vivo reaction of cells involved in the innate inflammatory reaction. When "sensitive" food antigens cross the tight junctions, neutrophils and macrophages are typically the first cells to react. They engage in the destruction of offending pathogens/antigens, ultimately releasing various cytokines and other pro-inflammatory mediators.

killer cells were shown to be active in food-induced migraine.[14,15]

Mediator Release Causes Volumetric Changes in White Cells

During an inflammatory reaction, phagocytic cells identify offending antigens as foreign, attacking and engulfing, and then eliminating them. During that process, whatever cells are involved release cytoplasm and chemical mediators, causing a volumetric change in reacting cells. This is true of all cells whenever they release mediators. Volumetric changes are typically subtle, in the range of 5 to 30 fl. (Figure 2).

Figure 2: Mediator Release Causes Volumetric Change

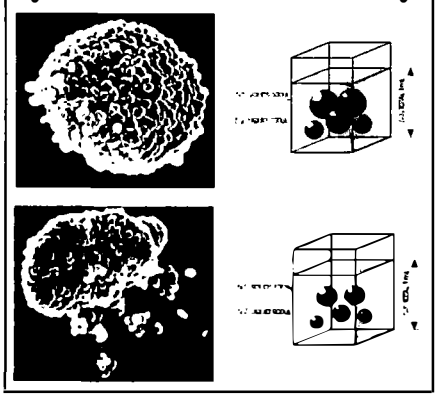


Figure 2 shows a peritoneal mast cell degranulating. Release of mediators invariably affects volumetric changes in reacting cells.

The Patented Mediator Release Test (MRT)

The Mediator Release Test (MRT), developed by Oxford Biomedical Technologies, is a new functional blood test designed to identify sensitive foods and food-chemicals. It utilizes two advanced methods of measurement: flow cytometry and ribbon impedance. The MRT is the only blood test in the world that tests cellular end-point reactions to foods, chemicals, and other foreign substances, quantifying the degree of the inflammatory response and simultaneously determining which types of cells are reacting. THE MRT provides the highest therapeutic value of any commercially available food-sensitivity blood test.

The Advantage of Ribbon Impedance over Normal Impedance

The ribbon method is a patented form of impedance-based measurement, developed by Oxford Biomedical Technologies. The ribbon method eliminates the baseline and threshold associated with every other impedance-based sizing technology (Figure 3).[16,17]

Impedance-based methods that employ a baseline and threshold have three main shortcomings:

1. They improperly size cells when dissimilar sized particles traverse the aperture near each other.
2. Impedance technologies that rely on a baseline begin their sizing from the level of the threshold, not from the when the actual start of the particle passing through the aperture occurs.
3. They are only capable of measuring size changes (2-D), not volumetric changes (3-D).

The ribbon method is extremely precise, measuring the entire flow of liquid and cells millions of times per second as they pass through the aperture. Because the ribbon identifies the true starting point and ending point of each cell (Figure 3), it is able to provide a volumetric determination of all tested cells. Incorporation of the ribbon method gives the MRT superior precision and accuracy over other impedance-based cell sizing methods of food-sensitivity testing.

Flow Cytometry Provides Vital Clinical Data

Impedance-based sizing methods cannot differentiate between different types of similar-sized cells (Figure 4). The use of advanced flow cytometry in the MRTIII is another area that helps provide vital clinical information to practitioners. Cytometry allows the measurement of all types of circulating white cells simultaneously (neutrophils, monocytes, eosinophils, lymphocytes). This is important because different types of white cells can act independently of each other.

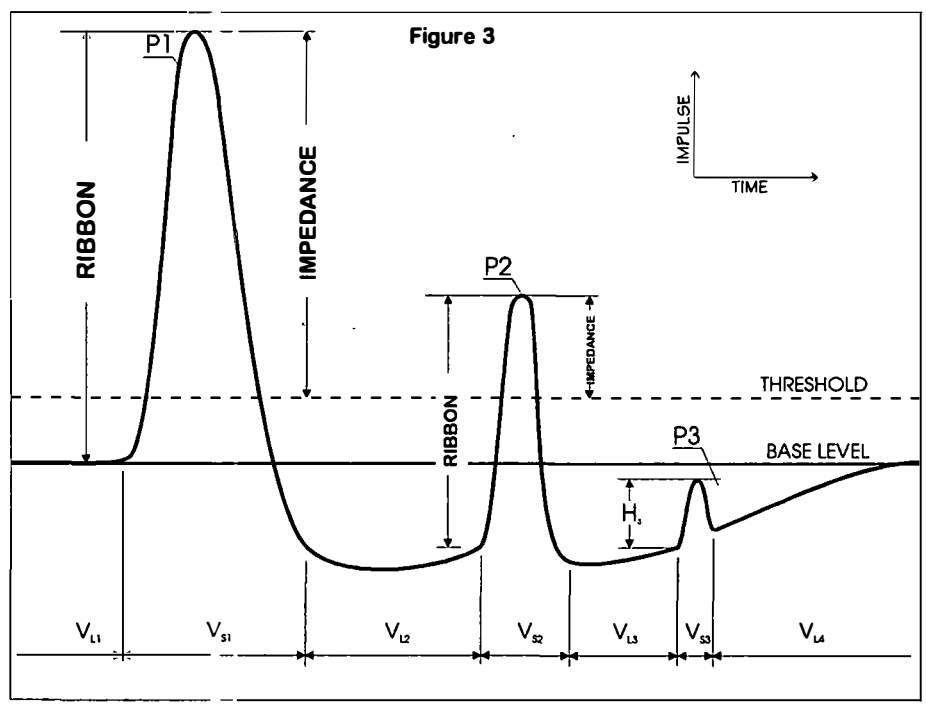


Figure 3 shows the difference in precision between typical impedance-based counting and sizing technologies, which rely on a baseline and threshold and the patented ribbon method, which is able to detect the true volume of each cell.

For example, monocytes, which comprise 1% to 7% of white cells, can strongly react to an antigen independent of any other group of white cells. So can any group of cells; that is, lymphocytes, neutrophils, eosinophils, and so on.

If neutrophils, which comprise between 55% and 75% of total white cells, have a cumulative 3% reaction (which would be nonreactive) and monocytes have a cumulative 50% reaction (which would be strongly reactive), the clinically significant monocyte reaction would not be recorded as clinically significant because the cumulative reaction of the monocytes is small relative to the total cumulative reaction (or nonreaction) of the neutrophils.

However, because the MRT can distinguish between reacting groups of cells, it is the only food–sensitivity testing technology that can deliver the most complete picture of cellular reactivity (Figure 5). Thus, the MRT provides practitioners and their patients the highest level of clinical utility.

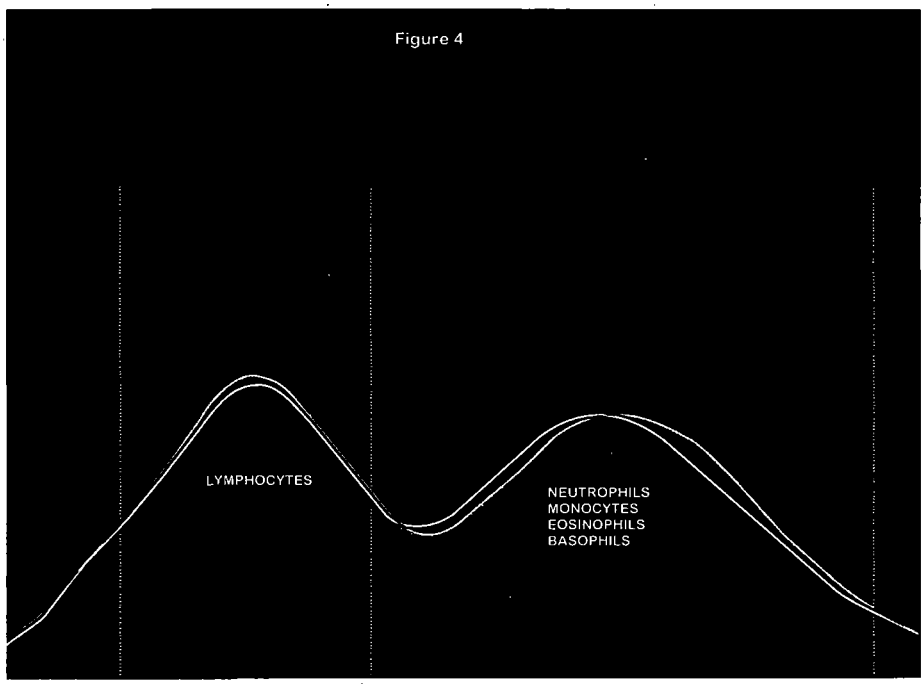


Figure 4 shows where the different cell types are sized using impedance-based sizing methods. Due to very similar sizes of various peripheral granulocytes, impedance-based technologies are incapable of distinguishing between different classes of reacting cells.

Advantages of the MRT over Other Food Sensitivity Tests

The MRT offers several important advantages over other sensitivity-based blood tests:

1. The MRT is a functional measure of sensitivity-based inflammatory responses, not just a measurement of a potential trigger that may or may not have clinical relevance.
2. Because the MRT is an end-point test, it is can account for the widest range of triggering mechanisms involved in sensitivity reactions, including both innate and adaptive pathways.
3. The MRT can test reactions to foods, food-chemicals, and other substances.
4. Because it is a three-dimensional volumetric measurement, the MRT can reliably quantify the degree of the inflammatory response. This is important because the MRT provides insight into dose-dependent reactions and subclinical reactions. These are clinically meaningful but virtually impossible to identify without the MRT.

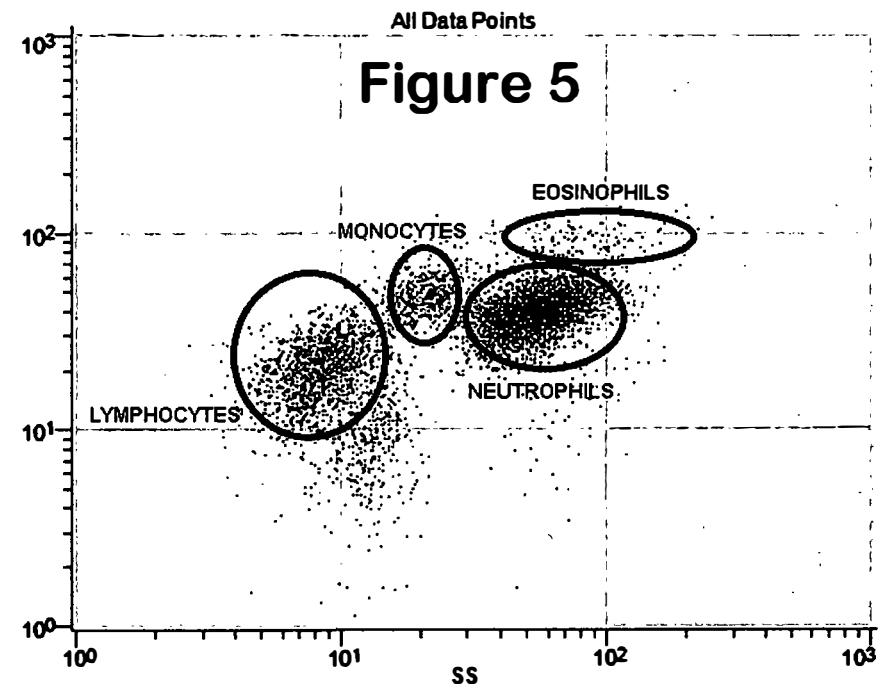
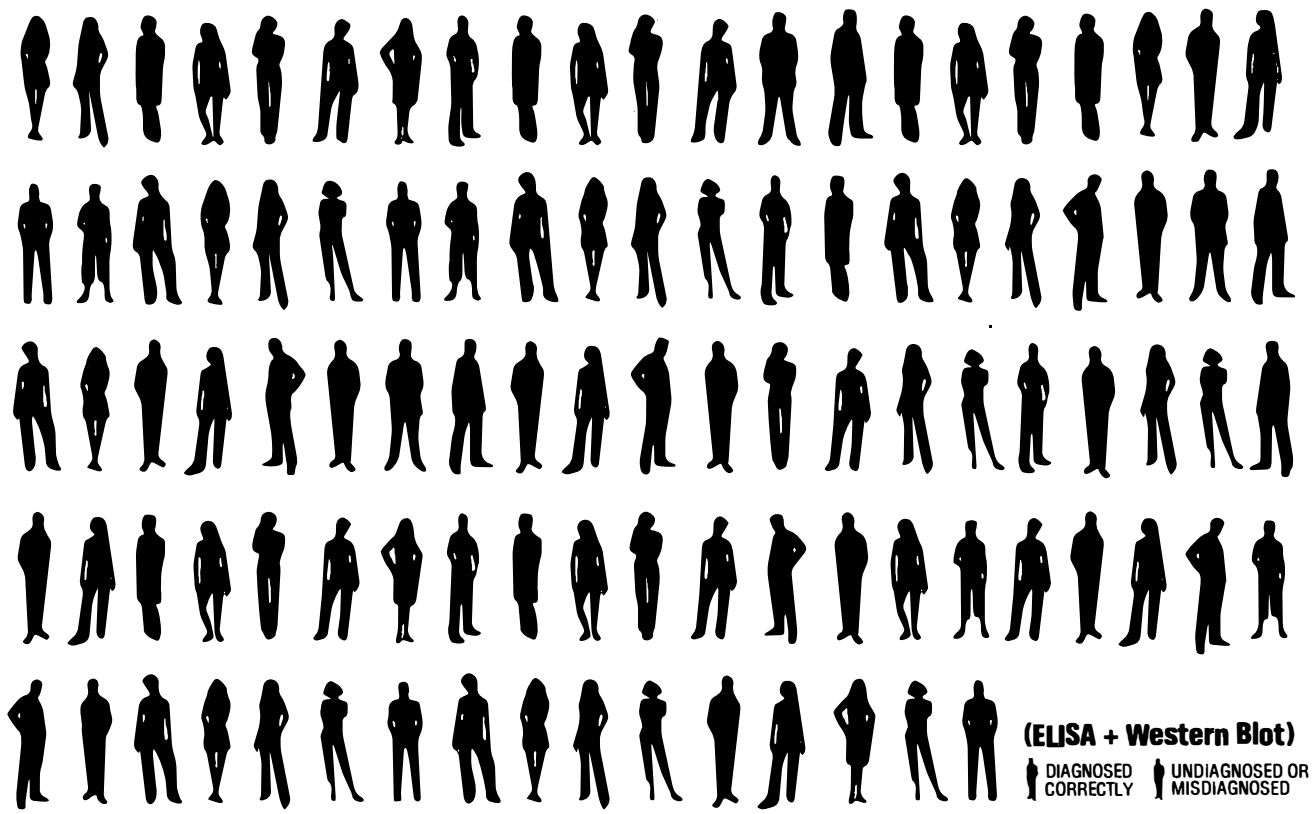


Figure 5 shows that the patented MRT, with the use of flow cytometry, is the only technology able to distinguish between different types of white cell reactions. This provides unparalleled therapeutic information for practitioners.

Don't take chances with Lyme disease

50-70% of patients go undiagnosed or misdiagnosed due to low sensitivity of traditional antibody-based testing.



Lyme is a difficult disease to diagnose because the bacteria are not always detectable in the blood, even in active disease, as the bacteria like to "hide." The current two-tiered antibody method for detecting Lyme identifies it 30% of the time in early stages and 50% in late stages. iSpot Lyme™ is a ***NEW*** breakthrough cellular immune diagnostic tool that can detect the bacterial infection of Lyme disease with 84% sensitivity and 94% specificity.

For greater accuracy, add iSpot Lyme™.
Rule it out, retest.
www.ispotlyme.com

iSpotLyme™

Innovation from Pharmasan Labs™

Case Study:
Sensitive Lyme Test Leads to Correct Diagnosis and Treatment for Patients with Intractable Illness

by Todd LePine, MD

Lyme disease, known as the great imitator, wreaks havoc on lives. Symptoms are diverse, severe, and – without an accurate diagnosis – intractable. Testing for the illness has been difficult due to a high false negative rate and low sensitivity. Because clinical proof of infection can be so difficult to obtain, chronic infection can often persist.

Lyme disease is the most prevalent tick-borne disease in the US, with an incidence higher than AIDS, West Nile virus, and avian flu combined. Caused by *Borrelia burgdorferi*, a bacterium of the spirochete class, Lyme disease is a zoonotic, vector-borne disease transmitted by the *Ixodes* (black-legged) tick. Classic acute symptoms may include an observed tick bite, a "bull's-eye" rash, flu-like symptoms, joint pain, neurological symptoms, heart palpitations, and severe fatigue. Patients not receiving adequate treatment may develop chronic infection or late-stage Lyme disease, which is truly the great imitator, manifesting as arthritis, fibromyalgia, chronic autoimmune diseases, or neuropsychiatric symptoms. The clinical manifestation of Lyme disease depends upon the infection load, duration, and potential coinfections.

Case Study: J. S.

J.S. came to me suffering from severe, refractory depression with no apparent cause. She lived for three years in Virginia and participated in frequent outdoor activities. She reported suicidal feelings that began at age 29.

History

- 10 different antidepressants were prescribed, including Adderall, Xanax, Abilify, and Zoloft.
- Of these antidepressants, J. S. found only Prozac and Wellbutrin to be somewhat helpful, and only for a short time.
- J. S. made two suicide attempts, and was hospitalized for one of them.
- J. S. reported achy joints, especially knees.

Laboratory Results

- I ordered a new test for *Borrelia burgdorferi*, iSpot Lyme, to determine if J. S. had been infected.
- J. S.'s iSpot Lyme test showed 79 spot-forming units, more than three times the diagnostic threshold for a positive case.
- Inflammatory cytokines can play a role in depression, and I suspect that her chronic Lyme infection was contributing significantly to depression symptoms.[1]
- Labs also showed elevated Epstein-Barr virus (EBV) titers and low immune function as measured by the CD57.

Treatment

- I initially prescribed doxycycline 200 mg b.i.d. along with artemisinin 400 mg b.i.d. for 2 months and recommended several supplements to support J.S.'s immune system, control inflammation, and treat EBV reactivation.
- When treatment works, patients can experience "die-off," a rise in symptoms due to neurotoxins released as Lyme bacteria die. I suggested that J. S take CharcoCaps three times daily if this happened.

Referrals

- I asked J. S. to schedule a SPECT scan to determine if brain scan abnormalities were present and if so to what degree. This can also be helpful to monitor success of treatment.[2]
- I referred J. S. to the International Lyme and Associated Diseases Society (ILADS) to connect with a local Lyme disease specialist; and after 3 months her regimen was changed to doxycycline, azithromycin, and cefdinir.

Treatment Results

- In early stages of treatment, J. S.'s depression symptoms improved by approximately 50%, though cycles of improvement and worsening are not uncommon in Lyme disease.

➤

➤

vitamins and minerals that are currently considered nonergogenic with their possible health benefits for the athlete.

Table 1: Potential Ergogenic Nutraceuticals for the Athlete

Vitamin C	Enhances immunity, protects from oxidative damage, supports connective tissue, may prevent upper respiratory infections after intense exercise
Vitamin D	Immune enhancement, protects against osteoporosis
Magnesium	May improve sleep, supports carbohydrate utilization, helps relax muscle tissue Deficiency may contribute to lower endogenous conc. of testosterone. It has yet to be demonstrated to boost hormone levels in someone with normal levels.
Vitamin B6	When combined with vitamins B1 and B12, B6 may increase serotonin levels and improve fine-motor skills.
Curcumin	Anti-inflammatory, possible aid for fat loss

Vitamin D

Special attention should be given to the athlete regarding vitamin D status. Vitamin D deficiency is now epidemic, and athletes suffer the same rates as the rest of the public. While vitamin D supplementation in those who are sufficient does not appear to improve performance, vitamin D delivered to deficient athletes does indeed improve performance.[6,7,10] In one study of elite female gymnasts, 77% were found to have vitamin D levels lower than 35 ng/ml and a full third had levels less then or equal to 10 ng/ml.[9] Vitamin D is stereotypically known for its role in bone metabolism. However, it is now known that there are vitamin D receptors all over the body, and as a consequence it affects the body in multiple ways. As far back as the 1930s, there were numerous reports of the beneficial effects of UV therapy on athletic performance.[10,11] There are also studies that suggest the season of training makes a difference. One of these studies showed that training in the summer months creates greater gains than the same volume of training in autumn or winter despite the same stimulus.[12]

In both older and younger individuals, adequate vitamin D status affects neuromuscular function and may have specific relationship to the maintenance of the fast twitch (type II) muscle fibers.[6,8,10,13,14] In a study on teenage athletes, vitamin D deficiency lowered muscle power and force.[15] Vitamin D levels are also related to myalgia, fatigue, and reduced motivation to exercise. Studies in older adults have shown that the level of vitamin D is correlated with the propensity to fall. A meta-analysis on vitamin D levels has shown a 20% reduction in the risk to fall.[16] This is likely due to vitamin D's ability to improve reaction speed, balance, and neuromuscular performance. Much of this may be explained by the ability of vitamin D to help maintain and even build type II muscle fibers.[6,8,10,13,14]

Athletes should be tested for vitamin D with a serum 25-hydroxy vitamin D test, with a target of between 50 to 100 ng/ml. If they are found to be deficient. then a combination of vitamin D supplementation and sun exposure is advisable.

Curcumin

Curcumin, one of the most well-researched nutraceuticals, is the active constituent in the herb turmeric. Curcumin sounds like the herb cumin, but has no relation to it. Curcumin is found only in turmeric.

The benefit for the athlete primarily comes from curcumin's powerful anti-inflammatory ability. Thus far curcumin has been studied against numerous anti-inflammatory medications and has done just as well or better.[18–21,23] Curcumin has a very real potential to support the athlete through its many anti-inflammatory effects while also supporting joint health.[22] Considering the numerous positive side effects and safety profile of curcumin, as opposed to the possible numerous negative side effects of most over-the-counter and prescription anti-inflammatories, one wonders why it is not recommended to athletes more.

Another possible benefit of curcumin is its effect on preventing fat gain. There are some intriguing studies showing that curcumin can help with fat loss.[24,25] To confirm this lipolytic effect of curcumin, many more studies are needed; however, this is just one of many potential benefits of taking curcumin for the athlete.

Although curcumin is not considered ergogenic, it can, at least in theory and based on current evidence, possibly support and extend the career of many athletes through its seemingly powerful anti-inflammatory effects.

Laboratory Evaluations for the Athlete

Individual nutrient deficiencies affect many aspects of physical performance, recovery, and immune function. Athletes, because of the imposed increases in metabolism, can be at higher risk for nutrient deficiencies. Serum testing is a reliable and useful tool for diagnosis of severe nutrient deficiencies but may be inadequate for certain vitamins and minerals.[17] Furthermore, serum testing does not give a clear picture of the functional status of the nutrient. In other words, to get a better idea of the intracellular status of a nutrient, other labs may be necessary. It can be useful for those working with athletes to use more functional tools for assessment of metabolism and nutritional needs.

As an example, doing a serum magnesium does not really tell the clinician anything about status of magnesium intracellularly unless it shows a frank deficiency. An analysis of intracellular nutrients can be a more valuable tool possibly indicating subclinical deficiencies or deficiencies not apparent on conventional lab tests. Functional lab tests can be extremely valuable for the athlete, and once any subclinical deficiencies are corrected, performance will most likely be enhanced.

There are now a wide range of laboratory analyses that can give more functional assessments of nutrition status. The ones that may be most beneficial are adrenal hormone profiles, organic acid testing, intracellular nutrient analysis, and amino acid testing.[17]

Critical Evaluation of Ergogenic Aids

It is important to be aware of the large gap that often exists between supplement marketing and supplement research. When evaluating whether a nutritional supplement might be useful, it is prudent to keep several things in mind.

A good first question to ask is, does the science make sense? Knowing the nutrient and its involvement in biochemical pathways is a key. If the mechanism of action makes sense from a biochemical perspective, then the supplemental aid may have merit.

The next question to ask is, can this nutrient actually be absorbed and utilized by the body? While a nutrient may seem as if it has ergogenic properties, if it cannot be delivered to the body in a safe, feasible, and usable form, it will not have much use. Other considerations include:

- Does it have any research suggesting an ergogenic potential?
- Are the studies in vitro or in vivo studies?
- Were they animal or human studies?
- Was the sample size big enough?
- How was the study designed?
- Was it well controlled?

Human clinical trials with a large sample size that are double blinded and placebo controlled are obviously most beneficial and should be weighed more heavily. Unfortunately, these types of studies often do not exist for sports performance supplements, thus accounting for much of the skepticism regarding ergogenic aids. Much of this skepticism is warranted, although discounting a supplement purely on the basis of lack of these types of trials is likely not wise.

Natural Ergogenic Supplements with the Most Evidence

The ISSN classifies ergogenic supplements in the following way[1]:

- **Apparently Effective**. Supplements that help people meet general caloric needs and/or that the majority of research studies in relevant populations show is effective and safe.
- **Possibly Effective**. Supplements with initial studies supporting the theoretical rationale but requiring more research to determine how they may affect training and/or performance.
- **Too Early To Tell**. Supplements with sensible theory but lacking sufficient research to support current use. Note: Most supplements marketed as ergogenic aids fall into this category.
- **Apparently Ineffective**. Supplements that lack a sound scientific rationale and/or research has clearly shown to be ineffective.

