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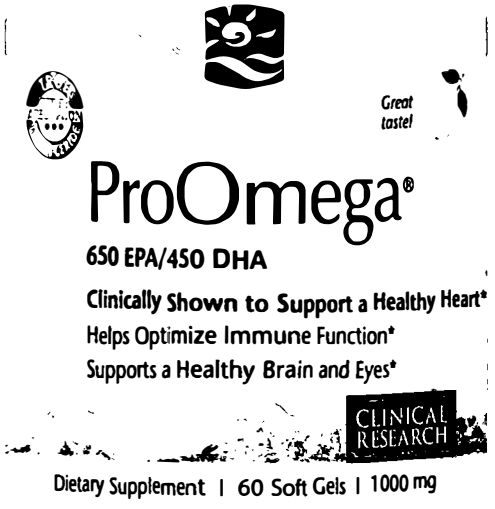

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NORDIC® NATURALS

Source: *Lipids in Health and Disease*, 2014

Think of Your Most *Chronically* ILL Patients

...We Challenge You To Try This Test!

15 minute Lactic Acid Reduction - How To Perform The Test in Your Clinic:

The product for performing these tests is called pHenomenal (www.phenomenalwater.com) It is made using heat, magnetism and a small amount of alkaline buffers (inert calcium that is not reported on the label because it is under the legal reporting limits). With this process the inventors have created a stabilized concentrate by removing a high percentage of the hydrogen - the acid part of water. This concentrate is an incredible 12.75 pH and yet is entirely non-caustic which is unprecedented in any other form of mineralized concentrate.

NOTE: It is very important to use patients with significantly elevated lactic acid levels before doing this test or the test will only have marginal results. It is best to choose a severe diabetic, a patient with significant and ongoing weight problems, or a patient that has an infection with a lactic acid bacterium (Staph or Strep) and is not currently on antibiotics.

Assuming you have a patient with elevated lactic acid, simply draw a vile of blood to perform a lactic acid blood test from your preferred lab. Then give the patient 32 ounces of mineral-free or steam-distilled water to drink that has 1 ounce to 1 ½ ounces of pHenomenal mixed into it.

Have them consume the mixed pHenomenal in as short an amount of time as they can comfortably drink it. Between 10 to 15 minutes from the time they finished the mixed water draw a second vile of blood for another lactic acid blood test.

In almost all cases you will find a significant drop in blood lactic acid from the first test to the second and this is further confirmed by how the patient will report "feeling". Generally pain will go down dramatically and increased energy and the symptoms of lactic acidosis (or sepsis) which was mentioned earlier will dramatically reduce.

What's happening? Since the pH scale is logarithmic the advantage of drinking mixed pHenomenal, 32 ounces at a mixed ratio of one ounce of concentrate to 31 ounces of mineral-free or steam-distilled drinking water, yields approximately one liter (946 milliliters) at a remarkable 11pH. The cost to the patient is approximately $1.20.

Compared to a 500 milliliter bicarbonate drip at an 8.5 pH, the mixed pHenomenal taken orally is approximately 867 times more alkaline or **867 times stronger neutralizing acidity in the body.**

Some of this alkalinity may be neutralized in the stomach, but with the overwhelming power of this product the neutralizing action that occurs in the stomach has proven to be insignificant.

Because pHenomenal is a "Hydroxide" meaning an unstable water molecule that is no longer H2O but has been modified to H1O (or properly "OH") when it finds a free hydrogen it simply binds the hydrogen to the empty valance and becomes H2O or water again. You can further research this on http://www.naturalpartners.com

The results produced by drinking pHenomenal as outlined above cannot be duplicated by using water produced from "Alkaline Water Machines". Perform a comparison test if you wish to confirm this statement.

Have QUESTIONS or want LAB SPECS?

Visit www.PHENOMENALWATER.com or CALL 1-(800) 620-3365

phenomenal

Lab Certified To Reduce Lactic and Uric Acid

LAB SPECS AVAILABLE AT PHENOMENALWATER.COM

It's very well-known in the medical community that...

"Acidity is the cause or byproduct of most diseases in the body"

But it doesn't take a PhD in science to know that acid = disease. With a little research *anyone* can quickly learn how the buildup of acid can have ill effects on the human body and it's ability to heal.

Diabetics, people with ongoing weight problems, those with bacterial infections, and others with elevated lactic acid levels are prime candidates for using pHenomenal.

Why Is pHenomenal *Different* Than Alkaline Water Drops, Alkaline Water Machines, And Intravenous Bicarbonate Drip?

With a double-patented process, it is made using heat, magnetism, and a small amount of alkaline buffers. This procedure allows the creation of a stabilized concentrate by removing a high percentage of the hydrogen - the acid part of water. This concentrate is an incredible 12.75 pH and yet is entirely non-caustic which is unprecedented in any other form of mineralized concentrate.

Because pHenomenal is a "Hydroxide", meaning an unstable water molecule that is no longer H2O but has been modified to H1O (or properly OH), when it finds a free hydrogen - acidity in the human body - it simply binds the hydrogen to the empty valance and becomes H2O or water again.

Also, pHenomenal remains stable in that it will never lose its alkalinity until it is consumed and binds with acid. It's 100% naturally derived from pure water with only a little calcium added as a stabilizer.

It's safe and completely non-caustic.

SEE OTHER SIDE >>

ALKALINE WATER
CONCENTRATE

1 liter of Concentrate makes 8 Gallons of drinkable pHenomenal (about 32 servings)

> *"I have been drinking pHenomenal Water for over 4 years. I refer phenomenal Water to over 90% of my patients. My brother was in intensive care for over 4 mos. Two of those months he was in a septic coma with a life threatening bacterial infection. Within 24 hours after adding Phenomenal Water he came out of the coma. He is doing just fine today. His life was saved from his high acidity level. Whether it is a chronic or acute case of acidity. We ALL can use some balance!"*
>
> **Dr. Rebecca Rogers N.M.D. PhD**
> **Dothan, Alabama**

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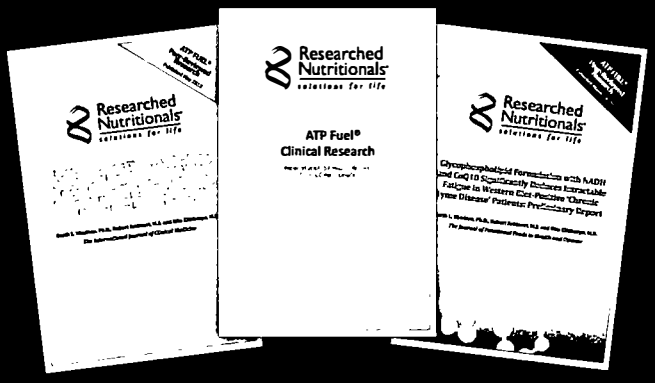
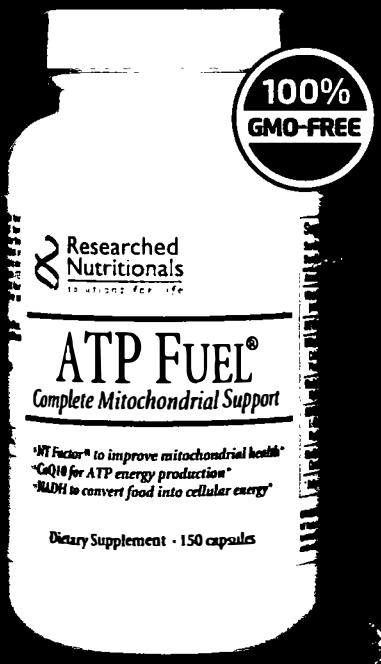
PEER-REVIEWED PUBLISHED RESEARCH





400 mg per soft gel

Your patients now have the option of high potency CoQ10 that is also GMO-free and Soy-free. Naturally fermented CoQ10 with all-natural ingredients--this is the only CoQ10 product that is GMO-free and Soy-free. Your patients deserve the best!

JOSEPH BURRASCANO JR., MD

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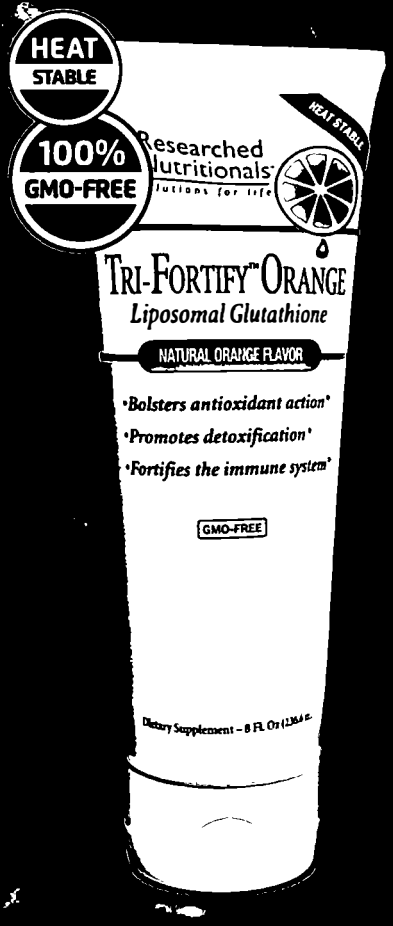


Oral Liposomal Glutathione GMO-free

Experience the only liposomal glutathione that you squeeze onto a teaspoon and enjoy. No need to mix in juice. Natural orange flavor & GMO-free

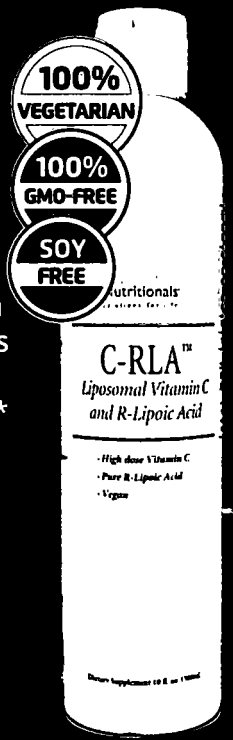
High Dose

Each serving offers:

- 450 mg of reduced glutathione
- 50 mg of Vitamin C

Heat Stable

We contracted with a third party lab to subject Tri-Fortify™ Orange to the most extreme conditions: 104˚F and 75% humidity for 90 consecutive days. ***The result:*** product met and exceeded the nutrient content on the label.



Liposomal 1,500 mg Vitamin C & R-Lipoic Acid

High Absorption, No Stomach Distress

Each serving contains 1500 mg of Vitamin C and 70 mg of R-Lipoic Acid in a natural, GMO-free liposomal preparation. As most oral Vitamin C doses above 250 mg are very poorly absorbed, the only efficacious high dose oral delivery system is via liposomes from natural phosphatidyl choline.* Many doctors 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.

Power-packed Antioxidant

High dose Vitamin C plus pure R-Lipoic Acid provides unparalleled antioxidant support.* R-Lipoic Acid, the "mitochondrial antioxidant", promotes healthy levels of oxidative stress & mitochondrial energy producing capability.*

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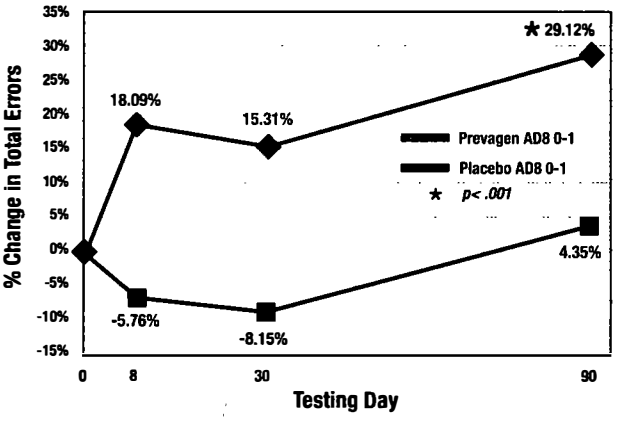
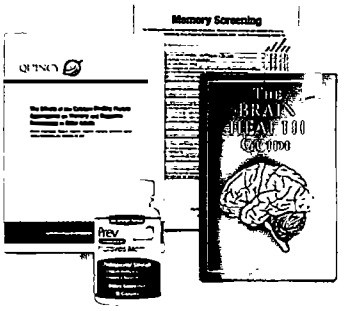
CLINICALLY SHOWN TO
IMPROVE MEMORY*

Shown Effective to Help Memory*



CALL TO GET A FREE PRODUCT KIT (888)-895-6463



"When people are experiencing the start of memory loss such as having difficulty remembering why they walked from one room to the next, **I suggest they take Prevagen®.**"

Henry Matick, M.D.
Matick Neurology Clinic

New Stronger Formula

Prev
Professional
(apoaequorin)
Improves Memory

Professional Strength
- Supports Healthy Brain Function*
- Supports a Sharper Mind*

Dietary Supplement
30 Capsules

Significant support for:

☑ *Mild Memory Problems Associated with Aging‡*

☑ *Word Recall‡* ☑ *Learning‡*

The Effects of Calcium-Binding Protein Apoaequorin in Memory ‡ and Cognitive Functioning in Older Adults. Quincy Bioscience, 2011

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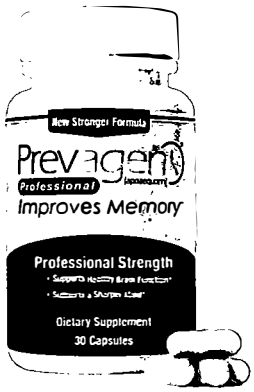

Prevagen® Professional (apoaequorin)

40mg apoaequorin per capsule
30 vegetarian capsules per bottle

PRODUCT BENEFITS

Supports:
Improved Memory*
Word recall*
Learning*

INDICATION

Prevagen Professional is for patients concerned with memory problems associated with normal aging and for patients who wish to support healthy brain function.*

PRODUCT DISCUSSION

Prevagen Professional is a first-in-class memory supplement which contains apoaequorin, a protein originally discovered in jellyfish, and shown to support neuronal calcium balance.

In a published, double-blind, placebo-controlled study, Prevagen improved memory, word recall and learning as early as 30 days. Prevagen Professional is exclusive to the healthcare practitioner market.

HOW SUPPLIED

Each Prevagen Professional vegetarian capsule contains 40mg of Apoaequorin.

QUINCY BIOSCIENCE

EVIDENCE

The positive effects of Prevagen on cognition were demonstrated in a published double-blind, placebo-controlled trial. 218 old adults with memory concerns were assessed over a 90 day period using a computer based cognitive testing protocol developed by Cogstate Ltd.

Overall, participants in the Prevagen arm saw a significant positive change over the three month study period in the following cognitive functions:

- ✓ ***Verbal Learning****
- ✓ ***Memory****
- ✓ ***Delayed Recall****
- ✓ ***Executive Function****

Additionally, the participants scoring 0-1 on the AD8 in the Prevagen arm experienced a statistically significant and robust reduction in total cognitive errors of 29% compared to baseline.*

SUGGESTED USE

Adults take 1 vegetarian capsule daily in the morning, with or without food, or as directed by a healthcare professional.

SAFETY

Prevagen Professional is a safe and well-tolerated supplement for better memory.* Prevagen has no known drug or supplement interactions. Prevagen is made without common allergens.

Supplement Facts
Serving Size: 1 capsule
Servings per container: 30

Amount per capsule		% Daily Value
Sodium	20 mg	<1%*
Apoaequorin	40 mg	†

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

Other ingredients: white rice flour, salt, magnesium stearate, acetic acid.
Manufactured & Distributed by Quincy Bioscience
301 S Westfield Road • Madison, WI 53717
Made without COMMON ALLERGENS
Suggested use: Take 1 vegetarian capsule daily in the morning, with or without food or as directed by your healthcare professional.

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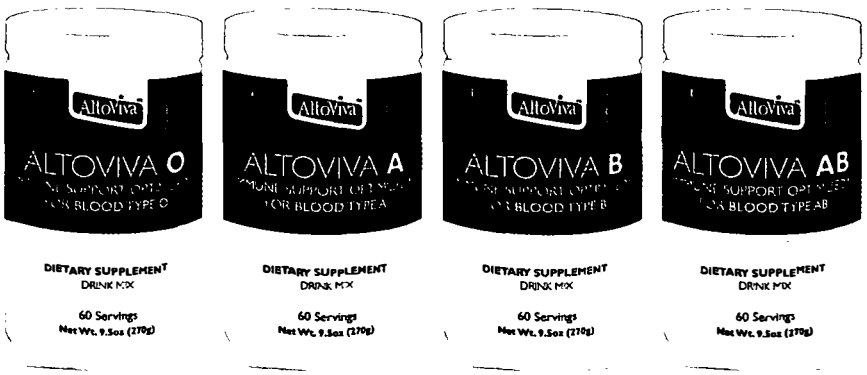
Discover Blood Type Formulation. **Find Clarity for the Most Perplexing Cases.** Each blood type responds to subtle but significant differences in nutritional balance. They even benefit from different probiotic strains. When immune health is your core objective, those differences become paramount. Blood type formulation can be the difference between achieving patient goals—or continuing the frustration. Isn't it time for some answers?* **When Life Feels Complicated, Supplementing Should be Simple!**



The All-in-One Reinvented: Probiotics & Prebiotics • Immune Health Botanicals Multi-Vitamin Blend • Enzymes & Amino Acids All ingredients optimized for each specific blood type.

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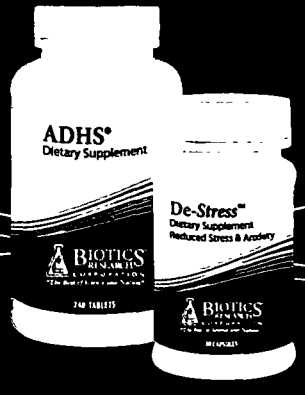
Feeling Holiday Stress?



The holiday season is a stressful time of year! Fortunately, there is **De-*Stress*™** from Biotics Research Corporation. **De-*Stress*™** supplies an all natural, bio-active decapeptide that has been proven safe and effective in reducing stress and anxiety!

Many factors affect the adrenal glands, especially stress. **ADHS®** from Biotics Research Corporation is an effective adaptogenic formulation designed to support normal, healthy cortisol levels and adrenal function.

Place your order for 6 De-*Stress*™ in the month of November and receive a FREE bottle of ADHS® (120T)!†

*Offer applies to healthcare professional customers of Biotics Research Corporation only.
† Products must be included in a single order. Offer expires on November 28, 2014.

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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.

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

broad-spectrum
(providing 29 strains of beneficial microorganisms)

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(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.

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NOURISH YOUR MITOCHONDRIA!*

AllergyResearchGroup®

Innovative Nutrition

NT Factor® EnergyLipids

Available as Powder and Chewable Tablets - Product #76710 & #76760)

- **Pure, food-based mitochondrial booster***
- **Supports cellular energy production***
- **Phosphoglycolipids in clinically validated ratios***
- **Supports healthy cell and mitochondrial membranes***
- **Available in Powder or convenient Chewable Tablets**
- **Chewables with Xylitol – no sugar, caffeine, ephedra**

Three more formulas that contain NT Factor® EnergyLipids, as well as friendly GI bacteria and prebiotic support*:

NT Factor® Advanced Physicians Formula - Product #76680

- With synergistic vitamins, minerals, α-ketoglutarate (AKG), L-carnitine, and L-tyrosine.*

NT Factor® Healthy Curb® - Product #76690

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- With enhanced cellular support from B vitamins, AKG, L-carnitine, and creatine pyruvate.*

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From the Publisher

The FDA Extends Its Oversight to Medical Laboratories

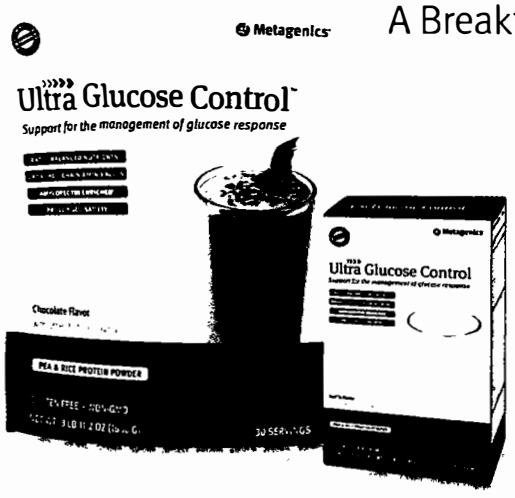
In July, the Food and Drug Administration announced its intention to regulate diagnostic laboratory testing. For many years, the FDA has limited its oversight to the largest commercial laboratories, neglecting to oversee the "in-house" diagnostic testing done by smaller laboratories and clinics. However, the agency has become aware that a growing number of smaller labs are developing and marketing specialized lab tests that assess "high risk" and "moderate to high risk" medical diseases. Given the possibility that these tests are inaccurate, based on flawed methodology, or lack adequate testing and medical evidence, the FDA wants them to be restricted or halted. The agency has become particularly concerned with laboratories marketing genomic testing directly to consumers advising their risk of developing disease. Without appropriate oversight, the FDA worries that incompetent and erroneous testing will reach the marketplace. The FDA also cites the example of a laboratory conducting putatively inaccurate testing for Lyme disease – such testing has led to possibly unnecessary physician and patient treatment. The

continued on page 8 ➤

Take Control

with Ultra Glucose Control™

A Breakthrough in Glucose Control Management



- RATIO-BALANCED NUTRIENTS
- BRANCHED-CHAIN AMINO ACIDS
- AMYLOPECTIN ENRICHED
- PROLONGED SATIETY

Take Control in Managing Glucose Response

Uncontrolled blood sugar affects approximately 160 million Americans.[1] Now you can help your patients take control with Ultra Glucose Control, the next generation of medical foods designed for patients who need additional support for blood sugar management.

This unique formula delivers a ratio-balanced combination of carbohydrates, protein, and fat (40-30-30) consistent with clinical centers.[2,3] Ultra Glucose Control also features MetaRelease™—a proprietary blend of slow-release, complex carbohydrates (UCAN SuperStarch™) and fiber—and a pea/rice protein blend enriched with branched-chain amino acids to support sustained energy release, satiation, and muscle-building capacity. Plus, it provides 22 essential vitamins and minerals to support overall health.

Help your patients take control of their health with Ultra Glucose Control.

1. Summarized from data published by ADA. Testing in Asymptomatic Patients. *Diabetes Care.* 2012;35 (Supplement 1):S14. Table 4.
2. Joslin Diabetes Center. Joslin Clinical Guidelines for Overweight and Obese Adults. 8/07/2011.
3. Hayes KC. Macronutrient ratios and insulin response for improved glucose control. Publication in process.

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Metagenics

Science-based Products + Lifestyle Medicine Programs + Breakthrough Research + Unsurpassed Quality + Practitioner Partnership = The Metagenics Difference

Letter from the Publisher

➤ continued from page 6

FDA aims to first scrutinize testing that assesses highest-risk disease. Once high-risk testing evaluation is completed, the FDA will study moderate-risk testing. Laboratories will be required to provide full documentation of testing methodology; in addition, the lab is expected to report testing "adverse events." A number of consumer groups and Congress members praised the FDA plan to oversee laboratory testing. However, pathologists from several medical schools criticized the plan, stating that restricting and regulating lab testing will likely stifle development.

Is there no end to the FDA's plan to disrupt integrative and naturopathic medicine? The FDA has long sought oversight and regulation over nutritional supplementation. In the past year, it has succeeded in gaining complete regulatory control over compounding pharmacies. Additionally, it is determining which drugs, chemicals, and biologics may be manufactured by compounding pharmacies; presumably those not permitted will be banned. Now the FDA intends to regulate and restrict lab testing. Many lab tests may be imperiled, including hair analysis, stool analysis, and metabolic testing. There is a clear-cut need to protest the increasing regulatory activity of the FDA. Perhaps there is a need to vote out of office our government representatives who approve this increasingly draconian FDA regulation.

Even Supplement Companies Attempt to Curry Special Favors from Governors

A supplement company seeking government approval gifted a governor and his wife with shopping sprees and vacation junkets. Former Virginia governor Robert McDonnell and his wife were indicted for "loans and gifts of money, clothes, golf fees and equipment, trips and private plane rides," estimated to be worth $165,000, from Jonnie Williams Sr., former CEO of Star Scientific.[1] The McDonnells are currently under trial for the aforementioned charges. McDonnell argues that his office was seeking "to promote the matter and cause of economic development for businesses and industries in Virginia."

Williams's Star Scientific has been facing the scrutiny of the FDA for its marketing of two supplement products: Anatabloc, touted for its "anti-inflammatory activity," and CigRx, for its "smoking cessation" use. In December 2013, the FDA sent Star Scientific a letter warning that these supplements were misbranded, claiming druglike activity.

Anatabloc contains anatabine, a natural nicotinelike chemical. Anatabine is derived from tobacco, and it has been used as a biologic lab marker for determining tobacco use during smoking cessation trials. It is found in nightshade plants, including potatoes, tomatoes, and eggplant. Some animal studies have found that anatabine can inhibit the production of inflammatory cytokines. In October 2012, there was a human experiment on anatabine's effect in

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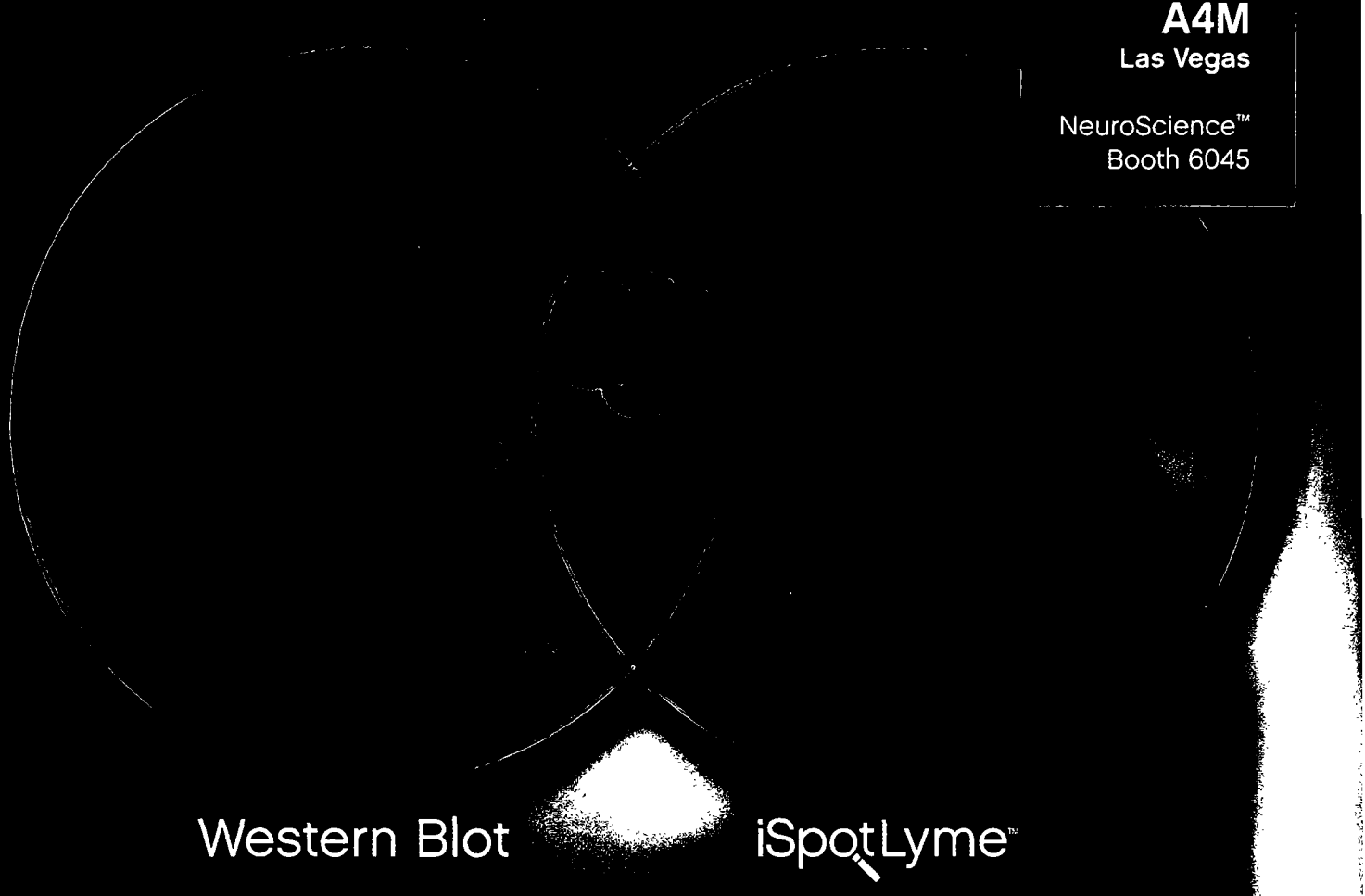
A4M
Las Vegas

NeuroScience™
Booth 6045



Get a clear picture of Lyme disease.

iSpot Lyme™ allows for better diagnosis, monitoring, and treatment when paired with Western Blot.

Western Blot can detect the presence of Lyme disease by testing for Lyme antibodies. But it's static: once a patient tests positive, she'll likely keep testing positive, even when the disease is controlled. iSpot Lyme can identify how active the disease is — and therefore how well your treatment is working — by measuring T cell response to Lyme antigens. iSpot Lyme also allows for earlier detection because the production of antibodies can take up to six weeks, while T cell response kicks in 4–6 days post infection. So for a clear picture, make sure to include iSpot Lyme.

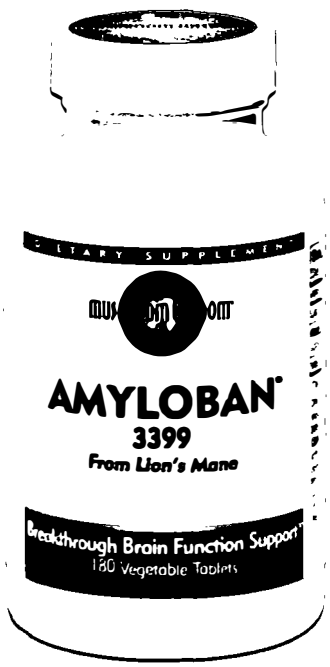
For improved patient care, add iSpot Lyme™.
Visit iSpotLyme.com for more details.

iSpotLyme™

Innovation from Pharmasan Labs™

A healthy brain is happiness!

There's never time to slow down. You can indeed "teach an old dog new tricks." Amyloban 3399® is a supplement your patients will love as their go-to healthy brain-support supplement.*



Amyloban 3399® contains unique, patented phytochemicals from the Lion's Mane mushroom — *hericenones and amyloban* — shown through research to support nerve cell health and healthy brain function.* Now you can help your patients enjoy being mentally fit, naturally. Amyloban 3399® from Mushroom Wisdom!