Table 2 below is a list of natural ergogenic supplements supported by research and given the "ergogenic" label by organizations such as ISSN. It ➤

Table 2

Supplement	Ergogenic	Benefits
Creatine monohydrate	Apparently Effective	↑ intensity, strength, power, lean mass, weight maintenance
Water and sports drinks	Apparently Effective	endurance, resists fatigue
Weight gain powders	Apparently Effective	body composition, muscle building, bulking
Protein (whey) supplements	Apparently Effective	recovery, lean mass, regulates hunger, ↑insulin, synergy with creatine, supports glutathione
Carbohydrate supplements	Apparently Effective	endurance, recovery, muscle gain via ↑ insulin
Essential amino acids	Apparently Effective	↑ recovery, ↑ protein synthesis, ↓ protein breakdown
Branched chain amino acids (BCAAs)	Possibly Effective	↑ recovery, ↑ protein synthesis, ↓ protein breakdown
Postexercise carbohydrate and protein	Possibly Effective	recovery, ↓ muscle breakdown
Low-calorie diet foods & supplements	Apparently Effective	body composition
High-fiber diet	Possibly Effective	body composition
Sodium bicarbonate	Apparently Effective	buffers lactic acid, resists fatigue
B-alanine	Apparently Effective	resist fatigue, ↑ force, ↑ training volume, ↑ carnosine levels
Sodium phosphate	Apparently Effective	resists fatigue, may ↑resting energy expenditure (weight loss)
Caffeine	Apparently Effective	↑ intensity, ↑ fat burn, improves mental focus and fine motor skills, ↑ endurance,
Green tea extract	Possibly Effective	↑oxidation of fat d/t catechins
Calcium	Possibly Effective	body composition
Conjugated linoleic acids (CLA)	Possibly Effective	body composition
β-hydroxy β-methylbutyrate (HMB)	Possibly Effective	protects muscle, may ↑ strength and muscle gain, may be synergistic with creatine
Glycerol	Possibly Effective	may help prevent dehydration

Cut

➤

lists all the "apparently effective" and "possibly effective" natural ergogenic supplements considered safe and not banned by most prestigious athletic associations, along with their possible ergogenic benefits.

Obviously, a full treatment of all the natural compounds purported to have beneficial effects in exercise and body composition could fill an entire book. We have selected supplements demonstrating the most and best research supporting their use as ergogenic aids that are also supported by the ISSN and other athletic organizations.

Conclusion

Due to limited research, most nutraceuticals are not considered to be ergogenic. Any athlete who is deficient in a nutrient will probably improve performance once the deficiency is adequately addressed; however, this does not mean that the nutrient in question is ergogenic.

Lab tests for essential nutrients rarely go beyond analyzing frank clinical deficiencies. Is there a difference between optimal nutrient status and adequate nutrient status? In our opinion, there is a huge difference. For the athlete this distinction is rarely made. Even though more research is needed in this area, common sense dictates that optimizing nutrient status can enhance performance. Functional lab testing can play an important role in this goal. Again, optimizing the levels of nutrients using functional lab tests whether deficiencies are subclinical or clinical does not mean that the nutrient in question is ergogenic. On the other hand, these functional test can give the athlete a significant advantage because most athletes never are functionally assessed with labs.

Whether or not functional testing is done, it is prudent to supplement athletes with a high-quality multivitamin, just as it is for the general public. Interestingly, most athletes are not doing this either, and have many more reasons than the average person to do so when considering training and performance schedules.

There are supplements that appear to have ergogeniclike effects, such as curcumin or vitamin D. These nutraceuticals can potentially extend the career of an athlete. Unfortunately, much more research is needed before labeling either one of these nutrients true ergogenic aids.

So what are the so-called ergogenic natural supplements as defined by the ISSN? Table 2 lists them primarily due to the number of studies done on them. With more studies being done every day, this list will grow and probably include nutraceuticals such as curcumin and vitamin D. In part 3 of this series, each ergogenic aid in Table 2 will be discussed, if it was not previously discussed in part 1.

Notes

1. Kreider et al. ISSN exercise and sport nutrition review:research and recommendations. *J Int Soc Sports Nutr.* 2010;7:7.

Keoni Teta, ND, LAc, is a naturopathic physician and acupuncturist practicing at the Naturopathic Health Clinic of North Carolina in Winston-Salem with his wife, Jillian, and brother, Jade, an integrative physician specializing in natural health, fitness, and body transformation. After graduating from Bastyr University, they cofounded Metabolic Effect, an international health and wellness company that focuses on balancing hormones for fat loss using rest-based exercise, sports nutrition, and lifestyle medicine. They are coauthors of *The Metabolic Effect Diet* and contributing authors to *The Textbook of Natural Medicine*, 4th ed.

2. American College of Sports Medicine position stand. Nutrition and athletic performance. *Med Sci Sports Exerc.* 2009;41(3):709–731.
3. Applegate et al. Effective nutritional ergogenic aids. *Int J Sports Nutr.* 1999;9(2):229–239.
4. Machefer et al. Multivitamin-mineral supplementation prevents lipid peroxidation during "the Marathon des Sables." *J Am Coll Nutr.* 2007;26(2):111–120.
5. Woolf et al. B-vitamins and exercise:does exercise alter requirements? *Int J Sport Nutr Exerc Metab.* 2006;16(5):453–484.
6. Bartoszewska et al. Vitamin D, muscle function, and exercise performance. *Pediatr Clin North Am.* 2010;57(3):849–861.
7. Larson-Meyer et al. Vitamin D and athletes. *Curr Sports Med Rep.* 2010;9(4):220–226.
8. Hamilton et al. Vitamin D deficiency is endemic in Middle Eastern sportsmen. *Public Health Nutr.* 2010;15:1–7.
9. Lovell et al. Vitamin D status of females in an elite gymnastics program. *Clin J Sport Med.* 2008;18(2):159–161.
10. Cannell et al. Athletic performance and vitamin D. *Med Sci Sports Exerc.* 2009;41(5):1102–1110.
11. Erikssen et al. Seasonal variation in work performance and heart rate response to exercise: a study of 1,835 middle-aged men. *Eur J Appl Physiol.*1979;42:133–140.
12. Sato et al. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovas Dis.* 2005;20(3):187–192.
13. Sørensen et al. Myopathy in bone loss of ageing: improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. *Clin Sci.* 1979;56(2):157–161.
14. Dhesi et al. Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing.* 2004;33(6):589–595.
15. Ward et al. Vitamin D status and muscle function in postmenarchal adolescent girls. *J Clin Endocrinol Metab.* 2009;94(2):559–563.
16. Bischoff-Ferrari et al. Effect of vitamin D on falls: a meta-analysis. *JAMA.* 2004;291(16):1999–2006.
17. Lord and Bralley. Laboratory analysis for integrative and functional medicine. 2nd ed. Duluth, GA: Metametrix Institute; 2008.
18. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytother Res.* 2012 Nov;26(11):1719–1725. doi:10.1002/ptr.4639.
19. Kuptniratsaikul V et al. Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. *J Altern Complement Med.* 2009 Aug;15(8):891–897. doi:10.1089/acm.2008.0186.
20. Satoskar RR et al. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. *Int J Clin Pharmacol Ther Toxicol.* 1986 Dec;24(12):651–654.
21. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. *Altern Med Rev.* 2009 Jun;14(2):141–153.
22. Henrotin Y et al. Biological actions of curcumin on articular chondrocytes. *Osteoarthritis Cartilage.* 2010 Feb;18(2):141–9. doi:10.1016/j.joca.2009.10.002.
23. Funk JL et al. Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis. *J Nat Prod.* 2006 Mar;69(3):351–355.
24. Ejaz A et al. Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. *J Nutr.* 2009 May;139(5):919–925. doi:10.3945/jn.108.100966.
25. Meydani M, Hasan ST. Dietary polyphenols and obesity. *Nutrients.* 2010 Jul;2(7):737–751. doi:10.3390/nu2070737.

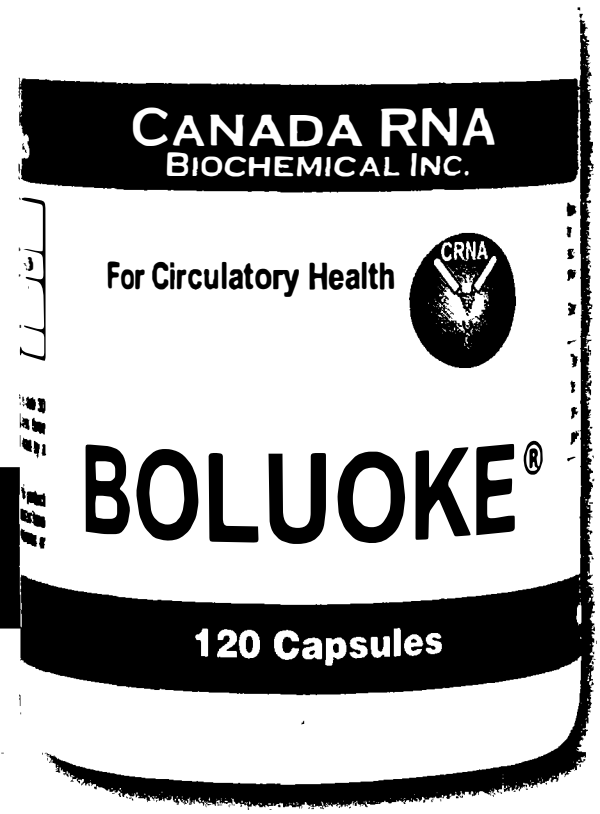
◆

Simply the Best

What More Can You Ask For?

SCELLÉ POUR VOTRE PROTECTION
SEALED FOR YOUR PROTECTION

- ✔ **Simply the best lumbrokinase**
- ✔ Now free of corn strach
- ✔ Extensively proven by clinical studies
- ✔ Suitable for patients with soy allergy
- ✔ Optimizes circulation:
  ↓fibrinoids, ↓endothelin, ↑CGRP
  ↓platelet aggregation, ↓blood viscosities
- ✔ Regulates inflammation: ↓C-RP, ↓TXA2, ↓Fibrinogen, ↓PAI-1
- ✔ Modifies CA-cell adhesion: ↓P-Selectin, ↓E-Selectin
- ✔ Decreases microbial resistance: breaks down biofilm
- ✔ No significant effect on INR or PTT



Your Patients. Your Reputation. Trust Nothing Less.

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

CRNA

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

Call Us Today **1-866-287-4986**

***Boluoke®** is also available through:*

International antiaging-systems.com
BIORESOURCE INC
MOSS NUTRITION
MP Mountain States Health Products, Inc.
Pro Health Network Your Gateway to Better Health
LONGEVITY PLUS Anti-Aging Products
Researched Nutritionals solutions for life
return health

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

FREE SUBSCRIPTION!
Canada RNA Biochemical Inc. is a proud sponsor of DMB. Sign up for a free subcription at the DMB website.

High-Affinity IgE Receptor Autoantibodies in a Patient with Chronic Fatigue Syndrome and Multiple Chemical Sensitivities

by Laurie Busby

I have chronic fatigue syndrome (CFS) and the hypersensitivities that sometimes accompany it, multiple chemical sensitivities (MCS). Like many CFS and MCS patients, I also have Hashimoto's thyroiditis (HT) and have had adverse drug reactions to multiple medications.[1-4] Based on my personal and family medical history, I asked to be tested for HLA-DR4 and autoantibodies to the high-affinity IgE receptor (Fc-epsilon RI), and both were positive. I believe that these autoantibodies have the potential to be positive in a specific subset of CFS patients who also have MCS and meet some of the criteria below.

These autoantibodies or a related test, the autologous serum skin test (ASST), have been associated with other hypersensitivity disorders: non-allergic asthma, chronic autoimmune urticaria (CAU), and multiple drug hypersensitivity, a.k.a. multiple drug intolerance or multiple drug allergy syndrome.[5-7] In some patients, Fc-epsilon autoantibodies have been associated with the ability to induce histamine release from basophils of donors. This test is known as a basophil activation test (BAT).[5-7]

These hypersensitivity disorders have similarities with CFS and/or MCS cohorts, including a female predominance, an increased frequency of thyroid disease or a positive ANA, an association with HLA-DR4 and HLA-DQ3, and reactions to medications.[1-8]

It might be worth testing for these autoantibodies in the subset of CFS patients who have MCS and meet some of these criteria. This test may be especially worthwhile in CFS patients prior to participating in the ongoing rituximab trials.[11-12]

In some CFS patients with MCS, these autoantibodies may be a piece of the puzzle and more importantly could open up several treatment options for some of the symptoms.

(Human leukocyte antigens [HLA] were immune system genes that play a role in response to infection, the development of autoimmune diseases, and the risk of adverse drug reactions.)

Laurie Busby received a BEd from the University of Missouri. At age 30, she developed chronic fatigue syndrome and the hypersensitivities that sometimes accompany it. Shortly thereafter, her aunt, a nurse anesthetist, handed her a huge medical dictionary and some studies, insisting that Laurie learn how to read them because she had something with no answers. Since that time, Laurie has asked for several tests that have given her incredible clues about her illness, conducted a family medical health survey among patients, testified before the CFS Advisory Committee to the US Department of Health and Human Services, and started a chronic illness blog, cfsfmmcsandrelatedstudies.tumblr.com, in an attempt to share what she has learned.

Notes

1. Hilgers A, Frank J. Chronic fatigue syndrome: immune dysfunction, role of pathogens and toxic agents and neurological and cardial changes. *Wien Med Wochenschr.* 1994; 144(16):399–406.
2. Galland, L. Biochemical abnormalities in patients with multiple chemical sensitivities. *Occup Med.* 1987;2(4):713–720.
3. Ferre Ybarz L, Cardona Dahl V, Cadahia Garcia A, et al. Prevalence of atopy in chronic fatigue syndrome. *Allergol Immunopathol (Madr).* 2005;33(1):42–47.
4. Ross GH. Clinical characteristics of chemical sensitivity: an illustrative case history of asthma and MCS. *Environ Health Perspect.* 1997;105 Suppl 2:437–441.
5. Comi, A.L., Tedeschi, A., Lorini, M., Miadonna, A. Novel clinical and serological aspects in non-allergic asthma. *Respir Med.* 2007;101(12):2526–2533. doi:10.1016/j.rmed.2007.07.010.
6. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA(2) LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy.* 2009:64(9):1256–68. doi:10.1111/j.1398-9995.2009.02132.x.
7. Asero R, Tedeschi A, Lorini M, Caldironi G, Barocci, F. Sera from patients with multiple drug allergy syndrome contain circulating histamine-releasing factors. *Int Arch Allergy Immunol.* 2003;131(3):195–200. doi:10.1159/000071486.
8. Nogue, S., Fernandez-Sola, J., Rovira, E., Montori, E., Fernandez-Huerta, J.M., Munne, P. Multiple chemical sensitivity: study of 52 cases. *Med Clin (Barc).* 2007;129(3):96–98.doi:10.1157/13107370.
9. Keller RH, Lane JL, Klimas N, et al. Association between HLA class II antigens and the chronic fatigue immune dysfunction syndrome. *Clin Infect Dis.* 1994;18(Suppl 1):s154–s156. doi:10.1093/clinids/18.Supplement_1:S154.
10. O'Donnell BF, O'Neil CM, Francis DM, et al. Human leukocyte antigen class II associations in chronic idiopathic urticaria. *Br J Dermatol.* 1999;140(5):853–858. doi:10.1046/j.1365-2133.1999.02815.x.
11. Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. *PloS One.* 2011;6(10):e26358. doi: 10.1371/journal pone.0026358.
12. Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. *J Allergy Clin Immunol.* 2011;128(6):1354–1355. doi:10.1016/j.jaci.2011.08.023.

◆

New Hope and Cure for Glaucoma Treatment

by Edith S. Marks and Gustavo De Moraes, MD

Although the tools for glaucoma care have become more sophisticated and advanced over the past two decades, the goal of cure is still beyond our reach, despite advanced technology and worldwide research. One of the problems lies in the fact that, unlike other medical problems wherein transplants have successfully restored an organ, the optic nerve – part of the brain – does not fall into this category. Nevertheless, the ophthalmological community has been hard at work assembling a medical tool kit that promises effective and less invasive care. As well, the pharmaceutical companies are constantly evaluating different substances in an effort to provide medications with greater efficacy and fewer side effects. Dr. Gustavo De Moraes, research associate professor at New York University Medical Center and senior researcher at the New York Eye and Ear Infirmary, and research fellow Dr. Camilla Netto reported on some of the current research for glaucoma treatment. De Moraes has authored over 75 research papers and authored/coauthored 7 book chapters.

The therapy today among practitioners consists of a number of strategies, with focus on lowering the intraocular pressure with medication, laser, and incisional surgery, but also on protecting the optic nerve from the ravages of toxic compounds.

The pharmaceutical community continues to develop improved medications. There are a few in the pipeline now in trial, and if these succeed in lowering the pressure sufficiently with minimal side effects, they will be introduced to the marketplace. In the past few years, we have witnessed a wider range of both laser treatments and incisional surgeries, especially with minute stents. Fortunately, these surgeries are minimally invasive and therefore possess fewer side effects, leading to quicker recovery periods. Newer forms of therapy using different sites in the eye offer better control, and the research on stem cell vision replacement continues apace. Nanotechnology offers new release methods inside the eye for medication.

Nitric oxide (NO) and other compounds that act synergistically with it to keep the intraocular pressure low and stable are among some of the newer medical approaches under investigation. Ongoing lab research on this substance indicates that NO successfully increases the outflow of the aqueous humor (fluid inside the eye) to the drainage system. It has not yet reached the marketing stage, although the researchers have demonstrated in animal models that outflow is increased. The study will need to move into human trials before it becomes publicly available.

The star of the less invasive operations appears to be the iStent. This infinitesimal unit creates a second pathway for the aqueous humor to seep from inside the eye to the outflow vessels, thus lowering pressure. Studies indicate pressure lowering of about eight points after a year of follow-up. This device is now available and may one day be an alternative to initial treatment of glaucoma.

Finally, an alternative therapy for nerve protection is being seriously examined. The botanicals *Ginkgo biloba* and resveratrol are being studied. *Ginkgo biloba*, long used as a natural extract to increase blood flow, is being studied to increase blood flow and protect the optic nerve from the detrimental effects of oxidative stress. There is evidence that insufficient blood flow to the tiny vessels in the eye may be depriving the optic nerve of nutrients and leading to death of neurons in the eye (retinal ganglion cells). This is especially true of low- or normal-tension glaucoma, but may very well apply to other forms of open-angle glaucoma (OAG). Research under way reveals that loss of vision in normal-tension glaucoma in particular is due to both intraocular pressure and low blood flow. Although *Ginkgo biloba* has been studied for its effects on memory and possibly slowing down Alzheimer's disease with varying results, its effects may be promising in the treatment of glaucoma, according to De Moraes, as numerous studies in animal models and humans have demonstrated its protective effect. Blood flow is improved, especially the microcirculation in small capillaries, such as those in the optic nerve. As well, ginkgo fights free-radical damage and platelet aggregation (platelet clumping), and can therefore help increase the flow and decrease the progression of the disease.

Resveratrol is being investigated in many labs for its effects on oxidative stress. As we age, we become more susceptible to oxidative stress that in the long run causes apoptosis (death of cells). Numerous studies have shown that antioxidative medications can slow down oxidative stress. There are currently hundreds of studies (in animals and humans) funded with millions of dollars that have shown

➤

➤

the benefits of resveratrol in chronic diseases such as cancer, Alzheimer's, and glaucoma.

Particular Risk Factors

There is a group of people who have consistent low blood pressure. While this condition may be the envy of those people taking medication for high blood pressure, abnormally low pressure can be detrimental to glaucoma patients. The researchers have been able to identify a relationship between glaucoma progression and this particular risk factor. During the nighttime hours of the nocturnal curve, blood pressure lowers and this condition may worsen the glaucoma, depriving the optic nerve of needed nutrients.

Maintaining the ideal blood pressure for people with normal-tension glaucoma may present a problem. Since the cardiologist is concerned with maintaining a low blood pressure to prevent strokes and heart disease, a contrary concern for ophthalmologists is to increase blood flow during nocturnal hours in patients suffering vision loss from a diminishing of nutrients delivered to the eye. It therefore becomes important for the ophthalmologist and cardiologist to confer on the best strategy to maintain both vision and heart health. Most important is maintaining an adequate blood flow during nighttime when blood flow slows. Blood pressure medications taken in the evening may lower the blood pressure to the point that the optic nerve is not protected.

Vision Restoration

Because retinal cells are an extension of the brain cells, they are incapable of self-restoration. Electrodes and stem cells fill this gap at present.

Electrodes: For those people who still retain some healthy cells in the retina, strategies are being investigated to activate this residual vision. One experiment conducted with mice, combining electrodes and exercise, attempted to increase and strengthen the remaining cells to compensate for the damaged area. A blind mouse received the device, and it was evident after the experiment that it had gained some vision, albeit not perfect; but it certainly was a promising development.

Stem cells are pluripotent; that is, they can develop into any kind of cell. One of the problems in glaucoma is that the outflow of fluid is clogging the trabecular meshwork. Replacing damaged cells with stem cells in the trabecular meshwork may well increase the outflow and thus lower the pressure and protect the optic nerve.

Within several years, it may be possible to harvest stem cells from one's own blood cells. This method appears to be superior to harvesting stem cells from the skin, liver, or other tissues and it bypasses ethical issues.

Replacement of cells is, of course, the ultimate goal for those who have lost a major portion of their sight. Researchers are trying to develop and differentiate the stem cells into retinal cells to restore the sight lost due to glaucoma, but this research still needs several years before results are clearly defined. Animal research indicates progress, but it is difficult to overcome the protocols established by the Food and Drug Administration (FDA). The problem remains of providing the FDA with sufficient documentation to satisfy the requirements of safety and effectiveness and move on to clinical trials in the human population. Then funding, most likely from National Institutes of Health (NIH), will be necessary to conduct wide-ranging clinical trials

Nanotechnology: At this stage, nanotechnology research has focused on providing a device that can be inserted into the eye loaded with medication that will be released over a period of months. This technology will eliminate the need for daily instillation of eyedrops and provide the exact amount of medication needed to maintain a steady eye pressure and minimize one of the main challenges in glaucoma: adherence. The steady supply of medication will act against pressure spikes, known to damage the cells. Devices already exist to treat macular degeneration and minimally invasive surgery. Delivery of medications to the right target with precise concentration will soon be commercially available and help improve pressure lowering and minimize the side effects.

Transorbital alternating current stimulation is a potential method to restore sight. This technology is not yet available in the US, but it does exist in Germany. It consists of placing electrodes on the forehead and skin around the eye (orbits) that transmit electric impulses which may "boost" retinal ganglion cells and neurons in the visual pathway to reestablish function.

Artificial vision: A light sensor connected to an array of electrodes has already been introduced into the eyes of blind people, allowing them to see shapes. This technology is moving rapidly. However, it does require implantation of the device inside the eye to connect to the optic nerve and has been reserved for cases of severe blindness.

Electrodes are used to simulate the cells. In a display projected on the screen, it was possible to see that the blind spots responded to stimulation with electrodes by providing a wider field, allowing better vision. Two kinds of electrodes are being explored: tiny small manual electrodes that are placed inside the eye during retinal surgery and those placed outside the eye. The purpose is to stimulate the cells to greater activity to compensate for their decreased function due to glaucoma or other blinding diseases.

The brain can also be stimulated, because the optic nerve is part of the brain. The area of stimulation is in the back of the head, where the visual center is located. During electrical stimulation, the patient simply gazes at the screen. This form of stimulation tells the researcher which part of

➤

➤

the brain is active. The researchers have found that modification of this stimulation of the brain provides information about the visual cortex, identifying which sick cells are still alive and working.

The research in this area is gaining momentum. It has moved from science fiction to reality. The problem remains that while research in animals in the laboratory often indicates positive results, the researchers must close the gap between research and clinical practice, so-called translational research. As stated previously, this can only be bridged with FDA approval of protocols developed in the laboratory, for safety measures must be met before the trials migrate to the human population

References

Arriola-Villalobos P, Martínez-de-la-Casa JM, Díaz-Valle D, et al. Mid-term evaluation of the new Glaukos iStent with phacoemulsification in coexistent open-angle glaucoma or ocular hypertension and cataract. *Br J Ophthalmol*. Epub 2013 Apr 20.

Boussommier-Calleja A, Bertrand J, Woodward DF, Ethier CR, Stamer WD, Overby DR. Pharmacologic manipulation of conventional outflow facility in ex vivo mouse eyes. *Invest Ophthalmol Vis Sci*. 2012;53(9):5838–5845.

De Moraes CG, Liebmann JM, Greenfield DS, Gardiner SK, Ritch R, Krupin T; Low-pressure Glaucoma Treatment Study Group. Risk factors for visual field progression in the low-pressure glaucoma treatment study. *Am J Ophthalmol*. 2012;154(4):702–711.

Du Y, Yun H, Yang E, Schuman JS. Stem cells from trabecular meshwork home to TM tissue in vivo. *Invest Ophthalmol Vis Sci*. 2013;54(2):1450–1459.

Kador KE, Montero RB, Venugopalan P, et al. Tissue engineering the retinal ganglion cell nerve fiber layer. *Biomaterials*. 2013;34(17):4242–4250.

Karl MO. The potential of stem cell research for the treatment of neuronal damage in glaucoma. *Cell Tissue Res*. Epub 2013 May 25.

Lee J, Sohn SW, Kee C. Effect of Ginkgo biloba extract on visual field progression in normal tension glaucoma. *J Glaucoma*. Epub 2012 May 16.

Lewallen M, Xie T. Cell-based therapies for retinal degenerative diseases: a thousand strategies. *J Glaucoma*. 2013;22(5):42–45.

Liu Q, Ju WK, Crowston JG, et al. Oxidative stress is an early event in hydrostatic pressure induced retinal ganglion cell damage. *Invest Ophthalmol Vis Sci*. 2007;48(10):4580–4589.