- **Manufactured in a cGMP facility in the U.S.**
- **Manufactured by the most trusted source in mushroom nutrition**
- **Practitioner Accounts Intro Discount - Code TN1014**

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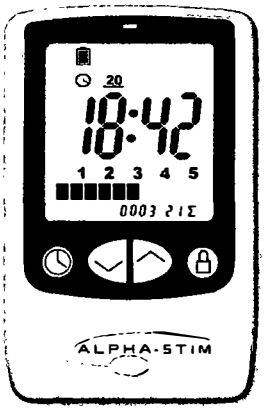

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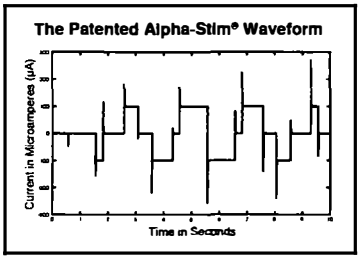

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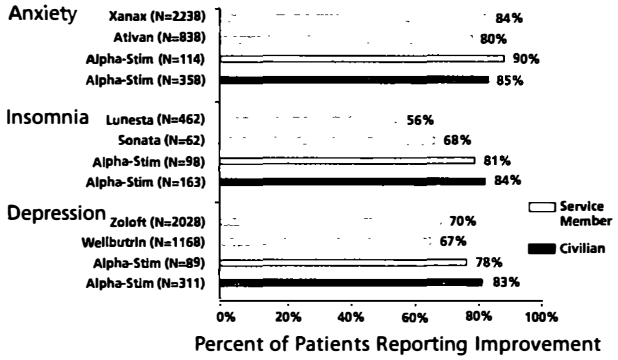

Patients who reported a positive response according to WebMD Drug Surveys, and Alpha-Stim Service Member and civilian surveys. Alpha-Stim Data from 2011 Military Service Member Survey (N=152) and Alpha-Stim Patient Survey (N=1,745). Conducted by Larry Price, PhD, Associate Dean of Research and Professor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

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Eupatorium Perfoliatum (Boneset)	*
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Supplement Facts Serving Size: 20 drops Servings Per Container: 120	
Amount Per Serving	**%Daily Value**
Cryptolepis Sanguinolenta	*
Lomatium Dissectum	*
Ceanothus Americanus (Red Root)	*
Juglans Nigra (Black Walnut hulls)	*
Stillengia Sylvatica	*

*Daily Value not established.

OTHER INGREDIENTS: Organic alcohol, distilled water, non-GMO sunflower phospholipids.

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Best of Naturopathic Medicine 2015

The *Townsend Letter* is pleased to announce our seventh Best of Naturopathic Medicine competition. Naturopathic students, faculty, researchers, and practitioners are invited to submit research papers, reviews, and articles. Selected papers will be published in our February/March 2015 issue. The author of the winning paper will be awarded $850. Runner-up papers will be published and authors will receive an honorarium.

Papers submitted should be 1500 to 3500 words and referenced. Author guidelines are available at the *Townsend Letter* website: www.townsendletter.com. Papers should be submitted digitally, preferably as a Microsoft Word document. Papers authored by multiple writers are acceptable; the lead author should be an ND graduate or candidate of an accredited four-year naturopathic school. Papers submitted for the competition may not be submitted to other publications or have previously been published. All entries must be submitted by November 20, 2014.

Send papers to editorial@townsendletter.com. The subject line should read: "Paper for Best of Naturopathic Medicine 2015."

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Letter from the Publisher

➤ continued from page 8

Hashimoto's thyroiditis; the results suggested a positive response in decreasing antithyroid antibodies. However, the results were very inconsistent. A Star Scientific news release reported that Johns Hopkins University was involved in conducting the anatabine studies. In fact, Hopkins did have a professor who commented on the Hashimoto's trial but was not involved in the experimentation.

The major problem for Star Scientific was that although anatabine has had limited studies, the company has marketed its products as food supplements despite making drug claims. The FDA demands that whenever a supplement claims to have drug activity, the supplement is subject to "new dietary ingredient premarket notification" as well as drug testing. The fact that Star Scientific filed for a patent for "improved method of synthesizing anatabine" did not improve its position with the FDA. Another problem for Star Scientific is that it was attempting to market its products under a two-tier system: one that would be for a food supplement and the other for a drug.

It is not clear what Williams was expecting from the Virginia governor. Presumably, he was looking for McDonnell to seek state authorization for further testing of anatabine. It shouldn't be surprising that a member of the supplement industry used cash to gain favors with a politician, but it is disappointing. Once again the FDA intends to wield its authority over supplement manufacturers who make claims – although "anti-inflammatory" activity seems quite reasonable. We should be prepared for further FDA warning letters to supplement manufacturers who make drug-related claims.

IV Therapies for Fibromyalgia and Chronic Fatigue

Paul Anderson, NMD, has directed the Bastyr University Clinic's IV clinic. Dr. Anderson has been lecturing about the use of nutrients administered intravenously for management of chronic illness. In this issue of the *Townsend Letter* he updates us on the use of injection therapies for chronic fatigue and fibromyalgia. Anderson's two decades of experience include the administering of 50,000 IV and IM injections as the basis for his report.

Anderson states that for many patients suffering from CFS and fibromyalgia, chronic dehydration underlies much of the symptomatology, including pain, myalgia, and brain fog. Although clinicians and patients make considerable effort to correct the dehydration through the use of oral minerals and electrolyte formulas, these efforts are frequently insufficient. The administration of IV fluids is generally very helpful. Anderson would argue that the solution should be isotonic or hypotonic to have the greatest benefit. Many patients arriving at the ER quite ill, treated with an IV solution, are benefited simply by receiving the infusion. Anderson would also argue that the addition of vitamin C and magnesium to the intravenous fluids would offer an even better outcome.

Anderson frequently uses IV ascorbic acid when treating the fibromyalgia patient. The ascorbic acid infusion need not be high dose; Anderson reports good outcomes using 5 to 15 grams of vitamin C. Similarly, Anderson writes that magnesium, as magnesium sulfate, is an important support for muscular relaxation, calcium channel functioning, and CNS activation. Anderson states that magnesium therapy needs to be titrated from a lower dose to a higher dose as the patient tolerates.

Anderson further writes on the benefit of using methylated forms of vitamin B12 and folic acid in managing chronic fatigue and fibromyalgia. He reports data showing improvement using infused vitamin B12 and folic acid, especially in patients showing genomic abnormalities. Of note, most of these patients do not show vitamin B12 or folic acid deficiencies as found in typical testing for serum B12 and folic acid levels. Anderson's article provides a clinical basis to treat chronic fatigue and fibromyalgia patients with IV nutrient therapies.

Jonathan Collin, MD

Notes

1. Kroll D. The McDonnell scandal: what's the dope behind Star Scientific Supplement Products? *Forbes*. Jan. 31, 2014.

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Send papers to editorial@townsendletter.com. The subject line should read: "Paper for Best of Naturopathic Medicine 2015."

Can Vitamin C Cure Ebola?

commentary by Steve Hickey, PhD; Hilary Roberts, PhD; and Damien Downing, MBBS, MSB

If there were a drug that worked on Ebola, you should use it. There isn't. There is only vitamin C. But you must be extremely careful what you believe, because, as it ever was, the Internet is full of dangerous loonies. For coming up to a decade now, the Orthomolecular Medicine News Service has reported on nutritional therapies; we leave the medical politics to one side and work from the facts. Here are the facts about vitamin C and Ebola.

1. Taking a gram or so a day of vitamin C won't protect you against anything except acute scurvy; it doesn't matter whether the vitamin is liposomal, nanoparticles, or even gold-plated. Beware of websites, companies, and YouTube clips making wild and unsubstantiated claims about the efficacy of vitamin C.
2. Clinical reports suggest that taking vitamin C almost to bowel tolerance every day (in divided doses) will help to protect you against all viruses. Reports by independent physicians have been consistent for decades. However, the doctors also stipulated most emphatically that the dose and the way you take it must be right – or it will not work. There is no direct, placebo-controlled "evidence" that massive doses of vitamin C will work on Ebola, and nobody would volunteer to take part in that study. But massive doses are reported to have helped against every virus that it has been pitched against. This includes polio, dengue, and AIDS, and it even makes vaccination work better. In the 1980s when no other treatment was available, it was reported that full-blown AIDS could be reversed and the patient brought back to reasonable health with vitamin C.[1,2]

At risk or worried about Ebola? This is what you should do.

Vitamin C

Vitamin C is the primary antioxidant in the diet. Most people do not take enough to be healthy. While this is true of many nutrients, vitamin C is a special case. Ignore governments telling you that you only need about 100 mg a day and can get this amount from food. The required amount of vitamin C varies depending on your state of health. A normal adult in perfect health may need only a small intake, say 500 mg per day, but more is needed when someone is even slightly under the weather. Similarly, to prevent illness, the intake needs to be increased.

The intake for an otherwise healthy person to have a reasonable chance of avoiding a common cold is in the region of 8 to 10 grams (8000–10,000 mg) a day. This is about 10 times what corporate medicine has tested in their trials on vitamin C and the common cold. Ten grams (10,000 mg) is the minimum pharmacological intake; it may help if you have a slight sore throat, but more (much more) may be needed. To get rid of a common cold, you may need anything from 20 to 60 grams (60,000 mg) a day. With influenza the need might be for 100 grams (100,000 mg) a day. Since it varies from person to person, and from illness to illness, the only way to find out is to experiment for yourself.

Dynamic Flow

The problem with oral intakes is that healthy people do not absorb vitamin C well due to what Dr. Robert Cathcart called bowel tolerance.[3] Take too much of the vitamin in a single dose and it will cause loose stools. In good health, a person might be able to take a couple of grams at a time without this problem. Strangely, when a person becomes sick, s/he can take far more without this side effect: as much as 20 to 100-plus grams a day, in divided doses.[4]

High dose vitamin C has a short half-life in the body. The half-life is the time for the level in the blood plasma to fall back to half its concentration. Until recently, some people claimed that the half-life of vitamin C was several weeks. We have shown that this long half-life applies only to very low doses.[5] By contrast, the half-life for high blood levels is only half an hour. This short half-life means that for high dose vitamin C the period between doses needs to be short – a few hours at most.

The aim is to achieve dynamic flow, to get vitamin C flowing continuously through the body. Dynamic flow requires multiple high doses taken throughout the day. When separated in time, each dose is absorbed independently. Two doses of 3 grams, taken 12 hours apart, are absorbed better than 6 grams taken all at once. Multiple large doses, say 3 grams 4 times a day, produce a steady flow of the vitamin from the gut, into the bloodstream and out, via the urine. Some of the intake is not absorbed into the blood and stays in the gut, as a reserve against the early onset of illness. As illness begins, the body pulls in this "excess" to help fight the virus.

The idea behind dynamic flow is that the body is kept in a reduced (antioxidant) state, using high doses. There is always vitamin C available,

to refresh the body and other antioxidants. Each vitamin C molecule (ascorbic acid) has two antioxidant electrons, which it can donate to protect the body. It then becomes oxidized to dehydroascorbate (DHA). This oxidized molecule is then excreted, so the body has gained two antioxidant electrons. The kidneys reabsorb vitamin C, but not DHA; the vitamin C molecule is absorbed, used up, and then the oxidized form is thrown out with the rubbish.

The effectiveness of vitamin C is not directly proportional to the dose; it is nonlinear. There is a threshold above which vitamin C becomes highly effective. Below this level, the effect is small; above it, the effect is dramatic. The problem is that no one can tell you in advance what intake of vitamin C you need. The solution is to take more – more than you think necessary, more than you consider reasonable. The mantra is dose, dose, dose.

Types of Vitamin C

Straightforward, low-cost ascorbic acid is the preferred form of supplement. Vendors may try to sell you "better-absorbed" forms with minerals or salts such as sodium, potassium or calcium ascorbate, and so on. These are irrelevant, if not counterproductive, for high intakes. It is worth noting the following:

1. Timing is more important than form. Two large doses of ascorbic acid taken a little time apart are better absorbed than a single dose of mineral ascorbate.
2. Mineral ascorbates are salts and do not carry the same number of antioxidant electrons. Ascorbic acid has two electrons to donate, while a salt typically has only one. With high doses, the "improved" forms are thus only about half as effective. This is consistent with reports that mineral forms are correspondingly ineffective in combating illness.
3. Ascorbic acid is a weak acid, much weaker than the hydrochloric acid in the stomach. Mineral ascorbates may be better tolerated, as they make the stomach more alkaline than ascorbic acid. However, an alkaline stomach is not a good idea – there are reasons that the body secretes hydrochloric acid into the stomach, including preventing infection. Furthermore, if you are coming down with a hemorrhagic viral infection, mild discomfort will not be of great concern.
4. For high intakes, capsules of ascorbic acid are preferable to tablets. This is because tablets are packed with fillers and it is not wise to take massive doses of these chemicals. Check the ingredients – you want to take ascorbic acid and very little else. Bioflavonoids are all right, and the capsules may be made with gelatin or a vegetarian equivalent.
5. The cheapest way to take ascorbic acid is as powder, dissolved in water. If you do this, use a straw to avoid it getting on the tooth enamel, as it is slightly acidic. You will need a set of accurate electronic scales to monitor the dose. If you do not weigh it carefully, it will be difficult to keep close to bowel tolerance.

Intravenous Vitamin C

Ideally, infected people would be given a continuous intravenous (IV) infusion of massive doses of vitamin C (sodium ascorbate is preferred, as ascorbic acid is irritant to veins).

1. People who are sufficiently ill will not be able to take vitamin C by mouth.
2. IV provides the highest possible blood levels.
3. IV means continuous drip, not an injection (short half-life).

Unless you are a medical professional who can treat yourself and your family, or are exceptionally rich, IV ascorbate will not be an option in an Ebola outbreak.

Rectal Vitamin C

Rectal administration of sodium ascorbate is a method that can be used in emergencies, and in developing-world circumstances, when IV is unavailable or unsuitable. Nurses can quickly be trained to mix 15 to 30 g of sodium ascorbate in 250 to 500 ml clean water, and give it by enema. It can be safely and effectively used in children. An enema also removes material that may be challenging from the bowel. This has been done successfully with aboriginal people in the Australian outback.

Liposomes

In healthy people, liposomes help the absorption of oral vitamin C; in some circumstances this is also true for sick people. However, we need to dispel some popular myths.

In a healthy person, higher blood levels (about 600 microM/L) can be achieved using liposomal vitamin C compared with standard ascorbic acid (about 250 microM/L). We were the first to demonstrate this fact experimentally.[6] However, the two absorption methods are different, and if both are used together the resultant ➤

plasma levels are additive (something like 600 + 250 = 850 microM/L). Since ascorbic acid is much cheaper than liposomal vitamin C, it is cost effective for a healthy person to start with ascorbic acid and top up with liposomes as required.

When a person becomes ill, he or she can absorb massive doses of standard ascorbic acid, using the dynamic flow approach. So if you are sick, taking a gram of liposomal vitamin C instead of a gram of cheap ascorbic acid will provide little extra benefit. Both will be well absorbed, and the liposome contains sodium ascorbate, which is less effective. Liposomes only provide added benefit once the sick person has approached bowel tolerance levels, using standard ascorbic acid.

Liposomal vitamin C is *not* more effective than IV for fighting acute infections. This suggestion is unscientific and unsupported by data. We prefer liposomes for chronic infections and cancer, but this does not extend to acute illness. There is also a lot of hype around the fact that liposomes can be absorbed directly into cells. Many liposomes are absorbed from the gut and pass into the liver, where they are stored and the vitamin C released. Liposomes may also float around in the bloodstream, lymph nodes, and so on, waiting to release their contents or be taken up by cells. But the cells that take up the liposomes are not necessarily those that are most in need of vitamin C. Moreover cells may suffer side effects; liposomes are basically nanotechnology and have additional theoretical issues.

Prevention

To have a reasonable chance of avoiding a major viral infection, a daily intake of at least 10 grams of ascorbic acid is needed. The idea is to start low, taking say 500 to 1000 mg four times a day. Build up the intake to close to bowel tolerance; increased wind and large soft stools will occur before diarrhea signals that bowel tolerance has been exceeded. At this stage, back off the dose a little, to a reasonably comfortable level.

At the first hint of an infection – feeling unwell, itchy throat, fatigue, and so on – take more ascorbic acid. If the hint of impending sickness is mild, take perhaps 5 grams every half hour or even more frequently. For anything more than a hint of infection, take as large a dose as you feel could be tolerated and follow this by taking 5 grams every half hour. The rule is to take as much as you can without going over the tolerated level: you will probably be taking too little, even though you are trying hard to take a massive dose.

If you are already in dynamic flow and want extra protection, then add liposomal vitamin C. Take it at the same intervals as the ascorbic acid; that is, several times a day. The limit is once again bowel tolerance – take too much and it will give you loose stools. This will provide the maximum preventive effect, for the lowest cost.

Treatment

We assume that you are not a medical professional and do not have access to IV ascorbate. However, if IV sodium ascorbate is available, it should be given slowly and as continuously as possible. For children, enemas may be the most practical method (we hope to publish practical instructions for this soon). Medical professionals can deal with such things with little difficulty, but others may do more harm than good.

The first important thing is to start the treatment early. The longer a person waits after the initial symptoms, the less effective the treatment will be. Also if the illness is allowed to develop, the sick person may become unable to take anything orally.

Once again, the idea is to get dynamic flow going with as much ascorbic acid as can be tolerated. In this case, the doses are massive. Five to 10 grams every half-hour, through the day, will provide 120 to 240 grams a day. Even at this high intake, the blood plasma levels may be low or undetectable; at most 250 microM/L will be achieved. So the question then becomes how much additional liposomal vitamin C the patient can tolerate.

A practical approach would be to start with 5 grams of ascorbic acid and a similar amount of liposomal vitamin C in very frequent doses. Remember the key is dose, dose, dose. More vitamin C!

How It Works

The mechanism of action of high dose vitamin C is known and understood. In normal healthy tissues, it acts as an antioxidant. In other tissues, it generates hydrogen peroxide, the chemical used to bleach hair platinum blond. This happens in sick and inflamed tissues; for example, in a malignant tumor. The process is typically a form of Fenton reaction, generating free radicals. The oxidation and free radicals arising from the hydrogen peroxide kill bacteria and inactivate viruses. In other words, vitamin C acts as a targeted bleach and antiseptic.

Vitamin C is unique, because it has low toxicity and can be taken safely in massive amounts. Other antioxidants and supplements will not have a similar effect. Do not be confused and think that echinacea, for example, will help. Yes, there may be supplements and herbs that provide a little immune system support, but this is Ebola we are talking about – get real!

Note, vitamin C is not some magical antitoxin; this idea is a metaphor. A disease such as Ebola is not caused by toxins that are inactivated by vitamin C. Free radicals are not toxins. Oxidants are not toxins. Vitamin C nearly always acts by transferring electrons, as an oxidant or antioxidant. It is just basic chemistry. Also, it does not matter if you have poor dental hygiene; this will hardly affect how massive intakes of vitamin C tackle an acute viral infection.

Interactions

Sugar interferes with the uptake of vitamin C. If you are using vitamin C to combat a viral infection, do not eat any sugar or carbohydrates (long-chain sugars) or the vitamin C will not be absorbed properly. We stress that this means no sugar and no carbs, at all.

Smoking releases enormous amounts of oxidants and free radicals into the bloodstream. The vitamin C will expend itself, trying to mop up the chemicals from the smoking. We have no moral objections to people's smoking; it is a personal choice. However, smoking will hinder even massive doses of vitamin C from preventing infection. Once you are infected with Ebola, smoking will stop the vitamin C from keeping you alive.

It is sensible also to supplement with a little chelated magnesium, such as magnesium citrate, which helps overcome the (largely theoretical) risk of kidney stones.

The reaction that generates hydrogen peroxide in sick tissues can be enhanced a little by taking selenium with the vitamin C. A little caution is needed, as too much selenium will cause diarrhea, fatigue, garlic breath, and hair and nail loss; severe toxicity can have more severe effects but is hard to achieve. Methylselenocysteine is a less toxic form, and this would be our choice. The normal intake is perhaps 100 to 200 micrograms (0.1–0.2 mg) a day; we would take 400 micrograms a day during an epidemic and up this to 1000 micrograms (1 mg) a day, at the initial onset of symptoms. It is possible to go up to 3 mg for short periods, with medical supervision.

Other supplements may be synergistic with vitamin C. Alpha-lipoic acid can be taken at high levels reasonably safely. We would take up to 1 or 2 grams a day (1000–2000 mg) in the short term. Vitamin K also helps with blood clotting and is safe in the recommended amounts; we would get the highest-dose vitamin K2 supplement available. Note that vitamin K is contraindicated in those with clotting disease or those on blood thinners such as warfarin.

Contraindications

The only established side effects of ascorbate therapy are wind, loose bowels, and chronic good health. There are some contraindications; people with kidney disease, iron overload disease, or glucose-6-phosphatase deficiency should not immediately take high doses of vitamin C. In the setting of an epidemic, they can start as we recommend but should increase more cautiously, with appropriate medical monitoring.

Why Put This Out?

People need to know that vitamin C is an option for fighting Ebola, and how it works. There is a great deal of misinformation, particularly on the Internet, both from vested interests and from "loonies." Moreover, in an Ebola epidemic, vitamin C supplements may be hard to source.

This account is intended for intelligent adults, who can make their own rational decisions and take responsibility for their health. We strongly promote the idea that medicine should be based on rational patients, rather than authoritarian doctors. Doctors are there to provide the information for patients, to help them choose between available options. This is information only – what you decide to do with it is up to you.

In our opinion the use of vitamin C in Ebola is a no-brainer. Get the illness and, it is said, you have at best a 50:50 chance of surviving without vitamin C-based therapy. Corporate medicine has no effective treatment. Furthermore, if a drug were available, it would be untested and almost certainly unavailable to you, dear reader. Vitamin C is considered safe and should do no harm. The cost of treatment is low. The clinical reports of vitamin C in viral infection are that if you get the dose right, you will survive. Vitamin C is known experimentally to inactivate viruses.

In the event of an outbreak, we hope that people make rational decisions.

For Further Reading

There are lots of other sources but these make a good fast start for a person beginning an investigation into the antiviral properties of vitamin C.

Hickey S, Saul A. *Vitamin C: The Real Story, the Remarkable and Controversial Healing Factor*. Basic Health; 2008. The book gives an easy readable account of the story of vitamin C.

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Compounding Outrage Upon Outrage

by Gretchen DuBeau, Esq.

Executive and Legal Director, Alliance for Natural Health USA

'It's Unsafe If We Say It's Unsafe!'

If you or your family uses compounded medications, you may well be out of luck – and you won't even have a say in the matter.

In a July 2014 article, I told you about the new changes to the Food, Drug, and Cosmetic Act (FD&C) with regard to compounded drugs and compounding pharmacies.[1] I said that it seemed likely that, once the US Food and Drug Administration completes the regulatory phase of the new provisions – wherein it creates the rules and guidances about how these new measures are implemented – practitioners would be increasingly limited in what medications they can prescribe.

I'm sorry to say that this is precisely what is happening.

The FDA has issued a slew of new regulations that broaden its powers well beyond anything Congress intended.[2] Specifically, the agency is proposing to empower itself with the ability to ban compounded drugs – any compounded medications that it wishes, carte blanche – without allowing public comment.[3]

Our organization, the Alliance for Natural Health USA, submitted formal comment to the FDA, arguing that this should be a consultative process, and that the new provision is potentially illegal. But as it stands now, all it has to do is call a compounded drug "unsafe" or "not effective" and it's banned, and the agency doesn't need any proof or justification for its actions.

Natural, Safe, Inexpensive ... and Under Attack

We only need look at the history of estriol to see what the future might bring.

Estriol is a natural and bioavailable form of estrogen replacement hormones. It is a naturally occurring hormone that is part of every human body. Estriol is approved in Europe for treatment of menopause and is the standard of care in most of the developed world. It is the weakest estrogen and generally accepted to be the safest estrogen treatment. The synthetic estrogen replacement product it is most often compared to is Prempro – a combination of a potent estrogen derived from pregnant mares' urine and a synthetic progestin.

A 2010 study published in the *Journal of the American Medical Association* shows that women who take Prempro are twice as likely to die from breast cancer.[4] A study published the same year in *Archives of Internal Medicine* shows that women taking Prempro or Premarin are also 21% more likely to develop kidney stones over 5 years.[5] A study published in the *Lancet* showed that Prempro raises the number of lung cancer deaths. And the government-sponsored Women's Health Initiative study was halted in July 2002 because long-term Prempro use was found to raise the risk of breast cancer, heart attack, and stroke.[6]

Despite the manifold dangers of Prempro, and despite the fact that the FDA has been unable to substantiate a single adverse event for estriol, the agency is still working diligently behind the scenes to ban estriol, not Prempro! That's because drug giant Wyeth (since bought by Pfizer) filed a petition with the FDA to remove estriol from the market. Ironically, when it filed the petition, Wyeth was marketing its own version of estriol in Europe as the "ideal therapy" for women.

The FDA seemed to grant Wyeth's petition, but then backpedaled in part because of the huge public outcry as we got the word out about this latest blatant example of crony capitalism. Efforts were made to shut down compounding pharmacy sales and to threaten doctors who prescribed estriol, and were then largely abandoned in favor of a so-called public awareness campaign about the risks and benefits of hormone therapy for the treatment of menopausal symptoms and other conditions.[7]

Keep in mind that FDA approval for a drug, with its mandatory double-blind, randomly controlled human trials, costs as much as $1 billion, and nobody will pay that for nonpatentable substances – including estriol – when they can never hope to recoup their investment. (We call this the "catch-22" of FDA approval.)

For the FDA to keep repeating that only FDA-approved drugs are safe or effective is total nonsense. Particularly when each year there are an average of 526,527 adverse events for prescription drugs, 275,421 of which have "serious outcomes," including

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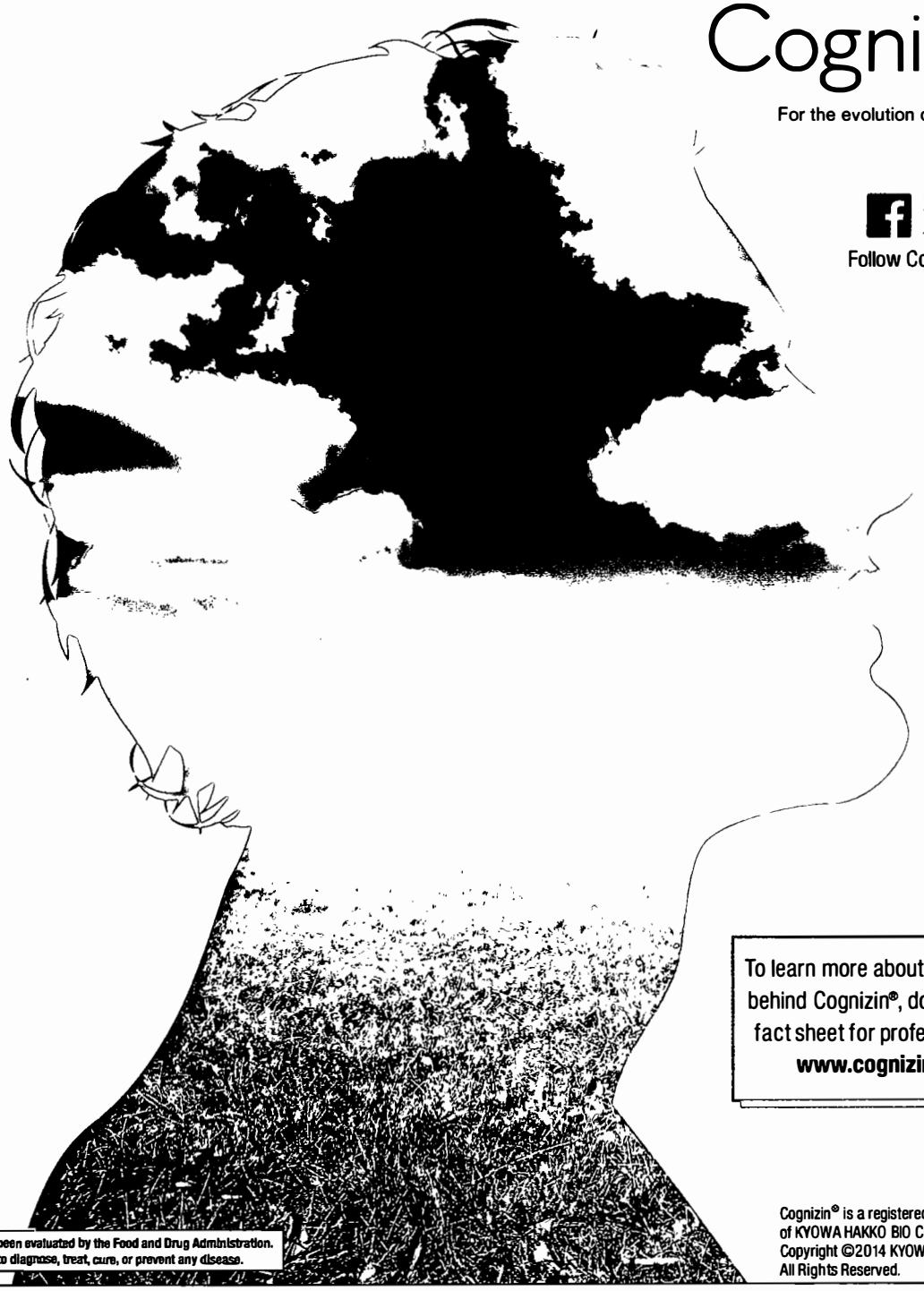

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death.[8] As noted above, estriol has not brought a single adverse reaction – ever. But the FDA needs an excuse to get rid of it.

This new law, if allowed to stand, gives the agency the very excuse that it needs. If the FDA should say, "We feel estriol is not safe" or "We don't find it effective," that's all it needs to do. It's gone if the agency wants it gone.

The FDA cites public health as the underlying need to fast-track drug removals, but the agency already has the ability to take any drugs off the market that are dangerous – in fact, the drugs that the FDA has added to the list so far are already illegal to make, so there's no public health concern there. The only other category is "not effective." Is it really a public health issue to take several months to properly determine whether a compounded drug is not effective?

Compounded Drugs Are Already Disappearing

The compounding legislation has already indirectly restricted availability of many safe and effective compounded drugs – through insurance companies and pharmacy benefit managers.

Pharmacy benefit managers, or PBMs, are companies that process prescriptions for insurance companies and corporations, and use their size to negotiate low prices with drug makers and pharmacies.[9] They act as intermediaries between the payor and everyone else in the health-care system.

One major PBM, Express Scripts, is dramatically decreasing its coverage for some bulk ingredients of compounded drugs.[10] It is citing high prices, and arguing that "by and large, compounded medications do not provide any additional clinical value over what is currently available."[11] The company will block coverage for approximately 1000 active ingredients.

Three other PBMs – Optum Rx (part of the insurance company United Health Group), CVS Caremark, and Catamaran – have placed restrictions on compounded drug ingredients. Harvard Pilgrim Health Care, the largest insurer in New England, ended coverage for compounded drugs altogether except for children and medically necessary drugs for adults.[12]

Note the language that these PBMs are using: "They don't provide any additional clinical value." "Only medically necessary drugs." Why in the world are insurers – or worse, their drug purchasing managers – determining what is "medically necessary" rather than one's personal physician? Pharmaceutical companies and insurance companies are negotiating prices and profits between themselves, without a single thought to the best interests of patients.[13]

As insurance companies drop coverage, and the new regulations diminish access to available compounding drugs, prices will inevitably increase for compounded medications, which in turn virtually *guarantees* a larger market share for Big Pharma.

The Law as a Tool for Bullying the 'Little Guys'

In May, the Senate Appropriations Committee criticized the FDA by issuing proposed new regulations on compounding pharmacies without sufficiently consulting the stakeholders: doctors, patients, and compounding pharmacists.[14] The language – which is worded more strongly than any report language that the ANH-USA staff has previously seen – also directs the FDA to consult with interested parties before moving forward.[15]

Since then – and probably because of our Action Alert that so many *Townsend Letter* readers participated in – the FDA held stakeholder meetings (which ANH-USA attended), and reissued some of its guidances. But with the appearance of the latest regulations, it has become clear the FDA isn't listening to anyone but its friends in the pharmaceutical industry.

In the new legislation, Congress divided compounding pharmacies into two categories – "custom" compounders and "outsourcing facilities." The latter would be allowed to sell across state lines but only from a restricted list of drugs. If those sales add up, drug companies may decide to offer their own version of the product, in which case the outsourcing facility may be barred from making it.

At issue right now is the approved list of "bulk ingredients" (drugs) that the FDA will allow to be sold by outsourcing facilities. Anyone can nominate bulk ingredients for the list (pharmacies are expected to be the most likely to do so), but the FDA is requesting supporting data for any ingredient nominated – and the new rules for this supporting information are so broad and complex, requiring so much time and research, that smaller organizations will find it difficult or even impossible to meet the agency's requirements.

This is a familiar scenario: large companies and regulators collude on rules designed to get rid of smaller competition and thus make life easier for both the large companies and the regulators.

Besides putting an intolerable burden on small, independent compounding pharmacies, this legislation suppresses innovation, as any new version of a compounded drug by an outsourcing facility will require permission from the FDA. Outsourcing facilities are extremely important, because they will be fulfilling the great majority of out-of-state patients' compounding needs.

For each ingredient nominated, the FDA wants info about both the bulk drug substance itself and the drug products that will be compounded using that substance.[16] The nominator must:

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Compounding Outrage

- show that there is an adequate clinical need for that specific drug product to be compounded, with evidence of the condition it treats;
- provide a list of FDA-approved drugs, if any, that address the same medical condition;
- if there are FDA-approved drugs, give an explanation of why the compounded version is necessary – that is, why the FDA-approved drug isn't suitable for a particular patient population; and
- come up with an estimate of the size of the population that would need this compounded drug product. Note that the FDA is saying that there must be an existing market for this product and it must be of some size. So new products, or old products that might prove useful in new ways or for new populations, will be barred.

The FDA may reject bulk ingredients based on any of the above criteria. What is particularly troubling is the implication that unless there is a large enough group of people who need a compounded medication, the answer will be an automatic no. This is the antithesis of personalized medicine, and defeats the whole purpose of compounding in the first place!

When did we as a nation decide that we no longer care about individuals' needs? If a compounder is willing to make a medication for an individual patient, what business is it of the government?

How You Can Fight Back

ANH-USA has and will continue to submit formal comments on these issues. In meantime, we want *Townsend Letter* readers to put pressure on the FDA and Congress. We suggest two separate counterattacks:

1. **Defend your access to compounded medications.** Tell FDA to stop intervening in the doctor/patient relationship, and ask Congress to carefully oversee the FDA's rulemaking process regarding compounding, and swiftly intervene where consumer and doctor access to compounded medications is threatened.
2. **Tell pharmacy benefit managers that compounded drugs are medically necessary.** Drug purchasing managers for insurance companies have no right to override the medical decisions of physicians. And attacking compounded medications simply gives more of a monopoly to FDA-approved drugs. Tell the major PBMs that they have no authority to countermand a doctor's health-

care directive with their own assessment of what is "medically necessary."

To take action and send your messages, please go to this link: http://www.anh-usa.org/compoundingrules. We also recommend that you subscribe to our weekly e-newsletter, the *Pulse of Natural Health,* where we keep you updated on troubling laws and regulations, and provide opportunities for action. Our Action Alerts are proven to be effective in influencing legislation and making federal agencies sit up and take notice. To subscribe to the *Pulse,* please visit www.ANH-USA.org.

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Shorts

briefed by Jule Klotter
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Animal-Assisted Therapy and Pain

Spending 15 minutes or less with a 40-pound certified therapy dog (a male wheaten terrier) decreased pain and improved mood in patients with fibromyalgia (FM) awaiting their clinic visit in a 2013 study. Like other certified therapy animals, the dog had a calm, friendly, and obedient temperament. Dawn A. Marcus, MD, and colleagues at the University of Pittsburgh School of Medicine conducted the study to see if interaction with a therapy dog and handler lessened pain, stress, and fatigue in people with FM specifically. Brief visits with a therapy dog had benefited patients with chronic pain in an earlier study.

Animal-assisted therapy, a complementary intervention provided by volunteer pet owners, produces measurable physiological effects on patients – even if they aren't animal lovers. Blood pressure and other signs of cardiovascular stress decline, as do stress markers such as cortisol and epinephrine. Endorphins, immune factors, and oxytocin levels increase. Animal therapy is being used to help people with depression, schizophrenia, Alzheimer's, cancer, cardiovascular disease, spinal cord injuries, cerebral palsy, and developmental and speech disorders, as well as those recovering from surgery or living in nursing homes.

This 2013 study, led by Marcus, took place in a tertiary outpatient pain management clinic. Notices placed in the waiting room invited FM patients to take part in the Therapy Dog Research Project. The notices said, "This research asks how you might spend time before your visit waiting in a room with a therapy dog." Before visiting with the dog and handler, patients completed a one-page survey that gathered demographic information and asked them to rate their current symptom severity for pain, fatigue, stress, aggravation, anxiety/worry, sadness/depression, irritability/frustration, calmness, pleasantness, and cheerfulness. "After completing their survey, therapy dog participants were provided with a chair in a designated room and introduced to the dog, which they were invited to pet," say the authors. More than one patient could visit at the same time. Conversation focused on the dog and pet-related topics and avoided patients' health issues. Patients did not have to remain in the room for a set time. All visits ended, however, when doctors were ready to see patients for their appointments. Visits lasted from 6 to 18 minutes, with over 60% of the participants remaining in the therapy room for 10 minutes or longer. Upon concluding the visit, patients again rated their symptoms. When the dog and handler were not at the clinic, FM patients were asked to complete the same one-page survey and then rate their symptoms again after waiting about 15 minutes. These patients acted as controls.

All 10 symptoms showed significant improvement ($p < 0.001$) in the dog therapy group. Only cheerfulness significantly improved in the control group ($p = 0.031$). The authors note that "clinically meaningful pain relief (≥2 points pain severity reduction [on the 11-point scale]) occurred in 34% after the therapy dog visit and 4% in the waiting room control." Such symptomatic improvements "may help prepare patients for a more successful clinic visit encounter," say the authors.

The authors recognize that their study has numerous limitations, including its open-label, nonrandomized design and the self-selected participant sample; but a meta-analysis of animal-assisted therapy found similar outcomes in both well-designed, controlled studies and nonrandomized, uncontrolled ones. It intrigues me that less than 15 minutes with a calm animal can produce such a change in physical symptoms and mood. Is it the animal's energy? Is it because patients focus on something nonstressful? Is it unique to the human–animal bond? Does animal-assisted therapy connect us to the healing power of the natural world?

Marcus DA, Bernstein CD, Constantin JM, et al. Impact of animal-assisted therapy for outpatients with fibromyalgia. *Pain Med*. January 2013;14(1):43–51. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3666031. Accessed August 31, 2014.

Beating Procrastination

Starting an exercise program, changing the diet, and other beneficial self-care actions often suffocate under the weight of procrastination. "Everyone procrastinates sometimes; yet, putting off something we set out to do can

leave us feeling unproductive, drained of energy, and often guilty," write Erik Peper, PhD, and colleagues in "Increase Productivity, Decrease Procrastination, and Increase Energy." Instead of chastising oneself for missing the mark (which is counterproductive), the authors offer a strategy to change self-blame into successful action.

The "Transforming Failure into Success" strategy involves mental rehearsal that lets us change our own behaviors. "Mental rehearsal is role-playing in your imagination. The more you imagine yourself performing the desired (or undesired!) behavior, the more likely it is that you will actually perform that behavior," the authors explain. " ... Every thought we think is a form of mental rehearsal that strengthens the neural connections in our brains. Even when you say, *I should not have done that*, in our brain you rehearse what you did *not* want to do, which increases the probability that you *will* do the same thing again!"

Becoming aware of the mental images and inner self-talk is the first step. Instead of criticizing oneself for failures and mistakes, the authors suggest acceptance: "When you notice yourself thinking, 'I wish I'd done that differently' – Stop! Give yourself credit that you did the only thing you could have done and that you could NOT have done it any differently given your history, skills, and environmental factors at that moment. Accept what happened and recognize that you are now ready to explore new options." The next step is to consider what action to take if the same situation recurs: "'If I could do this over, how would I do it now given the new wisdom I have gained?'" Mentally rehearse the new action repeatedly, step by step. Use details. Engage the senses. "Rewriting the past takes practice," say the authors. "During the mental rehearsal the old pattern often reasserts itself. Just let it go and practice again. If it continues to recur, ask yourself, 'What do I need to learn from this; what is my lesson?'" The last step is to smile" ... and congratulate yourself for taking charge of programming your own future."

Peper and colleagues report that thousands of their undergraduate students have used mental rehearsal to reduce procrastination and increase productivity. Mental rehearsal has also proved useful for patients in rehabilitation and those dealing with psychological disorders including depression, panic disorder, social phobia, posttraumatic stress disorder, somatoform disorders, and eating disorders.

Peper E, Harvey R, Lin I-M, Duvvuri P. Increase productivity, decrease procrastination, and increase energy. *Biofeedback*. Summer 2014;42(2);82–87.

Cognitive Behavior Therapy for Fibromyalgia

Cognitive behavior therapy (CBT) to address insomnia is more effective than sleep hygiene education, according to a 2013 randomized controlled trial involving 64 women with fibromyalgia (FM). Disrupted, nonrestorative sleep is a common symptom of FM. Numerous studies have indicated that poor sleep quality is linked to negative moods, increased pain and fatigue, and reduced cognitive performance and daily function. In the 2013 study, University of Granada (Spain) researchers used validated questionnaires to assess patient response to CBT or to a sleep hygiene education program (control).

In an earlier study, the Spanish researchers used polysomnography and found that CBT improved time in bed, wake percentage, sleep efficiency, and sleep architecture (more deep sleep and less light sleep) in patients with FM; but the objective data did not necessarily correspond to patients' perceptions. Patient self-reports provided more useful information than polysomnography. Because of this, the researchers decided to use multiple validated questionnaires in the 2013 study to assess sleep quality, pain, fatigue, FM impact, pain management, and psychological symptoms.

Both the CBT intervention and the sleep hygiene program consisted of 6 sessions. Thirty women in the CBT group and 29 in the sleep hygiene group completed treatment. The CBT program met the recommendations of the American Academy of Sleep Medicine. It consisted of information about the sleep-FM relationship, basic sleep hygiene education, sleep restriction, physiological deactivation procedures (i.e., slow breathing, passive relaxation, imagery training), and cognitive therapy to change negative thoughts about insomnia. The sleep hygiene control group received the same basic information about sleep and FM as the CBT group. In addition, they learned about environmental factors (noise, temperature, light) and lifestyle factors (diet, exercise, stimulant use, and other substances) that affect sleep. All participants completed the validated questionnaires four times: pre- and posttreatment as well as 3 months and 6 months after treatment ended. Patients in the CBT group showed significant improvement (pre- to posttreatment) in several sleep quality variables: sleep quality-total, subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, and daytime dysfunction. The sleep hygiene group only achieved significant improvement in subjective sleep quality.

Despite better sleep quality, pain intensity did not significantly improve in the CBT group. "It may be necessary for sleep to be normalized for a longer time before an effective change in pain can be observed," say the authors. They also suggest that CBT for insomnia (CBT-I) might be combined with cognitive behavior therapy protocols that have successfully managed pain in clinical studies. "The typical components of CBT-I can be combined with other elements of CBT for chronic pain ... providing potentially greater therapeutic benefits than each option separately," they write. Cognitive behavior therapy for chronic pain includes pain education, balancing activity and rest, communication skills, problem solving, managing emotion, and cognitive therapy for negative thoughts about pain.

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Shorts

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Congenital Hypothyroidism and Fukushima

Joseph J. Mangano and Janette D. Sherman published a 2013 study that found a correlation between congenital hypothyroidism (CH) in the US and fallout from the 2011 Fukushima nuclear meltdown. CH decreases intelligence and produces stunted growth, deafness, and neurological abnormalities unless treatment begins early. Newborns in developed countries are screened using a blood spot test. Several countries, including the US, UK, Australia, and Italy, have seen an increase over the past 20 years. CH incidence rose 75.3% in the US from 1987 to 2002. CH has been linked to dioxinlike compounds, organochloride pesticides, and prenatal exposure to radioactive iodine isotopes. "The fetal thyroid, the first glandular structure to appear in the human embryo, begins to concentrate iodine and produce thyroid hormones by the 70th day of gestation," Mangano and Sherman explain.

An airborne plume containing iodine-131 and other radioactive isotopes from Fukushima reached the US West Coast on March 15, 2011, four days after the meltdown began. I-131 is a short-lived isotope that enters the food chain primarily via dairy foods when cows eat contaminated forage. Being a form of iodine, I-131 concentrates in the thyroid gland.

For their study, Mangano and Sherman used gross beta measurements from EPA stations (for 2010 and 2011) to identify an "exposed" population and a "control" population. ("Beta measurements include a variety of radioisotopes, of which I-131 is a portion, meaning gross beta as a proxy for relative exposure to the thyroid gland.") They then called state newborn screening program coordinators and obtained the number of confirmed CH cases for 2010 and 2011 in 41 states, including all 5 "exposed" Pacific states. States that refused to share CH data typically had fewer than 10 cases per year and had patient confidentiality concerns.

"Highest levels of I-131 and airborne gross beta were documented in the five US States on the Pacific Ocean," Mangano and Sherman write. During March 15 through April 30, 2011, the average beta measurement for the Pacific/West Coast "exposed" sites was 7.345 times higher than the previous year's. In comparison, the average beta reading for the 31 control sites for the same period was 2.397 above the previous year's. "For the rest of the year, the 2010-2011 change was very small (0.983 and 1.018 respectively)," say the authors.

In the "exposed" states, the number of babies born with CH from March 17 through December 31, 2011, was 16% higher than for the same period during the previous year. In comparison, the "control" states experienced a 3% decline ($p < 0.03$). "The greatest divergence in these two groups (+28%) occurred in the period March 17-June 30 ($p < 0.04$)," write the authors. Babies born during this period were exposed to I-131 during their third trimester, when the thyroid is more developed.

Although Mangano and Sherman consider their findings preliminary, their study is by no means the only evidence that I-131 causes congenital hypothyroidism. I-131 from atmospheric nuclear weapons tests was first detected in the adult human thyroid gland and at higher concentrations in the fetal thyroid during the 1950s. After the Chernobyl reactor meltdown, CH rates in the US corresponded to I-131 content in milk; milk I-131 content was 3 times higher in Northwest states than in Southeast states, and CH rate change was +23.3 higher (1984–1985 vs. 1986–1987) in Northwest states compared with −1.0% in the Southeast. CH rates are also higher in the counties surrounding Indian Point nuclear plant in New York, which has a history of releasing I-131 and particulates.

Mangano and Sherman view congenital hypothyroidism as one of many possible health effects from the Fukushima meltdown that need to be investigated long term.

Mangano JJ, Sherman JD. Elevated airborne beta levels in Pacific/West Coast US States and trends in hypothyroidism among newborns after the Fukushima nuclear meltdown. *Open J Pediatr*. 2013;3;1–9. Available at http://www.scirp.org/journal/paperinformation.aspx?paperid=28599. Accessed August 31, 2014.

Dry Needling and Trigger Point Pain

Dry needling, a simple-to-learn procedure using acupuncture needles, reduces myofascial pain caused by myofascial trigger point (MTrP) activity. A MTrP is a painful spot located in a noticeably taut band of skeletal muscle fibers. Stimulating a trigger point produces referred pain and a local twitch response. "Numerous noninvasive methods – such as stretching, massage, ischemic compression, laser therapy, heat, acupressure, ultrasound, transcutaneous electrical nerve stimulation, biofeedback, and pharmacological treatments – have been used to alleviate chronic myofascial pain, but no single strategy has proved to be universally successful," according to Leonid Kalichman, PT, PhD, and Simon Vulfsons, MD.

During dry needling, an acupuncture needle is inserted directly into the trigger point. Local twitching in the muscle fibers during treatment (a sign of rapid depolarization and electrical activity) increases effectiveness. "After the muscle has finished twitching," say Kalichman and Vulfsons, "the spontaneous electrical activity subsides and the pain and dysfunction decrease dramatically."

A 2011 Taiwanese study used a combination of dry needling and muscle stretching to alleviate chronic myofascial pain. Ninety-two patients with myofascial pain syndrome took part in the observational prospective cohort study. All patients received 8 dry-needling treatments within 8 weeks. The acupuncture needle was inserted into the taut band at points that produced localized muscle twitching. Then the needle was partly withdrawn and reinserted repeatedly until the twitching become undetectable. Passive and active stretching of the muscle completed the treatment session. Patients completed questionnaires at baseline and after 2, 4, and 8 weeks of treatment, assessing pain intensity and interference, work

history (e.g., repetitive movements, cold environment), and lifestyle factors (e.g., smoking, drinking, nutrition, sleep deprivation).

Pain intensity scores (worst, average, and present pain) decreased significantly at 2 weeks ($p < 0.001$). Aggregated pain interference (defined as pain interference of general activity + mood + walking ability + normal work + relationship + sleep + enjoyment of life) also significantly improved from baseline to week 8. Patients with a long history of pain, high pain intensity, or poor sleep quality or who engaged in repetitive work tended to have poor outcomes. Dry needling alone cannot provide persistent pain relief unless underlying contributing factors such as repetitive occupational activity, postural abnormalities, mechanical disorders, metabolic abnormalities, and psychosocial factors are addressed.

Huang Y-T, Lin S-Y, Neoh C-A, Wang K-Y, Jean Y-S, Shi H-Y. Dry needling for myofascial pain: prognostic factors. *J Altern Complement Med.* 2011;17(8):755–762. Available at http://www.dryneedling.nl/media/Dry%20Needling%20for%20Myofascial%20Pain%20-%20Prognostic%20Factors.pdf. Accessed August 9, 2014.

Kalichman L, Vulfsons S. Dry needling in the management of musculoskeletal pain. *J Am Board Fam Med.* September–October 2010;23(5):640–645. Available at www.jabfm.org/content/23/5/640.full.pdf. Accessed by August 9, 2014.

L-Theanine

Catechins are not the only beneficial compounds in green tea. L-theanine, a nonessential amino acid, reduces anxiety and protects neurons, according to Anne L. Lardner, PhD. Lardner recently published a literature review of theanine's neurobiological effects, which she discussed in an interview with Kirk Hamilton (www.prescription2000.com). This green tea component increases GABA and glycine levels in the central nervous system, according to animal research. Both are neurotransmitter inhibitors that reduce neuron excitability and calm the brain, lessening anxiety. In addition to the CNS-calming effects, L-theanine appears to counteract some negative consequences of psychological stress, such as cognitive impairment and increased serum corticosterone and catecholamine levels. Few well-designed clinical studies of theanine's calming effects have been performed.

In addition to its antianxiety and stress-relieving effects, L-theanine has shown several neuroprotective effects in laboratory research. It increases brain-derived neurotropic factor (BDNF), a protein responsible for maintaining healthy nerve cells. Decreased BDNF is characteristic of early memory decline in Alzheimer's disease. Lardner reports that a few Japanese studies have reported improved cognitive function in elderly volunteers who drank several cups of green tea each day or who took theanine capsules. L-theanine also protects neurons against some environmental toxins. In laboratory studies, theanine reduced neuron cell death caused by toxins linked to Parkinson's disease

Lardner says that effective dosage is difficult to determine at this point. A study involving people with schizophrenia showed anxiety reduction and other psychological benefits when taking 400 mg/day for 32 months. Cognitive function improved in elderly people on a daily dose of about 50 mg/day. Theanine content in a cup of green tea varies from 20 mg to 45 mg, depending upon growing and processing conditions. "I could be wrong here," Lardner told Hamilton, "but my educated guess is that the amount of theanine required to affect a significant biological response will depend on the particular cohort examined and on the brain disorder or function being investigated."

L-theanine, as a single supplement, has no known adverse effects. Green tea can interfere with iron, folic acid, and possibly zinc absorption so Lardner recommends drinking the tea between meals. Because of green tea's caffeine content, she suggests that people with anxiety, insomnia, or caffeine sensitivity take a theanine supplement instead.

"Up until now I feel that theanine has been the 'Cinderella' to the other well known healthful components of green tea, the catechins!" says Lardner. "Perhaps it's now her turn to receive more overall attention from health professionals, and further research funding to investigate its full potential in neurobiological function and disorders."

Lardner AL. Neurobiological effects of the green tea constituent theanine and its potential role in the treatment of psychiatric and neurodegenerative disorders [abstract]. *Nutr Neurosci.* July 2014;17(4):145–155. Available at www.ncbi.nlm.nih.gov/pubmed/23883567. Accessed August 15, 2014.

Hamilton K, Lardner AL. Neurodegenerative and psychiatric disorders and theanine from green tea. July 27, 2014. E-mail communication.

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Pathways to Healing

by Elaine Zablocki

Homeopathy and CBT: Effective in Coping with Traumatic Stress

Nancy Gahles, DC, CCH, RSHom(NA)

Nancy Gahles, DC, CCH, RSHom(NA), lives and works in Far Rockaway, a narrow strip of land on the edge of New York City, looking out at the Atlantic Ocean. Many police officers and firefighters, active and retired, live in the area.

Gahles has been in practice for over 24 years, combining herbs, nutrition, yoga, and meditation along with structural correction for a variety of health issues. She first became interested in homeopathy when she found it effective in caring for her son, who'd developed allergic asthma. In addition to her training as a chiropractor, she trained in homeopathy. For several years she served as president of the National Center for Homeopathy, and she is on the board of directors of the Integrative Healthcare Policy Consortium.

On September 11, 2001, the Rockaways lost more people per capita than any other part of the city.

"Firefighters, cops, that's our community," says Gahles. "I practice family medicine here, and I saw the devastation." During the first stage of the process, when first responders were working the initial rescue, recovery, and cleanup efforts, Gahles reached out to battalion chiefs who lived in the neighborhood.

Aconite is a homeopathic remedy for acute shock, used when there's extreme fright or anxiety. "One of the battalion chiefs was taking tubes of aconite down to the pile as they were digging," Gahles recalls. "Each time they would unearth a finger with a wedding ring on it, the shock would reverberate through them. Then they would use the homeopathic remedy, calm down and get back to work."

But even after the site was cleared, 9/11 had long-term effects. "The loss of life was traumatic, but not only the loss of life," Gahles says. "I started to see pervasive effects: alcoholism, deteriorating family relationships, anger, children with supposed ADHD, anxiety, and depression."

She volunteered to work with these patients using homeopathic methods, but at the time no one was open to the idea. A fund had been set up for psychological services for first responders, but they weren't coming in for treatment. "Firefighters don't go for that. They go back into dangerous situations, they don't cry about them," Gahles says. "I watched this happening. I saw many symptoms of PTSD which weren't diagnosed as PTSD. Women would tell me that their husband has nightmares, he is angry, but he doesn't want to come in for treatment."

However, these patients were also experiencing physical symptoms such as back pain. Gahles began seeing patients for back pain, offering treatments that would be effective for the underlying traumatic situation, as well as the back pain.

In October 2012, the Rockaways were devastated by Hurricane Sandy. "Our whole neighborhood was destroyed. Houses flattened. It was beyond imagination," Gahles says. People were displaced, and for a year she didn't see many of her long-term patients, since they were living with relatives in other parts of the city. Over time, when they started to come back, they spoke frankly about the overwhelming stress in their lives. This stress expressed itself in physical disorders such as adrenal fatigue, thyroid dysfunction, cancer, chronic fatigue. "They have every manner of diagnosis but I know what happened to them; I know their trauma," Gahles says. "What they have is PTSD. Where is that being addressed? Nowhere."

Gahles is developing a collaborative care model for PTSD. She published her first book a couple of years ago;

she expects that recognizing and coping with PTSD will be the subject of her next book. "We know that a collaborative integrative model heals best. I have found that homeopathy combined with cognitive behavioral therapy and positive emotion psychology is enormously effective in dealing with PTSD," she says.

Homeopathic remedies are effective in helping people heal from stress, but then many people fall back into the same patterns. "Initially they feel well, but then they don't have the skill set to carry on in new patterns of behavior," she says.

Gahles's sister is a licensed psychologist who specializes in cognitive behavioral therapy (CBT), so they began treating patients as a team. Then they added positive emotion psychology techniques, which are able to undo the effects of stress. "We find this combination to be extremely effective," Gahles says. In addition, she perceives a trend moving in this direction: people are more open to these methods, compared with a few years ago. Nowadays Gahles speaks about this new work during every talk she gives. She's also in discussion with publishers about the reasons to describe these methods for a larger audience.

Common-Sense Self Care

In 2012, Gahles published *The Power of $elf Care: A Common Sense Guide to* YOUR *Wellness Solution*. This book covers the benefits of chanting, visualization and aware breathing when coping with many health conditions. Gahles discusses the benefits of homeopathic remedies, and the wide variety of methods that she used to help her daughter when special issues arose related to her learning patterns.

One of her patients, writing a review on Amazon.com, says: "I've known Dr. Nancy Gahles for many years and FINALLY, she has imparted so much of her wisdom in a book that is now available to everyone – hooray! The dollar sign in the title is a little misleading as this isn't a how-to book on saving money per se, but it does use the analogy of an investment portfolio to invest in yourself and your health now, in order to reap 'dividends' later."

The investment-portfolio analogy is quite useful, as we each think about our choices in terms of investing money and time in our own health. "You can't be spread too thin if you appropriately identified your assets and put them into different classes which are invested equitably," Gahles writes. She encourages readers to invest in both conventional and complementary health care, and to invest in both short-term and long-term aspects of care. For example, a person with diabetes needs to budget long term for health insurance and other medical expenses. The individual also needs to invest short term in high-quality nutrition, time for exercise, perhaps a gym membership, a yoga class, or a support group.

"We have to empower and inspire people to recognize their own ability to care for themselves," Gahles says. "That means to be consciously aware of what we're experiencing. You are not just your diagnosis: you're bigger than that. You have a whole body of experiences that have led to the current issue or diagnosis or stuckness."

Recently Gahles read a study about the Boston Marathon which showed that children and especially teenagers who experienced that event, or watched it repeatedly on television, are now experiencing symptoms of posttraumatic stress disorder. "Who is treating this? Who is thinking about it?" she asks.

"We must raise awareness of the levels of stress, and trauma related to stress, in our society. Most importantly, we need to change the way we think about it. Instead of framing this as 'posttraumatic stress disorder' we need to think about 'posttraumatic stress potential' and 'posttraumatic empowerment.' We are not static; we are dynamic. We have the ability to recognize trauma," she says. "We have the ability to heal our lives."

For many recent articles and news about Gahles's current projects, see her website.

Resources

Book: *The Power of $elf Care: A Common Sense Guide to YOUR Wellness Solution*
Website: http://askdrnancyg.blogspot.com
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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.

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Literature Review & Commentary

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

Melatonin for Temporomandibular Joint Pain

Thirty-two women (aged 20–40 years) with mild-to-moderate myofascial temporomandibular disorder were randomly assigned to receive, in double-blind fashion, 5 mg per day of melatonin or placebo at bedtime for 4 weeks. Compared with placebo, melatonin reduced (improved) the mean pain score by 44% ($p < 0.001$), decreased mean analgesic use by 66% ($p < 0.01$), and improved sleep quality ($p < 0.001$). The effect of melatonin on pain was independent of its effect on sleep quality.

Comment: Myofascial temporomandibular disorder is a subset of what is commonly called temporomandibular joint dysfunction. The results of the present study show that treatment with melatonin can decrease joint pain and improve sleep quality in women with this condition. The mechanism of action is not known, although melatonin has demonstrated analgesic effects in certain other painful conditions, including migraines and cluster headaches. The chemical structure of melatonin is similar to that of the anti-inflammatory medication indomethacin, and melatonin has been reported to be an effective treatment for certain types of indomethacin-responsive headaches (such as hemicranias continua). Thus, it is possible that the analgesic effect of melatonin is due to an anti-inflammatory mechanism. Melatonin should be administered at night, because taking it during the day can cause drowsiness.

Vidor LP et al. Analgesic and sedative effects of melatonin in temporomandibular disorders: a double-blind, randomized, parallel-group, placebo-controlled study. *J Pain Symptom Manage*. 2013;46:422–432.

Vitamin D for Fibromyalgia

Forty-two women with fibromyalgia and a serum 25-hydroxyvitamin D (25[OH]D) level less than 32 ng/ml (mean, 20 ng/ml) were randomly assigned to receive, in double-blind fashion, vitamin D or placebo for 24 weeks. The initial dose was 2400 IU per day if the serum 25(OH)D level was less than 24 ng/ml and 1200 IU per day if the level was 24 to 32 ng/ml. Serum 25(OH)D was measured again after 4 and 12 weeks, and the dosage of vitamin D was adjusted to achieve a target 25(OH)D level of 32 to 48 ng/ml. Supplementation was stopped if the 25(OH)D level was above 48 ng/ml. The patients were evaluated at the end of the treatment period and 24 weeks after treatment was stopped. Thirty women (mean age, 48 years) completed the trial. Treatment was stopped after 12 weeks in 47% of the women receiving vitamin D, because of elevated 25(OH)D levels. Compared with placebo, vitamin D significantly decreased pain severity ($p = 0.03$), but this effect was no longer evident 24 weeks after treatment was discontinued. Compared with placebo, vitamin D had no significant effect on the Short Form Health Survey 36 (SF-36), the Hospital Anxiety and Depression Scale, or the Fibromyalgia Impact Questionnaire.

Comment: The results of this study suggest that vitamin D supplementation can decrease pain in women with fibromyalgia and a low or borderline-low baseline serum 25(OH)D level. However, vitamin D did not improve overall health or overall fibromyalgia severity, as measured by questionnaires. Thus, while vitamin D supplementation appears to be of benefit for certain women with fibromyalgia, the effects are only modest.

It has been observed previously that the symptoms of vitamin D deficiency overlap with those of fibromyalgia and chronic fatigue syndrome. It is not possible to determine from the present study whether the improvement in pain was due to the correction of a deficiency or to a pharmacological effect of vitamin D.

Wepner F et al. Effects of vitamin D on patients with fibromyalgia syndrome: A randomized placebo-controlled trial. *Pain*. 2014;155:261–268.

Fibromyalgia and Gluten Sensitivity

Twenty patients with fibromyalgia who did not have celiac disease (as demonstrated by tissue transglutaminase antibody testing, HLA typing, and duodenal biopsy) improved when placed on a gluten-free diet. The improvements were

maintained during follow-up periods ranging from 5 to 31 months (mean, 16 months). All patients had intraepithelial lymphocytosis on duodenal biopsy, without villous atrophy. Clinical response was defined as 1 or more of the following: remission of pain, return to work, return to normal life, or discontinuation of opioids.