Liu XQ, Wu BJ, Pan WH, et al. Resveratrol mitigates rat retinal ischemic injury: the roles of matrix metalloproteinase-9, inducible nitric oxide, and heme oxygenase-1. *J Ocul Pharmacol Ther*. 2013;29(1):33–40.

Luna C, Li G, Liton PB, et al. Resveratrol prevents the expression of glaucoma markers induced by chronic oxidative stress in trabecular meshwork cells. *Food Chem Toxicol*. 2009;47(1):198–204.

Mozaffarieh M, Grieshaber MC, Orgül S, Flammer J. The potential value of natural antioxidative treatment in glaucoma. *Surv Ophthalmol*. 2008;53(5):479–505.

Pita-Thomas DW, Goldberg JL. Nanotechnology and glaucoma: little particles for a big disease. *Curr Opin Ophthalmol*. 2013;24(2):130–135.

Schmidt W, Kastner C, Sternberg K, et al. New concepts for glaucoma implants–controlled aqueous humor drainage, encapsulation prevention and local drug delivery. *Curr Pharm Biotechnol*. 2013;14(1):98–111.

Stamer WD, Lei Y, Boussommier-Calleja A, Overby DR, Ethier CR. eNOS, a pressure-dependent regulator of intraocular pressure. *Invest Ophthalmol Vis Sci*. 2011;52(13):9438–9444.

Contact:
Edith S. Marks
Author, *Glaucoma: Patient to Patient*
edithmarks@nyc.rr.com

Gustavo De Moraes, MD
Gus.Moraes@nyumc.org

◆

Celiac Disease and Gluten-Associated Conditions: Using Laboratory Measures to Clarify Etiology and Determine Course of Treatment

by Bethany Glynn, ND

The concept of gluten allergy has been around for many years, but only recently has the term become ubiquitous. More patients than ever are entering clinics with self-diagnoses of various reactions to gluten, leaving practitioners to decipher the intricacies of gluten-induced symptoms. Adding to the confusion is the assumption by many that gluten allergy and its autoimmune counterpart, celiac disease, are the same disease entity. This article will attempt to clarify this misconception in the exploration of terminology, pathophysiology, changing clinical picture, and differential diagnosis using laboratory medicine.

Appropriate Terminology for Gluten-Related Disorders

Historically, one of the greatest impediments to accurate assessment and treatment of gluten-induced symptoms was the lack of a standardized diagnostic criteria for food allergy in general. In 2010, the National Institute of Allergy and Infectious Diseases sought to remedy this situation, creating a schematic for the wide scope of adverse food reactions. Two main subcategories created by the expert panel are immune-mediated and non-immune-mediated, the former encompassing food allergy and celiac disease and the latter encompassing food intolerances. Under these guidelines, any abnormal antibody response to gluten would be considered an allergy. However, the guidelines go on to assert that IgG antibodies should not be used to assess patients for food allergy. The use of IgA is implied in the schematic by the term *non-IgE-mediated* but is never discussed as a marker of food allergy.[1]

Immunoglobulins Produced in Response to Gluten Exposure

Some discourse still exists over whether non-IgE-mediated reactions should be considered true allergy. IgE has long been the standard laboratory measurement for classical allergic response, its secretion in the body resulting in histamine release by mast cells and potential anaphylaxis. Skin-prick testing is the most common form of assessing IgE-induced allergy symptoms, although serum IgE assays can also be used in conjunction with other clinical and laboratory measures to identify allergy in children and adults.[1] IgE antibodies to gluten have been found in patients with atopic dermatitis and urticaria, and are beginning to be used in conjunction with skin-prick testing to diagnose classic wheat allergy.[2]

IgA is the first line of defense in mucosal immunity. It was discovered in the late 1960s that IgA-producing lymphocytes in the gastrointestinal system exist in 20 times greater quantity than those producing IgG. In a healthy gastrointestinal tract, enterocytes secrete IgA to inhibit colonization and invasion by various pathogens. IgA decreases antigen entry into the tissue space and activates lymphocytes; these cells then establish a common mucosal immunity by passage through the lymphatic system to other mucosal sites and subsequent secretion of antigen-specific IgA.[3] Because of this common mucosal immunity, salivary IgA offers a convenient way to screen for immune-mediated reaction to gluten in patients hesitant to complete a comprehensive elimination-challenge diet. It has been shown that total IgA can be elevated during states of inflammation such as inflammatory bowel disease, metabolic syndrome, and connective tissue diseases.[4,5] IgA has also been shown to be depressed in family history and/or clinical presentation of atopy, making it important to screen for total IgA when running allergen-specific IgA food allergy panels.[6] Currently, anti-TTG IgA is used as the primary antibody in the diagnosis of celiac disease.[7]

In the greater medical community, IgG has yet to be established as a valid marker of food allergy. In fact, oral and sublingual allergy desensitization studies show that IgG antibody rises in conjunction with decreases in IgE mast cell reactivity and basophil responses.[8] In line with this correlation, the European Academy of Allergy and Clinical Immunology (EAACI) asserts that IgG is more a marker of immunological tolerance than allergy.[9] The National Institute of Allergy and Infectious Diseases lists allergen-specific IgG4 testing under the heading "Non-Standardized and Unproven Procedures" in its *2010*

➤

➤

Guidelines for the Diagnosis and Management of Food Allergy in the United States.[1]

Despite the lack of wide-ranging acceptance for IgG-mediated food allergy, basic immunology tells us that in cases of mucosal endothelial cell destruction or when IgA is deficient, antigens from the lumen are complexed with IgG in the lamina propria.[3] These immune complexes activate complement in a type III hypersensitivity reaction and result in temporary movement of inflammatory mediators and IgG into the lumen between epithelial cells. Although the exact role of IgG in gluten allergy has yet to be elucidated in research, the immunoglobulin's connection to enterocyte destruction and subsequent inflammation may explain why some patients' symptoms resolve when elimination of IgG-positive foods takes place. For example, one study showed that when patients with irritable bowel syndrome (IBS) removed IgG-positive foods from their diets, they experienced relief of symptoms.[10] Furthermore, IgG to deamidated gluten peptide (DGP) and IgG to tissue transglutaminase (TTG) are used in cases of IgA deficiency under the new guidelines for diagnosis of celiac disease.[7] Patients with gastrointestinal symptoms and IgG-positive gluten assays are undoubtedly mounting an immune response. Whether IgG is acting in immune tolerance to gluten or as an indicator of allergy, however, may currently be clearer in clinical practice than in research.

Celiac Disease: Pathophysiology, Changing Clinical Picture and Diagnostic Criteria

In celiac disease, gluten intake leads to both (1) production of antibodies against TTG and (2) inflammatory cytokine release leading to enterocyte destruction. The process begins with gluten entering the tissue space of the small intestine through either paracellular or transcellular absorption. Gluten is then deamidated, forming DGP, or cross-linked to TTG, forming gluten-TTG. In the presence of HLA-DQ2 or HLA-DQ8 cell surface markers, DGP and gluten-TTG are presented to CD4+ Th1 cells by dendritic cells, initiating a type IV hypersensitivity reaction. These CD4+ cells release IFN-gamma, which leads to the activation of the humoral immune response through the clonal expansion of B-cells. The resulting plasma cells produce IgA and IgG to gliadin and TTG. The tissue destruction component of this process is also perpetuated by IFN-gamma, which subsequently triggers lamina propria cells and fibroblasts to secrete matrix metalloproteinases. The metalloproteinases begin to degrade cellular matrix and basement membrane, while simultaneously enhancing the cytotoxicity of intraepithelial lymphocytes and NK cells. The latter facilitate apoptosis of enterocytes.[11]

Celiac disease is therefore a mix of humoral and cellular immune responses, mediated by antibodies and various cytokines. The condition develops due to multiple factors, including genetic susceptibility, presence of antibodies to TTG and/or DGP, intestinal damage, and gluten as an environmental immunological trigger. HLA-DQ2 is positive in 95% of those with biopsy-confirmed celiac disease, and the remaining 5% have HLA-DQ8.[7] These genes must be present for autoimmunity to develop, as they are essential to the process of generation of anti-TTG/anti-DGP antibodies and enterocyte destruction. While absence of these markers can be helpful in exclusion of celiac disease from a list of differential diagnoses, the presence of either is not diagnostic as they are common in individuals of Caucasian European descent.[3] Positive HLA-DQ2 is found in approximately 25% to 30% of these individuals, making the assay useful for – but not conclusive of – diagnosis of celiac disease. It is clear that celiac disease is a very specific, genetically influenced, autoimmune sequence of events within the umbrella of immune response to gluten, much as Hashimoto's thyroiditis exists within the overarching diagnostic category of thyroid disease.

Along with our understanding of genetic factors, the clinical picture of celiac disease is changing. Celiac disease was originally considered a childhood condition, but the mean age of diagnosis as of 2010 was 45 years.[12] The condition may also be more common than most practitioners realize, as about 1 in 133 people in the US have the disease. In patients with a first-degree relative with celiac disease, prevalence increases to 1 in 22.[13] Celiac disease was once considered an exclusively gastrointestinal disorder, but we now know the condition can manifest with extraintestinal symptoms such as ataxia, peripheral neuropathy, skin eruptions, anemia, muscle weakness, and osteopenia. [14,15] The disease also has associations with other autoimmune diagnoses, including but not limited to type 1 diabetes mellitus, idiopathic pulmonary hemosiderosis, systemic lupus erythmatosus, IgA nephropathy, polymyositis, and Sjögren's syndrome.[12]

New diagnostic criteria from the American College of Gastroenterology (ACG) recommend anti-TTG IgA as the most sensitive and specific serologic marker for celiac disease. They also assert the significance of assessing total IgA in the diagnostic process. Separate diagnostic guidelines are laid out for IgA deficiency and include assays of anti-TTG IgG and anti-DGP IgG. In children younger than 2 years of age, anti-TTG IgG alone or in conjunction with anti-DGP IgG should be used due to high probability of insufficient total IgA. HLA-DQ2 and HLA-DQ8 genetic haplotypes continue to be recommended. Antigliadin antibodies are no longer endorsed in establishing the diagnosis of celiac disease; however, confirmatory endoscopy and biopsy of the duodenum are still

required. It is now necessary that 1 to 2 of the requisite biopsies be in the region of the duodenal bulb in order to identify an additional 9% to 13% of celiac disease patients.[7] A positive intestinal biopsy will reveal villous atrophy.[3]

Differential Diagnosis in Gluten-Sensitive Individuals

Because the presenting symptoms of gluten-related conditions can be complex, laboratory medicine can be an important tool for differentiating between autoimmune, allergic, and functional conditions. The following are some of the more common diagnoses and laboratory measures to consider when encountering a patient with gluten-induced symptoms:

Inflammatory Bowel Disease

Clinical characteristics of inflammatory bowel disease (IBD) are often similar to those in celiac disease and such functional bowel disorders as irritable bowel syndrome (IBS). The diseases comprising IBD – Crohn's disease and ulcerative colitis – share the common symptoms of abdominal pain, diarrhea, fatigue, fever, weight loss, and possible blood in the stool. Endoscopy and colonoscopy with biopsy are the current standards of diagnosis for these conditions, but a fecal assay of calprotectin can serve as a relatively noninvasive way to distinguish patients urgently in need of biopsy from those with functional digestive issues.[16] Calprotectin is a protein released from neutrophils during active inflammatory states, and has been correlated with a degree of intestinal inflammation. Patients between flares of the disease with elevated fecal calprotectin have been shown to be at greater risk of relapse within one year. Moreover, fecal calprotectin may indicate even subclinical mucosal inflammation, and therefore may help identify when an increase in naturopathic or conventional treatment is necessary. It should be noted that gastrointestinal bleeding has not been associated with levels of calprotectin, so clinical signs and symptoms must continue to be monitored to determine severity of disease progression.[17]

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is considered one disease within the spectrum of gluten-sensitive enteropathies. The clinical presentation of this condition can closely resemble that of celiac disease and includes abdominal pain, diarrhea, steatorrhea, and nausea and vomiting after meals. Weight loss is also common in adults and children. Eighty percent of patients with EoE will have symptoms of gastroesophageal reflux that do not respond to a 2-month trial of proton pump inhibitors (PPI).[18] An endoscopy would be indicated in these cases; a diagnosis of EoE would be made if biopsy revealed greater than or equal to 15 eosinophils per high-power field.[19]

Wheat Allergy and Nonceliac Gluten Sensitivity

Some experts argue that celiac disease, wheat allergy, and gluten sensitivity are conditions characterized by three distinct immunological responses to gliadin protein with three separate histological and prognostic results. Wheat allergy is IgE-mediated and associated with allergic symptoms minutes to hours after exposure to gluten.[2] Nonceliac gluten sensitivity (NCGS) is a diagnosis of exclusion to consider in patients with gluten-induced symptoms that improve on a gluten-free diet but lack genetic, immunologic, and endoscopic markers of celiac disease. Antigliadin IgA or IgG may be present in this condition.[20] NCGS is not typically associated with intestinal damage and permeability, in contrast to the overt enterocyte destruction that occurs in celiac disease. The elevated fecal lactoferrin level and lactulose/mannitol ratio frequently seen in IBD and celiac disease are typically normal in NCGS.[21]

Irritable Bowel Syndrome

Irritable bowel syndrome can manifest as reactivity to multiple foods, including NCGS.[21] The diagnosis of IBS is currently considered one of exclusion, but does have its own specific Rome III diagnostic criteria. According to these guidelines, a patient must have recurrent abdominal pain or discomfort (an uncomfortable sensation not described as pain) for at least 3 days per month in the last 3 months. This abdominal pain or discomfort must be associated with two or more of the following characteristics: improvement with defecation, onset associated with a change in stool frequency, or onset associated with a change in form (appearance) of stool. Moreover, the criteria must have been fulfilled for the last 3 months with symptom onset ➤

➤

at least 6 months prior to diagnosis.[22] Laboratory measures to rule out autoimmune and inflammatory conditions may include fecal calprotectin, an iron panel to assess for anemia, food immunoglobulin testing, stool testing for parasites and intestinal bacterial overgrowth, celiac disease markers, and intestinal biopsy.

Gluten-Associated Disorders: Beyond the Gluten-Free Diet

Complaints of adverse physiologic reactions to gluten are becoming more common in medical offices. Many health professionals question whether this trend is due to an actual increase in incidence, an improvement in diagnostic methods, or simply a rise in awareness. Which of these is true remains to be clarified by research, but there is no doubt that our tools for identifying food allergies and furthering our understanding of the immune system are rapidly expanding.

With any food-related symptoms or diagnoses, the astute physician would recommend identification and – at least temporary – removal of offending foods from the diet. And while it is essential to determine if gluten is a problematic food protein for patients, we must take further steps in laboratory diagnosis to determine a patient's exact immunological response to gluten in order to develop appropriate treatment plans and prevent further tissue destruction. The importance of identifying celiac disease is paramount, because if left untreated it may contribute to infertility, development of other related autoimmune disorders, and a higher incidence of certain cancers including lymphomas.[12]

We have yet to fully understand the implications of genetic susceptibility in autoimmune diseases, but it is known that specific HLA haplotypes are also associated with type 1 diabetes mellitus, multiple sclerosis, and Graves' disease.[23] Because of the potential for food to be antigenic, the impact of diet and genetics on autoimmune conditions can be pivotal in shifting the immune response. While gluten-free diets can alleviate symptoms, it is important that we continually review the literature and use of diagnostic testing, as this is an evolving discussion and recommendations are sure to change in the future. Researchers continue to discover immunologic and genetic etiologies of gluten-induced symptoms, leading to important branching points in treatment approach. Oral or sublingual immunotherapy, for example, may be a possibility in NCGS or IBS, while in celiac disease this therapy would be contraindicated due to the potential for autoimmune gastrointestinal and systemic sequelae.[8] Identifying the exact pathophysiology and category of immune response for each individual can aid not only in determining the necessary length and course of a gluten-free diet, but also in preventing comorbidities and improving autoimmune prognosis.

Bethany Glynn, ND, acquired her doctorate of naturopathic medicine from Bastyr University with specialty training in pediatrics, family health, neuropsychological conditions, autoimmunity, and environmental medicine. She is a licensed primary care physician to families living with autism, anxiety, and ADHD in the Greater Seattle area. She currently runs two active medical websites and hosts community outreach classes, summarizing and sharing the latest in natural health research with fellow practitioners and the public.

Notes

1. National Institute of Allergy and Infectious Diseases. *Guidelines for the Diagnosis and Management of Food Allergy in the United States*. December 2010. Available at: http://www.jacionline.org/article/S0091-6749(10)01566-6/fulltext. Published Dec 2010. Accessed September 8, 2013.
2. Sapone A, Bai J, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Medicine* 2012; 10:13.
3. Brostof J, Challacombe S. *Food Allergy and Intolerance*. New York: Saunders; 2002:127–162.
4. Kazemi-Shirazi L, Gasche C, Natter S, et al. IgA autoreactivity: a feature common to inflammatory bowel and connective tissues diseases. *Clin Exp Immunol* 2002;128:102–109.
5. Gonzalez-Quintela A, Alende R, Gude F, et al. Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities. *Clin Exp Immunol* 2007;151:42–50.
6. Sandin A, Björkstén B, Böttcher M, et al. High salivary secretory IgA antibody levels are associated with less late-onset wheezing in IgE-sensitized infants. *Pediatr Allergy Immunol*. 2011;22:477–481.
7. Rubio-Tapia A, Hill I, Kelly C, et al. American College of Gastroenterology Clinical Guidelines: Diagnosis and Management of Celiac Disease. *Am J Gastroenterol*. 2013;108:656–676.
8. Mousallem T, Burks A. Immunology in the Clinic Review Series;focus on allergies: immunotherapy for food allergy. *Clin Exp Immunol*. 2001;167:26–31.
9. Stapel S, Asero R, Ballmer-Weber B, et al. EAACI Task Force. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. *Allergy*. 2008;63(7):793–796.
10. Atkinson W, Sheldon T, Shaath N, et al. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut*. 2004;53: 1459–1464.
11. Bellanti J. *Immunology IV: Clinical Applications in Health and Disease*. Bethesda, MD: I Care Press; 2012:729.
12. Feldman M, Friedman L, Brandt L. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management*. Philadelphia, PA: Saunders; 2010:1797–1820.
13. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States. *Arch Intl Med*. 2003;163(3):268–292.
14. Hadjivassiliou M, Sanders D, Grünewald R, et al. Gluten sensitivity: from gut to brain. *Lancet Neurol*. 2010;9(3):318–330.
15. Bushara K. Neurologic presentation of celiac disease. *Gastroenterology*. 2005;128(4 Suppl 1):S92–S97.
16. Rheenen P, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. *BMJ*. 2010;341:c3369.
17. Burri E, Beglinger C, et al. Fecal calprotectin – a useful tool in the management of inflammatory bowel disease. *Swiss Med Wkly*. 2012;142:w13557.
18. Dellon E, Gonsalves N, Hirano I. ACG clinical guideline: Evidence based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. *Am J Gastroenterol*. 2013;108(5):679.
19. Dellon E. Eosinophilic esophagitis: diagnostic tests and criteria. *Curr Opin Gastroenterol*. 2012;28(4):382–38.
20. Lundin K, Alaedini A. Non-Celiac Gluten Sensitivity. *Gastrointest Endoscopy Clin N Am*. 2012;22:723–734.
21. Eswaran S, Goel A, Chey W. What role does wheat play in the symptoms of Irritable Bowel Syndrome? *Gastroenterol Hepatol*. 2013;9(2):85–91.
22. Drossman D. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology*. 2006;1377–1390.
23. Gough S, Simmonds M. The HLA region and autoimmune disease: associations and mechanisms of action. *Curr Genomics*. 2007;8(7):453–465.

◆

First Choice in Saliva Testing Since 1989

Trust your patients' well-being to Diagnos-Techs™, the saliva-testing lab that started it all. After nearly a quarter-century of pinpoint-accurate results, healthcare providers across the U.S. have come to rely on Diagnos-Techs for a wide range of patient hormone assessments, **including our:**

- **Adrenal Stress Index Panel**
- **Bone Health Panel**
- **Cycling Female Hormone Panel**
- **Peri and Post Menopause Hormone Panels**
- **Male Hormone Panel**
- **Food Allergy (Sensitivity) Panel**
- **Gastrointestinal Health Panel**

Diagnos-Techs is excited to announce that we are now offering testing for fecal CALPROTECTIN, a sensitive and non-invasive indicator of intestinal inflammation.

Call today and speak with one of our medical advisors for more information.

1.800.878.3787

www.diagnostechs.com

CLINICAL & RESEARCH LABORATORY DiagnosTechs™

THE LEADING LAB IN SALIVA TESTING SINCE 1989

Quality Testing You Can Trust

The Great Plains Laboratory, Inc. Presents

2nd-Annual Physician Educational Workshop

Are you a practitioner who knows the benefits of biomedical testing for improving patient care – and desires more education and tools to put it into practice?

SAVE THE DATE

Fri, April 11th - Sun, April 13th
Kansas City, MO

Save $100 on registration when you sign up before February 10th

This weekend workshop is designed for practitioners who wish to make a difference in the lives of individuals suffering from a variety of conditions including Autism Spectrum Disorders (ASD), mental health disorders, autoimmune diseases, and other chronic illnesses. Research studies have revealed that many disorders often have dietary and biological causes which contribute to symptoms. Patients have better outcomes when these causes are successfully identified and treated through a combination of specialized testing and nutritional therapies, even in conjunction with traditional approaches.

Featuring presentations by:

Kurt Woeller, D.O.

William Shaw, Ph.D.

Who should attend?

- MDs, DOs, NDs, NMDs
- Physician Assistants
- Clinical Nutritionists
- Nurses and Nurse Practitioners
- Chiropractic Physicians
- Other Health Professionals interested in biomedical testing

24 CME / CEU credits are available

24 American Medical Association PRA Category 1 credits are provided by Westbrook University.*

Special price:

EARLY BIRD PRICING (Ends February 10th)	Single Admission $295	Dinner on the Plaza Add $25

"I didn't know how to interpret test results before attending; now I have a foundation to study upon and confidence to explain the results to patients."
– Dr. Arlinda Koita,
2013 Physician Educational Workshop Attendee

"Excellent for practical pearls in an alternative and integrative practice that I will be able to implement right away."
– James Neubrander, MD,
2013 Physician Educational Workshop Attendee

For more information or to register visit
www.GPL4U.com/events

*It is the responsibility of the attendee to adhere to the CME/CEU requirements of his/her state licensing board. It is the responsibility of the attendee for checking with their own state, province, or region for continuing educational requirements. CME/CEUs are not APA approved.

Clinical Usefulness of IgG Food Allergy Testing

by William Shaw, PhD

Immunoglobulin G (IgG) food allergy testing has made vast advancements since 2003, when the American Academy of Allergy, Asthma, and Immunology published a statement that "Measurement of specific IgG antibodies to foods is also unproven as a diagnostic tool."[1] Most of the IgG food allergy throughout the world is done using the same immunochemical technique. First, soluble food proteins in solution are reacted to a solid phase that chemically binds to a variety of proteins. The use of plastic microtiter trays with one to several hundred wells has become the most common material used as the solid phase. Then these trays are washed, dried, and stored for later use. A sample of diluted serum is then added to each of the wells. Antibodies of all types in the diluted serum bind to the specific food molecules that are attached to the plastic wells of the tray. Next, the plates are washed to remove any nonspecific antibodies in the diluted serum. At this time, food antibodies from all of the five major immunoglobulin classes called G, A, M, E, and D may be attached to the food antigens on the plate. The next step confers specificity on the assay. Antisera from sheep, goats, rabbits, or other animals that specifically bind only to IgG (and not to IgA, IgM, IgE, or IgD) are added to microtiter wells. This antibody to IgG has previously been modified by the attachment of an enzyme that can be measured conveniently. The amount of enzyme bound to food antigen-IgG complexes on the plate is directly related to how much IgG antibody is attached to a given food. The overall technique is termed enzyme-linked immunosorbent assay (ELISA). If IgG4 is measured, an antiserum specific for IgG4 only must be used for the final step.

The usefulness of IgG food allergy to design customized elimination diets has now been documented in scientific studies. Irritable bowel syndrome (IBS) is a common, costly, and potentially disabling gastrointestinal (GI) disorder characterized by abdominal pain/discomfort with altered bowel habits (e.g., diarrhea, constipation). The major symptoms of IBS are abnormality of bowel movement, reduction in bowel sensitivity thresholds, and psychological abnormality.[1-3] Many IBS patients have psychological symptoms including depression, anxiety, tension, insomnia, frustration, hypochondria, and psychosocial factors.[3] Atkinson et al. evaluated a total of 150 outpatients with IBS who were randomized to receive, for 3 months, either a diet excluding all foods to which they had raised IgG antibodies (ELISA test) or a sham diet excluding the same number of foods but not those to which they had antibodies.[4] Patients on the diet dictated by IgG testing had significantly fewer symptoms than those on the sham diet after 120 days on the diets. Patients who adhered closely to the diet had a marked improvement in symptoms, while those with moderate or low

Of particular interest was the group of patients with chronic, disabling symptoms, unresponsive to other intensive treatments. Whereas 70% obtained 75% or more improvement, 20% of these patients obtained 100% relief.

The clinical usefulness of IgG testing in an array of illnesses is illustrated in an early article published by an otolaryngologist who reported that the majority of his patients had substantial health improvements after an elimination of foods positive by IgG food allergy tests.[2] The overall results demonstrated a 71% success rate for all symptoms achieving at least a 75% improvement level. Of particular interest was the group of patients with chronic, disabling symptoms, unresponsive to other intensive treatments. Whereas 70% obtained 75% or more improvement, 20% of these patients obtained 100% relief. Symptoms that most commonly improved 75% to 100% on the elimination diets included asthma, coughing, ringing in the ears, chronic fatigue, all types of headaches, gas, bloating, diarrhea, skin rash and itching, and nasal congestion. The most common IgG food allergies were cow's milk, garlic, mustard, egg yolk, tea, and chocolate.

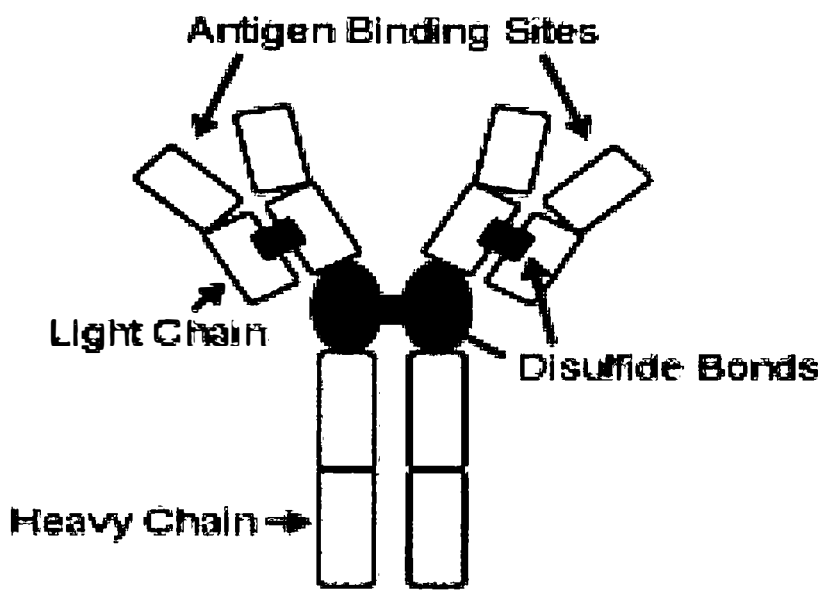
➤

adherence to the IgG test-dictated diets had poorer response. Similar results were also obtained by Drisko et al.[5] They used both elimination diet and probiotic treatment in an open label study of 20 patients with irritable bowel syndrome diagnosed at a medical school gastroenterology department. The most frequent positive serologic IgG antigen-antibody complexes found on the food IgG tests were: baker's yeast, 17 out of 20 (85%); onion mix, 13 out of 20 (65%); pork, 12 out of 20 (60%); peanut, 12 out of 20 (60%); corn, 11 out of 20 (55%); wheat, 10 out of 20 (50%); soybean, 10 (50%); carrot, 9 out of 20 (45%); cheddar cheese, 8 out of 20 (40%); egg white, 8 out of 20 (40%). Only 5 out of 20 reacted by IgG antibody production to dairy; however, the majority of patients reported eliminating dairy prior to trial enrollment, presumably clearing antigen-antibody complexes prior to testing. Significant improvements were seen in stool frequency, pain, and IBS quality of life scores. Imbalances of beneficial flora and dysbiotic flora were identified in 100% of subjects by comprehensive stool analysis. There was a trend to improvement of beneficial flora after treatment but no change in dysbiotic flora. The 1-year follow up demonstrated significant continued adherence to the food rotation diet, minimal symptomatic problems with IBS, and perception of control over IBS. The continued use of probiotics was considered less helpful.

IgG food allergy testing was also proved effective in the gastrointestinal disorder Crohn's disease. Bentz et al. found that an elimination diet dictated by IgG food allergy testing resulted in a marked reduction of stool frequency in a double-blind cross-over study in which the IgG-dictated diet was compared with a sham diet in 40 patients with Crohn's disease.[6] IgG food allergies were significantly elevated compared with normal controls. Cheese and baker's yeast (*Saccharomyces cerevisiae*) allergies were extremely common, with rates of 83% and 84% respectively. Main et al., focusing on the baker's yeast allergy, also found extremely high prevalence of IgG allergy in patients with Crohn's disease.[7] Titers of both IgG and IgA to *S. cerevisiae* in the patients with Crohn's disease were significantly higher than those in the controls. In contrast, antibody titers in the patients with ulcerative colitis were not significantly different from those in the controls. Among the patients with Crohn's disease there was no significant difference in antibody titers between patients with disease of the small or large bowel. Since IgG antibodies to *S. cerevisiae* cross-react with *Candida albicans*, *Candida* species colonization might be a trigger for the development of Crohn's disease.[8]

IgG food allergy to wheat, gluten, gliadin, rye, and barley are prevalent in the gastrointestinal disorder celiac disease. Virtually all patients with celiac disease have elevated IgG antibodies to gliadin if they currently have wheat or related grains in their diet. Celiac disease is confirmed by the presence of flattened mucosa with a lack of villi when a biopsy sample of the small intestine is examined microscopically. Another confirmation test with equal sensitivity is a blood test for IgA transglutaminase antibodies. The antibody confirmation test is equal in accuracy to the biopsy test with the exception that individuals with IgA deficiency may have false negative results. However, I would estimate that only 1% of people with elevated IgG antibodies to gliadin and other grains related to wheat have

Figure 1: In IgG1, IgG2, and IgG3, antigen-binding sites are for the same food antigen. In IgG4, the antigen-binding sites are for different antigens so that large immune complexes cannot be formed.



celiac disease. If the result is negative for the confirmation tests for celiac disease, many patients are frequently erroneously advised that they have no problem with wheat. Hadjivassiliou et al. argued that it is a significant clinical error to classify wheat allergy through the filter of celiac disease and argue that celiac disease is a subtype of wheat sensitivity.[9] Many of their patients with wheat allergy but celiac–disease negative had remission of severe neurological illnesses when they adopted a gluten-free diet and expressed that in these patients the gluten molecule causes an autoimmune reaction in the brain rather than in the intestinal tract, likely against the Purkinje cells that are predominant in the cerebellum.

A wide range of additional studies has proved the clinical value of IgG antibodies in autism, bipolar depression, schizophrenia, migraine headaches, asthma, and obesity.[10–15]

Total IgG versus IgG4 Food Allergy

IgG is classified into several subclasses termed 1, 2, 3, and 4. IgGs are composed of two heavy chain–light chain pairs (half-molecules), which are connected via inter–heavy chain disulfide bonds situated in the hinge region (Figure 1). IgG4 antibodies usually represent less than 6% of the total IgG antibodies. IgG4 antibodies differ functionally from other IgG subclasses in their lack of inflammatory activity, which includes a poor ability to induce complement and immune cell activation because of low affinity for C1q (the q fragment of the first component of complement). Consequently, IgG4 has become the preferred subclass for immunotherapy, in which IgG4 antibodies to antigens are increased to reduce severe antigen reactions mediated by IgE. If antigens preferentially react with IgG4 antibodies, the antigens cannot react with IgE antibodies that might cause anaphylaxis or other severe reactions. Thus, IgG4 antibodies are often termed *blocking antibodies*. Another property of blood-derived IgG4 is its inability to cross-link identical antigens, which is referred to as *functional monovalency*. IgG4 antibodies are dynamic molecules that exchange half of the antibody molecule specific for one antigen with a heavy-light chain pair from another molecule specific for a different antigen, resulting in bispecific antibodies that cannot form large cross-linked antibodies that bind complement and thus cause subsequent inflammation.[16] In specific immunotherapy with allergen in allergic rhinitis, for example, increases in allergen-specific IgG4 levels indeed correlate with improved clinical responses. IgG4 antibodies block not only IgE-mediated food allergies but also the reactions of food antigens with other IgG subclasses, reducing inflammatory reactions caused by the other IgG subclasses of antibodies to food antigens.

In IgG-mediated food allergy testing, the goal is to identify foods that can cause inflammation and thus trigger a large number of adverse reactions. IgG1, IgG2, and IgG3 can all cause inflammation because these antibodies do not exchange heavy and light chains with other antibodies to form bispecific antibodies. Thus, IgG1, IgG2, and IgG3 antibodies to food antigens can and do form large immune complexes or lattices that fix complement and increase inflammation. The presence of IgG4 antibodies to food antigens indicates the presence of antibodies to foods that will not usually cause inflammation even though high amounts of these antibodies do indicate the presence

of immune reactions against food antigens. Testing only for IgG4 antibodies in foods limits the ability of the clinician to determine those foods that are causing significant clinical reactions that are affecting their patients. The importance of measuring other subtypes of IgG antibodies is highlighted in an article by Kemeny et al.[17] They found that IgG1 antibodies to gluten were elevated in all 20 patients with celiac disease but none of the patients had elevated IgG4 antibodies to gluten.

Notes

1. Statement of the AAAAI Work Group Report: Current approach to the diagnosis and management of adverse reactions to foods [Web page]. October 2003. http://www.aaaai.org/ask-the-expert/usefulness-of-measurements-of-IgG-antibody.aspx. Accessed October 27, 2013.
2. Dixon H. Treatment of delayed food allergy based on specific immunoglobulin G RAST testing relief. *Otolorvngol Head Neck Surg.* 2000;123:48–54.
3. Nagisa Sugaya N, Nomura S. Relationship between cognitive appraisals of symptoms and negative mood for subtypes of irritable bowel syndrome. *BioPsychoSocial Medicine* 2008;2:9–14.
4. Atkinson W et al. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut.* 2004;53:1459–1464.
5. Drisko J, Bischoff B, Hall M, McCallum R. Treating irritable bowel syndrome with a food elimination diet followed by food challenge and probiotics. *J Am Coll Nutr.* 2006;25: 514–522.
6. Bentz S, et al. Clinical relevance of IgG antibodies against food antigens in Crohn's disease: a double-blind cross-over diet intervention study. *Digestion.* 2010;81:252–264.
7. Main J, McKenzie H, Yeaman GR, et al. Antibody to Saccharomyces cerevisiae (bakers' yeast) in Crohn's disease. *BMJ.* 1988;297:1105–1106.
8. Schaffer T, Mueller S, Flogerzi B, Seibold-Schmid B, Schoepfer AM, Seibold F. Anti-Saccharomyces cerevisiae mannan antibodies (ASCA) of Crohn's patients crossreact with mannan from other yeast strains, and murine ASCA IgM can be experimentally induced with Candida albicans. *Inflamm Bowel Dis.* 2007;13:1339–1346.
9. Hadjivassiliou M, Grünewald RA, Davies-Jones GAB. Gluten sensitivity as a neurological illness. *Neurol Neurosurg Psychiatry.* 2002;72:560–563.
10. Vladimir T et al. Higher plasma concentration of food-specific antibodies in persons with autistic disorder in comparison to their siblings. *Focus Autism Other Dev Disabl.* 2008;23:176–185.
11. Severance EG et al. Immune activation by casein dietary antigens in bipolar disorder. *Bipolar Disord.* 2010;12:834–842.
12. Severance EG et al. Subunit and whole molecule specificity of the anti-bovine casein immune response in recent onset psychosis and schizophrenia. *Schizophr Res.* 2010;118:240–247.
13. Huber A et al. Diet restriction in migraine, based on IgG against foods: a clinical double-blind, randomised, cross-over trial. *Int Arch Allergy Immunol.* 1998;115:67–72.
14. Vance G et al. Ovalbumin specific immunoglobulin G and subclass responses through the first five years of life in relation to duration of sensitization and the development of asthma. *Clin Exp Allergy.* 2004;34:1452–1459.
15. Wilders-Truschnig M et al. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. *Exp Clin Endocrinol Diabetes.* 2008;116:241–245.
16. Van der Neut Kolfschoten M et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science.* 2007;317:1554–1555.
17. Kemeny DM et al. Sub-class of IgG in allergic disease. I. IgG sub-class antibodies in immediate and non-immediate food allergy. *Clin Allergy.* 1986;16:571–581.

◆

William Shaw, PhD, is the director of the Great Plains Laboratory in Lenexa, Kansas, specializing in metabolic, toxic, and nutritional factors in a wide range of human diseases. He received a PhD in biochemistry, genetics, and human physiology from the Medical University of South Carolina. He is board certified in both clinical chemistry and toxicological chemistry by the American Board of Clinical Chemistry, one of a handful of individuals in the world to hold dual certifications. He has supervised large endocrinology, nutritional biochemistry, toxicology, and immunology departments in positions at the Centers for Disease Control (CDC) and SmithKline, one of the world's largest clinical laboratories, in Atlanta, Georgia. Dr. Shaw worked in the Health and Nutrition Examination Survey at CDC, the most comprehensive nutritional survey of the population of the US. He was director of clinical chemistry, endocrinology, organic acid testing, and toxicology at Children's Mercy Hospital, the teaching hospital of the University of Missouri at Kansas City School of Medicine, where he was an associate professor in the pathology department. Dr. Shaw has supervised the testing of over a million samples of blood and urine involving the use of virtually every modern technology in the field of laboratory medicine. Dr. Shaw was honored to recently receive the highest award from the International Academy for Child Brain Development in 2012.

Predictive Biomarkers in Personalized Laboratory Diagnosis and Evidence Based Best Practices Outcome Monitoring

by Russell Jaffe MD, PhD, CCN, and Jayashree Mani, MS, CCN

Predictive biomarkers are a few tests that can now be referenced to goal values whose interpretation can include a lifestyle action plan that enhances functional cost and outcome effectiveness, adding years to life and life to years.

This article addresses:

- what these predictive biomarkers are and why they are valid;
- interpretation of the test results based on goal values;
- how to reduce risk and bring tests value to or nearer to the safer value at least cost and best outcome effectiveness.

The existence of predictive biomarkers is the first conceptual advancement in lab medicine since sensitivity, specificity, and predictive index were introduced a generation ago. Integrative, comprehensive, personalized medicine seeks evidence-based objective predictive biomarkers to determine that both risk and response to therapy can be quantified. Each predictive biomarker is selected for its *sensitivity*; that is, its accuracy, and its *specificity*; that is, its lack of false results so that its clinical *predictive significance* – the product of sensitivity and specificity – is high.

Eight predictive biomarkers are proposed here along with their goal values, including which aspect of the metabolome and the microbiome are most affected, and the genes and epigenetic modulation of genetic expression. Strategies and tactics are presented to enable people to improve upon their biomarker values through virtuous cycles and health-enhancing habits of daily living.

Predictive Biomarkers

Predictive markers are independent and interdependent assessments of health risk and status. Together they cover the 92% of lifetime health that is based on lifestyle habits, or *epigenetics*, if you prefer. While 8% is genetic, over 9/10 of the quality and quantity of life is determined by the sum of what, how, and when people eat, drink, think, and do.

Predictive biomarker test results provide a comprehensive, accessible, actionable, and personalized plan for health with added value when the goal value and interpretation referenced here are included. Eight functional tests, each predictive of outcome, are useful in monitoring therapeutic responses to any program designed the help the person or evoke healing responses.

Usual (Statistical) Test Results vs. Predictive (Healthy) Goal Value Results

Prior to predictive biomarkers, conventional clinical lab tests provided information about "usual" or "normal" statistical ranges of a particular item analyzed. They are useful for population studies but not clinically as relevant or predictive. By contrast, these specific predictive biomarker tests provide information that extends the concept of "optimum," or "high-level health," reference ranges pioneered by Cheraskin and Ringsdorf or the biochemical

➤

➤

individuality concept documented by Roger Williams.[1-3] The goal values recommended here for each predictive biomarker are designed to improve predictive personal precision in practice and are set to be the least risk or highest gain value for each test. When predictive biomarker tests are at their goal value, all-cause morbidity and mortality are at their best outcome value; quality of life and lifespan are optimized. The specific predictive biomarker tests included have each also been validated on large numbers of people from all ethnic and socioeconomic backgrounds.

Predictive biomarkers referenced to goal values and interpreted with a focus on epigenetic opportunities and lifestyle habit changes can stimulate virtuous behavior cycles, and more cost-effective and outcome-effective care for each individual.

Table 1 gives an overview of the predictive biomarkers here suggested with their clinical significance.

This is important because frequently people have unremarkable blood sugar on the particular day that the test is run, but their Hgb A1c is elevated, or conversely stress may increase blood sugar at a moment while Hgb A1c is low, showing that "white coat" blood sugar elevations happen just as do blood pressure elevations. Day-to-day blood sugar levels can be distorted by many pre- and postanalytic variables such as exercise, meal timings, or medications. More importantly, we do not see high blood glucose levels routinely until prediabetes is far advanced. Hgb A1c gives more reliable indication of actual and future risk.[4] Accurate fasting blood sugar values require at least 12 hours of water only prior to the blood draw. In practice, this preanalytic variable is often ignored.

Hgb A1c is a marker of insulin sensitivity and resistance. Elevated Hgb A1c is strongly linked to inflammation as well as chronic, degenerative, autoimmune disease risks.

Table 1

Predictive Biomarker Test	Metabolome, Microbiome, Genes, & Epigenetics
Hemoglobin A1c (Hgb A1c)	Sugar, energy, diabetic risk & insulin resistance; epigenetic metabolic syndrome; syndrome X
High sensitivity C-reactive protein (hs-CRP)	Epigenetic inflammation, repair ability; calls for immune help; telomere length
Homocysteine	Epigenetic methylation, detox, transport, sulfur cycles
Oxidized LDL/HDL	Epigenetic CVD risk; lipid AO status
8-oxoguanine	DNA oxidative stress; nuclear AO status
Vitamin D	Epigenetic cell talk & adhesion, C, CVD, & AI risks
1st morning (a.m.) urine pH	Metabolic acidosis; mineral status; cell battery
LRA by ELISA/ACT	Immune tolerance or intolerance; delayed allergies

Legend: AI: autoimmune; AO: antioxidant; C: cancer; CVD: cardiovascular diseases; DNA: genetic code; deoxyribonucleic acid; ELISA/ACT: enzyme-linked immunosorbent assay/advanced cell technique; LRA: lymphocyte response assay

Predictive Biomarker 1: Glycosylated Hemoglobin/ Hemoglobin A1c (Hgb A1c)

Hemoglobin A1c (Hgb A1c) most accurately measures *average* glucose or blood sugar. Fasting and 2-hour postprandial blood sugar have long been measured to get information about moments in time. More recently, insulin and glucose/insulin ratios have been developed to better understand sugar energy metabolism. Hgb A1c *better* predicts average blood sugar level for the previous 3 months than any other lab test.

A Hgb A1c of $<5\%$ is the desired or goal value and reflects a 99% probability of living 10 years. The graphs below (Figures 1A and 1B, p. 95) represent the correlation between Hgb A1c levels, blood glucose levels, and 10-year survival probability.

When above goal value, an immunotolerant diet of whole foods enriched with super-foods and targeted full disclosure supplements directed to improve energy, glucose, and insulin balance, is included as part of the interpretation. Being active physically and

mentally is also included in the recommendations designed to evoke healing responses.

Predictive Biomarker 2: High-Sensitivity C-Reactive Protein (hs-CRP)

High-sensitivity C-reactive protein (hs-CRP) is one of the most predictive markers of inflammation systemically and particularly in the cardiovascular system. Levels of hs-CRP rise in response to repair need, also known as inflammation. Hs-CRP is more precise and predictive at low levels than CRP.[5]

When inflammatory repair deficit persists, often a chronic damaging process is slowly smoldering below the surface that is merely troublesome and not yet disabling progresses. Inflammation burdens the body's organ systems, especially the immune system, slowly wearing it down, taking a toll on daily quality of life, increasing risk, and reducing survival.[6]

The charts below (Figures 2A and 2B) represent the correlation between hs-CRP, Framingham 10-year CVD risk scores, and 10-year survival probability. Elevated hs-CRP is common in prediabetes and diabetes, reflecting insulin resistance and metabolic syndrome X, a continuum of conditions with increased inflammation and a high risk of cardiovascular complications due to cumulative repair deficits. Elevated hs-CRP levels may indicate a long-term chronic infection or host hospitality due to cumulative repair deficit; that is, inflammation.

As a predictive biomarker, hs-CRP reflects the effectiveness and efficiency of first line *innate* cellular immune defenses, responsible for neutralizing any sign of infection, repairing daily wear and tear, and identifying and eliminating cancerous cells.

Hs-CRP goal value is <0.5 mg/dl.

If hs-CRP is above goal value, our interpretation includes an immunocompetent diet of whole foods with an emphasis on repair-promoting super-foods, targeted supplementation directed toward adequate systemic repair, as well as mental and physical activities to evoke healing responses.

Predictive Biomarker 3: Homocysteine

Homocysteine is an amino acid whose balance with methionine reflects methylation status. Methylation controls many aspect of cell function, including expression of our genetic material; modulates RNA; and helps transport or deposit proteins. When this process is not working properly, homocysteine levels are elevated. Homocysteine reflects a deeper imbalance in two critical important aspects of metabolism, detoxification and methylation within all cells.

This marker reveals cellular function or dysfunction in regard to sulfur metabolism and methyl group migration at the most basic cell level. High homocysteine is associated with risks from heart disease and cancer to Alzheimer's disease and osteoporosis. Homocysteine measures all-cause morbidity and mortality; this test is an important predictor of long-term survival (Figures 3A and 3B, p. 96).

The good news is that elevated homocysteine levels reflect an imbalance usually easily correctable with diet and supplements. It is also encouraging to know that as homocysteine levels come back into a more normal range, risk is reduced after as short as a few months at the new, healthier levels after deferred repair as been completed.

Homocysteine goal value is $<6\ \mu$mol/L.

If homocysteine levels are above the goal value, our interpretation includes an immunotolerant whole-foods diet with an emphasis on sulfur-rich super-foods, targeted supplementation including methylation nutrients, along with mental and physical activities to evoke healing responses.

Additional five predictive biomarkers are discussed below that add independent predictive value to the above set of three. These are:

- oxidized LDL/HDL and 8-oxo-guanine for antioxidant status
- vitamin D level for cell communication
- pH for cell acidity and mineral reserves
- immune tolerance and intolerance by lymphocyte response assay (LRA)

Predictive Biomarker 4: Oxidized LDL/HDL

Oxidized LDL/HDL is a highly reliable indicator of oxidative stress, antioxidant status, and additionally cardiac risk. While traditional LDL cholesterol levels have been in use for a while to predict heart disease, ➤

➤

it is well documented now that the *oxidized LDL* test is a superior blood lipid test to identify risk among apparent healthy men and women.[7] Although the test has only recently become available commercially, the technology has been used in research studies for more than 10 years, and at least 400 papers have been published evaluating oxidize LDL cholesterol.

The test measures the health of DNA in our mitochondria, the "engines" within each cell that make energy. Are we burning up DNA faster than needed due to stress, toxic exposures, or poor diet? In essence, oxidized LDL is a measure of the health of our cells. Impaired function of the mitochondria is one of the central failures in practically every form of chronic illness. By being able to measure the health of our cells, we are measuring an important end point for chronic illness. This test answers the question, do we have increased stress in this critical area and, if so, how much stress?

Oxidized LDL is a preferred measure of oxidative stress and associated cardiac and metabolic syndrome risk with a healthy value of ~0 when adequate antioxidant protection is provided. If oxidized LDL/HDL levels are above the goal value, the interpretation includes an immunotolerant whole-foods diet with an emphasis on super-foods; antioxidant intake, especially buffered ascorbate and polyphenolics; along with mental and physical activities to evoke healing responses.

Predictive Biomarker 5: 8-Oxoguanine (8-Hydroxyguanine, 8-Oxo-Gua, or OH[8]Gua)

Along with oxidized LDL, testing for 8-oxoguanine provides important information about oxidative stress and its effects on DNA. The test is highly regarded as a measure of oxidative stress and well supported in the research literature.[8]

This indicator focuses on the acceleration of aging due to potential DNA damage and is an effective way to evaluate the success of an intervention, whether it involves dietary change or antioxidant nutrients. Tracking the results of this test provides an indication of:

1. risks due to oxidative stress in the DNA genetic code;
2. benefit or lack of benefit from therapies over time.

When antioxidant levels are sufficient, that prevents oxidative damage from free radicals. Healthy levels of antioxidants such as ascorbate mean efficient energy production in the cells.

The goal for 8-oxoguanine that we suggest is a value of <5.3 ng/mg of creatinine, indicating adequate antioxidant protection.

Both 8-oxoguanine and oxidized LDL/HDL indicate higher levels of inflammation, repair deficit, and oxidative stress throughout the body, factors that underlie almost any form of chronic illness.

If 8-oxoguanine levels are above the goal value, the interpretation includes an immunotolerant whole-foods diet with an emphasis on super-foods and antioxidant nutrients, along with mental and physical activities to evoke healing responses.

Predictive Biomarker 6: Vitamin D

It is estimated that anywhere from 30% to 100% of Americans, depending upon their age and community living environments, are deficient in Vitamin D. Vitamin D levels play a significant role in numerous systems in the body, including immune and neurological regulation and bone health. When levels of this nutrient are low, it increases the risk of cancer, heart disease, autoimmune disorders, and psychiatric and mood problems.

In addition, vitamin D:

- improves type 1 and type 2 diabetes, hypertension, multiple sclerosis, rheumatoid arthritis, and other conditions;
- moderates cell division as a hormone whose function is to provide vital communication links between cells, normalize cell growth, and avoid aggressive cell production;
- improves autoimmune disorders that are quieted by sufficient nutrients;
- reduces brain and nervous system inflammation, particularly important since the brain lacks other regulatory systems to moderate inflammation.

Knowing the status of vitamin D is essential to correct any nutrient depletion. The preferred test of vitamin D involves measuring the metabolite 25-hydroxycholecalciferol (25[OH]D). The predictive goal value range for 25(OH)D is 50 to 80 ng/ml.