Comment: In a recent report (Rodrigo et al.), 7 of 104 patients with fibromyalgia were found to have celiac disease. This prevalence of 6.7% is considerably higher than the approximately 1% prevalence of celiac disease among the general population. All 7 patients with celiac disease and fibromyalgia experienced marked improvement in their fibromyalgia symptoms when they went on a gluten-free diet. The results of the present study suggest that gluten consumption can also contribute to fibromyalgia symptoms in people who do not have celiac disease. In my experience, allergy to foods (including non-gluten-containing foods such as sugar, dairy products, and corn) is often an exacerbating factor, though not the main cause of symptoms, in many patients with fibromyalgia. An elimination diet followed by individual food challenges should therefore be considered for these patients.

Isasi C et al. Fibromyalgia and non-celiac gluten sensitivity: a description with remission of fibromyalgia. *Rheumatol Int*. Epub 2014 Apr 12.

Rodrigo L et al. Remarkable prevalence of coeliac disease in patients with irritable bowel syndrome plus fibromyalgia in comparison with those with isolated irritable bowel syndrome: a case-finding study. *Arthritis Res Ther*. 2013;15:R201.

Coenzyme Q10 Improves Depression in Fibromyalgia Patients

Twenty patients with fibromyalgia were randomly assigned to receive, in double-blind fashion, 100 mg of coenzyme Q10 (CoQ10) 3 times per day or placebo for 40 days. At baseline, CoQ10 and serotonin levels in platelets were significantly lower in these patients than in healthy controls. After CoQ10 supplementation, CoQ10 and serotonin levels in platelets increased significantly. At the end of the treatment period, the mean Beck Depression Inventory score was significantly lower (better) in the CoQ10 group than in the placebo group (6.2 vs. 24.1; $p < 0.001$).

Comment: Adenosine triphosphate (ATP) concentrations have been found to be low at sites of tenderness in patients with fibromyalgia, and it has been hypothesized that ATP deficiency plays a role in the pathogenesis of the disease. As a cofactor in the electron-transport chain, CoQ10 is required for ATP synthesis. The results of the present study indicate that CoQ10 supplementation can improve depression in patients with fibromyalgia, possibly by increasing serotonin levels. CoQ10 has also been reported previously by the same investigators to decrease pain and fatigue in fibromyalgia patients.

Alcocer-Gomez E et al. Coenzyme Q10 regulates serotonin levels and depressive symptoms in fibromyalgia patients: results of a small clinical trial. *J Clin Psychopharmacol*. 2014;34:277–278.

Vitamin B12 for Postherpetic Neuralgia

Ninety-eight patients (mean age, 67 years) with subacute postherpetic neuralgia on the torso (pain had been present for ➤

30 to 120 days after the onset of the rash) and a mean pain score of 7 on a scale of 0 to 10 (higher scores indicate worse pain) were randomly assigned to receive local subcutaneous injections of methylcobalamin (500 μg/ml) or 1% lidocaine, or oral methylcobalamin (500 μg 3 times per day) for 4 weeks. The subcutaneous injections were given with a 25-gauge needle once a day in the morning, 6 times a week; for each treatment, 0.5 ml was injected into a maximum of 4 painful areas, based on the patient's report. All patients had been treated with antiviral agents for 7 days after the onset of the rash. Mean improvements in overall pain, continuous spontaneous pain, and paroxysmal pain were significantly greater in the group receiving injected methylcobalamin than in the other 2 groups ($p < 0.05$ for each comparison). The proportion of patients who experienced at least a 50% decrease in pain was significantly greater ($p < 0.001$) in the injected methylcobalamin group (61%) than in the oral methylcobalamin (3%) and lidocaine (0%) groups. Oral methylcobalamin did not provide significant pain relief compared with baseline.

Comment: The present study is the first to demonstrate that postherpetic neuralgia can be treated effectively by injecting vitamin B12 directly into the painful areas. Intramuscular injections of vitamin B12 have been reported anecdotally to accelerate recovery from an outbreak of herpes zoster, but they have not been found to relieve the pain of postherpetic neuralgia. The mechanism of action of vitamin B12 is not known. Although methylcobalamin was used in the present study, one might reasonably expect that other forms of vitamin B12 (such as hydroxocobalamin) would also be effective.

Xu G et al. A single-center randomized controlled trial of local methylcobalamin injection for subacute herpetic neuralgia. *Pain Med*. 2013;14:884–894.

Vitamin B12 for Depression

Of 199 depressed patients in Iran who were screened for vitamin B12 deficiency, 73 (36%) had a low-normal serum vitamin B12 level (190-300 pg/ml). Those 73 patients (mean age, 37 years) were treated with antidepressant medication and were randomly assigned to receive or not to receive (control group) 1000 μg of vitamin B12 intramuscularly once a week for 6 weeks. The patients were reevaluated 12 weeks after the start of the study. Although the mean baseline score on the Hamilton Depression Rating Scale (HAM-D) was significantly higher (worse) in the vitamin B12 group than in the control group (23.2 vs. 19.4; $p < 0.01$), the mean final HAM-D score was significantly lower in the vitamin B12 group than in the control group (12.1 vs. 14.4; $p < 0.001$). The proportion of patients who showed at least a 50% reduction in the HAM-D score was significantly higher in the vitamin B12 group than in the control group (44% vs. 5%; $p < 0.001$). The beneficial effect of vitamin B12 remained significant after adjustment for baseline HAM-D scores.

Comment: Depression is one of the manifestations of vitamin B12 deficiency. In addition, previous research has shown that some patients suffering from depression have a deficiency of vitamin B12 in their cerebrospinal fluid, despite having normal serum levels of the vitamin. That finding suggests that some depressed patients have either an impaired capacity to transport vitamin B12 across the blood–brain barrier or an accelerated breakdown of the vitamin in the brain. In patients with vitamin B12 deficiency localized to the brain, intramuscular injections of vitamin B12 have produced clinical benefit, whereas oral vitamin B12 supplementation was ineffective. The results of the present study indicate that weekly intramuscular administration of vitamin B12, as an adjunct to antidepressant medication, was beneficial for depressed patients with low-normal serum vitamin B12 levels.

Syed EU et al. Vitamin B12 supplementation in treating major depressive disorder: a randomized controlled trial. *Open Neurol J*. 2013;7:44–48.

Human Milk for Premature Babies

Fifty-three extremely premature infants (mean gestational age, 27.6 weeks) whose mothers did not provide milk were randomly assigned to receive pasteurized donor human milk and human–milk based human milk fortifier or cow's–milk based preterm formula. The median duration of parenteral nutrition (27 vs. 36 days; $p = 0.04$), the incidence of necrotizing enterocolitis (3% vs. 21%; $p = 0.08$), and the incidence of necrotizing enterocolitis that required surgery (0% vs. 17%; $p = 0.04$) were lower in the group receiving human milk than in the group receiving cow's milk.

Comment: It is well known that breast milk is the preferred source of nutrition for infants. The present study demonstrates that human milk is particularly important for extremely premature infants. When combined with human–milk based human milk fortifier, human milk decreased the incidence of necrotizing enterocolitis, a serious and sometimes fatal condition that can occur in premature infants.

Cristofalo EA et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. *J Pediatr*. 2013;163:1592–1595.e1.

Fish Oil Supplements: Caution About Rancidity

Fifty-two women were randomly assigned to receive 2 capsules per day of less oxidized or highly oxidized omega-3 fatty acid supplements (600 mg of EPA + DHA per day) or no supplement for 30 days. The mean diastolic blood pressure and the mean serum cholesterol level decreased significantly ($p < 0.05$) with the less oxidized oil, and increased nonsignificantly with the highly oxidized oil.

Comment: These results suggest that oxidation of long-chain omega-3 fatty acids negates their beneficial effect on diastolic blood pressure and serum cholesterol levels. The long-chain omega-3 fatty acids present in fish oil are relatively unstable and prone to oxidation. Fish oil that has an unpleasant fishy taste and smell is likely to have some degree of rancidity. To minimize rancidity, look for supplements that use high-quality raw materials, purchase smaller rather than larger bottles, and keep the product airtight and refrigerated.

Garcia-Hernandez VM et al. Effect of omega-3 dietary supplements with different oxidation levels in the lipidic profile of women: a randomized controlled trial. *Int J Food Sci Nutr*. 2013;64:993–1000.

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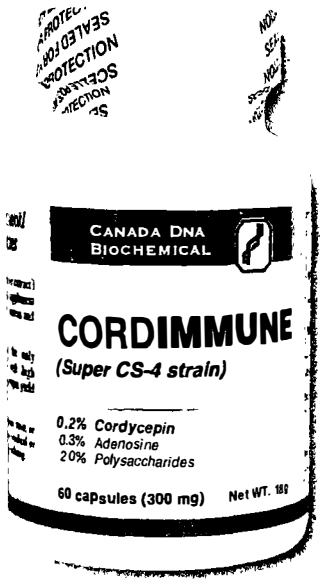

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Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

Chronic Fatigue Syndrome and Chemicals in Food

Introduction

Chronic fatigue syndrome (CFS) affects thousands of individuals in the US. CFS is characterized by an unexplained fatigue that does not improve with rest and lasts more than 4 to 6 months.[1]

Other symptoms of CFS may include headaches, unrefreshing sleep, pain, sore throat, and concentration or memory problems. It is a difficult condition to diagnose and treat. Typical causes of fatigue, such as anemia, thyroid disease, sleep apnea, adrenal dysfunction, depression, stress, and insomnia, are ruled out early on, often leaving patients with no explanation for why they are tired. Many suffer for years before finding help. The delay in diagnosis is often linked to physicians' reluctance to believe that CFS is a real condition. The current medical model in the US holds that symptoms are caused by underlying disease that can be measured by a definitive diagnostic test. CFS doesn't always fall within this model.

Etiology

The cause of CFS remains unknown, perhaps because there isn't one single factor linked to CFS but instead several factors, of which many are correlative and not causative. This is what makes CFS so difficult to diagnose. Recent research has linked mycotoxins, Epstein-Barr virus, sleep abnormalities, and herpesvirus-6 to CFS.[2-5] Since many physicians believe that the condition is psychosomatic, research has even been done to determine personality traits associated with CFS. A study on twins showed an association of emotional instability and extroversion with CFS.[6]

Alternative medicine has long considered the role of environmental chemicals in CFS. Exposure to solvents, formaldehyde, heavy metals, and pesticides has been linked to chronic fatigue.[7,8] A recent study looked at a case of a CFS linked to methylmercury from fish intake. This patient ate slices of raw tuna more than twice per week for 5 years. He complained of fatigue for the past year. After an extensive workup leading to no known cause for the fatigue, mercury testing was performed. Blood and urine tests were normal, but hair mercury was elevated. After the patient took dietary supplements, aimed at reducing mercury, his hair level returned to normal and fatigue improved.[9] The dietary supplement capsule contained zinc oxide, magnesium oxide, calcium, and L-cysteine. If mercury from fish can be linked to chronic fatigue syndrome, what about other chemicals in food?

Chemicals in Food

As previously stated, solvents, heavy metals, formaldehyde, and pesticides are linked to chronic fatigue syndrome. One major source of exposure to these chemicals is our diet. Not only are pesticides present as residue on fruit and vegetables, they are also in peanut butter, beef, butter, bread, ice cream, olive oil, and eggs. This has to do with the agricultural use of pesticides, which is a broad term for herbicides, insecticides, and fungicides. These are also used in and around homes. Pesticides can persist for years in the soil, contaminate groundwater and drinking water, and accumulate up the food chain.[10]

We are exposed to mercury, polychlorinated biphenyls (PCBs), and dioxins by eating fish. Other heavy metals such as arsenic, cadmium, and lead are also in our food. Heavy metals can be found in grains, flour, pasta, and vegetables due to contaminated soil and fertilizer. In the US, sewage sludge is commonly used as fertilizer and is contaminated with heavy metals. Fungicides containing mercury and runoff from industry-polluted waters are other sources of

heavy metal contamination. The amount of heavy metals in vegetables depends on the soil conditions and fertilizer. Cadmium is the most common contaminant. The US does not limit the amount of cadmium and lead that can be present in fertilizer. The toxicants phthalates and bisphenol A leach into food stored in plastic, cooked in plastic, handled with plastic gloves, and covered with plastic cling wrap. Most food cans in the US are lined with BPA.[10]

Additional chemicals found in food are linked to fatigue. Many of these are food additives or naturally occurring plant chemicals. The most studied natural chemicals known to cause adverse reactions are salicylates, biogenic amines, and glutamate.

The most common biogenic amines found in foods are histamine, tyramine, cadaverine, 2-phenylethylamine, spermine, spermidine, putrescine, tryptamine, and agmatine. Biogenic amines are present in chocolate, cheese, fish products, aged or processed meats, bananas, oranges, avocados, tomatoes, wines, and beer, among other foods.[11]

Free (i.e., non-protein-bound) glutamate is present naturally in many strongly flavored foods such as tomatoes, mushrooms, tasty cheeses, gravies, sauces, stock cubes, meat extracts, and yeast extracts; its purified sodium salt (MSG) is also used as a flavor enhancer.

There is a clear link between food additives/chemicals such as MSG, amines, and salicylates and CFS. Liblay and Swain published their work on food intolerance and CFS as a chapter in the book *The Clinical and Scientific Basis of Myalgic Encephalomyelitis: Chronic Fatigue Syndrome* (1992). Preservatives, nitrates, brewer's yeast, and tartrazine are also linked. Often it is difficult to differentiate between a true allergy and an intolerance to these additives. Food allergies can cause fatigue. A recent study of 38 patients with unexplained food intolerance and food hypersensitivity reported having symptoms of chronic fatigue compared with healthy controls.[12] It is proposed that they are associated through disruption of the neurological and immune systems. It could be the action of the food additive or toxicant such as pesticides and heavy metals, or these may simply be an antibody response to food.

Testing and Treatment

Given the fact that there is no singular cause for CFS, many are not sure where to begin with diagnostic tests. After ruling out causes of general fatigue and determining that the patient has chronic fatigue, testing for EBV, HHV6, mycotoxins, and sleep disturbances is a good starting point. Blood and urine testing for heavy metals, pesticides, solvents, and other chemicals are essential to finding the root cause. If toxicants are present in the body, detoxification methods to remove chemicals should be implemented. Food allergies and sensitivities need to be determined through both IgE and IgG antibody tests. Also, tests for reactions to food additives are available through several labs.

Summary

Fatigue is common in the general population. It is often described as an unusual or extreme sensation of tiredness that is not easily overcome, either by rest or by sleep. It becomes chronic when it lasts for more than 4 to 6 months. CFS affects thousands of people in the US. There is no know singular cause, yet several triggers or factors have been identified. Chemicals and additives in food are an often overlooked link to CFS. A simple food allergy test, tests for reactions to food additives, and body burden testing for chemicals can help identify this link. Avoidance of food triggers and environmental toxicants in food and detoxification may help improve the symptoms of CFS.

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Foods That Contain Salicylates

Fruits such as apples, avocados, blueberries, dates, kiwi fruit, peaches, raspberries, figs, grapes, plums, strawberries, cherries, grapefruit, and prunes

Vegetables such as alfalfa, cauliflower, cucumbers, mushrooms, radishes, broad beans, eggplant, spinach, zucchini, broccoli, and hot peppers

Some cheeses

Herbs, spices, and condiments such as dry spices and powders, tomato pastes and sauces, vinegar, soy sauce, jams, and jellies

Beverages such as coffee, wine, beer, orange juice, apple cider, regular and herbal tea, rum, and sherry

Nuts such as pine nuts, peanuts, pistachios, and almonds

Some candies, such as peppermints, licorice, and mint-flavored gum and breath mints

Ice cream, gelatin

Source: http://www.webmd.com/allergies/guide/salicylate-allergy

F.A.C.T. – Just the Facts

by Dr. Garry F. Gordon, MD, DO, MD(H)
Gordon Research Institute

Chronic Illnesses such as Fibromyalgia and Chronic Fatigue Have Multifactorial Etiologies

What are we learning today about the many apparently unrelated, chronic, and largely untreatable conditions that we are confronted with? The diagnostic list includes hundreds of autoimmune-related disorders such as rheumatoid arthritis, lupus, candida overgrowth, Lyme disease, adrenal insufficiency, chronic fatigue, fibromyalgia, multiple chemical and/or environmental sensitivity, and chronic pain syndrome. In a 2014 study, "Epigenetics and the Microbiome: Developing Areas in the Understanding of the Aetiology of Lupus," the researchers review the presence of altered levels of DNA methylation in lupus and rheumatoid arthritis, and the roles of key environmental factors in the development of these diseases. We could go further and call these conditions mitochondriopathies, as recent, concurring research has indicated that dysfunctional mitochondria may lie at the center of these and other complex illnesses, such as autism, Alzheimer's, and Parkinson's disease. *Toxicological Sciences* published a study in 2013 revealing that pharmaceutical drugs as well as environmental pollutants are major mitochondrial toxicants, causing epigenetic changes in mitochondrial DNA, leading to dysfunction and disease.

In addition to environmental pollutants, we are bombarded by a myriad of increasingly treatment resistant infections. We know that over 90% of adequately tested adults show the presence of cytomegalovirus (CMV), and nearly 70% show the presence of human papillomavirus (HPV). In the case of Lyme disease, the experts tend to agree that if a patient's history and symptoms are compatible, it is almost impossible to prove that there is no Lyme present. Then there are the latest pathogens to make headlines, with cases emerging here in the US, of Middle East respiratory syndrome coronavirus (MERS-CoV) out of Saudi Arabia, and the Ebola outbreak emerging from West Africa: both of these bear a high fatality rate among the infected, and there are no vaccines as of yet.

It is hard to know where and how to begin, but I believe that most chronic health conditions can be safely and effectively treated by following my F.I.G.H.T. For Your Health program – a multifactorial approach that addresses interrelated problems encountered in the areas of Food, Infections, Genetics, Heavy metals, Hormones, and Toxins together. As it is essential to any protocol, I always suggest that we must first do something about the body burden of heavy metals that we carry, which affects the immune system's TH1-TH2 ratio, setting the stage for vulnerability to persistent and recurring bacterial and viral infections.

Can oxidative therapies help us deal with today's chronic health challenges? I like to offer remedies such as chelation and oxidative therapies that assist in removing the body burden of toxins and lowering our viral load. Ozone therapy is particularly effective, and now we have ozone stabilized in ASEA water, which many find much easier than IV or rectal ozone treatments, with or without UVB irradiation. ASEA can also help the body deal with heavy metals, as studies have proved that it can increase the intracellular production of glutathione (GSH) and superoxide dismutase (SOD) by 500%!

For optimal results, I sincerely believe that we need to provide some form of oral chelation, daily for life. Parenterally, or IV administered, chelation works faster and is better absorbed, and in my opinion one cannot get too much IV chelation, but it only works to remove metals and toxins from our tissues. Today, we have 1000 times as much lead in our bones as our ancestors did only 100 years ago. In adults, bone remodeling proceeds at about 10% per year, with complete turnover occurring at around 15 years. During the remodeling time, lead is consistently leaching

back into the blood. This is why a daily oral chelation program is key, as without it, the lead only gets reabsorbed into the tissues and organs and eventually transported back into the bones.

When we consider the epidemic of chronic health challenges that we are confronted with today, there are no simple cures. Properly tested patients are all shown to carry some heavy metals, and there is no "safe" level of lead. Heavy metals cause immune system imbalances which increase the likelihood of acquiring viral infections. While striving to help heal our chronically ill patients, we need to always realize that merely masking the symptoms with drugs does very little to restore true health.

I continue to find that my F.I.G.H.T. program is a practical concept that helps health-care professionals and their patients avoid falling into the trap of using dangerous and toxic drugs that offer little benefit. Clearly, the most recent science supports the ties between environment and epigenetics, and the multifactorial nature of all chronic illnesses and disease.

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Here are a few examples of questions and additional alternative protocols, as discussed by our F.A.C.T. forum participants (names and responses redacted to protect member confidentiality).

Q: Fibromyalgia?

I have a patient who has been suffering from fibromyalgia for years. She has been treated by various doctors, but she still suffers from it. Nerve blockage, Botox, pain killers, myorelaxants have all been tried. Do you have any suggestions for her? Thank you, in advance.

Best regards, ~HB

A1: I see fibromyalgia as actually more than one disease/ syndrome. According to Robert Gerwin, MD, who teaches the Janet Travell Seminar Series, only about 2% of diagnosed fibromyalgia is actually "fibromyalgia." I mostly follow the school of Janet Travell, MD/Robert Gerwin, MD, but also that of Jacob Teitelbaum, MD. There are many possible causes of such pain syndromes & many times it is multi-factorial. I find that food, gut problems & sub-laboratory hypothyroidism are huge problems!

I start with getting people to "eat food with their meals" as many people simply eat junk. Avoid sugar, processed foods, grains, dairy, any foods they may be sensitive to & add organic whole foods. Add digestive enzymes, optimize nutrients–including EFA's, B-12, vitamin D & hormones–especially thyroid including T3, and others. (There is a Thomas Lowe, DC, in Colorado who believes it is mostly a thyroid issue–he has a website.) Resolve gut problems/infections. In addition, the patient might have a hypercoagulation disorder...see the website of HEMEX. And as in my understanding of Dr. Gordon's recent seminar, optimize what can be optimized & decrease the body burden of heavy metals, toxins & infectious agents. Once the internal milieu is improved, then physical medicine techniques e.g. trigger point injections, muscle techniques, etc, work better & can hold.

Sincerely, ~ LW

A2: I find that along with reducing the total body burden, ribose (15 gms/day) is really helpful. We use BioEnergy C, which also enables you to give lots of C as well. An alternative would be Corvalen-M, which also has Magnesium and malic acid in addition to ribose. A new product containing Seanol called Fibroboost seems to also be extremely effective (2 caps BID). ~RL

A3: Exclude food allergies/intolerance, and in the final analysis also toxic metal overload. ~S K T

A4: osteopathic manipulative medicine and homeopathic medicine helps. ~SD

A5: Xyrem, in that it gives a deep restorative sleep (stage 3,4) is very beneficial for minimizing the trauma of fibromyalgia. See www.xyrem.info for drug info and see www.ceri.org for info about the political economic aspect of stigmatizing this drug. Studies are undergoing for Xyrem and fibromyalgia. Best wishes, ~BW

A6: one cannot begin to consider a diagnosis and options without knowing the full history including age, BMI, habits, mental and hormone status. It's like asking advice for a fever. Why is she being poisoned by "Nerve blockage, Botox, pain killers" without a diagnosis? Regards, ~NB

A7: We've had great response to Fibromyalgia with 50mg of Iodine (25mg of Iodoral twice daily). Most docs would probably want to do an Iodine loading test first. This in addition to all of the support already mentioned here.

~WG

A8: Having been diagnosed with FM in 1994 at the age of 57, my personal experience with fibromyalgia is this:

After years of working with various physician-directed holistic approaches and finding some overall improvement with nutritional interventions, detoxing, etc. the most significant improvement came with several nutritional additions and a dietary change.

I tested low for vitamin D (18), began taking 2000 IU D3 and increased it over the course of 2 years to 6000 IU daily. My current level is 51. Levels are tested every 2 months. Much is written on the symptoms of a vitamin D deficiency mimicking fibromyalgia. In my case it was very true. I live in NE Ohio with many gray winter days but I golfed and gardened in summer so quite possibly was unable to convert because I had FM symptoms year-round.

In addition, a dietary change that eliminated all gluten/ gliadin-containing grains eliminated almost all of the morning stiffness and muscle aches as well as eliminated

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the tiredness that frequently remained even after 8-10 hours of quality sleep. I find I can now do with less sleep which is a welcome improvement.

I also found the addition of D-Ribose very significantly helped with energy, lack of muscle pain and fatigue. I experimented with dosing and found I am comfortable and have good strength and energy with one teaspoon before and after a daily workout. If I become fatigued or begin to ache, another teaspoon quickly resolves the symptoms. The work of Clarence Johnson, PhD, of Bioenergy Inc. indicates ribose enables CoQ10 efficiency (and other nutrients) in the mitochondria. I'm about 98% cured of all the FM symptoms which I attribute it to vitamin D supplementation, D-ribose and elimination of gluten/gliadin in addition to a core program of nutritional supplements which are undoubtedly all key in my success story. ~JB

Q2: Another Fibromyalgia Patient?

I have a patient's case that I would appreciate any insight on.

43 yo female with fibromyalgia symptoms, onset about 8 years ago, post high stress. Patient is depressed (sad, especially in morning), low energy, trouble concentrating, unremitting high pitch buzzing sound "in head" (not in ears), and widespread muscle pain. Previously been on antidepressants to no avail. Patient has sweet demeanor, feels like her cognition is analogous to that of a child. Patient is "big boned" and marginally overweight.

Currently mildly elevated TPO 54 IU/mL (RR: <35). TSH = 1.2, free T3 = 5.4 (RR: 3.5-6.5) (on thyroid).

Comprehensive · Parasitology · x 3 all negative for parasites, positive for gamma strep 4+, treated with botanicals. Neuroscience's · urine analysis of neurotransmitters demonstrated low epinephrine 3.9 (opt RR 8-12, observed RR 1-15), low normal NE 35.9 (opt RR 35-60, observed RR 15-106), low serotonin 80.3 (opt RR 150-200, obs RR 40-275), high GABA 6.1 (opt RR 1.5-4, observed 1.5-35), high histamine 20.5 (opt RR 10-20, obs RR 9-60). PEA & dopamine were WNR.

Chelation challenge with 2.4g CaEDTA. 100 mg DMPS IV demonstrated below average excretion of lead (15 ug/g creat) & mercury (1.5 ug/g creat). Meridian Valley IgG4/IgE food sensitivity panel demonstrated marginally elevated antibodies to cow's milk & pineapple, overall impression not mounting much of IgG4/IgE antibody response against foods. AM Cortisol low-normal at 7.7 ug/dL (RR 6-27). Full chemistry WNR. Recently found out that 1 room in house smells like mold and chewable multivitamins get "fuzzy" after awhile. Patient has been instructed to get a dehumidifier, and mold plate testing and mold sensitivity testing is soon to follow. Patient is not particularly sensitive to chemicals.

Patient is doing marginally better on Myers injections (q2wks), thyroid, 5-HTP, tyrosine. Patient has also completed round of p.o. DMSA, a few MAH treatments, but patient's symptoms appear to be resistant to treatments. Interesting thing is that this patient appears to be more "normal" according to testing than majority of patient base. What am I missing? Lead in cells (waiting for flood gates to open)? Mold sensitivity? Sublaboratory hypothyroidism/ hashimoto's? Any thoughts would be greatly appreciated. ~TW

A1: I have had outstanding results with MIHR. It stands for magnetically influenced homeopathic remedies. I've written about it in Second Opinion. In some cases, FM results are stunning. The remedies are activated with a special device and then injected into acupuncture points. ~RR

A2: Estimates suggest that anywhere from 30% to 70% of patients with fibromyalgia also suffer from irritable bowel syndrome (IBS), a chronic condition characterized by indigestion, irregularity, abdominal cramps, and diarrhea. Emphasize that patients with fibromyalgia have a high prevalence of gastrointestinal complaints that should be carefully assessed. I had many patients related to this problem. ~MU

A3: Adrenal insufficiency. I would suggest doing a challenge with ACTH or the synthetic version. Also, look for sleep apnea. I had a pt who was by all descriptions thin if not underweight and he had horrible sleep apnea, he had some brain injury which may have had an effect, but it pays to look. if other hormone levels are low, that also can be a sign (another pt with severe sleep apnea had drastically low testosterone and sky high estrogen levels and I have seen a similar pattern in women). it seems the pituitary doesn't get enough oxygen being in a watershed area and doesn't produce the stimulating hormones to make the other ones get produced. If you really want to see what kind of metals you are dealing with, check the stool after 3 grams of oral EDTA and a 3 gram Ca EDTA push. Give charcoal at the same time as the EDTA, orally so she/ he knows which stool to collect. ~JB

A4: I ran a small study 40 patients, 38 were women. All were toxic with copper. Any estrogen intake raises copper, and I would speculate that the birth control pill has elevated copper in most women, some to the point of wild emotional and mental reactions. Since the syndrome is relatively new, I suspect it is created by copper thru the pill; another bungle by the medical/pharma/cartel establishment. ~WR

A5: we had a patient misinterpret our castor oil pack instructions for treating their fibromyalgia. We requested them to wear a castor oil pack over their entire abdomen for 3 hours over 3 days. They wore it for 3 days straight. They returned to our clinic and reported 95% improvement by reduction of symptoms. When in doubt, treat the gut, decrease the toxic load. ~BL

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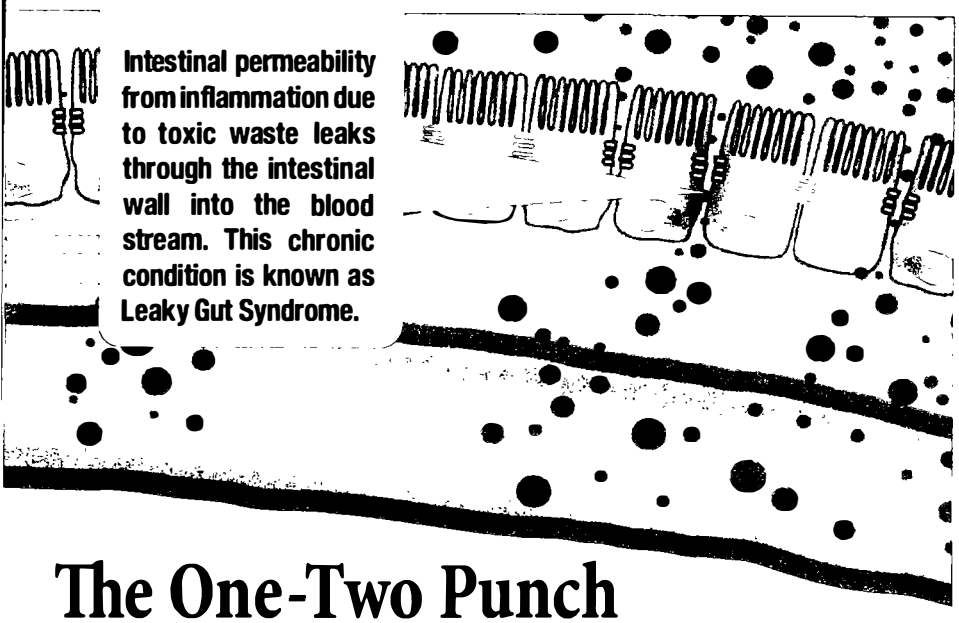


Intestinal permeability from inflammation due to toxic waste leaks through the intestinal wall into the blood stream. This chronic condition is known as Leaky Gut Syndrome.

The One-Two Punch for Chronic Conditions

Colostrum is the only substance clinically proven to prevent and repair Leaky Gut Syndrome, and healing a patient's permeable gut halts disease progression. But, that's only half the solution, and there's more work to be done. Existing cellular and tissue damage caused by Leaky Gut Syndrome (LGS) still remains, and inflammation resulting from a hyped-up immune system must be attenuated if true healing is to occur.