Figure 1A: Hgb A1c Levels and 10-Year Survival Probability

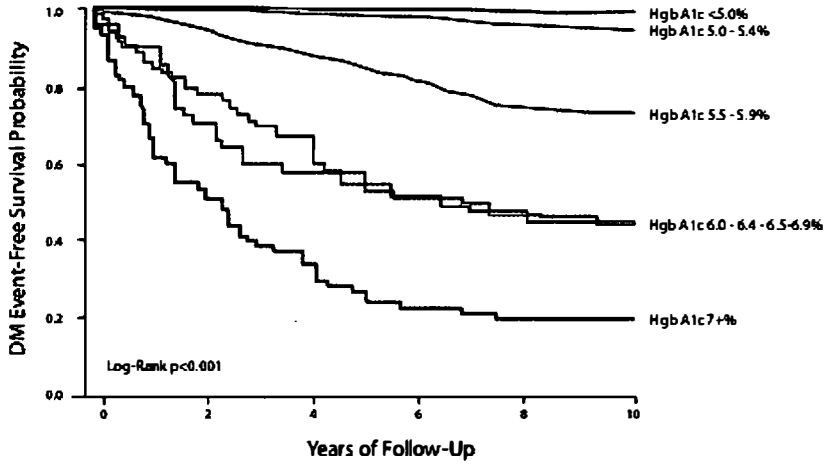


Figure 1B: Hgb A1c Levels, Average Blood Glucose, and 10-Year Survival Probability

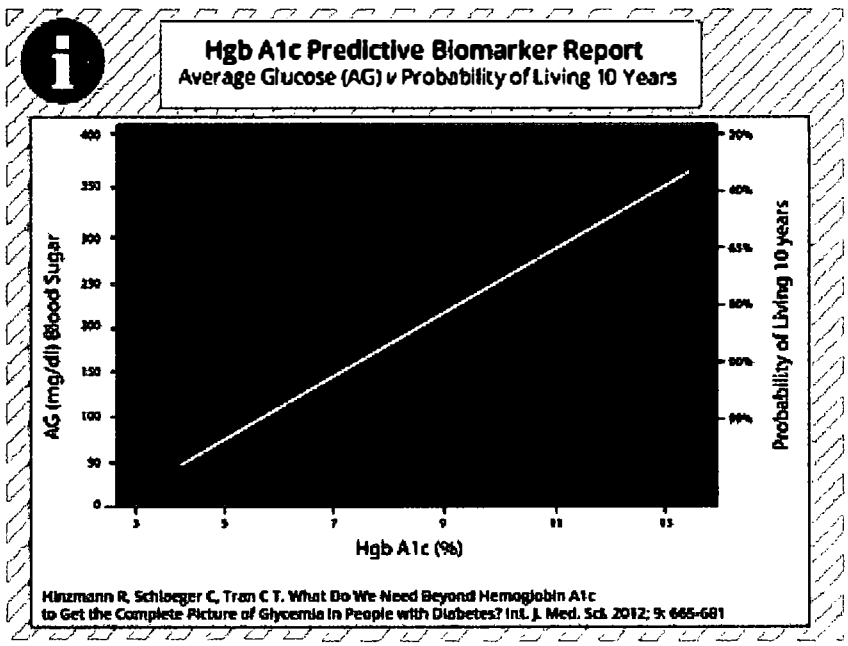
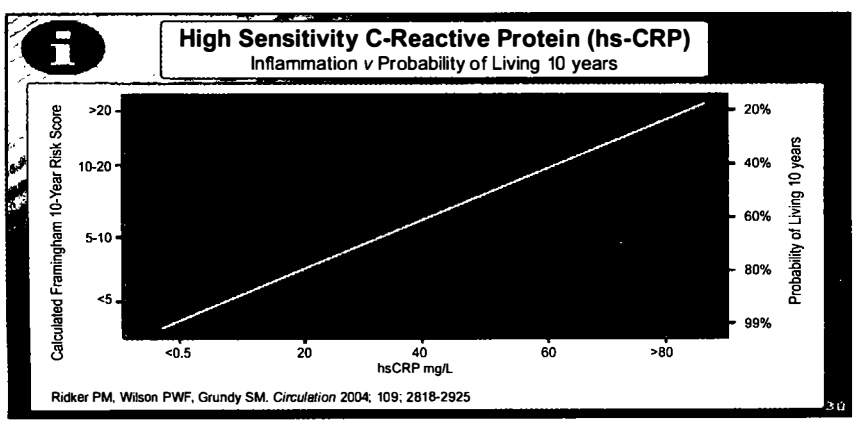


Figure 2A: High-Sensitivity C-Reactive Protein (hs-CRP) and Cardiovascular Risk



If vitamin D levels are below 50 ng/ml, vitamin D drops, 500 IU per drop with rosemary oil, sufficient to bring the vitamin D level into the goal range of 50 to 80 ng/ml, is part of the interpretation.

Predictive Biomarker 7: First pH After 6-Plus Hours' Rest in Urine

The pH level of urine after 6 hours of rest reflects pH throughout the body (Figure 4, p. 96). Levels below 6.5 indicate metabolic acidosis. Low pH also suggests mineral deficits, because minerals are pulled from bone and body fluid during metabolic acidosis to buffer and reduce acids and maintain pH within a health range.

Tiny changes in pH have profound implications for cell metabolism. Life exists poised exquisitely just above the neutral point of 7.0. Levels of pH above 7.5 can indicate catabolic illness in which amino acids are used as energy sources.

Any unusual variation in urinary pH is usually reflected in the first morning urine. This calls for changes in diet and/or nutritional supplements to restore acid–alkaline balance. Simply checking the pH level each day provides ongoing monitoring to see whether pH has been corrected. (fuph.perque.com). This is an important aspect of biochemistry; so if there is an abnormality, that has to be monitored regularly.

The predictive goal value range for urine pH is 6.5 to 7.5 after 6 or more hours of rest, typically first in the morning.

If pH levels are below the goal range, our interpretation includes an immunotolerant diet with alkalinizing whole foods and an emphasis on

➤

Figure 2B: High-Sensitivity C-Reactive Protein (hs-CRP) and 10-year survival

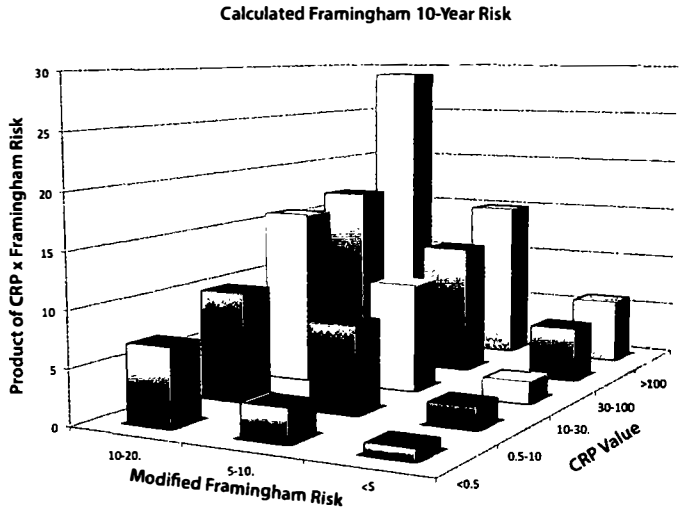


Figure 3A: Homocysteine Levels and 10-Year Survival

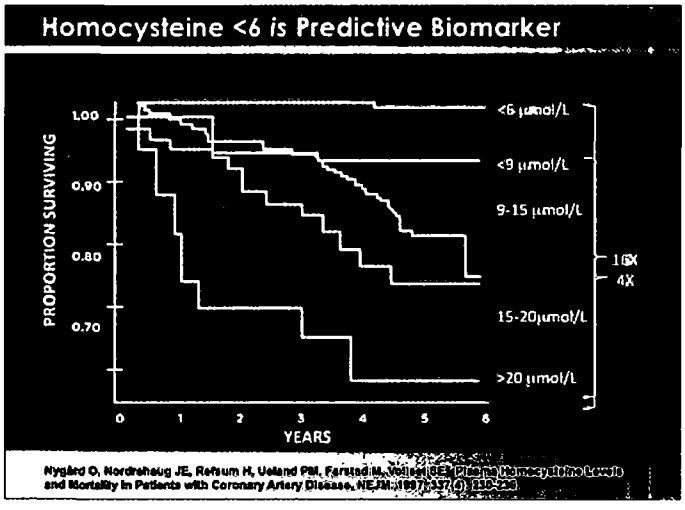
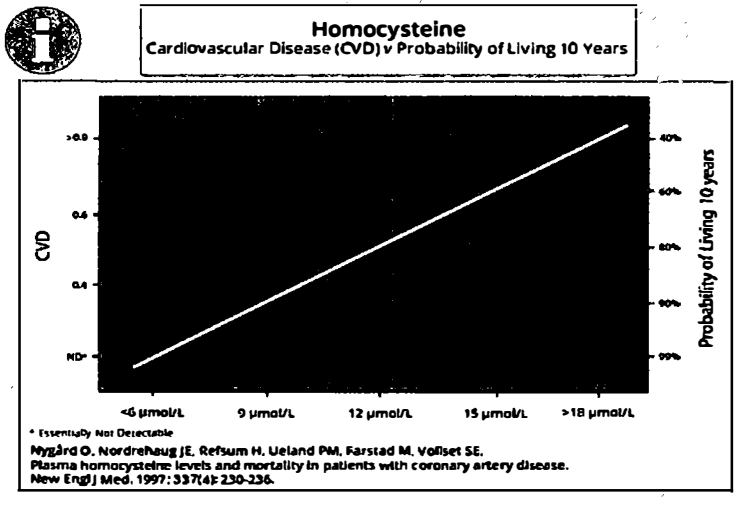


Figure 3B: Homocysteine Level, CVD, and 10-Year Survival Probability



Bostom AG, Silbershatz H, et al. Nonfasting plasma total homocysteine levels in all-cause and cardiovascular disease mortality in elderly Framingham men and women. *Arch Intern Med*. 1999;159(10):1077–1080.

➤

super-foods. Targeted supplementation, especially magnesium and choline citrate, along with mental and physical activities to evoke healing responses, are also key.

Predictive Biomarker 8: Tolerance or Immune Reactivities via LRA by ELISA/ACT Tests

Conventional therapies for autoimmune conditions involve some combination of immune suppressive therapies. In contrast, the LRA (lymphocyte response assay) by ELISA/ACT determines individual reactive foods or other chemicals that appear to

continued on page 99 ➤

Figure 4: Effect of First Morning Urine pH on Health Status

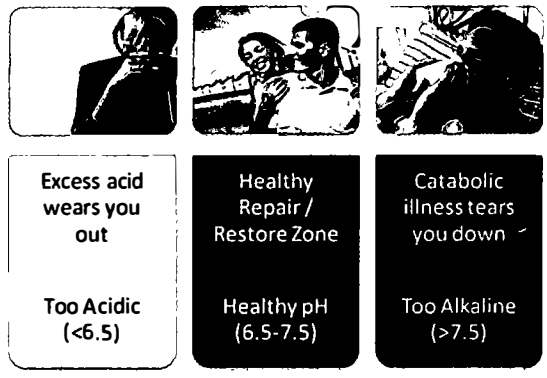
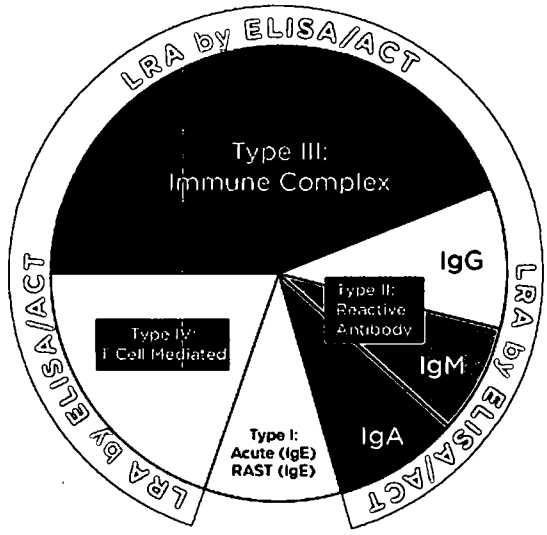


Figure 5: Wheel of Immune Response Mechanism



Better Lab Tests Now™

Lifestyle choices (epigenetics) determine 92% of your lifetime health risk and status.

Learn how to add years to life and life to years with the help of 8 key Predictive Biomarkers.*

Better Lab Tests Now offers a comprehensive Predictive Biomarker Panel with predictive goal values for each test

Hgb A1c (Hemoglobin A1c)
hsCRP (high sensitivity C-reactive protein)
Homocysteine
Oxidized LDL/HDL
8-oxo-guanine
1st AM urine pH
Vitamin D (25-OH)
LRA by ELISA/ACT tests

* See article by Dr. Russ Jaffe, "Predictive Biomarkers in Personalized Laboratory Diagnosis and Evidence Based Best Practices Outcome Monitoring" in this issue.

Better Lab Tests Now offers the highest quality testing at affordable prices, directly...without a doctor's prescription!

Convenient ordering online or by phone. Sample collection kits sent to you by mail. Easy-to-read test results in as little as 7 to 10 days!
Visit **www.BETTERLABTESTSNOW**.com to see our complete list of available tests.

Contact us now to learn how to add years to your life and life to your years!

877-894-8363

www.betterlabtestsnow.com

➤ continued from page 96

be burdening the immune system and an optional interpretation aimed at restoring immune competence, tolerance, and resilience.

The LRA tests measure all three delayed allergy pathways (Figure 5, p. 96) while avoiding false positives common in other types of delayed allergy tests:

- reactive antibody (IgA, IgM, and IgG)
- immune complexes
- direct T-cell activation

The LRA by ELISA/CT tests are fundamentally different from antibody serology or particle counting tests in that ex vivo LRA tests are substantially more sensitive, specific, and predictive.

Benefits of the LRA compared with other allergy tests include that it is:

1. comprehensive: Only clinical tests of all three delayed allergy pathways at one time (type II, type III, and type IV) able to perform up to 491 cell cultures on just 1 ounce of blood;
2. functional: Identifies only symptom provoking reactive substances, not merely harmful or protective while missing T-cell responses entirely;
3. ex vivo: Unique LRA tests are performed just as they occur inside the body.

Identifying the patient's specific sensitivities and delayed allergies that burden the immune system is a clinical breakthrough. Patients often experience a dramatic improvement in quality of life as a result of the individualized treatment plan, which includes an alkalinizing diet and targeted supplementation. After 6 months, a reevaluation of progress is recommended with three possible outcomes:

1. If patient is in remission, a guided gradual reintroduction of previously reactive items 1 per week is advised, ingesting an item 3 times in the first week because of amnestic responses.

2. If patient is better but not yet well, repeat LRA tests and treatment guidance every 6 months until in sustained remission. Since digestion and detoxification, among other systems, take time to recover, it is common for people to lose some reactive items and acquire new ones. A repeat program starting from a healthier base is likely to further improve health and sustain remission.

3. If patient reports following instructions carefully and avoiding reactive items but is still not better, look for toxins or hormone-disrupters that might inhibit to recovery. If a person reports making best efforts at following the program and does not report improvement, repeat testing is not indicated.

Healthy immune tolerance means no delayed allergic LRA reactions. Highly healthy people are tolerant. People can restore tolerance as part of a proactive prevention lifestyle. If reactions are found by LRA tests, our approach includes substitution of reactive foods along with an Alkaline Way whole-foods diet with an emphasis on super-foods, targeted supplementation to promote repair, and mental and physical activities to evoke healing responses. LRA by ELISA/ACT cell cultures are reproducible within less than 3% when different readers read split samples on different days.

Discussion and Conclusion

The eight predictive biomarkers discussed here are presented for use in clinical practice based on their *predictive goal value* and translated into years or decades of life at risk, retainable, or recoverable. Every health practice can benefit from learning about the value of personalized medicine and effective proactive prevention.

While each of the predictive biomarkers is predictive, when four or more are interpreted together, their predictive power increases, covering the 92% of lifetime health determined by choice and habit. While each biomarker is a separate marker of certain aspects of physiology, human systems are interdependent and usually consistent. When a biomarker shows higher risk, sooner rather than later is the time to take action and bring that marker back to or toward the goal value.

By example, hemoglobin A1c is highly predictive of certain aspects of sugar, insulin, energy metabolism, weight, metabolic syndrome, diabetes, cardiovascular, and other chronic diseases. Hs-CRP is highly predictive for other aspects of cardiovascular and chronic disease, particularly in regard to repair deficits that present as clinically as inflammation and to the person as stiffness or pain. Homocysteine rounds out

➤

➤

the remainder of cardiovascular risks as they relate to methylation, sulfur metabolism, detoxification, and epigenetic modulation.

Predictive biomarker goal values are best on best outcome and least risk variables that do not depend on age or gender. The usual or statistically normal ranges for homocysteine, for example, are usually based on age and gender. This means that there are more unhealthy people in the population as it ages. Age-conditional usual lab ranges often drift toward the less well with advancing age. Age, however, is a contingent variable. The significant variable is how many unhealthy people are present at each age. An important difference: chronology is fixed and most of function is choice.

Every test has a standard deviation or range within which the value exists. Typical variance for most classic ELISA based tests is 20% or more. This means that a value of 6 from a given specimen will cluster values around 6 with a large range of values from 4.8 to 7.2. The typical lab test variance is 20%. The more narrow the variance, the more predictive is the observed value. For predictive biomarker tests, a variance of 5% or less is desirable. For example, if the "true" value is 6 and the test technology allows for better precision and as a result a 3% variance, a single test value actually exists between a narrow range of 5.92 and 6.18. Improvement in preanalytic variables by reducing interfering substances, improved control of analytic conditions, use of improved curve fitting particularly at the lower end of the test range, often where the accuracy of measurement is most important. As a result, the predictive significance of any specific value becomes much greater. Such improvements in precision have been accomplished in higher-complexity tests such as lymphocyte response assay cell cultures (e.g., LRA by ELISA/ACT). As with all tests and particularly homocysteine, attention to details makes for better clinical results and improved human outcomes, particularly when therapy or management is based on lab results. Colleagues such as Alan Gaby have long pointed out that the best of tests done poorly or whose meaning is misunderstood by practitioners is unhelpful to the client. Mark Twain summed up the issue as follows: "Be careful about reading health books. You could die of a misprint." Those of us who are clinical, analytical, methodological, and metrological have an obligation to point out strengths and limitations of tests where results drive therapies or predict outcomes.

Separately, two people, each with a true hemoglobin A1c of 8%, one of whom has been diagnosed as a diabetic, both have an equally high risk of a cardiovascular or other health crisis within 10 years. Technically, both are diabetic and only one knows it. This is known as the difference between *incidence* and *prevalence*. Many diabetologists today are increasingly diagnosing the degree of diabetes based entirely on accurately performed Hgb A1c tests.

While each of these tests is a predictive biomarker, when they are taken together we can identify both where healthier resilience exists and also where risks that can be reduced are identified. Predictive biomarkers are each based on large-scale, long-term studies including all ethnic, economic, and cultural groups. There are no population exceptions of which we know. The predictive goal value for the biomarkers explained here is based on evidence from many studies covering all ethnic groups over long periods of time in regard to all-cause morbidity and mortality; that is, life expectancy. The probability of living 10 years for these predictive biomarkers is based on large-scale, long-term community-based outcome studies. The Health Studies Collegium includes links to review articles that address aspects of predictive personalized and potentially life-saving tests and what to do about them.

Predictive biomarkers are not age adjusted, because the interpretations of the test results reported here are based on least-risk, best-outcome healthier goal values. Healthy people at all ages have the same lab ranges. As people accumulate age, there are more unhealthy people in each progressive decade. This is why using predictive biomarkers based on goal values is an advancement of the previous statistical normality approach.

While too many people live in denial about their health until some catastrophe occurs, more and more professionals and consumers are using predictive biomarkers to help assure and guide their lifestyles. These proactive consumers of healthier caring are likely to live well and prosper.

Resources

Functional predictive biomarkers can be obtained through www.BetterLabTestsNow.com.

Link to the predictive biomarker table: http://betterlabtestsnow.com/pdf/Biomarkers.pdf.

Clinical protocols for these eight predictive biomarkers can be obtained by contacting PERQUE Integrative Health: 800-525-7372; clientservices2@PERQUE.com.

ELISA/ACT Biotechnologies: 800-553-5472; clientservices@ELISAACT.com.

Health Studies Collegium: 800-328-7372; info@4HSC.org.

Notes

1. Galen RS, Gambino SR. *Beyond Normality: The Predictive Value and Efficiency of Medical Diagnosis.* New York: Wiley; 1975.
2. Cheraskin E, Ringsdorf WM Jr, Clark JW. *Diet and Disease.* Emmaus, PA: Rodale Books; 1968.
3. Williams RJ. *Biochemical Individuality: The Key to Understanding What Shapes Your Health.* New Canaan, CT: Keats Publishing; 1998.
4. Hinzmann R, Schlaeger C, Tran CT. What do we need beyond hemoglobin a1c to get the complete picture of glycemia in people with diabetes? *Int J Med Sci.* 2012;9(8):665–681.
5. Silva D, Pais de Lacerda A. High-sensitivity C-reactive protein as a biomarker of risk in coronary artery disease. *Rev Port Cardiol.* 2012;31:733–745.
6. Jaffe R, Mani J. Rethink health: inflammation is actually repair deficit: using physiology first to achieve better outcomes, part 1: value and importance of understanding inflammation as repair deficit. *Townsend Lett.* 2013 Jun;359:68–74.
7. Holvoet P, De Keyzer D, Jacobs DR Jr. Oxidized LDL and the metabolic syndrome. *Future Lipidol.* 2008 December; 3(6):637–649.
8. Humphreys V, Martin RM, Ratliffe B, et al. Age-related increases in DNA repair and antioxidant protection: A comparison of the Boyd Orr Cohort of elderly subjects with a younger population sample. *Age Ageing.* 2007;36(5):521–526.

◆

Dr. Russell Jaffe received his AB, MD (with senior thesis honors), and PhD (In biochemistry and physiology) from Boston University. Dr. Jaffe served his medical internship at University Hospital and was awarded a the US Public Health Service Officer Commission, assigned to the Clinical Center of the National Institutes of Health, in June 1973. While at the Clinical Center, Dr. Jaffe served his residency in clinical pathology. He is board certified in clinical and subspecialty certified in chemical pathology. Dr. Jaffe remained on the permanent senior staff of the NIH Clinical Pathology Department, where he continued method innovation and was active in collaborative research with the Laboratory of Experimental Atherosclerosis (of the Heart, Lung, and Blood Institute). Concurrently, Dr. Jaffe's interests in the mechanisms of health and the evoking of human healing responses led him to apprentice in such healing arts as acupuncture; mindfulness; massage; music, art, and color therapy; and a variety of eclectic therapeutic approaches. In addition, Dr. Jaffe performed innovative studies of platelet function and blood clotting in relation to the origins of coronary artery and cardiovascular diseases. Among the tests that he developed are the early colon cancer-screening test using occult blood detection not interfered with by vitamin C consumption, as well as a variety of tests related to the blood clotting and immune defense and repair systems. Dr. Jaffe developed the first method of measuring cell-mediated immunity using a modified ELISA system in a lymphocyte mitogenesis/blastogenesis brief cell culture known as lymphocyte response assays (LRA). This LRA by ELISA/ACT provides an "immunologic fingerprint" of items to which the body is reactive or tolerant.

Dr. Jaffe has contributed over 100 symposium-invited talks, scientific articles, or book chapters. He received the J. D. Lane award for original research from the USPHS, the Merck Sharp and Dohme Excellence in Research Award, and in 2002 the International Research Scientist of the Year, among other recognitions for his investigations. Dr. Jaffe is a fellow of the Health Studies Collegium and director of ELISA/ACT Biotechnologies LLC and PERQUE LLC in Ashburn, Virginia. He may be reached at 800-525-7372 ext. 5101, and rjaffe@ELISAACT.com or rjaffe@PERQUE.com.

Jayashree Mani is a certified clinical nutritionist (CCN). She is experienced in the effective implementation of the comprehensive program described in this article involving these predictive biomarkers, LRA by ELISA/ACT tests, Health Appraisal Questionnaires (HAQ), Alkaline Way diet, and PERQUE nutraceuticals.

Defend and Protect your Eyes

review by Katherine Duff

The Vitamin Cure for Eye Diseases, by Robert G. Smith, PhD
Basic Health Publications Inc., 28812 Top of the World Drive, Laguna Beach, California 92651
© 2012; 198 pp.; $14.95

Diseases of the eye are usually regarded as the domain of medical specialists. Author Robert G. Smith, PhD, has combined his early influences in nutrition, his knowledge of orthomolecular medicine, and his deep knowledge about the eye to bring eye health and treatment of their diseases into the mainstream with his book *The Vitamin Cure for Eye Disease.*

Smith is a research scientist at the University of Pennsylvania, where he has focused on retinal circuitry. In this book, he is also a teacher. He begins with a tutorial on how the eye actually works. Here we learn that within this very intricate structure, there are components that have varying nutrient needs and different vulnerabilities, particularly to oxidative stress. Oxidative stress can be caused by physical injury, viral and bacterial infections, toxic chemical exposures, and light. The irony is that the eye needs light to see, but the light is also responsible for causing oxidative damage to the tissues. Over time, what we know as age-related diseases of the eye can develop, and this is due in part to oxidative damage. These diseases can lead to blindness.

The eye undergoes a continual process of oxidative damage and repair. As with damage caused by free radicals in other parts of the body, antioxidants and other nutrients can help prevent and slow progression of diseases in the eye. Vitamin C is most useful. It is found in the aqueous humor, the area in front of the lens, in levels much higher than blood serum levels. There it can help eliminate damage caused by light. The antioxidants lutein and zeaxanthin play multiple roles in maintaining the health of the eye. These carotenoids are found in the pigment of corn, peppers, and green leafy vegetables. They are also found in the outer segments of photoreceptors, where they serve as filters that remove the damaging blue light on its way to the retina, and in the retina, where they are thought to reduce oxidative stress. Lutein is found in the periphery of the eye and zeaxanthin is found in the macula. Vitamin E protects the photoreceptors and can reduce intraocular pressure.

There are several diseases discussed in this book, with the most serious being those that are caused by the degeneration of the photoreceptors: retinal detachment, macular degeneration, and retinitis pigmentosa, and those that are caused by degeneration of the retinal ganglion cells: glaucoma and diabetic retinopathy. For each of these conditions, the author describes what parts of the eye are affected, what the risk factors are for developing it, and which nutrients and antioxidants would be helpful.

Age-related macular degeneration (AMD) is the leading cause of blindness in people over 50. It is considered an incurable disease in which the photoreceptors near the center of the eye, or the macula, die. Smith describes the two forms of the disease. The wet form is a process that results in cellular waste products' collecting beneath the pigment epithelium. In this form, the choroid, a matrix of blood vessels that feed the pigment epithelium at the back of the eye, grows new blood vessels that push the retina away from the choroid. This results in retinal detachment.

"We know that supplemental antioxidants and nutrients are effective in preventing eye disease from literally thousands of studies over the past half-century."

Smith takes us through the progression of the disease, which may even start in infancy. He describes the series of oxidative damage that occurs in the eye over time that can result in AMD, but suffice it to say that both forms are thought to be caused by oxidative damage to the pigment epithelium and retina.

The risk factors for developing AMD are another clue to the role of oxidative damage, beginning with smoking. Some of the chemicals in cigarette smoke are known to cause cell death in the pigment epithelium, just where AMD starts its process. Other risk factors include high blood pressure, exposure to bright sunlight, and chronic inflammation. Smith notes that certain nutrients and antioxidants in a healthful diet and through supplementation can reduce the risk for AMD. Among these for a proactive approach include vitamins B, C, D, and E; lutein and zeaxanthin; omega-3 oils; zinc; selenium; and a low-glycemic diet.

An eye condition that we all experience to some degree is night blindness. Not many of us realize that when we see a bright light, the pigment molecule rhodopsin, which is in the outer layer of the rod receptors, is bleached by that light. It then takes a period of time before rods regenerate and we are able to see in the dark again. Whether during driving at night or coming into a darkened house from a bright sunny day, our inability to see right away is the time it takes for our rods to regenerate. Adequate levels of vitamin A are needed for this regeneration.

There are discussions of other, less serious eye conditions that can be treated with proper nutrients. For obtaining those nutrients, the author has suggestions for maintaining a proper diet and detailed information about the relevant supplements.

The fact is that most of us take our eyesight for granted until something goes wrong – but we should not. This marvelous organ needs to be a consideration in our overall health as much as any other organ that we work to preserve. At the least, this may mean that a jog outdoors on a sunny day should include a wide-brimmed hat and sunglasses. And our supplement regimen should include those vitamins and nutrients that will assist our eyes in the process of regeneration and repair.

Robert Smith has written an important book that has placed eye health into our own hands, where it should be. As a teacher, he has conveyed a respect and appreciation that is contagious. After reading this book, it would be impossible to take for granted the intricate performance of the eye that gives our lives so much. ◆

A Vital Bridge between Doctors and Patients

review by Neil Raff, MD

Your Blood Never Lies: How to Read a Blood Test for a Longer, Healthier Life, by James B. LaValle, RPh, CCN
Square One Publishers; 115 Herricks Rd., Garden City Park, New York 11040
© 2013; softcover; $16.95; 368 pp.

In an era when health care is being reduced often to imaging studies and lab tests, *Your Blood Never Lies* by James LaValle, RPh, CCN, emerges as a valuable tool to layperson and physician alike. It is a well-written and detailed book that serves as an excellent guide to blood tests, what information these tests provide, and how abnormal findings can be remedied and even reversed through lifestyle modification.

To get the most out of LaValle's book, you must read it carefully; ideally, it is best if the reader has a basic understanding of body chemistry. The detailed editorial format throughout is great if you have specific questions about specific tests. The various forms of treatment presented and outlined in the book are also very helpful.

Often, different readings on tests represent only minor variations and are best evaluated by a doctor. Just as often, however, these readings can stand as small but important early warning signs that may well be missed by a cursory and less detailed test assessment. As shown so well in this book, that small distinction between a minor variation and a major problem is a crucial one that should never go unrecognized.

If I have any criticism, it would be the book's lack of a section dedicated to the immune system and/or autoimmune diseases – an important but complex area of medical diagnosis – together with what seems an excess of choice pointed at nutrients, supplements, and any variety of alternative treatments now available.

In summary, though, the book is a thorough examination of an area in which far too many patients have known far too little for far too long. In a system increasingly dependent on any number of indecipherable medical tests, this new book serves as a clear and vital bridge between doctors and patients.

◆

Anti-Aging Medicine

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

An Anti-Aging Primer for GI Health

As we age, changes take place in our body systems. Cellular processes slow down, and our organs and tissues become less robust in performing their functions. Such is the case for the gastrointestinal (GI) system: with aging, there is a decline in the actual form of the intestines – the lower part of the gastrointestinal tract. Scientists have observed alterations in the structure and membrane composition of the intestine. This causes declines in the absorption of some nutrients, such as fatty acids and cholesterol. In addition, the following changes are common in the GI system during aging:

The human intestines remove toxins created by the digestive (as well as cellular) processes. The intestines are home to bacteria, known as intestinal flora. Representing 400 different species, these microorganisms typically comprise 2 to 3½ pounds of body weight. In all, the intestines may be home to as many as 100 trillion organisms – more than the total number of cells in the entire body!

We all have armies of "good" and "bad" bacteria in our intestines. The "good" (friendly) bacteria perform functions necessary to sustain life, from vitamin and enzyme production to enhancing digestion and absorption of proteins. Good bacteria also suppress potentially threatening microorganisms from multiplying and spreading. Of the 400 or so known species of bacteria that colonize the upper and lower gastrointestinal tract, *Lactobacilli* and *Bifidobacteria* are the most important and beneficial.

Bacteria coexist in the intestine with colonies of yeast. In fact, bacteria keep yeast growth in check. Frequent or prolonged use of antibiotics can kill enough bacteria to destroy this balance and cause an overgrowth of yeast, which leads to infections such as vaginitis and chronic diarrhea. Out-of-control intestinal yeast is also thought to precipitate allergic symptoms or to aggravate existing allergies.

This column reviews recent scientific evidence that reaffirms the notion that it is essential for overall health to maintain plentiful "good" bacteria in the GI system.

GI Bacteria Diversity Linked to Obesity

People who do not have a rich array of healthy gut bacteria may be more prone to metabolic dysfunction and low-grade inflammation. Oluf Pedersen and colleagues from the University of Copenhagen (Denmark) conducted DNA analysis on intestinal bacteria from 292 Danish patients, of whom 169 were obese and 123 were not. The researchers found that among the obese subjects, 23% had low "bacterial richness," with an average of 380,000 microbial genes, compared with an average of 640,000 genes in those who had more diverse microbiomes. Subjects with less diverse gut bacteria also had greater adiposity, insulin resistance and dyslipidemia, and a more pronounced inflammatory phenotype than those with high bacterial richness. Those subjects also gained significantly more weight over the previous 9 years. The study authors submit that these correlations help to "identify subsets of individuals in the general white adult population who may be at increased risk of progressing to adiposity-associated co-morbidities."

Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature*. 500:541–546; 28 August 2013.

Pine Tree Compound Aids GI Health

A polysaccharide from *Picea abies* (spruce) may selectively enhance the growth of beneficial gut bacteria. Researchers from the University of Turku (Finland) report that the spruce tree is abundant in galactoglucomannan, a type of hemicellulose that has been suggested by previous studies to exert prebiotic effects. L. Polari and colleagues showed that *Bifidobacterium* (beneficial bacteria) species could ferment the spruce-derived compound in a lab model. Additionally, the team observed that the amount of viable bacteria was nearly 100 times higher in samples exposed to galactoglucomannan, as compared with the control samples. Observing, "Bifidobacterium animalis subsp. lactis strain Bb12, a commonly used probiotic, was able to adapt to the galactoglucomannan leading to more efficient utilization of hemicellulose-derived saccharides," the study authors submit: "Our study demonstrates prebiotic properties for galactoglucomannan."

Polari L, Ojansivu P, Mäkelä S, Eckerman C, Holmbom B, Salminen S. Galactoglucomannan extracted from spruce (Picea abies) as a carbohydrate source for probiotic bacteria. *J Agric Food Chem.* 2012 Oct 24.

Dietary Fiber Supports GI Health

Microbes that live in the gut are responsible for fermenting fiber in the intestine, producing short-chain fatty acids and other metabolites beneficial for the body. It is therefore important that sufficient dietary fiber is consumed daily, in order to promote the growth of such beneficial bacteria. Kelly Swanson and colleagues from the University of Illinois (US) studied 20 healthy men, consuming an average fiber intake of 14 g a day, who were given snack bars to supplement the diet. A second group ate bars that contained 21 grams of polydextrose, a common fiber food additive; a third group received bars with 21 grams of soluble corn fiber; and a fourth group received bars that contained no fiber. The team collected fecal samples from the participants, and used the microbial DNA obtained to identify which bacteria were present. DNA was then subjected to 454 pyrosequencing, a technique that provided a snapshot of all the bacterial types present. The researchers found that certain bacteria grew as a result of the respective fibers consumed. Observing specifically that when soluble corn fiber was consumed, the numbers of *Lactobacillus bacteria*, often considered a probiotic for their beneficial effects on the gut, increased.

Hooda S, Vester Boler BM, Rossoni Serao MC, et al. 454 pyrosequencing reveals a shift in fecal microbiota of healthy adult men consuming polydextrose or soluble corn fiber. *J Nutr.* July 2012;142:1259–1265.

'Good Bugs' Battle Colds

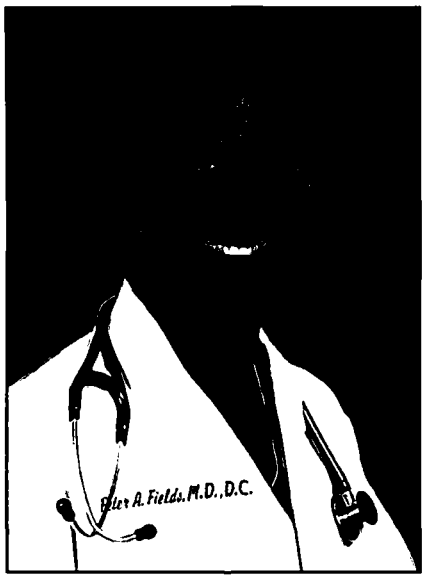
Previous studies have suggested the utility of probiotics, bacterial organisms that help maintain the natural balance of microflora present in the intestines, to help modulate the immune response. Tracey J. Smith and colleagues from the University of Medicine and Dentistry of New Jersey (US) recruited 200 college students, administering a supplement of 1 billion colony forming units (CFUs) of *Lactobacillus* and *Bifidobacterium* strains, for a 12-week period. When the participants contracted an upper-respiratory infection, the researchers observed that it lasted 4 days, as compared with 6 days in a control group who did not receive probiotic supplementation, equating to a 34% reduction in the duration of the common cold. The study authors suggest: "[Probiotic supplementation] may be beneficial among college students with [upper respiratory infection] for mitigating decrements in [health-related quality of life]."

Smith TJ, Rigassio-Radler D, Denmark R, Haley T, Touger-Decker R. Effect of Lactobacillus rhamnosus LGG(R) and Bifidobacterium animalis ssp. lactis BB-12(R) on health-related quality of life in college students affected by upper respiratory infections. *Br J Nutr.* 2012 Oct 1:1–9.

The gastrointestinal (GI) tract, the largest system in the body, is 28 to 30 feet long with a total surface area of almost 6000 square feet – about the dimensions of a tennis court! As the above studies suggest, abundant "good" GI bacteria help to achieve overall wellness and vitality.

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

◆



Orthopedic/Sports Medicine

by Peter A. Fields, MD, DC
www.DrFields.com

Low Back: Why Surgery May Not Be the Best Choice

80% to 90% of Americans experience low back pain at some point in their lives.

If you are in the 10% whom this does not happen to, then you have nothing to be concerned about. On the other hand, if this describes you or someone you know, then you may want to read the rest of this column. (Note: from this point, the term *back pain* will be used when low back pain is inferred).

We all take our backs for granted. Back pain will affect you no matter what you do: walking, sitting, standing, exercising, and even sleeping. So if you have back pain, it will be with you most, if not all, of the time. What to do about it when it gets to the "debilitating" stage is what we will address here.

Anatomy

The low back consists of the lumbar spine, the sacrum, and pelvis. *Lumbus* is derived from the Latin word *limbos*, meaning "lion," and the lumbar spine earns its name. It is built for both power and flexibility – lifting, twisting, and bending.

The spinal cord is housed in the vertebral column (spine) that protects it. The lumbar spine consists of five movable vertebrae. The complex anatomy of the lumbar spine is a remarkable combination of these strong vertebrae, multiple bony elements linked by joint capsules, and flexible ligaments/tendons, large muscles, and highly sensitive nerves.

The five vertebrae of the lumbar spine (L1–L5) are the biggest vertebrae in the spinal column, their size enabling them to support the weight of the entire torso. The lower the vertebra is in the spinal column, the more weight it must bear. The lumbar spine's lowest two spinal segments, L4–L5 and L5–S1, which include the vertebrae and discs, bear the most weight and are therefore the most prone to degradation and injury. The lumbar spine meets the sacrum at the lumbosacral joint (L5–S1). This joint allows for considerable rotation, so that the pelvis and hips may swing when one is walking and running. Below the lumbar spine are the sacrum and the pelvis. Although not technically in the spine, these last two bony structures make up the low back complex.

In between the vertebrae are the discs. They are there to cushion the pressure between each vertebra. They support the pressure when compressed (standing or sitting) and allow movement between the vertebrae. The discs are firmly embedded between the vertebrae and are held in place by the ligaments connecting the spinal bones and the surrounding sheaths of muscle. The disc is sometimes described as a shock absorber for the spine. It has a tough, fibrous outer membrane (the annulus fibrosus) and an elastic core (the nucleus pulposus). Although discs start off as gel- or fluid-filled sacs, they begin to solidify as part of the normal aging process, making the outer protective lining weaker and the discs more prone to injury.

Four major ligaments of the spine are the anterior longitudinal ligament, the posterior longitudinal ligament, the supraspinous ligament, and the capsular ligaments of the apophyseal/facet joints. These last ligaments are arranged to provide maximum resistance to flexion. They can support about twice body weight in the young, although their strength decreases with age.

A fifth and very important ligament in the spine, which is frequently overlooked, is the iliolumbar ligament. It connects the last lumbar vertebra (L5) to the pelvis. It strengthens the lumbosacral joint and basically helps stabilize the spine on the pelvis. The iliolumbar ligament is one of three vertebral-pelvic ligaments responsible for stabilizing the lumbrosacral spine in the pelvis, along with the sacrospinous and sacrotuberous ligaments. Along with these three are the sacroiliac (SI) ligaments, which also help to stabilize the spine.

An important joint in the spine is the apophyseal joint, commonly called the facet joint. This is a synovial joint (containing fluid) between the superior articular process of one vertebra and the inferior articular process of the

vertebra directly above it. This allows the two vertebrae "connect" to each other and glide/move together, and also limits motion. There are two facet joints in each spinal motion segment. In the lumbar spine, for example, the facet joints function to protect the motion segment from anterior shear forces and excessive rotation and flexion. These functions can be disrupted by arthritis, injury, trauma, and surgery. Due to the mechanical nature of their function, the facet joints undergo degenerative changes with the wear and tear of age, commonly known as facet joint arthritis, or facet arthropathy.

There are many important muscles that affect the lumbar spine's motion. They are divided into the extensors, forward flexors, lateral flexors, and rotators. There are too many individual muscles to name, but the groups are (1) extensors: stabilize posture and increase the efficiency of larger muscle groups; (2) forward flexors: their primary action is hip and trunk flexion; (3) lateral flexors: lateral flexion is normally a combination of side bending and rotation; (4) rotators: rotation is brought about by the unilateral contraction of muscles.

What Causes Back Problems?

Unfortunately, the answer here is almost anything. We are bipeds (walk on two feet), so there is a lot of pressure on the spine whenever we are upright. Gravity alone takes care of this. Generally speaking, the lower back is subject to a lot of mechanical stress and strain. The reason is the weight of the upper body, which always puts pressure on the low back. There is also pressure on the spine in the seated position. Most sports, hiking, yoga, driving, sitting, standing, and most other activities cause pressure on the back. At some point or other, this will build up, and one gets back pain. Being overweight, poor physical condition, decreased flexibility, poor posture, poor sleeping position, weight gain during pregnancy, and stress may also contribute to low back pain. The list goes on and on.

You've Tried Everything: Is Surgery the Answer?

Chiropractic, physical therapy, acupuncture, medicines, TENS units, muscle stim, distraction techniques, stretching, Pilates, and more. Now what do you do? Have surgery? Simple answer: *no*. Let's see why.

600,000 Americans have back surgery each year. $30.3 billion is spent on treatments to ease the pain. But while some of that money is spent on chiropractic visits, physical therapy, pain management, and other noninvasive therapies, a big chunk pays for spine surgeries; and complicated spine surgeries that involve fusing two or more vertebrae are on the rise. In just 15 years, there was an eightfold increase in this type of operation, according to a recent study.

The rate of back surgery in the US is at least 40% higher than in any other country and is more than 5 times that in England and Scotland. Back surgery rates increased almost linearly with the per-capita supply of orthopedic and neurosurgeons. Research suggests that of the 500,000-plus disc surgeries that are performed annually (a significant increase of late), as many as 90% might be unnecessary and ineffective. A US medical school professor notes: "It seems implausible that the number of patients with the most complex spinal pathology [has] increased 15-fold in just six years" and mentions that one strong motivation includes "financial incentives involving both surgeons and hospital." One article evaluated worldwide surgical attitudes. There were twice the number of surgeons per capita in the US compared with the UK. Sweden, despite having a large number of surgeons, was conservative and produced relatively few surgeries. The most surgeries were done in the US. In the UK, more than a third of nonurgent patients waited over a year to see a spinal surgeon. A lower rate of referrals in the UK was found to discourage surgery in general. Fee for service and easy access to care was thought to encourage spinal surgery in the US, whereas salaried position and a conservative philosophy led to less surgery in the UK.

Studies show that at best 50% will get relief (this may be all or just some) from back surgery, 25% will stay the same and 25% will get worse. These are not great odds. The ICD-9 codes (soon to be the ICD-10) are all the medical codes that insurance companies use to categorize illnesses, procedures, and surgeries. There are over 20,000 of them. But there is only one for a failed surgery. Guess which one? Yes, low back. It is called "failed low back surgery syndrome." Every year, there are 50,000 documented cases. This category should not even exist; but, sadly, after years of failed low-back surgeries, they had to put it in.

Of course, other problems that might happen with back surgery are device failure, loosening of a screw, infection, improper wound healing, and more. Then there are months and months of therapy afterwards, with no guarantee as to the outcome. In addition, many must take pain medicines. In what might be the most troubling study finding, researchers determined that there was a 41% increase in the use of painkillers, specifically opiates, in those who had surgery. Some of those go on to become addicted to these dangerous medicines and then need a pain management physician to help them. And if the surgery that you have does not come out to your liking, you cannot have the surgeon put it back the way it was. Surgery once done cannot be "undone."

I recently was treating a patient for his shoulder. One day he asked me if I worked on low backs, to which I replied yes. He then reminded me about his three low-back operations. Several years prior, they did surgery to fuse his L3–L4, L4–L5, L5–S1. This was done at a major medical center with some of the top surgeons in the US. Two days after discharge from the hospital, he developed severe pain going all the way down his leg. He was told by the surgeon to go to the ER. An X-ray confirmed his worst fear: a screw had come loose from the apparatus that they put in his low back. So it was back to the operating room for him. This time, he stayed in the hospital for a week. Several

➤

➤

days after this second surgery, he again began to have pain. And guess what? They found that another screw had come loose. This time the surgeon called in an "expert" to assist him, and they finally got it right. Total time in the hospital: 47 days! And the reason that he is asking me about all of this? Because he still has a lot of pain three years later. That is why he is now seeing me: to fix the cause and not just the effect.

Another misconception about back surgery is that if you have a disc bulge or herniated disc (most are partial and not complete), then surgery will solve your problem. A retrospective study looked at over 5000 backs. About half of them had bulging discs. The other half did not. In each group, about half of the people had pain and half did not. So that meant that there were people with bulging discs who did not have back pain and there were people without bulging discs who did have back pain. The conclusion of the study: a disc problem was no indication of whether someone would have back pain. So having surgery to fix the bulging disc would be of no consequence in resolving the problem.

As I stated in a recent column (October 2013), an MRI will show a problem (e.g., disc bulge) but not if that problem is the cause of the pain. And many times, that disc bulge is not the cause of the pain. An MRI will most commonly be used to determine the need for surgery, yet does not accurately diagnose ligament and tendon laxity, since they frequently do not show up on an MRI. In addition, MRIs have frequently shown problems when there are none. Over 50% of adults over age 45 will have some sort of disc problem but not any pain. The most likely suspect is ligament or tendon laxity not holding the structure in place, which needs to be addressed.

Although there are many reasons to avoid surgery, there is a place for back surgery when dealing with chronic pain. Patients who have excruciating pain from a truly pinched nerve causing weakness associated with decreased muscle mass, or in cases where there is evidence of bowel or bladder difficulties along with the pain, require a surgical evaluation. In addition, complete tendon/ligament ruptures usually require surgery as well.

What Regenerative Medicine Has to Offer

Prolotherapy, the main form of regenerative medicine, looks at fixing the cause and not just the effect. I have already addressed the three main forms of prolotherapy – dextrose, PRP, and bone marrow/stem cell – and will not go into it here (please see the June 2013 issue of the *Townsend Letter* on my website: www.Dr Fields.com). As stated above, many low-back surgeries address what is seen on the MRI. This is just the effect; an MRI does not address the cause. Again, thousands of people have bulging discs but do not have a problem. And when those who do have surgery to address it, guess what happens? It does not go away. Weakened or damaged ligaments and tendons are the most likely cause of many low-back problems, especially those not alleviated by conservative care mentioned above. Plus, one must look at all the supportive structures of the back, which include the ligaments and tendons of the sacrum and the pelvis. Most, if not all, low-back surgeries do not address this.

Prolotherapy is a better treatment than surgery, as it stimulates soft tissue repair of ligaments and tendons to alleviate pain. This is because most people have chronic pain due to ligament and tendon weakness.

Prolotherapy is the safest and most effective natural medicine treatment for repairing tendon, ligament, and cartilage damage. It stimulates the body to repair painful areas in the weakened attachments through the spine, pelvis and sacrum, and the SI joint. In the simplest terms, prolotherapy stimulates healing.

One Last Thought

I would like to share a story about a patient. He had been having back pain on and off for many years. Twelve years ago, it came back, and this time it was debilitating. He had tried chiropractic (several forms), acupuncture, physical therapy, muscle stim, pain medicines, and more. None of it relieved his pain. After 6 months of continued pain that radiated down his legs, sometimes awakening him up to four times a night, he finally decided to get an MRI. It was read as: desiccated (dried out) discs, bulging disc (9 millimeter), bilateral foraminal stenosis (closed-down holes where the spinal nerves exit the spine), arthroses (spinal arthritis), and more. He then went to see three different neurosurgeons, who all independently agreed that without surgery his athletic days were over and he would have trouble walking from time to time. This sounded like a death knell to him, as he was extremely athletic; he just could not accept it. He found out about prolotherapy and got treated. After three treatments, he was feeling better; after only seven treatments, he was pain free. He continued sports and his love for triathlons, finishing eight half (70.3) Ironman events. And last August, he finished his third full Ironman Triathlon, which consisted of a 2.4-mile swim, 112-mile bike ride, and 26.2-mile run. And this was after he was told by three surgeons either to have surgery or give up sports.

I guess he proved them wrong.

And I should know, as this is me.

So believe me when I say: Prolo first – surgery last.

Peter A. Fields, MD, DC, "The Athletic Doc," is an expert in the field of orthopedic/sports medicine. He is both a board-certified medical physician and chiropractor, one of only a handful of physicians in the US with both these degrees. Dr. Fields is the director of the Pacific Prolotherapy and Medical Wellness Center in Santa Monica, California. Orthopedic/sports medicine is the main focus of his practice. He also practices holistic medicine, which includes bioidentical hormones, anti-aging medicine, IV nutritional therapy, IV chelation therapy, natural alternatives to prescription medicines, and more.

◆

Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, DHANP, LCSW, and Robert Ullman, ND

www.healthyhomeopathy.com

Arthritis, Keratosis, and Morton's Neuroma: A Case of Constitutional Calendula

Calendula Cream: A Mainstay of Homeopathic and Naturopathic Practice

What is the natural topical preparation of choice in any homeopathic and many a naturopathic practice? Of course, *Calendula* cream, which we prefer to ointment preparations. We recommend it for cuts, scrapes, abrasions, lacerations, and to soothe the discomfort of eczema, burns, and many other nonfungal conditions. Not that it will do any harm with fungus – it just won't help. I, Judyth, was first sold on *Calendula* cream in 1981, during my second year of naturopathic training at Bastyr. I had the good fortune to work in a free medical clinic for destitute patients in Old Delhi, India. The neighborhood, the *Basti*, was populated by Islamic families living in the most basic housing without running water or an adequate sewage system. Our program provided milk to the undernourished children and free, basic medical care from a large tent with a dirt floor. We mostly dispensed soap and homeopathic medicines. I particularly remember an elderly man with a huge, angry gash on the front of his lower leg. We cleaned the wound each day, then applied *Calendula* cream and a fresh bandage. In a matter of a week, the skin had healed remarkably. Over the course of 30 years, we have seen many topical *Calendula* cures.