A balanced, optimally functioning immune system is key to health and well-being, and once again, it's colostrum to the rescue. This time, it's the Proline-Rich Polypeptides (PRPs) in colostrum that balance the immune system. This collection of short chain peptides are powerful immune modulators that help regulate the thymus gland and stimulate the production of either helper or suppressor T lymphocytes, depending on the need to either stimulate or suppress immune system activity. PRPs also induce the growth and differentiation of B lymphocytes and stimulate cytokine production, particularly IL-10, an anti-inflammatory cytokine. The most active PRPs in colostrum are the PRP-2s whose mechanism is primarily antimicrobial, and the PRP-3s whose mechanism is primarily anti-inflammatory. PRPs are not species specific, which makes bovine colostrum an excellent and abundant source.

The Total Gut Solution

First, Colostrum-LD® heals gut lining inflammation, decreases permeability, and increases the surface area of the small intestine for improved absorption of beneficial and critical nutrition. Second, IRM (Immune Response Modulator)® with its concentrated PRP-2s and PRP-3s inhibits the initiation of inappropriate inflammatory cascades associated with allergy and autoimmune responses. IRM® helps stop the destruction of body tissue associated with improper immune response and inhibits viruses known to be associated with autoimmune response.

Sovereign Laboratories is on the forefront of colostrum research and processing to maximize bioavailability of active components. Liposomal Enhanced Delivery system, an applied coating, allows powdered colostrum to readily dissolve in liquids and ensures powdered colostrum and oral colostrum spray will bypass digestion; will be transported through the bowel wall; will circulate throughout the body; will reach the organs and cells; and will remain bioavailable at the cellular level. "Liposomal Delivery makes colostrum (and other nutrients) up to 1,500% more bioavailable" (Robert R. Milne, MD). When used in combination, Colostrum-LD® and IRM® are clinically proven to provide the one-two punch for chronic conditions.

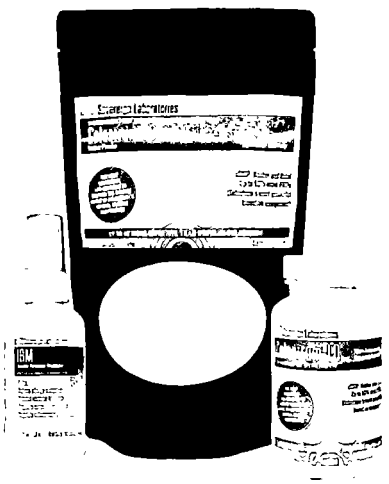
For more information, please see the article in the June issue or for professionals, go to www.ColostrumTherapy.com

The Doctor-Patient Agrees

Dr. Robert Y., MD, had been diagnosed with fibromyalgia by five doctors at the prestigious Mayo Clinic, where he was sent home with expensive prescriptions – and not much hope. He said his most serious symptoms were "muscle aches, fatigue, a decline in mental alertness connected with his inability to sleep at night, and severe depression." He tried Colostrum-LD®, and after taking it for about one month, he said "people in my community would stop me on the street and ask what I was taking because I looked so much better." He was able to stop taking all of his prescription medications, which were causing unpleasant side effects, including additional fatigue and pain. Dr. Y. feels that "Colostrum-LD® helps the body to do what it needs to do to heal," and after four months of supplementation, he reported an improvement factor of 100%.

FIRST STEP: Stop, Heal, and Prevent Leaky Gut Syndrome with Colostrum-LD®.

SECOND STEP: Restore Balance to the Immune System with IRM Immune Response Modulator®. Alleviate inflammation and pain and halt the body from destroying its own tissue and organs.



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Sovereign Laboratories

Potential Mechanisms of Autonomic Involvement in Subgroups of Chronic Fatigue Syndrome Patients

by Laurie Dennison Busby, BEd

Chronic fatigue syndrome (CFS) is a debilitating disease whose onset is often triggered by a flu-like illness. Signs and symptoms can include overwhelming fatigue, tremor, palpitations, and resting tachycardia. In some cohorts, there is postural orthostatic tachycardia syndrome (POTS) or orthostatic hypotension (OH), and in addition to autonomic dysfunction, there is also evidence of endocrine or cardiac involvement and possibly a genetic predisposition. In some CFS patients with a particular genetic predisposition, a virus may have triggered the development of autonomic dysfunction. Similar mechanisms to those in other diseases accompanied by autonomic dysfunction may play a role in CFS. Pursuing these could open up new avenues in CFS research.

Often CFS patients and approximately one-third of POTS patients have reported an infectious trigger.[1,2] In one CFS study, "The onset of autonomic symptoms occurred within 4 weeks of a viral infection in 46% of patients. ... "[1] CFS patients also show evidence of a "heritable" predisposition.[3]

Human leukocyte antigens (HLA) play a role in the response to infection and the development of autoimmune diseases. Viruses can lead to the expression of HLA on tissues that do not normally express them like the thyroid in thyroiditis and the heart in myocarditis.[4,5] In an animal model of virally induced myocarditis, "The development of inflammation takes place only in mice with a predisposing genetic background."[5]

Among HLA found in CFS, HLA-DR4 has been found in a cohort with evidence of viral reactivation.[6] HLA-DR4 has also been associated with risk of dilated cardiomyopathy (DCM), Hashimoto's thyroiditis (HT), and type 1 diabetes, with HLA-DR4 being "significantly more common" in familial cases of DCM.[5,7-10]

In some CFS cohorts, endocrine findings include abnormal thyroid biopsies, autoantibodies to thyroid peroxidase (TPO), and genes indicating thyroid involvement.[11-13] Autonomic findings include POTS or OH.[14-18] Cardiac findings include cardiopulmonary exercise (CPX) test results described as similar to those of heart failure (HF) patients, evidence of left ventricle dysfunction and possibly dilation, and heart failure tied for one of the top three causes of death among CFS patients at a mean age of 58.7 years.[19-24]

An increased incidence of endocrine diseases had been found among CFS patients' family members.[25] In an unpublished CFS family medical history survey, patients frequently reported Hashimoto's thyroiditis and/or autonomic dysfunction in themselves and endocrine and/or cardiac involvement in family members. In families where the type of enlargement and failure was known, it was due to DCM.

Up to this point, findings thought to contribute to the POTS or OH in CFS include increases in norepinephrine (NE), decreases in hormones (renin, aldosterone, or antidiuretic hormone [ADH], a.k.a. arginine vasopressin) that affect the kidneys, hypovolemia, or an exaggerated response to acetylcholine (ACh) with prolonged vasodilation.[14,25-28] "Prolongation of ACh-induced vasodilation is suggestive of a disturbance to cholinergic pathways, perhaps within the vascular endothelium of patients with CFS, and might be related to some of the unusual vascular symptoms, such as hypotension and orthostatic intolerance (OI), which are characteristic of the condition."[28]

In a CFS cohort predominantly made up of those with an infectious trigger, gene expression was tested before and after moderate exercise. Most patients had increases in gene expression for some adrenergic receptors and catechol-O-methyltransferase (COMT).[29] In a subgroup, who had decreases in gene expression for a-2A adrenergic receptors, the majority also had OI.[29] In adolescents with CFS, "CFS might be related to polymorphisms

of COMT and the beta 2-adrenergic receptor."[30]

Autonomic dysfunction is often seen alongside cardiac and sometimes endocrine diseases. The autonomic dysfunction in CFS and in the diseases that run in CFS patients' families may potentially share some similar mechanisms.

Increased sympathetic activity, also known as a hyperadrenergic state, is seen in several CFS cohorts, POTS, many of the cardiac conditions, including DCM, and in some cases of diabetic autonomic neuropathy (DAN).[31-35] One potential mechanism involves changes in the norepinephrine transporter (NET). A decrease in the density or activity of NET has been linked to many of these same conditions. It has been found in some cases of OI, cardiac conditions (DCM, post myocardial infarction [MI], degenerative mitral valve prolapse [MVP], sustained ventricular fibrillation, arrhythmia), and possibly diabetes or DAN.[33-35] In addition, a mutation in NET has been found in a family with OI.[33] When researchers have used pharmaceutical agents to inhibit NET, they have reported results that resemble OI with signs and symptoms that include fatigue, palpitations, headache, dry mouth, nausea, and urinary urgency.[36]

Another potential mechanism is through autoantibodies. In POTS patients, autoantibodies have been found to "cross-react with a wide range of cardiac proteins and may induce alterations in cardiac function." "Many of the proteins have previously been implicated in cardiac dysfunction or cardiac disease. ..." Of the 10 POTS patients studied, one had CFS plus fibromyalgia (FM), one had FM, and both had some of these autoantibodies.[37]

In OH, most patients had autoantibodies to at least one of the following receptors: beta 1-adrenoceptors (B1AR), beta 2-adrenoceptors (B2AR), muscarinic 2-recptors (M2R), or muscarinic 3-receptors (M3R); and 25% had more than one autoantibody.[38,39] These autoantibodies may act as agonists, "causing or enhancing peripheral vasodilation (mediated by B2AR and/or M3R activation) or inhibiting compensatory rise in pulse rate (M2R)." "These data support the concept that circulating agonistic autoantibodies serve as vasodilators and may cause or exacerbate orthostatic hypotension."[38] This team noted, in one study, 4/6 patients had other autoimmune diseases, and in another study, diabetics were included because autonomic dysfunction can occur in association with diabetes.[38,39]

Autoantibodies to beta adrenergic receptors and/or muscarinic receptors have also been linked to some cases of DCM, Chagas, post MI, ischemic HF, atrial fibrillation, ventricular tachycardia, and DAN.[40,41] In one study, over half the patients with ventricular arrhythmias had autoantibodies to beta 1- and beta 2-adrenoceptors.[41] In HLA-DR4 positive DCM patients, up to 72% had beta 1-adrenoreceptor autoantibodies.[7] In addition, in one study, 38.8% of DCM patients were found to have M2R autoantibodies.[42] In DCM, "A highly significant correlation was found between the presence of antimuscarinic receptor-2 autoantibodies and anti-beta-adrenoceptor-1 autoantibodies in the patients' sera."[42]

In other diseases with autonomic dysfunction, researchers are looking at autoantibodies and the norepinephrine transporter, and looking into similar mechanisms could open up new research avenues in CFS as well.

(The autonomic nervous system is regulated by adrenergic and cholinergic receptors in the sympathetic and parasympathetic nervous systems respectively. Beta 1-adrenoceptors and muscarinic 2 receptors primarily affect heart

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rate, and beta 2-adrenoceptors and muscarinic 3 receptors primarily affect blood pressure. In addition to these receptors, the NET and the enzymes catechol-O-methyltransferase [COMT] and monoamine oxidase [MAO] also influence adrenergic activity. If in the density or activity of the NET is decreased, and allows norepinephrine to stay in the synaptic space longer, or if there are lower levels or activity of the enzymes COMT or MAO, which would allow catecholamines to accumulate rather than be broken down, these could result in a hyperadrenergic state. Hormones [renin, aldosterone, ADH]b that affect the kidneys influence blood pressure through their effect on blood volume.)

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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.

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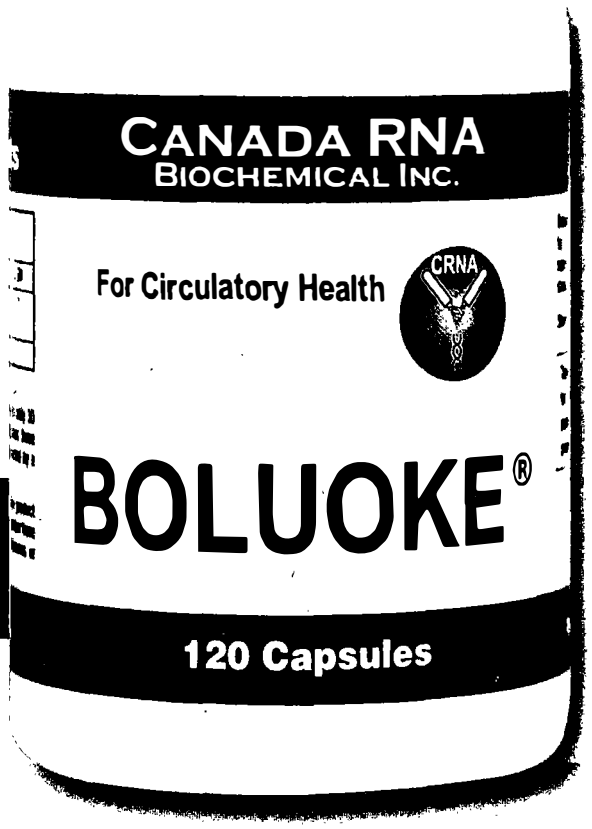
- ✔ Modifies CA-cell adhesion: ↓P-Selectin, ↓E-Selectin
- ✔ Decreases microbial resistance: breaks down biofilm
- ✔ No significant effect on INR or PTT



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Update: Injection Therapies for Chronic Fatigue and Fibromyalgia

by Paul S. Anderson, NMD

Introduction

The purpose of this review is to collate and summarize some of the available scientific data regarding potential causes, aggravations and therapies in the fibromyalgia/chronic fatigue (FMS/CFS) and like syndromes. This review is not intended to be encyclopedic in scope but rather to give some data-driven rationale for common therapies clinically recognized as useful in these syndromes. Additionally, the data presented are limited to injection therapies. As injection therapies are a broad topic and the technical points of safe administration are numerous and beyond the scope of this article, limited discussion of technique-oriented data (such as dose and administration) will be given. It is assumed that if practitioners wish to use this information to treat patients, they have the prerequisite training in the safe administration of any substances mentioned by injection therapies.

Additionally, it should be noted that noninjection therapies typically crucial to the treatment of FMS/CFS, while not discussed in this review, are assumed to be known and practiced concurrently. These include but are not limited to endocrine support, immune and infectious therapies, sleep hygiene and therapies, digestive support and diet therapy, as well as many others. And finally any injectable nutrient mentioned below should be added to the oral repletion therapy of the FMS/CFS patient both between and after the injection therapy if the individual patient gastrointestinal function allows.

Basis of the Disorders

Much has been published regarding the potential causes of FMS/CFS. Most clinicians agree that these conditions are multifactorial and patient specific. Potential partial causes or aggravations of FMS/CFS include hippocampal dysfunction, neurotransmitter imbalance and autoimmune attack, lifestyle and physical activity deficits, oxidative stress and mitochondrial dysfunction, methyl cycle defects, seasonal affective disorder, anemia, and many others.[1–15,36,52]

Given the broad base of data regarding potential cause and the logical conclusion that FMS/CFS are therefore multifactorial, anecdotal positive clinical experience in broad-based therapies, both oral and injection, match the available data and make logical clinical sense. The discussion below attempts to give scientific and clinical rationale to common injection therapies that address the above causal relationships in FMS/CFS. When the term *clinical experience* is used in this review, it refers to the author's two decades' experience in treating FMS/CFS with multiple therapies including over 50,000 IV and injection administrations.

As a small number of reviews or studies on injection therapies in FMS/CFS exist, this review will focus on updated information regarding potential biological indications for injection therapies commonly employed in the integrative medical setting.[18–20]

Therapeutic Targets for Injection Therapies

Therapeutic targets for injection therapies are well suited to access some of the common potential causes of FMS/CFS. These include neurotransmitter imbalance and autoimmunity, oxidative stress and mitochondrial dysfunction, methyl cycle and other genomic defects, anemia, dehydration and like comorbidities.

Hydration

Dehydration is known to aggravate many of the CNS manifestations of FMS/CFS such as "brain fog" and to decrease quality of life in ill people.[16,17] Although many nutrient formulas are hypertonic and thus not hydrating, our clinical experience shows that the desired IV formula can be made hydrating if the osmolarity is adjusted to isotonic or mildly hypotonic (170–310 mOsm/L) and that this adjustment can improve tolerance and outcome of the IV therapy. While oral hydration is always a primary goal of therapy, the addition of a hydrating type IV formula can additionally be beneficial in this population.

Vitamin C/Ascorbic Acid (ASC)

The use of ASC in IV therapy is well known and reasonably well studied and reported on elsewhere in the literature and clinical experience. Limiting the discussion to symptoms related to FMS/CFS, such as fatigue, pain, and immune deficits, ASC infusion can be a helpful addition. Use of ASC IV has been shown to improve pain in viral infections and fatigue, as well as oxidative/redox balance.[7,21,22] Doses in studies were moderate (5 to 15 grams) and are amenable to admixture in other water-soluble nutrient infusions. In clinical practice, the author has seen similar results with these relatively low-dose strategies, as well as higher-dose oxidative ASC infusions in treating infectious comorbidities of FMS/CFS.

Magnesium

Long a staple of oral and injection therapies in FMS/CFS, magnesium enjoys great clinical popularity in most clinicians' assessment. Some of the things that injected magnesium can add to the therapy of FMS/CFS include NMDA/glutamate receptor activity decrease, causing lower nociception and CNS arousal, and acetylcholine blockade, causing skeletal muscle relaxation, cardiac muscle calcium channel downregulation, as well as increased cell ATP and glutathione activity.[23-27] An additional benefit of injected magnesium is a relatively long therapeutic window following injection. In a human study of IV magnesium, Silver reported that tissue levels rose for 24 hours following infusion and distributed for another 24 hours, giving a total postinfusion therapeutic window of at least 48 hours following one infusion.[27] The author's clinical experience has been that IM doses of 0.5 to 2 grams magnesium sulfate 50% are tolerated as well as IV doses of between 2 and 8 grams of magnesium. IV doses of this magnitude need to be appropriately diluted and started at lower doses and escalated to the patient's cardiac tolerance.

The Amino Structures Taurine and Carnitine

While many amino acids are necessary in the therapy of FMS/CFS, in the author's clinical experience, two amino structures found to be exceptionally helpful are taurine and carnitine.

Carnitine (either in the L form or the more bioavailable acetyl-L form) is useful in varied targets affecting the FMS/CFS patient, including decreasing neurotoxicity, decreasing lactic acid buildup, as well as its more commonly known biochemical function of transporting fatty acids into the mitochondria for beta oxidation-based energy production.[28,29] The L-carnitine form in our clinic is administered IV at doses of 500 to 4000 mg and the acetyl-L-carnitine form at doses of 100 mg to 1000 mg in most cases.

Taurine is the master osmolyte in the human body and as such regulates distribution of the excitable ions (Na, K, Ca, Mg and Cl) to their appropriate sides of the cell membrane.[30,31] In this role, the author's clinical observation has been that the addition of taurine to IV formulas containing magnesium and other excitable-tissue acting minerals causes a greater benefit as reported by patients. For example, the addition of taurine to a formula with magnesium will be perceived by patients to have a more muscle-relaxing effect in many cases. Taurine is used constantly at the cell membrane and thus depleted both in low dietary intake as well as by oxidative stressors.[31] Taurine in our clinic is dosed between 200 and 1000 mg in most IV formulas.

Methyl Cycle and Genomic SNP Support

In a scientific presentation by the author, a trial was reported investigating the incidence of MTHFR defects in the general population versus a sample of race-matched patients with known FMS/CFS (n = 88).[6] The incidence summarized in Table 1 was much higher for homozygous C-677 defects as well as compound heterozygous defects in the FMS/CFS sample than the general population.

Once this association was established, an active comparator interventional trial was conducted to assess what if any support of the damaged methyl pathways via nutrients would add to clinical outcomes. Addition of a balanced methyl support oral formula as well as methylated forms of injectable B12 and folate resulted in data summarized in Table 2.

The intervention in the 88 patients already receiving treatment in an integrative medical clinic for their FMS/CFS already included all the comorbidity therapies mentioned in the introduction above. Prior therapy time frame was from 1 to 5 years, and all patients were not progressing with respect to additional positive

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Table 1

Incidence Data	Hetero A1298C	Hetero C677T	Compound Hetero	Homo A1298C	Homo C677T
Study n = 88	23	12	19	9	22
% CFS/FMS Participants	26	13	23	10	25
% Normal population	43	43	15	11	11
% Incidence Difference	−40	−70	+53	−1	+44

Table 2

Result of treatment – Active comparator	Hetero A1298C	Hetero C677T	Compound H+etero	Homo A1298C	Homo C677T
Intervention % (of n)	22	25	47	50	27
% outcome improvement	+55%	+75%	+56%	+56%	+71%

treatment or symptom outcome prior to the methyl support.

Well-rounded support for methylation (MET) as well as cystathionine beta synthase (CBS) pathways appeared well tolerated in this study. This fact creates the need for more than simple injection of a methyl donor such as 5-MTHF or methyl B12 in these patients. A therapeutic injection strategy is listed below.

Care should be taken to titrate the doses of supportive parenterals up to patient tolerance. Some younger patients will tolerate a faster titration to full dose and some not. Most patients with higher-grade defects (homozygous, compound heterozygous or heterozygous with CFS, FMS, chronic neuroinflammatory disease, and any with elevated homocysteine) who are over 35 to 40 years of age will require a slower titration but ultimately higher dosing based on our observations. Additionally, in some patients with numerous additional SNP defects, a lower and more inclusive formula may be required in order to support the other SNP defects. In our clinical experience, this is most common in patients with COMT/MAO and other like SNP defects.

Data regarding injection/parenteral support of methylation defect treatment in this setting cover a span of two decades, but due to the lack of available active-form nutrients for parenteral administration, some interpretation is necessary. Older recommendations were generally safe but lacked the agents available currently such as parenteral 5-MTHF and methyl B12.[32–34] Newer interventional trials used injection-grade 5-MTHF and hydroxyl-B12 with success and patient tolerance.[35]

Injectable Treatment Strategies

(Note: Oral supportive agents are recommended to augment these parenteral agents if tolerated by the patient.)

Methyl donor support including methyl B12 2.5–5 mg IM once to twice weekly (methyl B12 can be compounded from 2.5 to 5 mg/mL).

Direct 5-MTHF pathway support: 5-MTHF ramp up 1–10 mg IM once to twice weekly (5-MTHF can be compounded as 2.5 to 5 mg/mL). In patients in whom 5-MTHF and/or methyl B12 are too stimulating (as in COMT/MAO SNP defects), substitution with folinic acid (calcium folinate) and hydroxo-B12 can be made.

Collateral pathway (CBS) support with pyridoxine HCl 25–50 mg IM once to twice weekly is useful (Pyridoxine is generally 100 mg/mL).

B2 and B3 as obtained in parenteral B100 complex (1 mL B100 contains 100 mg thiamine HCl; 2 mg dexpanthenol; 2 mg riboflavin 5 phosphate-Na; 100 mg niacinamide; 2 mg pyridoxine HCl).

Sample IM formula:

0.5 mL: Methyl B12 (5 mg/mL)
0.25 mL: Pyridoxine HCL (100 mg/mL)
0.25 mL: 5-MTHF (10 mg/mL)
0.5 mL: B100 complex

Notes:

- This may be painful due to the pyridoxine and B100. Recommend injecting into the deep hip muscles or lateral thigh if patient is administering at home. Additionally, 0.5 mL plain procaine or lidocaine may be added.
- May precipitate. Recommend adding the 5-MTHF to the syringe first, then the other additives. If that does not stop precipitation, the 5-MTHF may need to be in a separate syringe.
- This may be given as a slow IV push diluted with 10 mL sterile water (or normal saline). Ideally in a push syringe, add sterile water, then the 5-MTHF, then the other additives. In a higher-volume IV formula, the above doses are generally higher.

Iron Status and Ferritin

Ortancil et al. include a statement that significantly correlates with the author's clinical experience "Our study implicates a possible association between FM and decreased ferritin level, even for ferritin in normal ranges. We suggest that iron as a cofactor in serotonin and dopamine production may have a role in the etiology of FMS."[36] Most commonly, oral repletion of iron stores via diet and supplement interventions is preferred. In the author's experience, in those with the other mentioned comorbidities and low ferritin of over 5 years' duration, injectable iron may be required. Clinical experience and the study by Ortancil indicate that a ferritin level over 40 (and ideally 50–75) is required to replenish the mitochondrial iron reserves as well as hematologic requirements. Both primary targets of iron stores (mitochondrial and hematologic) contribute significantly when iron stores are low.

Injectable iron is known to have a higher incidence of anaphylaxis and other high-grade adverse events than most other nutrients. As such, the clinician should have very specific and proper training before attempting injectable iron formulas, as well as available emergency medications and interventions should an adverse event occur.

In the author's clinical experience spanning over 3000 iron injections, the use of iron dextran is limited to Z-Track IM injection (due to the high rates of anaphylaxis when dextran is infused), and the gluconate and sucrose forms of iron are reserved for IV infusion. Used appropriately, all forms can raise ferritin and iron status faster than any oral repletion ever can, and clinically are associated with faster positive outcomes in low-ferritin patients.

Glutathione

A favorite IV additive, glutathione is known by those who use it to have extremely positive effects in the treatment of a wide range of illnesses. In the FMS/CFS setting, it

also is known to be a helpful addition to most IV protocols. Although much has been written about the potential benefits of glutathione augmentation in medicine, the FMS/CFS patient may have a greater need for glutathione augmentation due to higher oxidative stress loads as well as a greater need for appropriate cell regulation.[37,38] In addition to these factors, a connection between FMS/CFS and MCS is clinically noted in many patients. Glutathione is one factor in aiding repair of cell metabolism in MCS as well as damaged redox states in FMS/CFS.[45,51,52] These and other likely reasons for inclusion are why the author includes glutathione IV in all FMS/CFS patient protocols. General doses are between 1 and 3 grams and may be as high as 6 to 10 grams in some cases. Clinically, the use of glutathione IV appears to be more efficient when support nutrients (such as are found in the general nutrient IV formulas) are given before the glutathione infusion. As some patients will have sulfation SNP defects and other reasons not to tolerate glutathione, the author typically uses a lower test dose on the first IV infusion of glutathione ranging from 100 to 500 mg.

The Lipoic–Acid Based Thiols

Alpha-lipoic acid (ALA): ALA is a thiol and as such is known in basic science to support levels of glutathione in the liver and other tissues. In experimental models, ALA has been shown to be helpful in pushing the redox balance in a positive direction via modulation of inflammatory cytokines such as tumor necrosis factor and NF-kappaB.[39,40] Like glutathione, the lipoic acid molecules bring a high level of respect for clinical efficacy from those who use them. Due to recent changes in pharmacologic compounds of ALA, it is recommended that practitioners discuss dosing and potential reactions based on the available form of ALA from their individual compounding pharmacies before administration.

Lipoic acid mineral complex (LAMC): Known in North America as the proprietary formula Poly MVA, LAMC has shown to be helpful in cell repair, mitochondrial repair, and radioprotection.[41–44] The author has found that low IV doses (5–15 mL) combined with low oral doses (5–10 mL b.i.d.) improve energy and other quality of life measures in FMS/CFS patients. Like ALA, LAMC does take time to work, so most patients are advised that either therapy (like all others) may need to be continued for a number of months for a positive effect to be noted.

DMSO

The sulfur-containing molecules DMSO and MSM have been reported as potentially therapeutic in FMS/CFS as well as useful in pain syndromes for palliation.[46,50] DMSO is also used to transport drugs and nutrients across membranes including the blood–brain barrier.[47–49] Given these data, as well as a long clinical history with both substances, the author utilizes both in the therapy of those with FMS/CFS. IV MSM is water soluble and mixes with most any water-soluble IV formula. DMSO is fat and water soluble and mixes well with most water-soluble formulas as well. As DMSO is a solvent, special handling and administration guidelines as taught in standard IV training should be observed. The author favors DMSO for acute and neuropathic pain syndromes and MSM for long-term therapies in FMS/CFS.

Summary

It is clear that there are many potential therapies both oral and parenteral for the patient suffering from FMS/CFS. Both the data presented and the author's experience would speak to the utility and improvement in outcomes when the above, and many other, interventions are used in a well-

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planned comprehensive care plan for these patients. Basic training and understanding of the biochemistry and pharmacology of these agents allow for safe and effective use in the IV or IM setting.

Notes

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Effective Treatment of Pain and Fibromyalgia: Treating the Root Causes

by Jacob Teitelbaum, MD

With pain medications causing over 45,000 preventable US deaths a year, it is time to recognize that there are far more effective, and safer, ways to get rid of pain!

And 45,000 deaths is a conservative estimate. Arthritis medications cause over 16,500 deaths a year from bleeding ulcers, along with a massive 40% to 300% increased risk of heart attack and stroke.[1,2] Meanwhile, over 15,000 people a year die from overdoses of prescribed codeine medications.

It is important to recognize that, like the flashing red oil light on your car's dashboard, pain is your body's way of saying that something needs attention. If you have your hand on a hot stove or have a broken leg, the cause is obvious. But most of the time with arthritis, migraines, fibromyalgia, or other common pains, the cause is less obvious. So what do most doctors do? Simply throw an often-toxic pain medication at the person!

Simply giving a pain medication without treating the cause of the pain is like putting a Band-Aid over a flashing red oil light. It looks better, but then you burn your motor out a few miles later. In the same way, if you give the person's body what it needs, the pain goes away – just like the oil light goes out when you put oil in the car. This has been shown in our research, using fibromyalgia as one pain model.[3,4]

In addition to the personal costs of pain, the financial costs are also staggering. A study in the August 2012 issue of the *Journal of Pain* showed that the economic costs of pain in the US are about $600 billion dollars a year, a huge figure that is more that the total costs of cancer and heart disease combined![5] Yet most physicians are very poorly trained in treating pain, while being indoctrinated with a dogmatic belief that any holistic or non-MD practitioners who can help pain patients must be quacks. It's no surprise then that around ¼ of adult Americans suffer unnecessarily with poorly treated pain.

Let's begin by looking at how to treat the root causes of pain to get relief, using fibromyalgia (FMS) and myofascial pain syndrome (MPS), or muscle pain, as a model. These same principles also appy to treating fatigue and chronic fatigue syndrome (CFS). FMS, CFS, and MPS are common names for an overlapping spectrum of disabling syndromes. It is estimated that FMS alone affects 3 to 6 million Americans, and as many as 12 million in milder form, causing more disability than rheumatoid arthritis. Myofacial pain syndrome (MPS) affects many millions more. Although we still have much to learn, effective treatment is now available for the large majority of patients with these illnesses.[3,4] CFS/FMS/MPS represents a syndrome, a spectrum of processes with a common end point, and I will often refer to the three together.

Research has implicated mitochondrial and hypothalamic dysfunction as common denominators in these syndromes.[6] Dysfunction of hormonal, sleep, and autonomic control (all centered in the hypothalamus) and energy production centers can explain the large number of symptoms and why most patients have a similar set of complaints.

FMS/CFS/MPS

Essentially, these three conditions represent an energy crisis in one's body. Treating the root causes requires treating the underlying problems that deplete energy or interfere with energy production.

To make it easier to explain to patients, we use the model of a circuit breaker in a house: if the energy demands on your body are more than it can meet, your body "blows a fuse." The ensuing fatigue forces you to use less energy, protecting you from harm. On the other hand, although a circuit breaker may protect the circuitry in the home, it does little good if you do not know how to turn it back on or that it even exists.

This analogy actually reflects what occurs in CFS/FMS. As energy stores are depleted, hypothalamic dysfunction occurs early on, resulting in the disordered sleep, autonomic dysfunction, low body temperatures, and hormonal dysfunctions commonly seen in these syndromes. In addition, inadequate energy stores in a muscle results in the muscle shortening (think of rigor mortis) and pain that is further accentuated by the loss of deep sleep. Therefore, restoring adequate energy production, and eliminating the

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stresses that overutilize energy, restores function in the hypothalamic "circuit breaker," and also allows muscles to release – allowing pain to resolve. Our placebo-controlled study showed that when this is done, 91% of patients improve, with an average 90% improvement in quality of life, and the majority of patients no longer qualified as having FMS by the end of three months.[4]

In addition to muscle pain, about half of those with FMS have a secondary neuropathy called small fiber neuropathy (SFN). Chronic pain in general can trigger SFN, and in my experience most with FMS begin with muscle pain and MPS, which then progresses in some cases to SFN. Interestingly, SFN also is being commonly seen in association with antibody deficiencies (mostly IgG1 and -3) in clinical work being done by Dr. Mark Sivieri, and may supply a "missing link" connection between the nervous system, immunity, and even autonomic dysfunction. More on this in future articles and in an upcoming webinar (see below).