We are talking about the beautiful gold and yellow marigolds that provide the colorful centerpiece for flower and vegetable gardens as well as containers overflowing with eye-catching annuals. *Calendula*, along with *Arnica* (also yellow, but smaller and less showy) are members of the *Compositae*, or aster, family, known to treat injuries. The name *Calendula* derives from the opening of the blooms on the *calends*, the first day of the month. Marigold is associated by some authors with the Virgin Mary and by others with Queen Mary Stuart. The flowers are edible, freshly gracing salads or dried for use in soups. The old herbalists, such as Culpepper, referred to the plant as "a comforter of the heart and spirit." Classical homeopaths who practice the sensation method of Rajan Sankaran recognize the need for these and other *Compositae* members when the patient's chief focus is on hurt and pain. Words commonly used are *hurt, pain, injury, excruciating, ache,* and others describing sensitivity to pain. *Calendula*, along with *Arnica*, is particularly useful in acute injuries, especially excessively painful lacerations or cuts and ragged, suppurating wounds. It has been used effectively for over 200 years to prevent infections of open wounds, such as on the battlefield or during childbirth. It can be used either internally or as a dressing made from a weak solution of tincture and water, sometimes with the addition of *Hypericum* (St. John's wort). This plant is the best-known herbal wound dressing and antiseptic, tried and true. *Calendula* has also been used for superficial burns and scalds, inflamed ulcers with excessive secretion of pus, bedsores, and hemorrhages in scalp wounds or follow dental extraction. It is known, when applied topically, to prevent scars and keloid tissue and to promote healthy granulation.

We have recommended *Calendula* cream to most of our patients at one time or another. But the following case is the first time in 30-plus years of practice that we have prescribed *Calendula* homeopathically. The results, you will see, were quite rewarding, for the patient and the prescriber.

Revisiting Homeopathy at the Age of 65

Helen, a community college instructor from Portland, had been helped by us for several years in her 40s, likely benefiting from *Calcarea carbonica* (calcium carbonate; oyster shell). We are not sure because we had disposed of her long-outdated chart, but that is our recollection. She was one of those patients whom we had long forgotten about but who had continued taking her remedy, with benefit, over the years. We were surprised and pleased to see her again two years ago. ➤

➤

The remedy helped. Now I am having trouble with my memory. The other day I couldn't remember that I had a ruptured appendix. Even as a little girl my memory wasn't great. I have anxiety for no reason. My back acts out. I think I have arthritis in my big toes. I cough and sneeze and my voice becomes gravelly when I'm around dust. I don't sleep well at night – I wake between 1 and 4 a.m. I have a big lump in my foot from the Morton's neuroma. I ache when I walk. Orthotics has helped somewhat and I received a cortisone injection. I had a number of breast biopsies in the past, but no lumps for a number of years. I don't have any one big thing ... just a bunch of little ones.

It's the tightness of my body. I have scoliosis in the top of my back. The muscles are *tight. It feels like I'm just wires inside – instead of your muscles being how you can manipulate them. Like big, thick wires that don't want to give ... don't want to bend, move. Maybe rods, rather than wires.* I don't move as easily. Like if you scrunch your fist up and you hold it like that. I have to be so careful about how I move. I've gone through a lot of chiropractic care. *Tight ... restricted movement.* When I get up in the morning, I have to move slowly. More stiff than flowing. Like I'm carrying a big load ... like the character with the bag on his back. All humped over. I think I've always felt tight. My movement has always been restricted.

Since the sensation should permeate all of the patient's case, we asked if Helen experienced tightness in any other area of her body.

My root canal. I had to keep my mouth open so long. I've always had a tight jaw. It just clenches down. Or when I'm on a plane. I can't wait to get out. I like to sit on the aisle. Otherwise I feel hemmed in. When I drive it always feels good to get out of the car and walk. ... My neck gets really stiff on the right side, sometimes to the point of waking up with a migraine. And my right jaw keeps clicking and going out of joint.

I'm colder than I used to be. I used to be a snow skier.

I have gobs of keratosis on my nose. And all over my body – arms, legs, back, face, chest. A year ago I was diagnosed with basal cancer. They dug a big hole in my skin. I have scaly marks all over my face. As a child I had eczema inside my elbow. My dermatologist gave me a new topical medication for it, but it makes me turn beet-red and I have to stay inside. ... I had eczema on my arms when I was younger.

Calamine lotion made it better.

Helen feared being alone, suffering, someone coming into her house, and illness, especially dying from skin cancer. She mentioned her longtime love of nature and plants.

The emphasis on tightness, restriction, inability to move freely, and a desire to get up and move around frequently matched quite well the *Anacardiaceae* (cashew) family. There were no indications of a need for a mineral or animal medicine, which seemed to confirm a plant prescription. We prescribed a common homeopathic medicine for joint and skin complaints: *Rhus toxicodendron* (poison ivy) 12C to take in a plussed form daily. We also recommended vitamin D, essential fatty acids, CoQ50, and an excellent calcium/magnesium/boron supplement.

Response to *Rhus Tox*

Five weeks later, Helen reported that her memory was improving. She had discovered black mold in her bathroom, which she was having removed. The neuroma was less intense and painful. "My lower back seems to be staying in place better." Helen had a somewhat positive response, but not convincing to a homeopath. Ten weeks after starting the *Rhus tox*, she was still experiencing some improvement. The moderate improvement continued and we did not change the medicine, nor the potency. In retrospect, we would have raised the potency to 30C much earlier. Six and a half months into the course of treatment, Helen told us that her big toe joints were doing great, the low back pain was 75% to 80% better since starting the *Rhus tox*, and the Morton's neuroma was almost gone. Her migraines had decreased somewhat. The keratosis had not been significantly affected by the homeopathy, but topical vitamin E was helping. At that point we did increase the potency to *Rhus tox* 30C daily.

It may sound as if Helen was feeling a great deal better, but we were just not convinced that we had found the best medicine for her. When we prescribed the first dose of *Rhus tox*, the sensations did point clearly to *Anacardiaceae*, specifically *Rhus tox*. But, despite some positive strides, we decided to do a retake. This is when we meet again with a patient for an hour or so to take the case from scratch. It is an excellent way to see whether the same symptoms and sensation present and the same kingdom, family, and miasm are confirmed. In many cases, when the response to the medicine has been lackluster, we are treated to a surprise. That was the case with Helen.

Retake: New Family and Prescription

This was now 10 months after Helen had come back to see us. She was not unhappy with her response to the homeopathy, but we felt unsettled about it. We expect excellent, not mediocre, results from a constitutional medicine. The new information:

"I'm not depressed anymore. The Morton's neuroma is much better, but it still feels like a wad in the bottom of my right foot. Thick and uncomfortable. Like clay. Massaging helps. It is irritating ... I still feel *sharp pain* at night in my lower back. It wakes me up. *Like if you hit me with a wooden stick. Like somebody punched me and hit my bone. Like a jolt to my back. If somebody knocked you in the chin and made you see stars. Like an unmovable part in the shoulder blade.*" Helen had never before shared these sensations.

We asked what the Morton's neuroma had felt like at its worst. "A *sharp pain. Pinching.* I couldn't wear shoes. *Like*

when you take something and pinch it. It's all squeezed together. A lump that wasn't movable."

"I have hemorrhoids. It's uncomfortable to go to the bathroom. *Tender.* I have to be really gentle and careful. Thin protection. It makes me feel irritated. It's *harsh. Hurtful. Painful."*

We delved more deeply into the pain. "Horrifying. You would want to leave your body. *The pain is too horrible. Very sharp. Extremely painful. Hurtful. Something's being damaged. It would be bloody, swollen. It could sting ... harsh, mean. ...* My dad used to hit me with a switch. It left red marks. So bad that I couldn't sit down and go to the bathroom. *Extremely painful."* Helen them mentioned having nearly escaped a serious car accident as a teenager.

All of the references to pain and hurt suggested a *Compositae,* far different from the *Anacardiaceae* family. We considered which member of this plant family would best fit Helen, including the keratosis, and came upon *Calendula.* Given its fame for lacerations, wounds, and postsurgery, we asked Helen about any history of surgeries. "I suffered a ruptured appendix 15 years ago. Surgery wasn't performed until after it ruptured. I told the doctor that my siblings had also experienced ruptured appendixes, but he didn't catch it in time. I was in so much pain that I think I was not much in my body. *Painful, sharp, intense.* Five days later he opened me up and found the appendix had ruptured. I was very angry about the delay." We changed the prescription to *Calendula* 30C daily.

Follow-Ups After Calendula

One month following the new prescription: "You know how I had brown spots all over? They turned scaly and are starting to disappear. I had gobs of them all over. Nothing else has ever worked in the past ... I felt two weeks ago and ended up wracking my body. I am still sore. My hemorrhoids are 90% better. I also started using astringent pads." We prescribed a dose of *Calendula* 1M for the contusion and Helen continued the 30C daily.

Three months: "I was good until last night, when my shoulder went out. I was hardly going to see the chiropractor. The keratosis is much better. I have about three spots on my face and one on my back. Still some brown spots but no flaky keratosis. ... My memory is so much better. So is the arthritis in my hands and toes. There is not as much leakage with the hemorrhoids even though I stopped using the astringent pads. I so appreciate your help. It's wonderful." She continued the *Calendula* 30C daily.

Nine months: "A lot of my symptoms are better. My left foot, lower back, and shoulder blade are all less painful. Before I had keratosis all over my face, back, arms. I don't see any on my arms now, my face is much improved, and my legs look much lighter. And my nose is so much better. ... I still suffer from anxiety, but not like before. My memory continues to improve. It seems like the remedy is even helping my toenail fungus." We again prescribed *Calendula* 1M and Helen continued the 30C.

One year: "The spots on my skin are even better. Just one the size of a dime on my right leg and it's fading, too. The arthritis in my big toe is just about gone. That lump in my back, the one I was born with, is hardly there. The remedy is helping with the neuroma, too. I would say it is 80% improved from when we started. I think it comes from wearing hand-me-down shoes as a little girl that were too small for me. ... My hemorrhoids are getting steadily better, too." Plan: Continue *Calendula* 30C.

Ten and a half months (most recent appointment): "I only have two or three small spots on my back. Before they were all over. And on my mouth. They're 95% better. The scoliosis pain is also much less. The Morton's neuroma is not bothering me like before. It's no longer difficult finding shoes. The arthritic nodule on my left foot has gone down in size. My MD tested my memory and says it's fine. I don't think I mentioned that my stools were black before. Now they're a normal color. And my fingernails are hard. I have to cut them all the time. Before they had ridges. They wouldn't grow but just broke easily. That's one of the first things I noticed with this remedy, 'Wow. I've got fingernails that I need to cut!'" Helen continues to take the *Calendula* 30C liquid plussed as well as *Calendula* cream as needed.

The Value of a Retake

Helen reminded us to not make assumptions about the prescription. Even though *Rhus tox* seemed to be the obvious choice and did produce improvement over time, we listened to our intuition that it was not the best homeopathic medicine for Helen. It is important to not hesitate to do a retake if there is any doubt about the constitutional prescription. And to do so without any prejudice about what might emerge. Allowing our cases to be new and fresh rather than continuing with a prescription that is producing only partial results is the most rewarding part of our work.

Judyth Reichenberg-Ullman and Robert Ullman are licensed naturopathic physicians, board certified in homeopathy. Their books include *Homeopathic Self-Care, The Homeopathic Treatment of Depression, Anxiety and Bipolar Disorder, Whole Woman Homeopathy, Ritalin-Free Kids* (new edition soon), *Rage-Free Kids, A Drug-Free Approach to Asperger Syndrome and Autism, The Patient's Guide to Homeopathic Medicine,* and *Mystics, Masters, Saints and Sages: Stories of Enlightenment.* Look for all of their books on Kindle soon. They live on Whidbey Island, Washington, and in Pucón, Chile, and practice at the Northwest Center for Homeopathic Medicine in Edmonds, Washington. They treat patients by phone and videoconference as well as in person. They can be reached by telephone at 425-774-5599, drreichenberg@gmail.com, or drbobullman@gmail.com. Their website is www.healthyhomeopathy.com.

◆

Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

Environmental Global Health: The Impact of Chemicals Abroad

Introduction

"Think globally, act locally" is a phrase coined several decades ago. It gave rise to awareness that the world is interconnected and disease can spread easily from one country to another. One country's health problems affect those outside its borders. Acting locally is a call for people to become active participants, not only to improve health locally but also globally. Global changes can affect health locally as well. This concept is of utter importance in the area of environmental medicine and environmental health. One country's chemical emissions affect other countries hundreds to thousands of miles away.

Environmental Impact

Chemicals are usually emitted locally but their impact can be felt globally, creating both an ecological and human health risk. There is a global impact of chemicals released into the air. Soil, groundwater, and drinking water can be contaminated, affecting humans and animals and ecosystems.[1] Food imported into the US from other countries may be contaminated with pesticides that are no longer used in the US due to their adverse health effects. Countries exporting produce to the US are required to adhere to US pesticide tolerance limits, but testing of imported produce is in reality very limited. There is little information on the extent to which these imports may expose US consumers to elevated levels of pesticide residues, relative to domestically grown produce. A recent study looked at pesticide residue that could enter the US if exporters followed originating-country requirements but not US pesticide tolerances.[2] It found that for the top 20 imported produce items, 120,439 kg of pesticides in excess of US tolerances could potentially be imported to the US, in cases where US regulations are more protective than those of originating countries. Based on low level dietary exposures, the selected pesticides in this study are associated with health effects on 13 organ systems, and several are associated with cancer.[2]

High-dose exposure to pesticides, such as occupational exposure, has the most harmful effects on humans. Most poisonings and deaths from acute pesticide exposure occur in developing countries, not the US. This is due to many factors, including: developing countries have a higher proportion of the population involved in agriculture, they have poorer pesticide handling practices, they commonly use unsafe equipment (such as leaky backpack sprayers), and they generally employ more toxic pesticides than those used in developed countries.[3] They are using highly toxic pesticides that have been banned in the US but may be reentering it through imported produce.

Traveling to other countries for work or vacation may also be a source of exposure to harmful chemicals not used in the US. Air pollution in some countries is significantly higher than in the US. There may not be any regulation of chemicals found in water or used in food manufacturing and preparation. Another risk to travelers is the fact that some countries spray them with disinfecting chemicals while on the plane. Many countries have required aircraft disinfection since the early 1930s, treating the landing aircraft with insecticides to minimize the spread of potential disease. The most common product used contains a 2% synthetic pyrethroid insecticide. Pyrethroid can affect the nervous and immune systems, and is suspected to be an endocrine-disrupting chemical.[4] The World Health Organization (WHO) and most countries and airlines have deemed pyrethroid safe for aircraft disinfection with passengers either on or off the plane. In September 2001, *USA Today* published an article detailing the use of insecticides on aircraft traveling to other countries. Six countries required spraying while passengers were still on board: Grenada, India, Kiribati, Madagascar, Uruguay, and Trinidad and Tobago.[5] The flight attendant was not even allowed to exit the plane, thus creating an occupational hazard for those who work flights overseas. A recent study investigated the urinary pyrethroid metabolite levels of flight attendants working on US domestic and

international commercial aircrafts to assess whether those on disinfected flights have elevated pyrethroid body burden compared with those on planes not treated with pesticides and the US general population. It was concluded that working on commercial aircrafts disinfected by pyrethroids resulted in elevated body burden of 3-PBA, *cis*- and *trans*-Cl2CA, two urinary metabolites of pyrethroids.[4]

Pesticides and insecticides are not the only chemicals used locally that are having global effects.

Air pollution is a major threat to every country, as it can negatively affect human health and wildlife ecosystems. WHO estimates that more than 2 million people die every year from inhaling tiny particles present in indoor and outdoor air pollution. Dr. Maria Neira, WHO director for Public Health and Environment, has stated, "Across the world, city air is often thick with exhaust fumes, factory smoke or soot from coal burning power plants. In many countries there are no air quality regulations and, where they do exist, national standards and their enforcement vary markedly." Air pollution can travel from one country to another. Several studies have determined that the air quality over parts of North America is being affected by the pollutants transported from Asia.[6,7] A recent study showed that the trans-Atlantic transport of North African dust by summertime trade winds increases ambient particulate matter (PM) concentrations in Texas above air quality standards.[8] Due to loosened restrictions on coal plants in Mexico, the airborne pollutants from coal-burning power plants along the US–Mexico border affect air quality and health in the US.[9] It is clear that one country's chemical emissions, environmental policies, education, and awareness have global effects.

Solutions

The world's entire atmosphere is connected, bringing pollutants across borders. Identifying and implementing global solutions is not an easy task, given differing cultures, awareness and education, governments, environmental controls and regulations, and economics.

"Local actions, national policies, and international agreements are all needed to curb pollution and reduce its widespread health effects," said Dr. Michal Krzyzanowski, head of the WHO European Centre for Environment and Health in Bonn, Germany. The US Environmental Protection Agency (EPA) runs a collaborative program with Mexico called Border 2012, to improve the environment and protect the health of the nearly 12 million people living along the border. The binational program focuses on cleaning the air, providing safe drinking water, reducing the risk of exposure to hazardous waste, and ensuring emergency preparedness along the US–Mexico border. Many other countries are working on curbing emissions as well. Even China, known for air pollution and poor environmental regulations, has taken steps in the right direction. In February 2012, China's Ministry of Environmental Protection (MEP) issued two major new regulations: a revision to the ambient air quality standards to include PM2.5, and a new definition of China's Air Quality Index. By the end of the year, China had completed and begun operating a network of real-time PM2.5 monitors in 74 cities through the country.

Think globally, act locally, sometimes needs to be turned around. Educating people in developing countries on simple steps to decrease environmental pollutants is often a task left up to a small group of concerned individuals. One such group is Naturopaths Without Borders (NWB; www.naturopathswithoutborders.org), a group of physicians and medical students whose mission is to provide naturopathic health care to impoverished communities while empowering those communities through education, supporting growth, and cultivating sustainable resources. In Cap-Haïtien, Haiti, the group is working on environmental concerns as well. One area of education is trying to curb the use of use of hazardous chemicals (hydrochloric acid) for drain cleaner and bleach. There is no safe method of disposal of such toxic chemical cleaners in Haiti. The bottles typically get burned as trash, contributing to poor air quality and health issues. In Haiti, NWB is spreading the word about trying not to drink out of plastic bottles, which end up being burned as trash. The group is educating people not to burn plastics and Styrofoam – a difficult task, since there is no alternative method of disposal. There is limited city garbage collection and disposal. These grassroots efforts will hopefully make way for larger governmental regulations.

Summary

It is clear that in this age of technology, the world is interconnected through the Internet. Most people do not consider that the world is also connected through a shared environment, which may affect health locally and globally. Environmental global health includes regulations, policies, research, education, and training directed at health problems related to environmental exposure. The goal of improving health for all people, by reducing global environmental exposures that lead to avoidable disease, needs to be a priority of all humankind.

Notes

1. Huijbregts MA et al. Geographical scenario uncertainty in generic fate and exposure factors of toxic pollutants for life-cycle impact assessment. *Chemosphere.* 2003;51(6):501–518.
2. Neff RA et al. A comparative study of allowable pesticide residue levels on produce in the United States. *Global Health.* 2012;8.2 Published online 2012 January 31.doi:10.1186/1744-8603-8-2.
3. Pesticide Health Risks. World Resources Institute. Accessed online Sept 24 2013. http://www.wri.org/publication/content/8437.
4. Wei B, Mohan KR, Weisel CP. Exposure of flight attendants to pyrethroid insecticides on commercial flights: urinary metabolite levels and implications. *Int J Hyg Environ Health.* 2012;215(4):465–473.
5. Woodyard C. Fumes over planes treated with pesticides. USA Today. 2001;9. Accessed online Sept. 24, 2013. http://usatoday30.usatoday.com/travel/business/2001/2001-09-10-pesticides.htm.
6. Wuebbles DJ, Lei H, Lin J. Intercontinental transport of aerosols and photochemical oxidants from Asia and its consequences. *Environ Pollut.* 2007 Nov;150(1):65–84.
7. Carmichael GR, et al. Asian aerosols: current and year 2030 distributions and implications to human health and regional climate change. *Environ Sci Technol.* 2009;1;43(15):5811–5817.
8. Bozlaker A et al. Quantifying the contribution of long-range Saharan dust transport on particulate matter concentrations in Houston, Texas, using detailed elemental analysis. *Environ Sci Technol.* 2013;47(18):10179–10187.
9. Blackman A et al. Health impact of power-exporting plants in northern Mexico. *Energy Policy.* 2012;44(C):34–45.

Dr. Marchese is the author of *8 Weeks to Women's Wellness: The Detoxification Plan for Breast Cancer, Endometriosis, Infertility, and other Women's Health Conditions.* Dr. Marchese graduated from the National College of Naturopathic Medicine. She maintains a private practice in Phoenix, Arizona, and teaches gynecology at Southwest College of Naturopathic Medicine. She was named in *Phoenix Magazine*'s 2010 Top Doctor Issue as one of the top naturopathic physicians in Phoenix. Dr. Marchese is a contributing author for the *Townsend Letter* and lectures on topics related to women's health and environmental medicine throughout the US and Canada. She is past vice president of the Arizona Naturopathic Medical Association and current member of the board of directors for the Council on Naturopathic Medical Education. ◆

Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Cancer-Related Research

Ginseng and Cancer-Related Fatigue

This multisite double-blind phase III trial was conducted to evaluate the effectiveness of American ginseng (*Panax quinquefolius*) on cancer-related fatigue. Three hundred sixty-four patients were randomized to receive 2000 mg of American ginseng or placebo twice per day for 8 weeks. Patients were men and women who had cancers other than brain or CNS lymphoma and were undergoing or had undergone treatment, had been diagnosed within the last 2 years, and had cancer-related fatigue scores of 4 or more on an 11-point scale. Patients were included only if they had pain or insomnia not higher than 4 on an 11-point scale. Other exclusions included steroids, opioids, prior/current ginseng or other treatments for fatigue.

The primary end point was the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). This is a 6-item scale to measure the patient's subjective experience of fatigue. Other outcomes included the Profile of Mood States (POMS), in particular the fatigue-inertia and vigor-activity subscales, and the Brief Fatigue Inventory (BFI).

The ginseng product contained 3% ginsenosides and was grown in Wisconsin.

In the MFSI-SF, changes from baseline to 4 weeks was 14.4 in the ginseng arm and 8.2 in the placebo arm. At 8 weeks, there was statistically significant improvement in fatigue in the ginseng group vs. placebo with change scores of 20 vs. 10.3. More patients had a positive response to ginseng and more had at least a 30% clinical improvement in the ginseng group compared with placebo. In the other outcomes, ginseng also performed better and had statistically significant improvements in fatigue over placebo for the fatigue-inertia and vigor-activity subscale of the POMS. The BFI total score did not differ between groups. In addition, greater benefit was reported in those patients who were actively receiving cancer treatment vs. those who had already completed their treatment.

Comment: Fatigue in cancer patients undergoing chemotherapy is reported to be between 59% and 96% and for patients receiving radiation therapy, between 65% and 100%. This fatigue is not necessarily short term, but can easily last 1 to 2 years, and up to 5 to 10 years after diagnosis and treatment. Fatigue symptoms have a profound impact on the quality of life for these patients, and even with this degree of frequency and impact on quality of life, there is no evidence for effective pharmacologic treatments.

The clinically significant results of the current study are especially realized after 2 months of the ginseng with improvement in cancer-related fatigue, especially for those receiving radiation or chemotherapy. There is a long tradition of use for ginseng in the treatment of fatigue of numerous causes. The two major species of ginseng, Asian (*Panax ginseng*) and American (*Panax quinquefolius*) have constituents common to both, including ginsenosides, but in different amounts, strengths, and varieties of ginsenosides. In addition to the substantial historical use of ginseng species, in vitro, animal, and two previous pilot trials in cancer survivors provide other reports relevant to the current study. This study clearly lends support to the use of American ginseng to address cancer-related fatigue, especially in light of a lack of conventional pharmacologic agents to address this common situation.

Barton D, Liu H, Dakhil S, et al. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: A randomized, double-blind trial, N07C2. *J Natl Cancer Inst.* 2013;105:1230–1238.

Curcumin for Radiation Dermatitis in Breast Cancer Patients

This small randomized, double-blind, placebo-controlled clinical trial was conducted in 30 breast cancer patients to assess curcumin's ability to reduce the severity of radiation dermatitis. Women with noninflammatory breast cancer or carcinoma in situ and receiving radiotherapy were randomized to receive either 2.0 grams 3 times per day of curcumin or placebo during their course of radiation treatments. The Radiation Dermatitis Severity (RDS) score was assessed weekly, along with the presence of moist desquamation, redness, and results from the McGill Pain Questionnaire-Short Form and Symptom Inventory questionnaire. The average age of the women was 58.1, and 90% were Caucasian.

Curcumin reduced RDS at the end of radiation therapy compared with placebo. The mean RDS scores for curcumin patients were 0.8 lower than the placebo-treated

patients; that is, 2.6 vs. 3.4. There were also fewer curcumin-treated patients with moist desquamation (28.6% vs. 87.5%). There were no significant differences in pain scores in total sensory pain or intensity of pain at the treatment site, and oral curcumin did not reduce erythema. Curcumin was not effective at reducing the severity of radiation dermatitis in those women who had a total mastectomy prior to radiotherapy.

Comment: Radiation dermatitis is one of the most common side effects that patients acquire from radiotherapy. It occurs in approximately 95% of women receiving radiotherapy for breast cancer, and 10% of those are severe cases. Current conventional treatments include washing with lukewarm water and mild soap, and applying unscented lanolin-free, water-based moisturizers, hyalauronate cream, and possibly topical corticosteroids. Practitioners of natural medicine have been using many options, including topical aloe preparations, topical vitamin E, and topical calendula lotion. Calendula lotion in particular has one French study demonstrating efficacy.

Oral curcumin has low bioavailability and, according to at least one publication, an oral dose less than 4.0 grams is not detectable in the blood. In the current study, patients had to take 12 capsules per day to achieve the 6.0 grams per day. There are at least three technologies that enhance the bioavailability and thus would then require a much lower number of capsules. These are: lecithin bound to curcumin, a "phytosome" process (e.g., Meriva), curcuminoids/turmeric essential oil/lecithin (e.g., BCM-95), and a curcumin nanoparticular colloidal dispersion (e.g., Theracurmin).

Ryan J, Heckler C, Ling M, et al. Curcumin for radiation dermatitis: A randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. *Radiat Res.* 2013;180:34–43.

Pelvic Ultrasound Monitoring to Help Avoid Surgery in Pelvic Masses

Transvaginal ultrasounds have a central role in evaluating adnexal masses. The problem is the high number of false positives and a high number of surgeries. To evaluate the results of serial transvaginal ultrasounds, data were analyzed from 39,000 asymptomatic women whose average age was 56. After one abnormal screening sonogram, repeat images were scheduled at intervals from 6 weeks to 6 months. If the mass increased significantly in volume, the characteristics of the mass progressed, or the onset of pain occurred, women underwent surgery. The abnormal ultrasound data revealed that 12% had simple unilocular cysts, 10% had cysts with septations, 7% had cysts with solid areas, and 2% had mostly solid masses. Cysts with solid areas and solid masses are considered high risk for malignancy, whereas simple cysts and cysts with septations are considered low risk. Within the first year of follow-up, 38% of the low-risk masses and 79% of the high-risk masses had resolved. In total, 85 true positive malignancies, and 472 benign findings were recorded. Over the 25-year study period, 557 women eventually had pelvic surgery and 15% had malignancies. This study illustrates that in asymptomatic women, even those women with ovarian masses with complex features, the majority resolve. Serial ultrasounds in some cases should be done sooner (every 6 weeks) and in others, every 3 months or 6 months. An experienced gynecologist can best make these recommendations. Complex masses that increase in size or complexity should indeed be removed, but simple unilocular cysts and even cysts with septations have a high degree of resolution on their own. Even masses thought to be higher risk can have a high rate of resolution. It can be a difficult decision as to have surgery or not, but 2 if not 3 to 4 serial transvaginal ultrasounds can facilitate a clearer decision.

Pavlik E et al. Frequency and disposition of ovarian abnormalities followed with serial transvaginal ultrasonography. *Obstet Gynecol.* 2013 Aug;122:210.

Herzog T. Enhancing the needle count in the haystack: Serial ultrasonography for low-to moderate risk adnexal masses. *Obstet Gynecol.* 2013 Aug;122:198.

Dr. Tori Hudson graduated from the National College of Naturopathic Medicine (NCNM) in 1984 and has served the college in many capacities over the last 28 years. She is currently a clinical professor at NCNM and Bastyr University; has been in practice for over 28 years; and is the medical director of the clinic A Woman's Time in Portland, Oregon, and director of research and development for Vitanica, a supplement company for women. She is also a nationally recognized author, speaker, educator, researcher, and clinician. ◆

Calendar

Please submit an announcement of your event 90 days in advance. Event publication must be limited to 25 words or less. Multiple event listings require paid advertising.

JANUARY 10-12: BIORESONANCE ANALYSIS OF HEALTH with Thomas K. Szulc, MD in Portland, Oregon. 24 CME Category I Credits Available. CONTACT: Innovative Medicine, LLC, 800-605-1798;info@innovativemedicine.com; http://innovativemedicine.com/bioresonance-analysis-of-health/bahcourse/#.UcpPx_lwqSo

JANUARY 10-12: BASTYR UNIVERSITY presents AROMATHERAPY & ESSENTIAL OILS – Foundations in Kenmore, Washington (near Seattle). Also, **APRIL 11-13**. CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

JANUARY 11-12: KLINGHARDT ACADEMY presents AUTONOMIC RESPONSE TESTING (Level 2) in Kenmore, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

JANUARY 18-19: NEW KLINGHARDT PROTOCOLS in Warren, New Jersey. Open to non-ART practitioners. Also, **OCTOBER 11-12** in Kenmore, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

JANUARY 23-FEBRUARY 7: INTENSIVE HOMEOPATHIC CLINICAL TRAINING in India CONTACT: http://www.homoeopathy-course.com/index.php/training-courses/india-homoeopathy-training

JANUARY 24-26: 3RD ANNUAL INTEGRATIVE ONCOLOGY CONFERENCE & EXPO – IV Therapies in Costa Mesa, California. Sponsored by Park Compounding and Southwest College of Naturopathic Medicine. CONTACT: http://www.ivtherapies2014.com

JANUARY 29-FEBRUARY 1: SCRIPPS CENTER FOR INTEGRATIVE MEDICINE presents 11th ANNUAL NATURAL SUPPLEMENTS: An Evidence-Based Update in San Diego, California. CONTACT: 858-652-5400; med.edu@scrippshealth.org; http://www.scripps.org/NaturalSupplements

JANUARY 31-FEBRUARY 2: IMMUNE ADVANCED PRACTICE MODULE-The Many Faces Of Immune Dysregulation And Chronic Inflammation: Chronic Infections, Atopy, And Autoimmune Disorders in Phoenix, Arizona. CONTACT: https://www.functionalmedicine.org/Immune

FEBRUARY 15-16: BASTYR UNIVERSITY presents FACIAL DIAGNOSIS: New Tools for Clinical Practice in Kenmore, Washington (near Seattle). CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

FEBRUARY 22-23: BASTYR UNIVERSITY presents THE ART & PRACTICE OF NARRATIVE MEDICINE in Kenmore, Washington (near Seattle). CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

FEBRUARY 28-MARCH 1: FORDHAM PAGE NUTRITION STUDY CLUB – Hormones & Supplements That Can Change Your Life with Jorge Flechas, MD @ Crowne Plaza Dulles Airport in Washington DC. CONTACT: 800-832-9901

MARCH 6-8: ANNIE APPLESEED PROJECT presents its 8th EVIDENCE-BASED COMPLEMENTARY & ALTERNATIVE CANCER THERAPIES CONFERENCE in West Palm Beach, Florida. CONTACT: 561-749-0084; http://www.tinyurl.com/ny63uur

MARCH 7-9: KLINGHARDT ACADEMY presents AUTONOMIC RESPONSE TESTING (Level 3) in New York City, New York. Refresher course (Levels 1 & 2) on **MARCH 6**. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

MARCH 7-9: AIH-SHMA-NYMC SEMINAR – PREDICTIVE HOMEOPATHY: Case Taking, Follow-Ups, Theory of Suppression in New Orleans, Louisiana. AMA PRA Category 1 credits. CONTACT: 888-445-9988; http://www.homeopathyusa.org

MARCH 13-16: PHYSICIAN'S ROUND TABLE – Accentuating the HEAL in Health in Tampa, Florida. The best in exhibitors, 24 expert speakers. CMEs. CONTACT: Sue Vogan, 717-254-1953; peerobmagazine@aol.com

MARCH 13-16: 3RD LATIN AMERICA CONGRESS ON CONTROVERSIES TO CONSENSUS IN DIABETES, OBESITY, & HYPERTENSION in Panama City, Panama. CONTACT: codhyLA@codhy.com; http://codhy.com/LA/

MARCH 15-16: BASTYR UNIVERSITY presents AYURVEDIC PULSE ASSESSMENT: INTERNAL ORGAN PULSE & METHODS OF HEALING WEAK ORGANS in Kenmore, Washington (near Seattle). CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education ➤

Classified Advertising

FOR SALE

JOINT PAINS Try ARTH-HIT; Heart Problems.Try CARDIACT; Liver Issues Try LVR- NORM; Menopause Victims Try MENOPAUSEX. ALL Natural, No Preservatives, No Side Effects. $$ Back Guarantee. 775-337-2987, herborigins.com

EMPLOYMENT OPPORTUNITIES

YORK, PA SEEKS INTEGRATIVE MD, contact willa@sonnewald.org

SEEKING MD/DO OR FNP w/experience in Classical Homeopathy &/or Integrative Medicine to join reputable practice in Albuquerque NM. Inquiries or resumes to drweissadmin@gmail.com

UNIQUE OPPORTUNITY FOR AN M.D. OR D.O. to join well established practice in stunning Sedona Arizona. If interested e-mail narizona11@gmail.com

HELIOS INTEGRATED MEDICINE OF BOULDER, CO would like an Integrative Pain Specialist and/or an Orthopedist to join well established practice. Located in health oriented community receptive to traditional and alternative medicine. Lease term to facilitate & support needs of practice growth. Please visit: Heliosintegratedmedicine.com. Send CV to Tia: contact@heliosintegratedmedicine.com

SEMINAR

WISDOM DAY 2014, Washington DC; seminar before Psychotherapy Networker Symposium 2014; 03/19/2013; www.DCNN.pro

Please Support the Advertisers in this Issue

Calendar

➤

MARCH 19: WISDOM DAY 2014 SEMINAR in Washington DC. How to help people have stronger physical bodies so that the mind has a firmer foundation. Precedes 4-day Psychotherapy Networker Symposium 2014. CONTACT: http://www.dcnn.pro/WisdomDay2014.en.html

MARCH 28-30: CARDIOMETABOLIC ADVANCED PRACTICE MODULE-Transforming the Assessment, Prevention, and Management of Chronic Metabolic And Cardiovascular Disorders in Boston, Massachusetts. CONTACT: https://www.functionalmedicine.org/Cardiometabolic

APRIL 4-6: 9TH ANNUAL JOINT AMERICAN HOMEOPATHIC CONFERENCE in Long Beach, California. Presented by the National Center for Homeopathy. CONTACT: http://www.homeopathycenter.org

APRIL 5-6: KLINGHARDT ACADEMY presents AUTONOMIC RESPONSE TESTING (Level 1) in Jenkintown, Pennsylvania. Also, **APRIL 12-13** in Kenmore, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

APRIL 10-12: 37TH ANNUAL HOLISTIC DENTAL ASSOCIATION SYMPOSIUM – Healing Through Dentistry in Dallas, Texas. CE credits. CONTACT: 305-356-7338; director@holisticdental.org

APRIL 11-12: BASTYR UNIVERSITY presents TREATING EATING DISORDERS-CONCEPTS & APPLICATIONS in Kenmore, Washington (near Seattle). CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

APRIL 26-27: BASTYR UNIVERSITY presents TREATING TRAUMA WITH CHINESE MEDIICNE: UNTYING THE KNOT in Kenmore, Washington (near Seattle). CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

APRIL 28-29: INTERNATIONAL VITAMIN D CONFERENCE – Vitamin D, Sun and Human Health in Oslo, Norway. CONTACT: http://oslo2014.d-vit.eu/

MAY 2-4: BIOLOGICAL MEDICINE 2014 LYME CONFERENCE in Bellevue, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

MAY 10-11: BASTYR UNIVERSITY presents AURICULOTHERAPY ADVANCES IN PAIN & ADDICTION TREATMENTS in Kenmore, Washington (near Seattle). Also, **JUNE 6-7**. CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

MAY 28-30: METABOLISM, DIET AND DISEASE 2014: Cancer and Metabolism in Washington, D.C. CONTACT: http://www.metabolism-diet-and-disease.com

MAY 29-31: THE INSTITUTE FOR FUNCTIONAL MEDICINE ANNUAL INTERNATIONAL CONFERENCE-Applying Clinical Nutrition Through The Functional Medicine Lens in San Francisco, California. CONTACT: https://www.functionalmedicine.org/AFMCP

Douglas Laboratories to Distribute Sedona Labs Pro Line of Products

Douglas Laboratories is proud to announce the addition of Sedona Labs Pro formulas to its existing line of nutritional supplements and will now distribute well-respected, clinically researched iFlora Multi-Probiotic and Colostrum products exclusively to healthcare professionals.

The formulas include: Sedona Pro™ iFlora Multi-Probiotic, iFlora Multi-Probiotic Powder, iFlora Multi-Probiotic YC-7, iFlora Multi-Probiotic KIDS, SinuPro 6, and Sedona Pro Colostrum in both powder and vegetarian capsule form.†

For further information on the Douglas Laboratories Sedona Pro formulas available to health-care professionals, please visit douglaslabs.com.

† These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure, or prevent any disease.

MAY 30-JUNE 1: KLINGHARDT ACADEMY presents AUTONOMIC RESPONSE TESTING (Level 2) in Horsham, Pennsylvania. Also, **AUGUST 23-24** in Kenmore, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

JUNE 7-8: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION SPRING CONFERENCE in Tempe, Arizona. CONTACT: 480-921-3088; http://www.AzNMA.org

JUNE 7-8: BASTYR UNIVERSITY presents ESOTERIC ACUPUNCTURE in Kenmore, Washington (near Seattle). CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

JUNE 27-29: KLINGHARDT ACADEMY presents INJECTION TECHNIQUES & SKILLS 2014 – Neural Therapy in Bellevue, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

JULY 11-13: HORMONE ADVANCED PRACTICE MODULE-Re-establishing Hormonal Balance in The Hypothalamic, Pituitary, Adrenal, Thyroid, and Gonadal Axis in Denver, Colorado. CONTACT: https://www.functionalmedicine.org/Hormone

JULY 11-13: DETOX ADVANCED PRACTICE MODULE-Understanding Biotransformation And Recognizing Toxicity: Evaluation And Treatment In The Functional Medicine Model in Denver, Colorado. CONTACT: https://www.functionalmedicine.org/Detox

SEPTEMBER 8-12: APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE-A Five-Day Foundational Course in Functional Medicine in Scottsdale, Arizona. CONTACT: https://www.functionalmedicine.org/AFMCP

SEPTEMBER 15-17: PREVENTING OVERDIAGNOSIS @ Oxford University in Oxford, United Kingdom. CONTACT: http://www.preventingoverdiagnosis.net

SEPTEMBER 22-27: KLINGHARDT ACADEMY WHIDBEY ISLAND RETREAT in Clinton, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

NOVEMBER 6-9: ENERGY REGULATION ADVANCED PRACTICE MODULE in Miami, Florida. CONTACT: https://www.functionalmedicine.org/Energy

NOVEMBER 6-9: GI ADVANCED PRACTICE MODULE-Restoring Gastrointestinal Equilibrium: Practical Applications for Understanding, Assessing, and Treating Gut Dysfunction in Miami, Florida. CONTACT: https://www.functionalmedicine.org/GI

NOVEMBER 8-9: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION FALL CONFERENCE in Tempe, Arizona. CONTACT: 480-921-3088; http://www.AzNMA.org

DECEMBER 5-7: KLINGHARDT ACADEMY presents APPLIED PSYCHONEUROBIOLOGY in Redmond, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; http://www.klinghardtacademy.com

◆

MarketPlace

2014 Editorial Calendar

February/March 2014, #367/368: WOMEN'S HEALTH. DIET & WEIGHT MANAGEMENT: Hormone replacement therapy. Breast health. Anti-aging strategies for women. Hypothyroidism. Endometriosis and Uterine Disorders. Osteoporosis. Depression and anxiety disorders. Managing weight loss.

April 2014, #369: METABOLIC SYNDROME/DIABETES. LIVER DISEASE. DETOXIFICATION: Hypertension, hypertriglyceridemia, abdominal weight gain. Nutritional support for diabetes. Hepatitis C. Liver fibrosis. Alcoholism and drug addiction. Detoxification strategies. Managing drug treatments and botanicals.

May 2014, #370: CARDIOVASCULAR HEALTH. SEASONAL ALLERGIES: Coronary artery disease, stroke and cerebral atherosclerosis. Hypertension, hypercholesterolemia, and inflammation. Atrial fibrillation and cardiac arrhythmias. Nutritional and homeopathic treatment for seasonal allergies.

June 2014, #371: INFLAMMATION. AUTOIMMUNE DISEASE. G.I. DISORDERS: Inflammation versus infection. Immune system abnormalities. Role of Nutrition and Epigenetics in inflammation. Probiotics. Lupus, Rheumatoid Arthritis, and Inflammatory Bowel Disease. Role of Inflammation in Chronic Infection.

July 2014, #372: LYME DISEASE. INFECTION. SKIN DISORDERS: Lyme disease and co-infections. Diagnosis of Lyme Disease: Borrelia, Babesia, and Bartonella. Bio-film and infection. Alternatives to antibiotics and use of probiotics. Antibiotic resistant infection. Dermatitis and chronic skin disorders.

August/September 2014, #373/374: CANCER: TREATMENT AND PREVENTION: Integrating nutritional treatments with chemotherapy, radiation, and biologic treatments. Cancer protocols. Treating and preventing side effects of cancer treatment. Strategies for cancer prevention.

October 2014, #375: BRAIN HEALTH. DEMENTIA/ALZHEIMERS. AUTISM. ADHD: Nutritional approaches to maintaining cognitive functioning and preventing neuro-degenerative disorders. Alzheimer's and Parkinson's syndrome. Autistic disorders. Attention deficit disorders. Insomnia.

November 2014, #376: FIBROMYALGIA. CHRONIC FATIGUE. PAIN MANAGEMENT: Multiple chemical sensitivity disorder. Coping with Environment Allergy Avoidance. Candida disorder. Pain management beyond drugs. Adrenal deficiency. Depression versus pain disorder.

December 2014, #377: ARTHRITIS. PNEUMONIA/FLU. EYE DISEASE. Osteoarthritis and rheumatoid arthritis. Inflammation. Respiratory infection/ flu. Antibiotic treatment for arthritis. Non-antibiotic treatment for infection. Macular degeneration. Cataract prevention.

January 2015, #378: LABORATORY TESTING. Salivary, Urine and Blood Testing. Toxic element evaluation. Food allergy testing. Energetic and Electro-acupuncture testing. Dark field microscopy. Metabolic and genomic testing.

Things Go Better with Coke

New York City Mayor Michael Bloomberg and others have been unfairly critical of soft drinks, which can have enormous health value under certain circumstances. For example, a beneficial effect of Coca-Cola was recently demonstrated in a study published in *Alimentary Pharmacology and Therapeutics*.

A bezoar is a hard mass that gets stuck in the gastrointestinal tract, usually the stomach. Approximately 1 in 250 people develops a bezoar at some time in his life. The most common type of bezoar is a phytobezoar, which consists of the fibrous portion of fruits and vegetables. Conservative treatment of phytobezoars includes proteolytic enzymes, cellulase (an enzyme that digests cellulose), and fragmenting the mass by endoscopy. If conservative treatment is unsuccessful, or if the phytobezoar causes intestinal obstruction, surgical removal by laparotomy or laparoscopy may be necessary. Impaired gastric motility secondary to diabetes resulting from gastric surgery is a risk factor for the development of phytobezoars.

In 2002, a report was published demonstrating the efficacy of Coca-Cola in dissolving gastric phytobezoars. Since then, more than 20 other reports regarding this treatment have been published. Investigators therefore conducted a systematic review of these studies to determine whether Coca-Cola was indeed effective. The review included 24 papers, with a total of 46 patients.[1] The daily amount of Coca-Cola administered ranged from 500 ml to 3000 ml, and the duration of treatment ranged from 24 hours to 6 weeks. In 50% of the patients the phytobezoars dissolved with Coca-Cola treatment alone, and in an additional 41% the combination of Coca-Cola and endoscopic procedures was successful. Only 4 patients (8.7%) required surgery because of intestinal obstruction. No serious adverse events were reported, but it was not stated whether any of the patients consuming 3 liters of Coca-Cola per day developed anxiety, insomnia, hypertriglyceridemia, or fatty liver disease. No follow-up information was provided regarding recurrences of phytobezoars, although it is assumed that some of the patients became addicted to Coca-Cola and therefore engaged in long-term phytobezoar prophylaxis.

The mechanism of action of Coca-Cola in dissolving phytobezoars is not certain, but it is believed to be related to its strong acidity (pH 2.6) and possibly to an enhancement of the dissolving mechanism by the carbon dioxide bubbles. Considering its low cost and relative safety (it is safer and less expensive than battery acid, for example), Coca-Cola should be considered first-line therapy for gastric phytobezoars. Also, because people with phytobezoars can return to normal gastrointestinal function after drinking Coca-Cola, there is unquestionable truth in the old adage "Things go better with Coke."

Another health benefit of Coca-Cola is its capacity to enhance cognitive function. Specifically, I have observed that many children develop a newfound interest in chemistry and physics after watching the miracle of a bottle of Coca-Cola mixed with Mentos candies taking off like a rocket. Claims that soft drinks are associated with impaired cognitive function are based entirely on observational data (which cannot prove causality), and anyone who would rely on such flawed evidence truly deserves the label "*non compos* Mentos."

There are many other beneficial effects of Coca-Cola that are largely ignored by Bloomberg and his ilk. For example, it is remarkably effective for removing grease spots and blood stains from clothing and fabric. In addition, it can be used to loosen rusty bolts: just pour some Coke on and wait a short while. Anecdotal evidence suggests that it can neutralize a jellyfish sting, although that treatment has not been subjected to randomized controlled trials. Another use for Coca-Cola is to remove chewing gum stuck in your hair. Just dip your hair in a small bowl of the soft drink, leave it there for a few minutes, and then gently wipe off the gum. Coke can also be a worthwhile addition to summer picnics. Pour a small amount in a cup and set it out an hour before the picnic, away from your site; it will attract wasps and bees so that they stay away from you and your food. Finally, this versatile liquid can be used to mop floors to make them sticky. Coke-mopping is commonly employed in the movie industry to prevent actors from slipping, and thereby breaking a leg, as it were.

One might presume that Pepsi and other cola beverages would have similar benefits, although it is possible that the effectiveness of Coke is due to that special secret ingredient.

Alan R. Gaby, MD

Notes

1. Ladas SD. Systematic review: Coca-Cola can effectively dissolve gastric phytobezoars as a first-line treatment. *Aliment Pharmacol Ther.* 2013;37:169–173.

◆

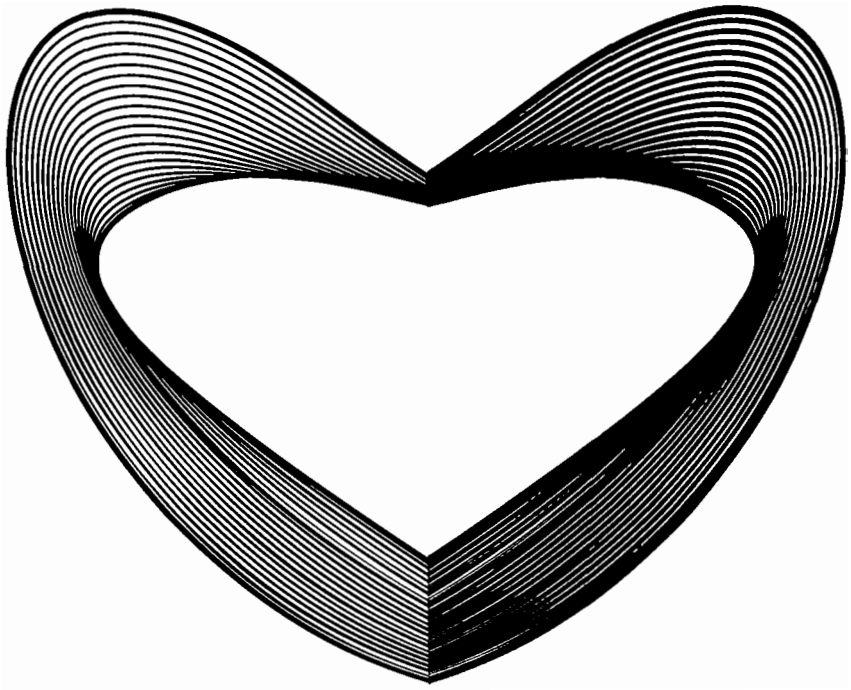
pure encapsulations®

— Your Trusted Source —

The PureHeart™ Protocol

Screening + Supplements = Success™

The PureHeart™ Protocol brings together innovative screening and innovative supplements that go ***beyond lipids***. Half of all individuals faced with a cardiovascular event had normal values on their standard lipid panel. While routine lipid screening plays an important role in cardiovascular assessment, it doesn't provide the full picture.



Her Heart. His Heart.
Your Heart. PureHeart™.

YouTube

NSF GMP Registered

*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.

800-753-2277 | PureEncapsulations.com

The information contained herein is for informational purposes only and does not establish a doctor-patient relationship. Please be sure to consult your physician before taking this or any other product. Consult your physician for any health problems.

TRUST. IN NUTRITIONAL HEALTH.

SEDONA PRO™ SUITE

Specialized Colostrum & iFlora® Formulas

Douglas Laboratories is proud to announce the addition of the Sedona Pro™ Suite to our existing line of nutritional supplements.

Sedona Labs Pro® supplements have been the healthcare professionals' source for premium probiotics and New Zealand colostrum for more than 20 years. These innovative, clinically-supported products have been formulated for use in integrative practices to meet the natural health needs of patients.

Multiple formulas offered to meet the exact needs of your patients.
1.800.245.4440 | douglaslabs.com

ConsumerLab.com 2013 Survey -
Douglas Laboratories® awarded the#1 Rated Healthcare Practitioner Brand Based on Consumer Satisfaction

†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.

DOUGLAS LABORATORIES®

You Trust Douglas Laboratories®. Your Patients Trust You.