Common Causes of the Energy Crisis that Leads to Fibromyalgia May Include

infections
nutritional deficiencies
disrupted sleep
pregnancy
hormonal deficiencies
stress
toxin exposures
injury (especially brain and neck)

Diagnosis

The criteria for diagnosing FMS/CFS are readily available elsewhere. There is a simpler approach to diagnosis that is very effective clinically. If patients have the paradox of persistent widespread pain and severe fatigue combined with insomnia (if one is exhausted, one should sleep all night), they likely have an FMS related process.

Treatment

Two studies (including our RCT) have shown an average 90% improvement rate in FMS/CFS when using the "SHINE" protocol.[3,4] SHINE stands for Sleep, Hormonal support, Infections, Nutritional support, and Exercise as able. Using the acronym SHINE will simplify treatment of these patients. This article will give you an excellent start in treating CFS/FMS/MPS, and there are other tools available for simplifying and improving treatment of these complex conditions.

Tools to Simplify Care of these Complex People

1. **Free treatment tools**. These include:
   A. intake questionnaires that elicit symptoms by diagnosis (e.g., thyroid, adrenal, candida) so that you can quickly determine the underlying contributing conditions;
   B. treatment checklists. Are you repeatedly (and illegibly) writing down the same treatment recommendations over and over? Instead, simply check off the treatments that you want. They include detailed recommendations such as dosing, side effects, etc. Simply e-mail me at Endfatigue@aol.com and ask for the free treatment tools, and I will send them to you.
2. Our free **Practitioners Alliance Network (PAN)**. This is a free membership organization for health-care practitioners. Our mission is to provide a common platform for bringing together health-care professionals from widely diverse backgrounds in order to foster communication and to help practitioners grow their practices.

   PAN members participate chiefly through a private, members-only website where practitioners gain access to many free benefits that include:
   A. membership in the PAN Forum, a practitioners-only social website and discussion forum where members can ask and answer questions – including questions for Dr. Teitelbaum;
   B. access to the PAN Buyers Club, a group of companies that offer PAN members special discounts on nutritional supplements and office supplies for their practices (typically at rates of 7.5%–15% below wholesale);
   C. opportunities for cross-referrals through a growing community of PAN members;
   D. access to free live webinars conducted by Dr. Teitelbaum and guest presenters on health topics of interest to practitioners;
   E. opportunities to help suggest, design, and participate as study authors in PAN-sponsored research studies. PAN has just launched a study on Alzheimer's treatment using a holistic protocol. There will be many more.
3. **Online training**. There is an 8-hour online training that you can take at your leisure which will make you an expert on treating FMS/CFS/MPS and also get your name on our patient referral list. See www.vitality101.com/PAN for info.
4. **Our free online Energy Analysis Program** (at www.EndFatigue.com), which will analyze the person's symptoms and even pertinent labs if available, determine the factors contributing to the person's energy crisis, and tailor a program to optimize that person's energy. The questionnaire that the person fills out is the same as the one in the treatment tools, so your staff can enter the info if you like and have the detailed analysis and treatment protocol come from you instead of the online program. That allows you to be "the Wizard"!

All involved in the healing arts in any and all forms are invited to come and share what you know while learning from each other. Let's come together to heal our health-care system!

Treating the Root Causes of Pain with SHINE

S – Sleep: Sleep is when tissue repair occurs, and is *critical* for the resolution of most types of chronic pain. A foundation of FMS/CFS is the sleep disorder. Using treatments that increase deep restorative sleep, so that the person gets 7 to 9 hours of solid sleep each night, is critical. Start treatment with natural therapies or with a low dose of sleep medications that do not decrease stage 3–4 sleep. Continue to adjust the treatments each night until the patient is sleeping 8 hours a night without a hangover.

The natural remedies that I recommend you begin with include the following:

1. Herbal preparations containing a mix of valerian root, wild lettuce, Jamaican dogwood, passionflower, hops, and theanine. These are all combined in an excellent product called "The Revitalizing Sleep Formula" by Integrative Therapeutics. Patients can take 1 to 4 caps at bedtime. These six herbs can help muscle pain and libido as well as improving sleep.
2. Melatonin: ½–1 mg at bedtime.
3. 5-HTP (5-hydroxytryptophan): 200 to 400 mg at night. Limit to 200 mg if on antidepressants or other serotonin-raising medications.
4. Magnesium at bedtime. A hot bath with 2 cups of Epsom (magnesium) salts and some lavender oil can be very helpful.

If natural remedies are not adequate to result in at least 8 hours a night of sleep, consider these medications:

- Zolpidem (Ambien): 2.5 to 10 mg q.h.s.
- Gabapentin (Neurontin): 100 to 900 mg h.s. can help sleep, pain, and restless leg syndrome (RLS) as well.
- Cyclobenzaprine (Flexeril): 3 mg.
- Trazodone (Desyrel): 50 mg. Use a half to 1 tablet q.h.s.

There are over 30 other helpful natural and prescription sleep aids.

Most people with insomnia do well just with the natural sleep support. In those with CFS/FMS, the added medications may be needed. Because of next-day sedation and each medication's having its own independent half-life, FMS/CFS patients do better with combining low doses of several medications than with a high dose of one.

Although less common, three other sleep disturbances must be considered and, if present, treated. These are sleep apnea, UARS (upper airway resistance syndrome), and RLS, which is also fairly common in fibromyalgia.[7]

H – Hormonal support: Hormonal imbalances are associated with FMS. Sources of imbalance include hypothalamic dysfunction, adrenal exhaustion from chronic stress, environmental toxins, and autoimmune processes such as Hashimoto's thyroiditis. Most blood tests use two standard deviations to define blood test norms. By definition, only the lowest or highest 2.5 % of the population is in the abnormal (treatment) range. This does not work well if over 2.5 % of the population has a problem.

The goal in pain management is to restore optimal function while keeping labs in the normal range for safety. One way to convey the difference between the "normal" range based on 2 standard deviations and the optimal range which the patient would maintain if he/she did not have FMS is as follows:

Pretend that your lab test uses 2 standard deviations to diagnose a "shoe problem." If you accidentally put on someone else's shoes and had on a size 12 when you wore a size 5, the normal range derived from the standard deviation would indicate that you had absolutely no problem. You would insist the shoes did not fit although your shoe size would be in the normal range. Similarly, if you lost your shoes, the doctor would pick any shoes out of the "normal range pile" and expect them to fit you.

Thyroid Function

Suboptimal thyroid function is very common, and it is important to treat *all* chronic myalgia patients with thyroid hormone replacement if their free T4 blood levels are below even the 50th percentile of normal (Janet Travell – personal communication). Many CFS/FMS patients also have difficulty in converting T4, which is fairly inactive, to T3, the active hormone. Additionally, T3 receptor resistance may be present, requiring higher levels.[8] In most CFS/FMS patients, I give an empiric trial of Armour thyroid, ½ to 2 grains every morning, adjusted to the dose that feels best to the patient as long as the free T4 is not above the upper limit of normal.

TSH testing is not reliable. Iodine support (I use Tri-Iodine 6.25 mg a day) can be helpful. Optimizing ferritin (iron) levels by keeping them over 60 is needed for proper conversion of T4 thyroid to active T3. Selenium 200 mcg can help in Hashimoto's, but otherwise I limit selenium to 55 mcg a day, as higher doses are associated with a modestly increased diabetes risk.

Adrenal Insufficiency

I find the most reliable indicator of the need for adrenal support to be sugar cravings associated with irritability when hungry.

An excellent glandular/herbal mix for adrenal support that is very safe and effective is Adrenal Stress End (from Integrative Therapeutics). I also consider bioidentical prescription Cortef, 5 to 12.5 mg a day if needed.

Low Estrogen and Testosterone

These have been discussed at length in other *Townsend Letter* articles, so I will simply note that bioidentical and herbal support when needed is very helpful.

I – Immune Dysfunction, Infections, Inflammation, and Impingement: Immune dysfunction is part of the ➤

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FMS process. Opportunistic infections present in FMS/CFS include yeast/candida, chronic sinusitis, nasal–toxin producing *Staph aureus* infections, numerous bowel infections, and chronic, low-grade viral and antibiotic-sensitive infections (e.g., Lyme disease). These may need to be treated, especially candida, though many infections resolve on their own as immune function improves.

Inflammation also needs to be addressed, and natural remedies do so brilliantly. My favorites are below.

Treating Inflammation Naturally

My favorite natural anti-inflammatories are:

1. BCM95 highly absorbed curcumin
2. boswellia
3. willow bark
4. omega-3 EFAs

These are contained in:

Curaphen (by EuroMedica): This mix of highly absorbed curcumin, boswellia, DLPA, and nattokinase has been a pain relief miracle – sometimes helping when morphine has not. It continues to build in effectiveness over 6 weeks, but is often effective in 30 minutes. For severe chronic pain, I give 2 tabs 3× day for 6 weeks, then lower the dose or give as needed.

Pain Formula (by Integrative Therapeutics): This mix of willow bark, boswellia, and cherry is especially helpful for arthritis and back pain. For severe chronic pain, I give 2 tabs 3× day for 6 weeks, then lower the dose or give as needed.

EurOmega 3 (by EuroMedica): This vectorized omega-3 is what I use for omega-3 support. One pill delivers the same effective level of omega-3s as 8 regular fish oil capsules, containing the EFAs but leaving out the unneeded triglycerides. So 1–2 a day are plenty, with lower cost, better compliance, no toxicity or rancidity, and no fish oil burps.

I combine all 3 of the above in those with pain and add them to any pain meds that the person is on. After 6 weeks, the pain meds can often be tapered down or stopped, and the dose of the herbals lowered (or taken as needed). In a head-on study, the components of Curaphen were much more effective than Celebrex for arthritis. At the beginning of the study, 79% of the people taking Celebrex were in moderate to severe pain, dropping to 50% after 12 weeks. In those who took Curaphen equivalent, these numbers were 86% and 21%, respectively. Basically, the medication resulted in major pain reduction in only 29% in the Celebrex group vs. 65% in the herbal group![9]

Meanwhile, in another head-on study, willow bark was twice as effective as ibuprofen for back pain.[10] Besides being more effective, the herbals result in "side benefits" instead of side effects!

N – Nutritional Deficiencies: FMS/CFS patients are often nutritionally deficient. B vitamins, magnesium, ribose, iron, coenzyme Q10, malic acid, and carnitine are essential for mitochondrial function. These nutrients are also critical for many other processes. Although blood testing is not reliable or necessary for most nutrients, I do recommend that you check B12 and ferritin levels.

I begin people with FMS/CFS on the following nutritional regimen:

1. A quality multivitamin suited for their needs. It should contain at least a 50 mg B complex, 150 mg of magnesium glycinate, 900 mg of malic acid, 2000 IU of vitamin D, 500 mg of vitamin C, zinc 15 mg, selenium 50 mcg, chromium 200 mcg, and amino acids. Because there are dozens of important nutrients, and patients got tired of taking handfuls of tablets each day, I now use a powdered multivitamin called the Daily Energy Enfusion (by Integrative Therapeutics) in almost all of my patients (even those without CFS) for overall nutritional support. It contains over 50 nutrients in a single drink, replacing over 35 tablets each day. This should be taken long term with 1 EurOmega 3 daily.
2. If the ferritin is under 60 mg/ml, supplement with iron (with added vitamin C for absorption and not within 2–6 hours of a thyroid dose).
3. If the B12 level is under 540 pg/ml, I recommend B12 injections, 3000 mcg IM three times a week times for 15 weeks, then as needed based on the patient's clinical response or 5000 mcg (5 mg) SL daily.
4. Coenzyme Q10: 200 mg a day.
5. Acetyl-L-carnitine: 500 mg twice daily for 4 months.
6. The person should avoid sugar and caffeine, and water intake should be increased.
7. An especially important nutrient? Ribose (Corvalen by Douglas Labs). This is one of the single most important nutrients for treating fibromyalgia, A study that we authored published in the *Open Journal of Pain* showed that ribose not only significantly decreased fibromyalgia pain but also increased energy an average of 61% at 3 weeks.[11]

It is also very effective for heart disease as well. *I consider ribose the most important nutrient discovery of the decade!*

A Few Final Points

Topical Pain Relief

When dealing with localized pain, it is often neither needed nor desirable to soak all 200 pounds of a person to treat 3 ounces of painful tissue, and topical treatments can be excellent. A few of my favorites include:

1. Comfrey topical (Traumaplant by EuroPharma). This is an amazing and often quickly effective treatment for many kinds of pain, and a top priority for everyone's medicine cabinet. Try it and prepare to be amazed
2. Topical menthol creams (such as Tiger Balm) can help for tension headaches and other muscle pains
3. Compounded pain creams. For prescribing practitioners, this can be helpful for nerve and tendonitis pain.

A Few Specific Pain Conditions

Neuropathies

Nutrient	Amount
Vitamin B6 (P5P)	50 mg/day
Acetyl-L-carnitine	1500–3000 mg/day
B12	500+ mcg/day
Alpha-lipoic acid	300 mg 2×/day for 6–2 weeks (diabetic & other neuropathies

Migraines

1–2 g IV magnesium sulfate over 15 minutes gives immediate elimination of the migraine in 85%![12,13]

Migraines: Acute

Excedrin Migraine	Amount
Acetaminophen	500 mg
Aspirin	500 mg
Caffeine	130 mg
Butterbur (Petadolex)	You can give 100 mg every 3 hours to eliminate an acute migraine Give 50 mg 3× per day for 1 month and then 50 mg 2× per day for prevention

Migraines: Prevention

Nutritional support and treating food sensitivities are very important

Nutrient	Amount
Vitamin B2 (riboflavin)	400 mg/day (67% decrease)[14]
Butterbur	50 mg 2× per day
B12	1000 mcg (43% decrease)
CoQ10 and Magnesium	200 mg/day of each may also help

Conclusion

Effective treatment is available for almost all pain, just not from standard physicians. Although this article focuses on metabolic aspects of pain relief, applying structural therapies (e.g., chiropractic and osteopathic manipulation and numerous forms of body work), biophysics (e.g., acupuncture and frequency specific microcurrent), and other modalities can also be dramatically effective. People with pain do best, as do their practitioners, when practitioners speak with each other, cross-refer, and share information!

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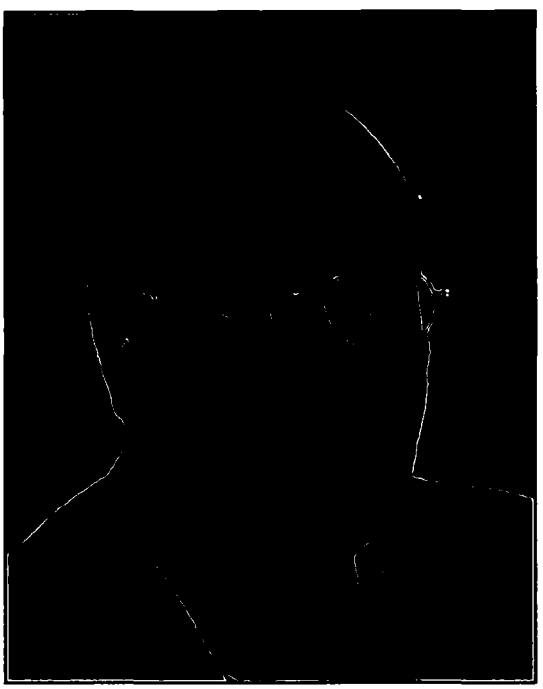
Phenotypes and Therapeutic Outcomes: Neurofeedback and Medication

Jay Gunkelman, QEEG

Based on an interview with Nancy Faass, MSW, MPH



The *DSM-5* was developed with the idea that the correct diagnosis leads to the proper treatment. The problem is that although behavior patterns tend to be reliably mirrored in the *DSM*, the resultant diagnosis fails to indicate how patients will respond to treatment. In the ADD population, for example, of two patients with the same *DSM*-based diagnosis, one may respond positively to a stimulant and the other may react negatively to that same drug, and might require a different medication or even a different therapy.

Rather than basing treatment on behavioral symptoms, in my own work I have developed treatment protocol guided by patterns in the brain's electrical activity, reflected in the EEG (electroencephalogram). This enables targeted use of medications, supplements, and therapies. For example, only 35% of the general population has a good response to SSRIs. However, if you target antidepressant prescriptions using EEG patterns, that success rate increases to approximately 80%. This approach can also be applied in orthomolecular therapies.

The Phenotype Model

At this point in my career, I have analyzed far more than 500,000 EEGs, passing that number in the 1990s. As I reviewed trends in the EEGs over the years, I noticed patterns of EEG activity associated with common "failure modes" in clinical cases. Over time I identified eleven distinct EEG patterns, two of these having known genetic correlates. In a retrospective paper in 2005, I hypothesized that these eleven patterns were phenotypes, and that nine of these clusters had unidentified genetic correlates. Since not all genes are expressed, evaluation of genetic patterns tends to be less fruitful than the study of epigenetics and phenotypes when looking at genetic expression. These phenotypes are seen as an intermediate step between genetics and behavior, reflecting actual expression of the underlying genetics.

In a phenotype model of patients with addiction, for example, I proposed that people sharing the same EEG pattern (phenotype) were likely to respond to the same therapy, regardless of their psychological history or their "story" as reflected in the *DSM* categorization. Therapy could be selected based on the EEG pattern, rather than the *DSM*-based diagnosis alone. Applying this approach in the clinical setting, we found that therapeutic outcomes were optimized. Patients not only achieved sobriety, they also showed measurable improvements in neurocognitive function.

Today we know a great deal about patterns of brain activity through the extensive research on monozygotic twins, who have virtually identical EEGs (unless one of the twins has an acquired condition such as traumatic brain injury). A clinician can match monozygotic twins in pairs simply by looking at their EEG patterns.

Since the 2005 retrospective paper, we have prospectively tested the phenotypes' predictive accuracy in clinical therapy. The phenotypic patterns test out extraordinarily well, to such an extent that we have been able to identify clusters for which we now have genetic correlates, previously unidentified.

Using our EEG phenotyping, Johnson & Johnson drew blood on 100 patients, from an original sample of 126 research patients identified with the *DSM*-based diagnosis of depression, further subdividing them using our EEG phenotyping. The researchers found an unexpectedly powerful application of the EEG phenotypes in categorizing these patients into genetic clusters and will be publishing

these outcomes. We found, for example, that beta spindles seen in the EEG corresponded with a gene that regulates the enzyme that degrades serotonin (5-HT), dopamine (DA), and norepinephrine (NE). This enzyme, catechol-O-methyltransferase (COMT) has three forms: COMT-0, 1, and 2, referring to the number of allele pairs. We found COMT-2 to be associated with the beta spindle, and a negative response to SSRIs, unlike COMT-0 which predicts a strong SSRI response. As we had hypothesized, the EEG patterns and the genetic testing paralleled specific clinical behavior patterns and responses to treatment. The COMT-2 patients, for example, did not respond well to SSRIs, with a tendency to overarousal. This research was published retrospectively in 2005, and has been validated in subsequent published prospective research on ADHD, depression, addiction, and also non-clinically in peak performance applications.

Subsequent research involved more than 400 psychiatric patients using EEG and qEEG (the numerical analysis of electroencephalography data and associated behavioral correlates). We were able to successfully predict which patients were likely to fail with psychiatric medications and to determine how to treat these medication nonresponders effectively without drug therapy. Traditionally, treatment of any psychiatric condition can be an extended process involving medication trial and error, and a series of treatments or treatment combinations. That can also involve a number of side effects before the patient stabilizes. However, if we examine brain activity before we treat, we can use information gained from EEG patterns and the associated phenotypes to select optimum treatment.

Targeting Treatment

Phenotypes by definition occur in both normal and clinical populations, cutting across *DSM*-based categories. Each phenotype has specific underlying neurochemistry, making identification of chemical approaches to normalization quite straightforward. Within any single *DSM* category there are multiple clusters of EEG phenotypes and their associated variety of neurochemistry. Consequently, diagnosis alone is incapable of predicting the right pharmaceutical or nutraceutical approach.

Medications. EEG patterns can be used to effectively predict which medications are most likely to be effective (or not) for any given patient. In psychiatry, treatment failure is common, as seen in the STAR-D study on depression. This ➤

QEEG Patterns/Phenotypes and Interventions

QEEG Profile	Description of Pattern	Medication	Neurotransmitter Support	Neurofeedback
Diffuse slow activity, with or without low-frequency alpha	Increased delta and theta (1 – 7 Hz) with or without low posterior dominant rhythm	Stimulant	Dopamine (DA) and norepinephrine (NE)	Inhibit midline frontocentral activity below 10 Hz Reward anterior beta frequencies
Focal abnormalities not epileptiform	Focal slow activity or focal lack of activity			Inhibit slow activity (<10 Hz) Reward higher frequencies (>12 Hz)
Mixed fast and slow	Increased activity below * Hz Lack of alpha Increased beta activity	Both stimulant and anti-convulsants		Inhibit slow frequencies Reward middle frequencies Reward sensori-motor rhythm
Frontal lobe disturbances	Frontally dominant excess theta or alpha frequency activity	Anti-depressant or stimulant	DA Serotonin (5-HT)	Inhibit midline frontocentral activity below 10 Hz Reward anterior beta frequencies
Frontal asymmetries	Variable asymmetry L>R or R>L, primarily at F3, F4	Anti-depressant	5-HT, DA, NE	Reward F3 beta, Inhibit F3 theta and alpha frequencies
Excess temporal lobe alpha	Increased alpha activity generated in the temporal lobe	Stimulant	DA Limbic activity	Inhibit 9 – 12 Hz activity over affected temporal region(s) Inhibit frontal slow activity
Epileptiform	Transient spike/wave Sharp waves Paroxysmal EEG	Anti-convulsants		Inhibit low and high frequencies over affected regions Central strip training Reward SCP(slow cortical potentials)
Faster alpha variants, not low voltage	Alpha frequency greater that 12 Hz over posterior cortex		Excess NE or excitatory neuro-chemistry	Reward 9 – 10 Hz alpha at Pz Shift alpha frequency lower with shift in alpha/theta protocol
Spindling excessive beta	High frequency beta with spindle morphology, often with anterior emphasis	Anti-convulsant	COMT-2 genetics; DA, NE, epinephrine	Inhibit beta frequencies Inhibit a broad frequency band
Generally low magnitudes (fast or slow)	Low voltage EEG overall	Metabolic support	Nutraceuticals	Reward posterior alpha activity
Persistent alpha with eyes open	Lack of appreciable alpha Lack of alpha attenuation with eyes open			Reward beta frequencies Inhibit alpha Reward higher frequency alpha

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large study found that patients had a 25% chance of having the right drug prescribed the first time, with success rates dropping precipitously with each added trial. For patients who did not respond well by the third drug trial, there was a high likelihood that they would never be effectively treated with medication. Among people suffering from depression, approximately 36% either had a negative response to drugs or never responded appropriately.

Supplements. Of interest to orthomolecular providers, the eleven EEG phenotypes also suggest which neurotransmitters are imbalanced. For example, one cluster of the ADD population has a genetic marker involving dopamine transporter genetics. Their dopamine levels are insufficient at the level of the striatum (deep basal areas of the frontal lobe), and as a result, elevated theta levels appear in the EEG, an indication that the patient needs more dopamine. This particular pattern can be improved by giving dopamine reuptake inhibitors such as Ritalin, a form of stimulant. Not all stimulants have this effect, as amphetamines have a different mechanism involving increased norepinephrine, which speeds up the alpha frequencies and is not related to the theta rhythm. Practitioners expert in orthomolecular therapy who are knowledgeable regarding amino acid supplementation and nutrition can use their approach to alter the level of the appropriate precursors and support resultant neurotransmitter levels if they know which systems to target.

Neurofeedback. The phenotype approach can also be efficacious in predicting what type of neurofeedback is needed, based on peer-reviewed and published classic neurofeedback protocols. This approach increases the efficacy of the therapy by indicating protocols that match the client's physiological pattern. Neurofeedback protocols which match the phenotype patterns were published in 2005.

Research Funding

The challenge in this field is the fact that the U.S. has not funded neurofeedback research since the 1970s. The E.U., Germany, and Korea have ongoing international studies that are well funded. There is a large consortium research project that was just funded by the NIH, primarily due to the positive outcomes reported from the European research. International neuroscience is re-leveraging interest in neurofeedback research.

The Treatment of Pain

There is no EEG signature specifically associated with pain. There are no patterns that would indicate pain being experienced in one patient as compared with the next, nor any discernable pattern that might suggest the presence or absence of pain in a particular patient. However, this lack of specificity does not mean the brain is uninvolved in the perception of pain, or that changing brain function won't improve the perception of pain for an individual

Neurofeedback. On the EEG "tracings" the baseline indicates the level of direct current (DC) in the brain. This direct current (DC) system was first described In the *British Medical Journal* in 1875 (issue #2) by Richard Caton, decades before the human EEG was developed in 1924, based on the work of Hans Berger.

When an area of the brain is in use, it shifts to an electronegative state. (In the vocabulary of electronics, negative current is referred to as "down." However, in describing an EEG, negative voltage is "up.") In an EEG, when the baseline goes up (negative), that brain is more active in that particular area. To reduce pain, the somato-sensory strip can be shifted from an electronegative state in which the cortex is active, and the patient is perceiving the pain, to an electropositive state in which the brain is "off," dialing down pain sensitivity. This type of change can be taught with neurofeedback or induced through a variety of treatments.

I experienced this directly when I had the unfortunate occurrence of a severe hand injury. Being fully immersed in the field of biofeedback, I learned how to dial down pain working on myself. At the time, I was in charge of the first state hospital-based biofeedback lab in the world, which gave me access to an exceptional resource. I used neurofeedback to interrupt the pain peripherally, turning off the generation of the pain at the source, and also in the central nervous system, to change my perception of the pain.

This concept of turning off the perception of pain can be seen in the work of Kowakami, a Japanese Kundalini expert (noted for inserting large metal skewers in his neck and tongue, apparently oblivious to pain). I had the opportunity to track his responses on an EEG at one of the demonstrations he gave in the U.S. for a professional society. The data showed that he shifted into an electropositive state, turning off sensation, inserted the skewers, and then turned back on brain activity so that he was fully conscious, but pain-free.

Neuromodulation. In addition to neurofeedback training, the brain can be treated with DC current stimulation, the treatment essentially turning the brain area being treated on or off, depending on the polarity used for treatment. This is an ancient technique used by the Greeks at the time of Christ. Claudius Galen's writings report that Pliny the Elder treated patients with epilepsy or migraine headaches using torpedo fish (electric eel). He would place the eel on the head of the patient and the creature would "shock" the patient, knocking them unconscious. When the patient awoke, their migraine headache or seizure was effectively treated.

Although our technology is clearly more sophisticated, treatment today still involves applying electrical stimulation to the cortex through the skin, skull, and meninges. We use neuromodulation techniques that include transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Approximately 10% of the current applied to the scalp goes to the cortex, the rest absorbed by skin, bone, and cerebrospinal fluid. This technique changes the excitability of the cortex, promoting a 30% to 40% increase or decrease from a baseline level, which represents 60% to 80% of the total signal. Using this approach, patients can be trained to dial down the pain.

Professionals who wish to refer patients with pain issues will want to seek out neurofeedback experts working in the area of neuromodulation, using techniques such as mag stim or DC stim. This can be a viable approach to reduce excitability in the cortex, particularly for patients who have shown an adverse reaction to medication.

Acupuncture. Techniques such as acupuncture also have neuromodulatory effects, but are beyond the scope of this paper. The electromagnetic nature of acupuncture points is well-documented. If you measure the body with a DC microvolt meter/null detector and look for areas that have higher electronegative charge, those areas turn out to be acupuncture points. The points are highly specific: moving the detector merely a millimeter or two off the point, the current source drops by orders of magnitude. This DC field system does not follow the structure of the nervous system: it is an energetic system with a distinct structure unto itself.

Therapeutic Outcomes

There are a number of different protocols for neurofeedback. Some practitioners take a highly statistical approach, such as the use of univariate scores from databases of an age-matched healthy reference population that guide their training, though these emerging protocols have yet to validate their efficacy and remain experimental. Earlier methods are well-validated in neurofeedback efficacy literature, having passed the field's own standards, based on well-designed outcome studies and also on meta-analysis review of published outcomes. The newer, statistically driven techniques may have efficacy, but it will take time for the peer review and publication process to show which approaches have appropriate levels of support.

ADD/ADHD

Pediatricians recently published a consensus position that neurofeedback has achieved level-1 evidence for efficacy in the treatment of ADD/ADHD. (Note that this is a fairly unbiased group of providers who neither suggested superiority over medication nor lesser effect than medication.) The vote of confidence was based on their review of multiple, well-controlled studies and meta-analyses. The meta-analysis literature includes a recent evaluation which reported a greater effect size for neurofeedback than for medication. The majority of the funded studies reviewed in this recent meta-analysis were done outside the USA at academic centers in Europe.

Neurofeedback and Medication

Addictions

The use of neurofeedback in addiction treatment dates back to the 1970s: I used it in my first lab and subsequently wrote an NIH grant for alpha training (which was not funded at the time). There is a robust efficacy literature for neurofeedback applied to addiction, with a history of innovative therapies and positive outcomes, reflecting the work of researchers such as Eugene Peniston and more recently Bill Scott, as the field developed the so-called "alpha/theta" protocol to treat addiction. The level of efficacy has been judged as "probably efficacious" according the hierarchy of standards in the field of applied psychophysiology.

Peniston reported a 30% recidivism rate. To provide a context for this outcome statistic, in the field of addiction treatment, Twelve-Step Programs have an 83% to 87% recidivism rate. Another challenge in judging efficacy in addiction is the fact that outcomes are generally only judged based on sobriety. Although people may be clean and sober, they still may not be fully functional.

In 2008, we published research using a standard model of addictions treatment that included group and one-on-one therapy, as generally seen in modern treatment programs, with the addition of neurofeedback. Our goal was to determine which of the eleven identified phenotypes occurred most frequently in the addictions population and to document the effect of NF guided by the phenotypes. We found that two-thirds of the addicted population had an overarousal drive mechanism. There are three phenotypes associated with overarousal, with the other one third having cingulate dysfunction, suggesting an obsessive/compulsive drive for those individuals. The overarousal individuals received classical alpha/theta training, but the other third needed a different approach. Peniston showed in his study that 70% of patients would be successfully treated using this approach, but the intervention was not effective for 30% of participants. Our findings may explain these failures as well as explaining the mechanism for the alpha/theta training efficacy.

The other third of the study population had a disorder involving a different neurological mechanism: a cingulate dysfunction located in the area of the midbrain, which manifests as an obsessive-compulsive drive, rather than as overarousal. If the cingulate is not addressed, the patient's addiction to drugs can be resolved, but they will still have a tendency to addictive behavior and typically will seek another form of addiction such as the internet, sex, or gambling. Functionally, these patients continue to have a dysfunction, even when they are not drinking or using drugs. Sobriety does not equal health... though it helps.

We found that once the brain is actually functional, whether that originally involved overarousal or cingulate dysfunction, not only are the clients sober/abstinent, they have better brain function. In our study of 30 patients with a history of mixed addiction to drugs and alcohol, all 30 of these patients were

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clean and sober at the study's completion (identified by blood work), and also at one-year follow-up. They were all still clean at three years, which is a speciously high success rate. At the time of the one-year follow-up, we also administered the Woodcock-Johnson III and found on average a 21 standard-point increase in GIA (an IQ 'equivalent'). The mean group standard score increased from 98 to 120. There was an average 20-point increase on all neuro-cognitive measures, and no scores degraded. Delayed recall increased from 60 to above 100. Not only were these patients clean and sober, they were more functional.

My conclusion: "When you help the brain work better, it works better." These gains and sobriety persisted because the patients no longer had the drive toward addiction and their brain function was optimized based on their personal phenotype. Personalized medicine aspires to this approach with the provision of effective evaluation and individualized therapy.

This methodology is based on the use of data from the EEG, applying the phenotype to define the nature of the dysfunction and pairing that with the appropriate treatment – in contrast with a psychodynamic approach to addiction that relies on the individual's "story." Given what we now know about neurochemistry and the electrochemical nature of the brain, neurofeedback provides a deeper layer of information relevant to the treatment of addictions based on reliable, repeatable measures. The effect of the therapy is pervasive, with an impact on every area of life requiring brain function. The changes are seen in the functioning of the patient, reflecting the intertwining of physiology and psychology, body, mind, and consciousness.

Autism

Our work with autism includes patients who have both affective and language issues, from the earlier classification of "Asperger's autism" (no longer in the *DSM*) to those with a fully mute presentation. Although it can take one to two years of training, we typically help patients progress to the point where they can no longer be diagnosed as autistic. These are not patients merely experiencing a little social awkwardness. Often they are individuals who essentially have no hope – clients fully on the spectra. In many cases, we are able to get them off the spectra. When we use this approach with "just Asperger's" clients we generally have much less difficulty resolving their symptoms. Treatment for autism is not fast: it is a learning approach which takes time and effort to slowly climb the EEG learning curve, step by step. Behaviors improve gradually, fading away or occasionally improving in a series of breakthrough experiences. We definitely see strong positive outcomes for our autistic clients.

Epilepsy

Only about one-third of those diagnosed with epilepsy have effective medication control of their clinical presentation, and one-third are considered "intractable." In the treatment of epilepsy, neurofeedback offers an important and viable adjunctive treatment along with medication or as an alternative to surgery. Today, brain surgery is an increasingly common form of therapy for these conditions. At three-year follow-up, meta-analysis of neurosurgery for epilepsy found a 50% chance of a 50% or greater reduction in seizure rates. Neurofeedback has an 82% chance of a 50% or greater reduction in seizures for patients *with intractable epilepsy*. In our centers, we have seen excellent results for patients with epilepsy and for those with autism.

Peak Performance

EEG patterns that mirror brain chemistry are characteristic of both normal subjects and patients. Consequently the EEG

Dual Diagnosis: Intractable Epilepsy and Autism

In our experience, individuals with the dual diagnosis of epilepsy and autism spectrum disorder are treatable. Consider the case of a severely impaired child whose family contacted one of our professional trainees in Israel. This was essentially a young person with no hope. She was experiencing multiple seizures every day and was placed on anticonvulsant medications to no effect, with an extreme level of disability. This was not a mild case of Asperger's, but rather full-blown autism.

The little girl, eight years old, could not speak and was unable even to tie her shoes. The child suffered from multiple seizures and she experienced more than 250 electrographic seizure episodes within the first 10 minutes of the baseline EEG. We applied an algorhythm in recording the data to assure consistency across repeated measures, and the reports were also confirmed by visual analysis.

At session 20, there were 115 spikes, reflecting less seizure activity. Clearly no one would describe this as improvement. However, at session 42, there were no spikes, confirmed using both the algorhythm and visual evaluation.

When the treatments began, the child was totally mute. That is the nature of intractable epilepsy and autism, a life essentially without trajectory. These are children who never really find their wings and take off. There is no altitude gained. The expectancy is that adulthood will be more of the same. However, at session 42, the child is riding a bicycle, speaking fluently, seizure-free, and no longer on anticonvulsant medications.

This is not cherry-picked data: this is one of the therapist's initial dual-diagnosis clients. We flew the therapist to the States to present her work at a meeting on Catalina Island of SABA (Society for the Advancement of Brain Analysis). An epileptologist and a neurologist specializing in autism were present, and they were amazed by the results. The therapist has video tapes of these children at various stages of treatment. What you see at the beginning is a child who has no hope and at the end, a young person who is fully functional.

can be used not only to treat psychiatric issues, but also to optimize normal functioning. To enhance performance, we treat normal subjects with the same phenotype-driven approach that we would use for clinical patients with a similar EEG pattern. At our treatment centers, we see not only patients with clinical issues, but also athletes and business professionals focused on performance. Another interesting client group is researchers studying consciousness. We do not change the treatment model when a different person walks through the door.

Ultimately, peak performance is not about achieving at the mean. It is a unique outlier state. How many Olympic athletes would be described as "average"?

Goals of Treatment

To assume that treatment takes the patient from an outlier state to the mean is a theoretical model. When you are dealing with a multivariate system such as the brain, you cannot characterize it using univariant measures. Yet today we apply Gaussian statistics from the 1950s to describe brain function. The brain has skew, kurtosis, and a level of complexity that simply cannot be described with a normal distribution.

In a realistic model of healing, we are not moving patients toward the mean, we are identifying their divergence and optimizing their function within their genetic pattern. Healing occurs within the patient's divergent genetic cluster.

Phenotype research provides the opportunity to define subsets of patients based on the genetic, neurological, neuroelectrical, and neurochemical characteristics within each patient population. Phenotypic modeling gives us the information we need to treat the patient before us, by providing data that indicates which medications, supplements, and therapies will be most effective. For patients with a complex presentation such as autism, this information is essential, given the enormous number of causal factors that can be involved.

We cannot currently alter our patients' genotypes. However, we can change behavior, genetic expression, and the severity of that expression. This work reflects the convergence of evidence-based medicine and outcomes research, applied in the practice of personalized medicine.

Jay Gunkelman, QEEG

Jay Gunkelman, QEEG Diplomate, is recognized as one of the top leaders in the field of EEG and QEEG, and has processed over 500,000 EEGs since 1972. He has served as president of The International Society for Neurofeedback and Research, as well as a board member and treasurer of the Association for Applied Psychophysiology and Biofeedback and is past-president of the Biofeedback Society of California. Jay was the first EEG technologist to be certified in QEEG (1996) and was granted Diplomate status in 2002. He has conducted, published, or participated in hundreds of research papers, articles, and books, including seminal work on EEG endophenotypes. Jay is co-founder and Chief Science Officer of Brain Science International and is a popular lecturer worldwide on the topic of QEEG and the phenotype identification of neurological disorders.

Neurofeedback and Medication

Brain Science International

BSI provides EEG training, as well as analysis and consultations on EEG recordings for clients in the U.S. and around the world on issues ranging from autism to consciousness research. We focus on EEG and phenotype analysis. Although we do not use neurochemical biomarkers in our own work, we have clients who do use this approach in working with the EEG data.

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Resources

Certification. Biofeedback Certification International Alliance (BCIA) offers training, examination, and certification in biofeedback and neurofeedback. States such as Washington require BCIA certification for neurofeedback providers, whereas in other states, licensed psychologists may perform neurofeedback without additional training (Note: buyer beware).

Website: BCIA.org

Pain Therapy. When seeking a health professional who works with chronic pain, it is helpful to know about the training program at Harvard, the Berenson-Allen Center for Noninvasive Brain Stimulation, which offers coursework in the use of mag stim and DC stim. It is important to make referrals with care. This is emerging technology across the board: just because a provider is good with one area of application does not mean that they are good in another. Not only do they need to know the stimulation techniques, they need to be knowledgeable in the application of these techniques to the diagnostic area of interest.

Website: tmslab.org

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Editorial. Nancy Faass, MSW, MPH, provides support for authors in the development of articles, books, manuals, white papers, and writing for the Web via her company and can be reached at info@HealthWritersGroup.com or by phone at 415-922-6234.

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Stress, Pain, and Addiction Affect the HPA, HPG, and HPT Axis: Part 2

Addiction and the IV Amino Acid Miracle Therapy

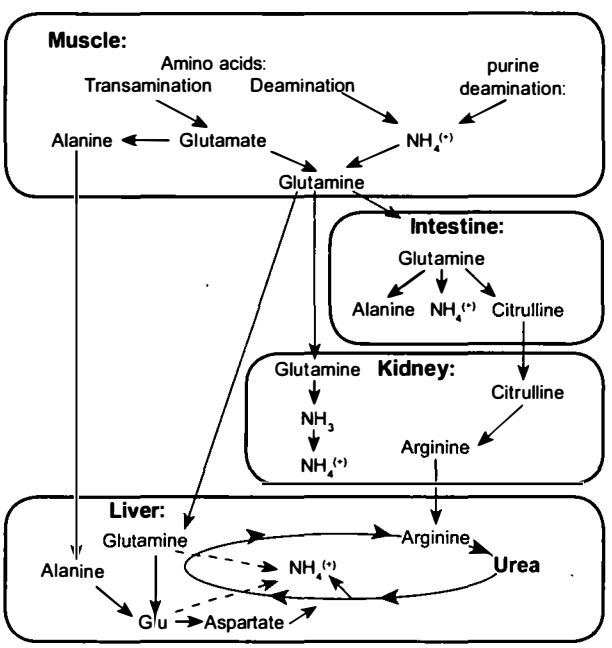
by Dalal Akoury, MD

The problem of addiction has found its way into all societies globally, and it causes great medical and social problems to all people either directly or indirectly. It respects nobody and does not care for one's social position. It cuts across all directions of life indiscriminately. Most addicts are unaware of their addiction. Using drugs makes a person very vulnerable. Addiction is a progressive chronic disease; it usually reaches a point at which it is harmful not just to addicts but also their neighbors, friends, and relatives as well as to society as a whole. Addiction is not only a physical consumption disorder involving drugs or alcohol use, but also an emotional and spiritual chaos that fundamentally alters any and every fraction of one's psyche.[1] Addiction is a spectrum of disorders that create a state of total loss of control, dependency, and even slavery to not only material things such a drugs or alcohol but also more abstract passions such as gambling, sex, texting, or video gaming.[2,3] In other words, *addiction* may refer to a substance dependence, such as drugs, or to a behavioral addiction.

The common denominator in addiction is slavery, loss of control, and perpetual suffering that affects the addict and anyone who has any relationship, direct or indirect, with that person.

Addiction treatment is of complex medical, psychological, and public concern.[4] An optimal addiction recovery program should be comprehensive, integrative, and holistic. The only way that we can overcome this epidemic of addiction is through addressing the root causes, by using not only pharmacological methods but also nutritional tactics, psychological approaches, and rehabilitation exercises. Although the word *addiction* is merely nondiscriminatory, each kind of addiction causes somewhat different neuroendocrine-immune dysfunction and has a constitutionally different neuroendocrine fabrics stamp.[5,6] As an example, alcohol withdrawal syndrome is due to hyperactivity of the central nervous system.[7] Abrupt reduction of alcohol consumption causes violent autonomic imbalances, mainly sympathetic overtone responses affecting the brain (causing seizures) and the gastrointestinal tract, causing diarrhea and vomiting. Furthermore, alcohol syndrome encompasses several manifestations ranging from depression to delirium tremens, to polysubstance abuse, to liver diseases, to acid-base disturbance, to seizures, to coma, to stupor, to Wernicke-Korsakoff syndrome with alcohol cravings.[8]

Figure 1



Prior to effectively addressing treatment of addiction, an integrative approach should consider restoring the body–acid base balance, hydration, and appropriate nutrition, mainly

IV nutrition, to address the universal vitamin deficiency, in particular the B vitamins, which are completely depleted in addicts.[9-12] The next phase of treatment should include safe detoxification. A proper detoxification process will minimize stormy withdrawal states. A successful detoxification begins by effectively replacing the essential elements needed for a smooth phase 2 liver detoxification. Proper and effective phase 2 liver detoxification depends on an appropriate repair of all the cofactors and amino acids pool as necessary. Considering the severe malfunction of the digestive tract and its minimal efficiency to absorb the necessary nutrients for proper detoxification, one should resort to an aggressive, well-crafted restorative intravenous nutrition protocol. The well-documented inefficiency of the GI system obligates the treating physician to construct the ultimate detox intravenous cocktail. This carefully designed brew will produce the ideal nutritional environment that stimulates and enhances suitable liver detoxification correcting dehydration and cofactors deficiencies, and insuring adequate supply of the essential amino acids necessary to enhance liver detox capability. The liver-appropriate amino-acid balance is the key to healthy liver support and bowel decontamination.

We are beginning to scratch the surface of the amino acid revolution and its major role in the treatment of addiction. The purpose of this article is to unveil the crucial role of amino acids in the treatment of addiction.

So what are amino acids? And why will amino acids therapy revolutionize the field of integrative addiction medicine?

Amino acids are the undiscovered miracle of healthy living; this area of natural addiction therapy is still unexplored but offers great potential for not only overall health but especially brain health. These benefits include proteomics, enzyme therapy, and brain health. The central nervous system (CNS) is almost completely regulated by amino acids and peptides.[13] The importance of amino acids within the brain is now being recognized, and as a result amino acid therapies are transforming the treatment of psychiatric disease. Later on we will look into the specifics of how amino acids are being used as therapy for brain functions.

Amino acids are the building blocks of proteins; proteins are the building blocks of our bodies. There are over 100 amino acids that have been found to occur naturally; each of them differs in R group. Of these 100 amino acids, there is a group involved in making up a protein. There are two classifications within this group: nonessential and essential amino acids. Nonessential, or dispensable, amino acids are synthesized in the body. They are alanine, arginine, aspartic acid, asparagine, cysteine, glutamic acid, glutamine, glycine, proline, serine, and tyrosine. These nonessential amino acids may become essential when the body cannot synthesize them; in this case they must be supplemented either orally or intravenously.

Essential, or indispensable, amino acids cannot be synthesized in the body and can only be obtained through food. The essential amino acids are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine.

The most exciting area of amino acid research is their role in brain function and metabolism. The communication within the brain and between the brain and the rest of the nervous system occurs through chemical "languages," called neurotransmitters. There are about 50 such languages. Amino acids, manifesting as precursors, neurotransmitters, or peptides, account for the majority of them.

When the brain and other organs such as muscles communicate with each other, amino acid-related neurotransmitters are again the primary language. Throughout the body, the amino acids function as precursors for the manufacturing of other important substances. This precursor functionality of amino acids is where amino acids derive their potential value in medicine and surgery.

The Neurotransmitters Communication Network Is an Intricate Ecosystem

The neurotransmitters communication network is organized into micro- and macrosystems, interconnected and interdependent. Neurotransmitters are synthesized inside the neurons. Signals from the neuron travel out a threadlike extension called the axon, which ends in several terminals.

Just over the gap (synapse) are the target neurons with many protruding spines called dendrites waiting for the message.

Presynaptic and *postsynaptic* neurons communications are as follows the presynaptic neuron, whose axon is primed for releasing neurotransmitters.

There are some 100 types of neurotransmitters in the brain.[14] On release from the axon, certain neurotransmitters leap across the synapse and momentarily bind to specialized receptors along the dendrites of the postsynaptic neurons. From there, a complex series of signaling cascades follow that switch on or off or maintain no end of functions inside the target neuron.

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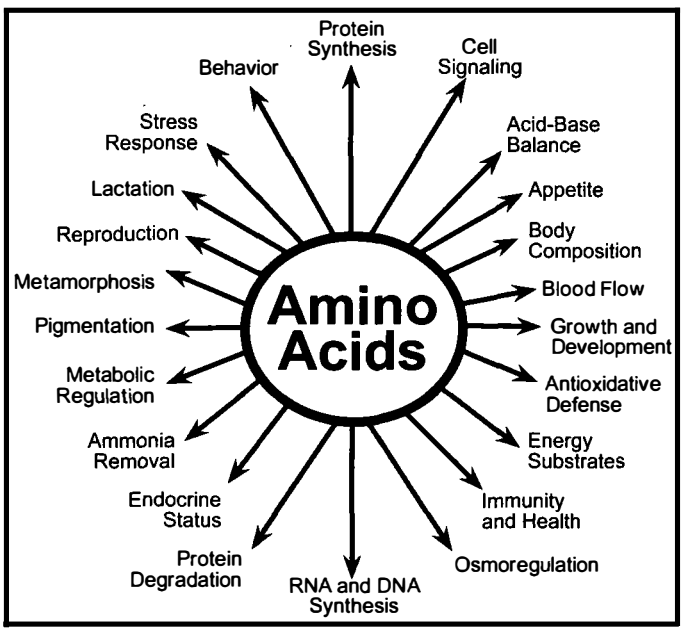
Figure 2



Stress, Pain, and Addiction

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Fast synapses are roughly divided into *excitatory* and *inhibitory*, with glutamate as the main excitatory neurotransmitter and GABA as the main inhibitory neurotransmitter.

The neurotransmitters that we are most familiar with are dopamine, serotonin, and norepinephrine; they involve slow and more complex transmission. They interact with signaling proteins found inside the cell membrane in a way which allows the receiving neurons to process signals from glutamate and GABA.

The ultimate complexity of the brain is that it is not static but dynamic, constantly changing. Every time we learn something new, we alter the structure of the brain. Any experience noticeable enough to cause memory creates new synaptic connections, prunes old ones, and strengthens or weakens existing ones.[15] Let us conceptualize how addiction deregulates this complex neurotransmitter symphony.

Inhibitory/ Excitatory Glutamate and GABA Network

Glutamate (excitatory) and GABA (inhibitory) represent the yin-yang of the neurotransmitters, with both present in nearly all synaptic functions throughout the brain.[16] The mood stabilizers used to treat bipolar are thought to act on one or the other or both.

There are two types of glutamate receptors: the ionotropic (iGluR) receptors, including NMDA, kainate, and AMPA, and the metabotropic (mGluR), which mediate numerous neurometabolic chemical actions. When the NMDA receptor is working properly, both glutamate and glycine bind to the receptor, which in turn opens up its corresponding ion channel and permits calcium entry into the neuron. This well-designed GABA glutamate NMDA receptor unit promotes the intracellular signaling, which is essential to plasticity and survival.

In response to stress and mood instability episodes, glutamate reuptake in the synapses is compromised, resulting in increased calcium influx through the NMDA receptors and ion channels into the neuron and the activation of certain calcium-dependent enzymes that can result in cell atrophy and death.[17]

GABA is formed in the brain from glutamate, glucose, and glutamine. It binds to one of two receptors on the postsynaptic neuron. GABA A receptors regulate excitability and anxiety, panic, and stress and are the targets of benzodiazepines such as Ativan, as well as alcohol. When alcohol and/ or benzodiazepines are consumed over time, the neurons structurally change to accommodate increased GABA supply, setting up the potential for dependence and abuse.[18] Many

Alcohol Addiction Treatment

Assess patient alcohol addiction stage: determine the risk for liver diseases, acid-base disturbance, seizures, Wernicke-Korsakoff syndrome with alcohol cravings. Prior to proper detoxification process, withdrawal symptoms should be effectively managed with proper oral nutrition, intravenous fluids to correct dehydration, supplementation, amino-acid balance, liver support, bowel decontamination process, exercise, psychosocial support, and meditation practices

A. Acute Induction Treatment

1. **Mitochondrial Restoration Is Phase I**
   - Use Coenzyme 1, NAD IV therapy for 5–10 days, depending
   - **Poly MVA IV**: titrate up initially from 5 cc then 10, 15, 20, depending on their condition.
   - CoQ10
2. **Seizure Precautions: Phenobarbital or Dilantin**
3. **Oral nutrition**
   Nausea therapy including Zofran, high-protein diet, rich in amino acids. Oral fluids can be given to prevent dehydration and associated electrolytic disturbances.
   Vitamin B replacement orally and IV, especially tetrahydrofolate, thiamine should be given. In patients with poor nutritional status, parenteral administration of thiamine should be considered due to poor intestinal absorption.
   Cysteine-rich foods such as eggs can be prescribed to facilitate acetaldehyde metabolism.
4. **Intravenous fluids**
   In hypovolemic patients, volume deficits should be replaced with isotonic fluids to achieve euvolemia: parenteral with multivitamin/mineral preparations including folate, phosphate, potassium, and magnesium.
5. **Liver Support**
   Nutritional care with treatment of dopamine is essential during recovery process. Alcohol withdrawal can cause delirium tremens with ketoacidosis, and hepatic failure may occur in about 5% of individuals. Hypoglycemia with irritability, nervousness, fatigue, and aggression are common during withdrawal. IV NAC and glutathione.
6. **Bowel Decontamination**
   Bowel decontamination process should be considered before detoxification to reduce withdrawal symptoms. The aim of the intervention is to decrease GI absorption of the addictive substance.
   Magnesium antagonizes calcium entry into the neurons after NMDA activation. This results in reduced morphine-induced dopamine release and pharmacodependence. The antimorphine effects of magnesium have been confirmed through studies.

other drugs of overuse and abuse work indirectly on GABA receptors.

Gerard Sanacora, MD, PhD, of Yale has used magnetic resonance spectroscopy to measure GABA in the brain, finding that people suffering from melancholic depression show low GABA concentrations in the occipital cortex. On the other hand, the depletion of GABA is not as pronounced in individuals experiencing atypical depression; this finding indicates a diagnostic potential for subtypes of depression.

The Phenylalanine Tyrosine Energetic Reward Cascade Network: Dopamine

Dopamine, the elixir of life and survival, is a spin-off from L-DOPA.[19–22] L-DOPA is created from L- tyrosine, a progeny of L- phenylalanine. This master recycling plan is the originator of our essence and survival. More precisely, L-DOPA is converted to dopamine by action of DOPA decarboxylase (DDC). L-DOPA itself is converted from tyrosine by the action of tyrosine hydroxylase (TH). Dopamine release can either be phasic or tonic. "Phasic" dopamine release is characterized by burst firing and is thought to occur in response to behavioral stimuli, such as those that may predict reward.[23,24] In contrast, "tonic" dopamine release is slow and irregular. Dopamine is a neurotransmitter implicated in addiction, depression, bipolar, schizophrenia, psychosis, Parkinson's, ADHD, substance use, and aggressive behavior.[25–28]

Most dopamine-producing neurons are located near the brainstem. Their axons extend in one of three specific but overlapping paths (via the medial forebrain bundle) to stimulate specific cortical and subcortical structures. In contrast, serotonin and norepinephrine patterns of distribution are far more diffuse.

The nigrostriatal pathway of dopamine (in the subcortical areas of the brain) has a prominent role in motor planning and movement, plus cognition.[29,30]

The mesocortical pathway of dopamine, which projects to the frontal and temporal cortices, is believed to be vital to concentration and executive functions such as working memory.[31] The mesolimbic pathway of dopamine, which projects into the limbic system, including the hippocampus and amygdala, is particularly important for motivation, experience of pleasure, survival, and reward.[32]

Cocaine and various forms of methamphetamine are infamous for enhancing dopamine production; however, medications used for ADHD and Parkinson's enhance dopamine generation less dramatically. Likewise, antipsychotic pharmacologic agents bind to dopamine D2 receptors; consequently, they inhibit too much of a good thing. Imprudently, antipsychotic agents don't just limit themselves to blocking the D2 receptors[44] in the mesolimbic pathway, but also block all receptors in the brain's dopamine pathways, causing what Stephen Stahl of UCSD calls a "high cost of doing business."[33–35]

With the use of street drugs, neurons structurally change over a short time to accommodate the increased dopamine supply, setting the scene for dependence and abuse. Furthermore, other drugs of overuse and abuse may work primarily on other neurotransmitter systems; but ultimately, all drugs of abuse exert their tasks through a downstream effect by increasing the production of dopamine

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7. **Herbs**
   - Herbal tea or extract of passionflower
   - Silymarin
8. **Vitamins**
   - Thiamine

   Oral or intravenous administration. Thiamine deficiency is common among alcohol addicts due to malnutrition, altered gut microbiome, and impaired alcohol metabolism. In chronic alcoholics, we use only parenteral administration of thiamine which can increase the absorption rate and reduce withdrawal symptoms
9. **Intravenous Amino-Acid restoration**
   Amino acid restoration is vital for the alcohol withdrawal process due to its health benefits. Administration of L-glutamine can reduce alcohol cravings and anxiety symptoms among alcoholics. GABA soothes excited nerves and reduces sugar and alcohol cravings to reduce addiction predisposition. IV L-glutamine can reduce mood disturbance and behavioral disorders among heroin addicts and improve addiction recovery.
10. **Magnesium Sulphate Intravenously**
    Intravenous magnesium ions reduced ethanol and morphine dependence in controlled-clinical trials.
11. **Adrenal support**
    IV Vitamin C 25–50 grams daily for 3 days.

B. Maintenance

1. Monthly: Supplements, including niacin, B-vitamins
2. Weekly: IV amino acids for 2 months, then monthly for 3 months, then every other month ×6
3. Nutrition
4. Lifestyle modification
5. Exercise
6. Meditation, biofeedback therapy
7. Alpha-Stim

C. Consolidation Every 3 Months for 1 Year, Then Every 4 Months

in the pleasure and reward circuits.[36] In contrast, in case of depression, the lack of dopamine, among other things, would account for lack of pleasure; however, in the manic stages, too much dopamine acts as a rocket fuel.

Norepinephrine: The Stress Hormone – a Link to Addiction

Norepinephrine is a neurotransmitter released from the sympathetic nervous system in response to stress.[37-39] Norepinephrine, also known as noradrenaline, the king of stress, a stress hormone that affects every organ in the body. Norepinephrine is produced in the neurons by enzymes that act on tyrosine, which converts it into L-DOPA, then to dopamine. Some of the dopamine is then converted to norepinephrine.[40] As soon as norepinephrine is created by enzymes, it gets destroyed by other enzymes, such as MAO (which also destroys serotonin and dopamine).[41,42] Hence the MAO inhibitors represent the first family of antidepressants.[43] Another class of first-generation antidepressants, the tricyclics, such as Elavil, have a dual reuptake action on both norepinephrine and serotonin. The later-generation SNRIs such as Effexor work in a similar fashion.

Most of the norepinephrine action takes place in an area of the brainstem known as the locus coeruleus, which referees external stimuli and human responses to such external stimuli (such as fight or flight) and pain.[44] Norepinephrine and the locus coeruleus are also believed to play a role in cognition, mood, emotions, movement, and blood pressure. Difficulty concentrating, fatigue, apathy, and depression are some of the symptoms that can result from norepinephrine going AWOL.

In depression, the prevailing theory is that lack of norepinephrine accounts for psychomotor retardation. In anxiety, too much of the neurotransmitter is seen as part of the stress reaction.

The Tryptophan, Serotonin, and Melatonin Circadian Circuitry

Serotonin is synthesized in the neuron from tryptophan, which is first converted to 5-HTP.[45-48] Serotonin is then released into the synapse in a similar fashion to norepinephrine. Serotonin has some 17 different types and subtypes of receptors, which underscores its importance as a neurotransmitter. Serotonin-producing neurons project from the raphe nucleus in the brainstem to the basal ganglia, frontal cortex, hypothalamus, and limbic system, and down the spinal cord. Serotonin is also found in abundance in the GI tract, thus implicated in a host of functions, from mood to anxiety to sleep (serotonin makes melatonin, which regulates sleep) to sexual response and to food craving and (in)digestion.

A presynaptic transporter sucks up excess serotonin from the synapses in preparation for the next release of this ubiquitous neurotransmitter.[49]

In depression, lack of serotonin would explain obsessing on grieving thoughts. Not surprisingly, serotonin-enhancing medications such as SSRIs also help with OCD. SSRI antidepressants are believed to work by binding to this reuptake pump, thus keeping more serotonin in circulation. If this were completely true, why would antidepressants not have an immediate effect, instead of taking at least 2 weeks to start making an impression and another 2 to 6 weeks to achieve full clinical benefit? One explanation would be that blocking the serotonin transporters desensitizes the neurons in a way that dampens normal firing for 4 weeks. Another is that antidepressants also work on intracellular processes downstream of the neurotransmitters.[50]

Serotonin stimulant drugs of abuse include ecstasy and LSD.

Other Neurotransmitter Systems

Acetylcholine: Damage to this system has been linked to Alzheimer's. Cholinesterase inhibitors such as Aricept are believed to work by preventing the breakdown of acetylcholine. Specific nicotinic receptors in the acetylcholine system are linked to nicotine addiction, but safe alpha7 nicotinic agonists (for improving cognition) are being investigated for the treatment of schizophrenia.

Oxytocin and Vasopressin: As both neurotransmitters and hormones, these two peptides mediate a range of physical and mental functions, but their role in pair-bonding has earned them the reputation as the "love hormones."

Opioids: *Endorphins* is a popular term to describe complex chemical activity involved in killing pain, inducing sleep, and creating sensations of pleasure.[51] Opiates such as heroin and morphine and opiate-derived painkillers such as codeine and oxycodone appear to mimic natural endorphin activity by binding to opiate receptors. The immediate effect is blocking pain and causing drowsiness. A domino effect results from reduced GABA release failing to inhibit dopamine release.[52] Medications such as methadone are aimed at mimicking the mimickers. Naltrexone, on the other hand, works by countering the opiate effect and blocking cravings.

Adenosine: Caffeine gets its effect by binding to these receptors, thus blocking fatigue-inducing adenosine neurotransmitters. A downstream effect is mild dopamine release. Once the blockade wears off, however, adenosine comes back into play, which is why coffee is only a temporary fix. The only cure for missing out on sleep is – drum roll – catching up on sleep.

Hypocretins: Also called orexins, these neuropeptides have recently been identified in sleep regulation. Breakdown in hypocretin function is believed to result in narcolepsy. The novel wakefulness agents Provigil and Nuvigil are believed to act on hypocretin.

Substance P: In spring 2003, this peptide, which is released in response to stress, was ready for prime-time.

Again, the Brain Is Not a Neurochemical Soup

Even though the focus of this article is on amino acids therapy and neurotransmitters, this focus may tend to blind us to the convolution and sophistication of the brain machinery. The brain is an intricate ecosystem, not just an artificial

intelligence engine, but the CEO of a complex intelligence machine that encompasses a microuniverse inside each neuron, dynamically interactive systems, and networks of neurosystems – a continuous and dynamic interplay between genes and the environment. But because of our focus on neurotransmitters, I will recap dopamine, epinephrine, and the adrenal and HPA system. Hormonal systems create the symphony of our being; the ventral tegmental area sends dopamine to other areas of the brain such as the nucleus accumbens and the prefrontal cortex. When we are exposed to pleasurable things such as brownies, new clothes, a shiny new car, sex, or drugs, dopamine is shunted to the nucleus accumbens. This area of the brain is highly associated with pleasure, motivation, and the reward system. (I.e., I did this action, I got this awesome reward.[38] Lots of feel-good dopamine hormone was sent to the nucleus accumbens; now I'm motivated to do that again. And again. And again.)

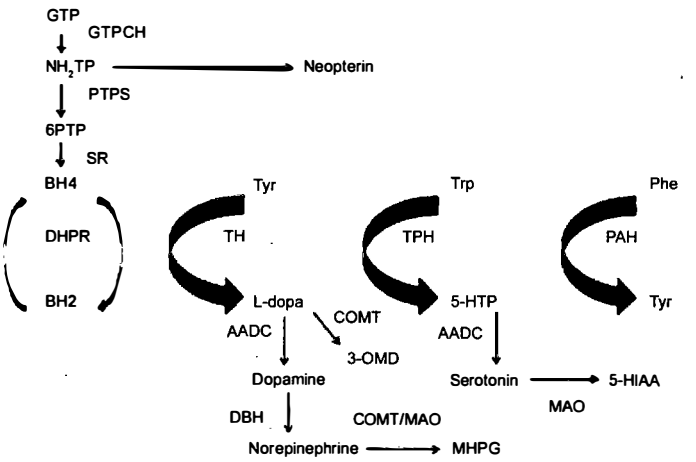
Drugs such as cocaine and other stimulants hit those reward centers hard, and addiction is likely. There is a growing body of knowledge showing that people who have an extroverted personality and are more in tuned to the dopamine-related reward system are more daring, reward[38]-seeking-behavior explorers.[53,54] Also keep in mind that if one ever feels an overwhelming desire to work out, especially if one knows that one shouldn't, this may mean that one is a dopamine junkie and could be at higher risk for addiction – what may be called an addictive personality.

Dopamine acts as a hormone specifically in the hypothalamus. When dopamine is released, it inhibits the hypothalamus from releasing prolactin.[55] Prolactin stimulates lactation or milk production and is also involved in sexual satisfaction. Dopamine is related to sexual arousal. Dopamine is high before sex and then drops once orgasm is achieved.

It is worth noticing that dopamine cannot cross the blood–brain barrier, so it is useless for treating Parkinson's or any other disease related to dopamine shortage. Amino acids such as phenylalanine or L-tyrosine or L-DOPA, on the other hand, are viable precursors in the formation of dopamine, norepinephrine, and epinephrine and can cross the blood–brain barrier.[56–58] L-DOPA effectively treats several diseases and symptoms.

Now that we've discussed what dopamine is and the important role it plays in the body, let's talk about how we produce it. Just as with norepinephrine and epinephrine, L-phenylalanine, L-tyrosine, and L-DOPA are crucial for dopamine to be synthesized in the body.[59,60] Here's the breakdown of this whole synthesis pathway (Figure 4):

Figure 3



L-phenylalanine is converted to L-tyrosine.

L-tyrosine is then converted to L-DOPA.

L-DOPA is converted to dopamine.

Dopamine will move down the conversion chain to yield norepinephrine and epinephrine.

Now, let's review the dopamine transporters and receptors, or, in simpler terms, how dopamine actually gets from point A to B to so it can "do work."[61] Dopamine is released from presynaptic vesicles, given the correct stimulus, and then binds to postsynaptic receptors. There are several types of dopamine receptors, including D1, D2, D3, D4, and D5.[62–65] These receptors are either excitatory or inhibitory if stimulated, although the end result is not always so straightforward.[67] Dopamine is taken up by the protein DAT (dopamine active transporter), then undergoes enzymatic breakdown by MAO into DOPAC, or is repackaged into the presynaptic vesicle and recycled.[68] Cocaine, amphetamines, and methamphetamines inhibit DAT from uptaking

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dopamine, so that it continues to stimulate the receptors, causing euphoria and hyperactivity.[69,70]

The Revolutionary Amino Acids Treatment Accelerates Neuroendocrine Restoration (NER)

Amino acids addiction treatment can hasten neuroendocrine restoration (NER).[71–74] NER is gaining steam as an effective natural addiction treatment. Three recent studies, one on compulsive gambling and two about cocaine addiction, examine the role played by simple amino acids in the treatment of addiction. These amino acids taken regularly in the diet can also help normalize the brain chemistry of people addicted to drugs and alcohol.[75] Amino acids treatment for addiction thereby offers much hope for a nontoxic, relatively economical option.

Scientific research supports that restoration of cystine/glutamate exchange by intracranial perfusion of cystine or systemically administered N-acetylcysteine normalizes the levels of glutamate in cocaine-treated subjects.[76] The role of amino acids in the treatment of addiction and restoration of brain chemistry is well documented. Amino acids restore neurotransmitter imbalances and cement the desire to quit drugs and helping individuals modify their behavior.[77]

The biochemical imbalances resulting from substance abuse can be restored with the suitable and skillful administration of lithium, B vitamins, amino acids, and dietary manipulations. The field of optimizing brain chemistry has continued to receive a boost with many doctors venturing into finding the natural, inexpensive, safe, and effective nutrients to help treat addiction.

Note that if we are missing out on any of the amino acids required for this biosynthesis, the resulting hormones and neurotransmitters will also have deficiencies and imbalances. With dopamine being as important as it is on its own, and also being a precursor to the norepinephrine/epinephrine, we can rest assured that keeping these neurotransmitters/stress hormones in balance is crucial to the adrenals and overall health.

So where does this all put us? The adrenal system, including all the hormones and neurotransmitters that go with it, is a very complex system that can greatly affect every system and organ in our body. Because of the massive changes that it can cause in other systems, any major issues with the adrenal system can affect virtually any function in the body. This is something that extends past just having a bad workout or one's body composition suffering a bit. We're talking about the possibility of severe mental illness or life-altering neuromuscular diseases. By keeping this in mind as we continue to learn more about the pieces and parts of our bodies that make up the adrenal system, we also learn that seeking balance and ways to nurture our bodies and prevent stress are key in long-term health and physical and mental well-being.

The adverse effects of stress and addiction on the HPA, HPG, HPT axis should not be overlooked when we treat patients suffering from any addictive disorder.[78] The effects on neurotransmitters/amino acids networks are so complex, intricate, and misunderstood, physicians must take an innovative fresh approach to properly addressing the disease of addiction. More physicians need specialized training in understanding the dynamic changes happening in the entire being of an addict.[79] Taking into account the makeup of the psychoneuroendocrine-immune system, the addiction physician of tomorrow should be able to maintain a harmonic balance between homeostasis and the allostatic load.[80]

Training Physicians to Handle Drug Addiction Is Becoming a Necessity

In summary, with the prevalence of addiction and substance abuse in society today, we need to reevaluate our action plan to ascertain that restoration of spirit, mind, and body is properly addressed to prevent and treat addiction. The purpose of this article is to raise the awareness about the magnitude and complexity of the problem of all types of addictions from drugs and alcohol to gambling, sex, and the Internet. I cannot emphasize enough the importance of a fresh training system offering physicians the tools to better assess, diagnose and effectively treat addictions, naturally and safely. Understanding the complexity of this epidemic of the disease of addiction is the beginning. Equipping all practitioners with innovative tools to help them affect the course of addiction treatment should be our goal. This education endeavor should begin by raising the awareness of addiction in general. Natural recovery training should and will focus on better understanding the amino acid revolution in addiction medicine, and how to create, tailor, and individualize IV amino therapy for different kinds of addiction while respecting patients' individuality. The proper understanding of IV amino acids and peptide therapy in all phases of addiction training will be emphasized. The creative manipulation of amino acids therapy and how to individualize integrative addiction medicine is our only

Dalal Akoury, MD, is the founder of AWAREmed Health and Wellness Resource Center and the director of the Wellness U program. Dr. Akoury is board certified in anti-aging, functional, and regenerative medicine, as well as having accumulated more than 20 years of experience in emergency medicine and pediatrics, and a master's degree in public health. Dr. Akoury has also served fellowships in pediatric hematology/oncology and performed research in leukemia and the effects of smoking. This lifetime of experience, along with a unique sensitivity, genuine compassion, and driving passion to inspire health in everyone, has prepared "Dr. Dolly" to be in this place at this time. About developing her dream, AWAREmed and Wellness U, Dr. Akoury says, "My mission is to ignite the spark of health deep within everyone, and to allow this sparkle of wellness to shine through everyone's eyes, becoming one with the universe, and aligning body, mind, and spirit."

salvation. For us to overcome the addiction crisis, and save generations from the *pain* and *chaining* of addiction, we must comprehend it from a different prospective.

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FCT Cured Case of Severe Multiple Chemical Sensitivities

by Savely Yurkovsky, MD

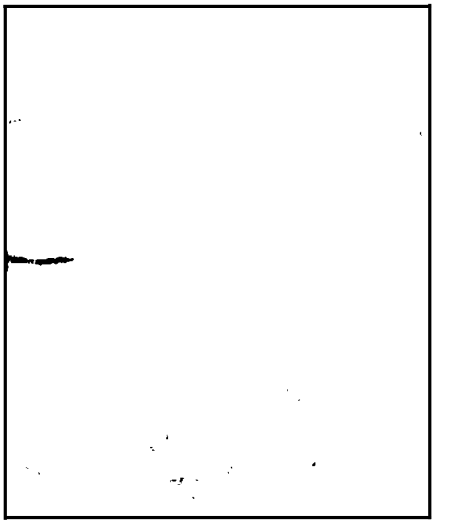
A young, handsome dentist was thriving both professionally and financially in a lucrative practice, yet was resigned to a life of misery due to multiple chemical sensitivities. Any exposure to chemicals via touch or smell would literally turn his face and the rest of his body into a bloodbath, covered with countless itchy, disfiguring sores oozing blood.

Both his personal and professional lives were seriously compromised, and the only clothing that he could barely tolerate was 100% cotton surgical scrubs. His words, "It ruins my life," said it all. Conventional dermatology, using cortisone and other creams, had stopped working; and he was even offered chemotherapy! He refused and opted for alternative treatments, yet trying quite a few of these for years offered no reprieve.

As is the case with any chronic disease, one must delve beneath its generic name or label to determine the specific causes that ultimately created and sustained it, with the complex of causes being unique to each individual patient. The only way to accomplish this correctly is via skillful bioresonance testing, which besides just visibly or logistically sick organs (such as the skin and liver, in this patient's case) can also screen all of the poisoned, infected, or electrocuted organs. Each of these invariably contributes to and becomes a big part of an individual chronic disease.

Findings of Bioresonance Testing During First and Subsequent Visits

Testing discovered severe staphylococcal and herpetic skin infections, and an intoxication of herbicides, solvents, pesticides, mercury (both inorganic and, its most toxic form, organic), toxic metals – including silver – benzene, diesel, car exhaust fumes, hexachloride, formaldehyde, hydrocarbons, methyl alcohol, DDT, and polyurethane. Also antibiotic residues, as well as parasitic, yeast, and bacterial infections in the gut; a dental infection; and electromagnetic stress affecting his brain, skin, and gastrointestinal organs. Following some of these findings, he shared that besides being a city dweller, in his youth he used to mow golf course lawns; and this must have given him a good head start in inhaling exhaust and petroleum fumes, along with the pesticides and herbicides generously sprayed there.



This patient's skin reacted severely to chemical exposure.

Savely Yurkovsky, MD, graduated from II Moscow State Medical Institute in 1975 with a degree in pediatric medicine. He completed his training in internal medicine and cardiology at Coney Island Hospital of Downstate Medical School, and is board certified in internal medicine. He has been in private practice since 1984 with a special focus on identifying and successfully treating the main causes of chronic diseases via bioenergetic modalities – bioresonance testing and homeopathy, correspondingly, or FCT. Dr. Yurkovsky founded a teaching organization, SYY Integrated Health Systems Ltd., dedicated to training in FCT. It was presented extensively in the US and Europe to medical practitioners since 1999 and has demonstrated numerous documented reversals in a variety of chronic diseases. His book, *The Power of Digital Medicine*, was endorsed for scientific validity by two prominent physicists, MIT Professor George Pugh, PhD, and former chairman of materials science at Stanford University, Professor William Tiller, PhD, and also by Mehmet Oz, MD, from Columbia University Medical School. Its diagnostic and homeopathic aspects were also presented at the annual BTR (bioterrorism) conference in 2005: Unified Science & Technology for Reducing Biological Threats & Countering Terrorism, affiliated with the Department of Homeland Security and the US Army, as well as at the Department of Psychiatry of Massachusetts General Hospital, Harvard Medical School, and many other professional symposia. In collaboration with the Department of Gastroenterology of Johns Hopkins University School of Medicine, Dr. Yurkovsky has contributed a chapter on homeopathy to the textbook *Integrative Gastroenterology* (Oxford University Press; 2011) and authored numerous articles on different medical topics. His book in progress explains the inevitability of the current epidemics of autism and numerous other brain and somatic diseases, and how to solve them.

Malfunctioning Organs

Practically all bodily systems were "hit" in various degrees: detoxifying, immune, excretory, gastrointestinal, immune, neurological, musculo-skeletal, vascular, skin, and even urogenital, according to the testing.

Treatment

The patient was treated exclusively with FCT's homeopathic approach, aimed at the release of all toxicological and infectious agents and the restoration of all of damaged organs.

Other therapeutic measures were provided via his removing his only mercury filling and purchasing memon electromagnetic-protective devices to address the severe electromagnetic stress in his apartment, office, and car and from his computer and cell phone. When electromagnetic stress is ignored, this places the body in a no-win physiological situation, since these destructive fields disorient and disorganize the body's innate cellular energy fields, which ultimately run its body chemistry and maintains homeostasis, which sustains our health and life itself.

Following homeopathic FCT treatment cycles, he would often report: "Doctor, some weird things are going on. My fiancée says I smell like a gas station; something must be coming out of me. By week's end, I see layers of soot covering the floor of my shower stall. I scrub it off, but then, it comes back. This homeopathy thing is weird. I've never see anything like this. I know I am new to this, but this is all really weird."

The End Result

Today, the good doctor lives a normal life as, besides his multiple chemical sensitivities, his chronic low energy and spinal problems have also ceased. This is evidenced in his own words: "Your great talent brought me back from the dead – and I mean that! I have my life back which I never thought I would have again – after 5 years I had forgotten how nice it can be just to be normal without 24 hours of burning, itching, and bleeding all over my sheets and waking up with my face stuck to my pillow. It was truly a nightmare that I never could wake up from. You saved me and I mean that in the true sense of the word. After all of my drastic efforts before finding you, I was helpless and TRULY, LITERALLY, dying – I don't know what it is but when you are dying suddenly you know it and your body and your mind changes. My family thanks you as well and I am so glad I believed in you and your philosophy. Thanks again for saving my life because it was gone for years!"

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Eliminate Electromagnetic Pollution to Eliminate Disease

by Connie Strasheim

www.ConnieStrasheim.com

Did you know that babies are born with more than 200 chemical toxins in their bodies? If babies have this many toxins, imagine how many more those of us who have been on this earth 40, 50, or 60 years have accumulated in our bodies!

Many of us are aware that environmental toxins of all kinds are harming us and that they are one of the foremost causes of most chronic and degenerative diseases. I talk about toxins in my recently released book, which I coauthored with W. Lee Cowden, MD, titled *Create a Toxin-Free Body and Home, Starting Today* (www.ConnieStrasheim.com). In this book, we provide a broad overview of the many different types of toxins that are contaminating our bodies and homes, along with simple tools and strategies for eliminating them, so that we can heal faster from whatever ails us.

While all toxins are harmful to the body and damage it in their own unique way, I've become particularly passionate about sharing what I know about what I believe is one of the most dangerous, insidious pollutants of our time: electromagnetic radiation (EMR).

Some of us don't take EMR that seriously, even though we've probably heard that it's bad for us. If we did, we wouldn't be carrying around our cell phones in our pockets in the "on" mode, or talking on them for hours daily. We wouldn't be using Wi-Fi in our homes, forgetting to turn off the circuit breakers in our bedrooms at night, or ignoring the smart meters installed outside our homes.

I suspect that this is because even if we have heard about how harmful excessive EMR exposure is, we figure that we have to function in this world with all the radiation-producing gadgets, so there's not much that we can do about it. Or, because EMR is a silent, invisible toxin and we often don't immediately feel its effects upon our bodies, we don't really believe that it's all that harmful.

Unfortunately, I think that EMR may be harming us more than some of us believe. Every month, I interview cancer doctors for a podcast interview that I do for the Alternative Cancer Research Institute, and those who have been practicing for over 20 years will often tell me that back when they started practicing medicine, it was rare to see children with cancer, and rare to find people with brain tumors. Now, they say, brain tumors are common – among the young and the old – and are a direct result of cell phone use, because the tumor always appears on the side of the head where the person uses his or her cell phone.

Numerous studies substantiate this finding, as well as others, which link different types of cancer with specific sources of EMR, such as leukemia and power lines. But because evidence about the damaging effects of EMR hasn't been widely published in mainstream media, people have been falsely led to believe that Wi-Fi, smart phones, and all the latest and greatest technological gadgets aren't that bad for you.

Anyway, these gadgets are fun, and make most of our lives easier because we can multitask while driving, cooking, or exercising, which makes it hard for us to say no to using them. A decorated smart phone or iPad that allows you to access Facebook or e-mail anytime, anywhere, is really hard to put down. So it's just hard to imagine that these fun, helpful gadgets are really causing cellular mutations and cancer. And even harder to believe that the radiation that we're exposed to from them could be what's keeping those of us with chronic health conditions from a full recovery.

However, if you take a look at the BioInitiative Report (www.bioinitiative.org), a 650-plus page report compiled by a group of scientists and researchers from 10 nations, you'll find plenty of evidence – over 2000 studies – about the damaging effects of cell phones and other sources of EMR, and the diseases that have been linked to them.

In my 2012 book, *Beyond Lyme Disease: Healing the Underlying Causes of Chronic Illness in People with Borrelia and Co-Infections* (www.beyondlymedisease.com), I also write about the dangers of electromagnetic pollution, and mention the late Dr. Professor Neil Cherry of New Zealand, a foremost pioneer in environmental health. According to Cherry, "EMR confuses and damages the cells' signaling system, which produces symptoms such as headaches, concentration difficulties, memory loss, dizziness and nausea, and long-term diseases such as Alzheimer's dementia, brain tumors and depression." Other researchers have confirmed Cherry's findings.

Lynn Quiring, RPh, CCN, NMD, in her paper "The Cell Phone Poisoning of America," lists a variety of conditions that can result from prolonged exposure to or are caused partly by EMR. These include Alzheimer's, autism, Parkinson's, heart disease, brain tumors, leukemia, fatigue, depression, immune system disorders, learning disabilities, memory loss, sleep disorders, lowered sperm counts, DNA damage, hormonal imbalances, and cancer. She cites over 66 scientific references in her work proving these associations.

Further, Dr. Thomas Rau, of the renowned Swiss Paracelsus clinic in Switzerland, stated in a 2009 interview published on www.emrstop.com that "... cultures of normal human endogenous bacterial cultures grow much less when exposed to EMR." This means that our bodies produce less beneficial bacteria when exposed to EMR.

Rau then states that this results in an overgrowth of bad bacteria that can bring about conditions such as Lyme disease. So he seems to be implying in his interview that EMR plays a huge role in allowing Lyme disease organisms to flourish in the body, and that by reducing our exposure to it, our bodies can mount a better defense against the microbes.

Some doctors and researchers, such as Cowden, have also found that infections such as mold multiply faster in the presence of EMR. Therefore, it is essential for all of us to avoid EMR as much as possible, so that our bodies have the best chance of recovery from chronic infections or other health conditions.

It doesn't help that the amount of EMR in the environment is increasing exponentially, as we construct new telecommunication and microwave towers, allow smart meters to be installed on our homes, use Wi-Fi instead of hardwired Internet, buy smart phones and computers for round the clock use, and so on.

I've experienced firsthand the detrimental effects of EMR upon my health. For years, I've lived in condominiums or apartment complexes, which are often awash in a sea of EMR from a multitude of Wi-Fi connections that come from the neighbors above, below, and adjacent to me.

But what has hurt me the most hasn't been the Wi-Fi exposure (although that in itself can be quite harmful), but rather the wiring in the ceiling in my most recent home – wiring connected to a huge outdoor lamp mounted on the exterior of my condo building.

Interestingly, I had measured the electromagnetic fields in my condo during the daytime, before I moved into it, but I failed to measure them at night, when that powerful outdoor lamp gets switched on. Which goes to show how challenging it can be to identify EMR sometimes!

It took me a while to figure out why my body was "buzzing" and vibrating during my sleep – and then I discovered that it was because of the powerful low-frequency electromagnetic fields from the wiring connected to that lamp! Imagine my dismay, when I'd thought I had finally found a home that was low in EMR.

The insomnia that had I suffered from, and which had been mild to moderate prior to my move to this home, suddenly became severe; and for over two years, my recovery from chronic illness was hindered as I lost the ability to function from severe sleep deprivation. To be sure, EMR wasn't the only reason that I wasn't resting and recovering, but it was a major one.

Some people might argue that I was susceptible to the effects of EMR because I've had chronic Lyme disease. Maybe so, but consider this: Lee Cowden, who is a very healthy, strong person, noted in our recent book that when a smart meter was installed on his home, within a very short period of time afterward, he became fatigued, and brain-fogged and developed atrial fibrillation (which is a potentially dangerous heart rhythm disturbance). Incredibly, his symptoms continued until he was able to get the smart meter removed from his home, at which time he returned to feeling healthy and energetic.

Not all of us can afford to live in a house out in the countryside, and putting our cell phone in airplane mode during the day is inconvenient, as is having to sit down to talk on a landline or use a computer on battery power. However, I believe that more of us would recover faster from our chronic health conditions and illnesses if we did whatever we could to reduce our exposure to electromagnetic pollution.

It's not easy. It's not a matter of doing just one or two things, but every step that you can take to reduce your exposure will ➤

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bring you one step closer to total wellness. Below I mention some strategies that I have found to be helpful, which you can learn more about in Cowden's and my book, since it is beyond the scope of this article to describe them in great detail. I also mention these in my 2012 book, *Beyond Lyme Disease*. (www.beyondlymedisease.com).

First, turn off your bedroom circuit breakers at night. This reduces the amount of low-frequency fields to which you are exposed from your appliances and even the wall wiring while sleeping. Consider Graham-Stetzer filters to neutralize or mitigate the effects of the wall wiring (www.stetzerelectric.com).

Next, use a landline connection instead of Wi-Fi Internet, and use your cell phone only for emergencies, preferably on speakerphone. Headsets or Bluetooth devices will not protect you from the radiation emitted from cell phones, so I personally would not use these either. I have measured the fields that radiate from the headset using a Trifield meter and found them to be similar to when I hold the phone to my ear.

So-called radiation-free headsets that use air tube headset technology might be a bit safer, but it is more like using the speakerphone option on your phone than not talking on it at all, since the frequency signals still run up most of the length of the headset cord.

Sleeping under a metallic-lined Faraday cage at night is also a good idea. Faraday cages filter out high-frequency electromagnetic fields, such as those from microwave towers and Wi-Fi. If you are like me, though, and are exposed to low-frequency fields from appliances or wall or ceiling wiring, you'll also want to consider Graham-Stetzer filters or memon technology (mentioned later in this article). The Faraday cage will not filter out low-frequency radiation, which is just as dangerous as high-frequency radiation.

Also, avoid living close to microwave and other telecommunication towers. You can see how many antennas and towers are within a 4-mile radius of your home by doing a search on www.AntennaSearch.com. An area that is less densely populated might have 4 towers; denser areas might have 45 or more.

Next, do whatever you can to get the smart meter (if you have one) removed from your home. Some states, such as California, have created legislation that allows you to do this. For more information on how to get a smart meter removed from your home, visit www.stopsmartmeters.org.

During the day, when you are working, use a laptop computer on battery power whenever possible, rather than a desktop computer or laptop plugged into an outlet. Never place the laptop on your lap.

Connie Strasheim is a medical researcher and the author of two books on Lyme disease: *Insights into Lyme Disease Treatment: Thirteen Lyme-Literate Health Care Practitioners Share Their Healing Strategies*, a best-seller within the Lyme disease community. She is also the author of the newly released book *Defeat Cancer: Fifteen Doctors of Integrative and Naturopathic Medicine Tell You How*. More information on this and her other books can be found at www.cancerbooksource.com and www.lymeinsights.com. She also maintains a blog on Lyme disease: http://www.lymebytes.blogspot.com.

Finally, consider a technology such as memon transformers (www.memonyourharmony.com; note that the company's name is not capitalized), which are devices that will partially neutralize the effects of the EMR in your home or work environment. Not all EMR-protective devices are effective, and some can even be dangerous, especially when used improperly. Choose a company and device that have testimonials, studies, and a reputation to back their effectiveness.

I mention memon here because it has been studied in at least one university in Europe, and been approved for use in some schools in Europe. I have also personally benefited from this technology. (Note: I receive no financial compensation from memon for mentioning its products in this article).

Finally, you might want to try wearing an EMR-protective device, such as a pendant. I haven't personally found most of these devices to be effective, and some can even misalign your body's own energy even further, but you may find one that works for you.

One EMR expert whom I interviewed for the Alternative Cancer Research Institute, Dr. Elizabeth Plourde, a clinical laboratory scientist, medical researcher, and advisory board member of the American Anti-Cancer Institute, uses a product called bioDOT, which apparently has a homeopathic-like effect upon the body.

According to Plourde's website: "The bioDOT is programmed with powerful resonant Phi Technology®. The natural, coherent frequencies used in this programming harmonize your biofield. They remind it of its optimal functioning state, making it more coherent and resilient. It is like recharging your battery, restoring and rebalancing your energy." Thus, the technology is somewhat different from that of other devices that aim to block EMR.

Plourde sells these devices on her website, but she is also electrosensitive and believes that this product has been the only one of many that has enabled her to function and go out in public, when all kinds of other gadgets failed. I believe that there is no one-size-fits-all solution when it comes to protecting the body against EMR, but the bioDOT may be helpful for some of us.

We can't avoid electromagnetic pollution, but by taking steps to mitigate its effects upon our bodies, I believe that many of us will find our energy increasing, sleep improving, and brain fog dissipating, among other positive benefits. I also believe that reducing our exposure to EMR will help those of us with chronic health conditions, such as Lyme disease, to heal faster, better, and more thoroughly.

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Statins and Breast Cancer

by Jacob Schor, ND, FABNO

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Over the last few years, the question of how statin drugs affect breast cancer has gone through several flip-flops. One day statins are promoted as a cure for cancer; the next, blamed as the cause. Numerous large, seemingly well-done papers provide arguments for both sides. This issue confuses our patients, who depend on us to provide advice on the drugs that their doctors want them to swallow; it behooves us to make some sense of this.

It is often the case in medical research that understandings and opinions change over time. Drugs once thought safe are discovered to have unwanted side effects. But when it comes to statins and cancer, opinions swing further and faster than usual. One month they are good, the next bad, back and forth like tides, or pendulums moving from one extreme to another.

The statin and cancer excitement took off with Nielsen's November 2012 study, which reported that people in Denmark who took statins had a lower risk of dying from cancer than non-statin users. Causes of mortality were assessed among all Danes diagnosed with cancer between 1995 and 2007 and followed through 2009. Of patients aged 40 years or older, 18,721 had used statins regularly before the cancer diagnosis and 277,204 had never used statins. Statin users had a 15% lower risk of dying from any cause and from cancer. Reduced cancer deaths were seen for 13 cancer types.[1]

Then in April 2013, Murtola reported that statin use was associated with a 66% reduction in the risk of dying from breast cancer. Murtola's retrospective study looked at statin use and breast cancer mortality among the 31,114 women with breast cancer who were diagnosed in Finland between 1995 and 2003. During follow-up, 6011 of the women died, 3,169 due to breast cancer. The death rate among statin users was 7.5%, while among non-statin users it was 21%.

Women with localized disease who took statins were 67% less likely to die than nonusers (hazard ratio, 0.33). Among those with metastatic disease, statins use was associated with a 48% decreased risk of death. Finland's national health database allowed calculation of hazard ratios risk by the type of statin taken, including simvastatin (HR, 0.47), atorvastatin (HR, 0.27), fluvastatin (HR, 0.35), and pravastatin (HR, 0.50). Median follow-up was about 3 years but ranged from less than 1 year to 9 years.[2] These numbers suggest that atorvastatin (Lipitor) worked best.

An earlier study had reported similar but less dramatic decreases in breast cancer occurrence. Researchers analyzed data from 156,351 postmenopausal women enrolled in the Women's Health Initiative with 4383 confirmed invasive breast cancers. Statins were used by 11,710 (7.5%) of the women. Nonsignificant trends toward lower breast cancer risk were seen in the statin takers. Breast cancer incidence was 4.09 per 1000 person-years among statin users and 4.28 per 1000 among nonusers. Hydrophobic statins (i.e., simvastatin, lovastatin, and fluvastatin) were used by 8106 women, and this was associated with a significant 18% lower breast cancer incidence. Use of other statins (i.e., pravastatin and atorvastatin) or non-statin lipid-lowering agents was not associated with breast cancer incidence.[3] In this study Lipitor did nothing.

Statins Were Supposed to Cause Cancer

18 years ago, we were pretty sure that statins caused cancer. This belief originated with Newman and Hulley, who quoted rodent data from the *Physicians' Desk Reference* to suggest that statins might cause cancer in people.[4]

Their suspicions were seemingly confirmed in 2007 when Alsheikh-Ali et al. reported a significant association between low levels of LDL cholesterol and cancer among patients taking statins. After evaluating 23 drug trials, yielding 309,506 person-years of follow-up, they found that "... the risk of cancer is significantly associated with lower achieved LDL-C levels ... the cardiovascular benefits of low achieved levels of LDL-C may in part be offset by an increased risk of cancer."[5]

This convinced many that statins cause cancer, but not Alsheikh-Ali. A year later, in a second publication, Alsheikh-Ali amended the initial conclusion: "There is no evidence that statin use causes cancer, although patients who reduce their LDL cholesterol level with statins appear to have a significantly increased risk of the disease. ..."

Alsheikh-Ali's first paper only used data from patients taking statins.

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The second paper, from 2008, was a larger meta-analysis and included data from both people taking statins and from people not taking them. Fifteen randomized, controlled trials provided data from 97,000 patients yielding 437,000 person-years of follow-up.

During these trials, 5752 patients developed a new cancer. The cancer incidence was 4% to 27% per 1000 person-years for those taking statins and 6% to 24% per 1000 person-years for the people not taking statins; both groups had the same risk. People who had low LDL cholesterol levels had an increased risk for cancer, even patients taking placebo and not statins. The statins were not to blame. LDL cholesterol levels drop when cancer is developing; it is an early warning: "... cancers can significantly lower cholesterol levels as much as 10 years before they surface clinically."[6] Cancer cells consume LDL cholesterol faster than normal cells. Statins were not the culprit. In hindsight, this is easy to see; using Framingham data, Williams had reported in 1981 that low cholesterol levels predict the occurrence of colon cancer.

New News

In the months since Nielsen and Murtola were published, other papers suggested similar benefit.

Brewer et al. reported that hydrophilic statins (more about hydrophilic vs. lipophilic later) improved progression free survival in patients with inflammatory breast cancer (IBC). Data from 723 IBC patients treated at M. D. Anderson from 1995 to 2011 were analyzed. Statins were classified by Ahern's system ranking them from hydrophilic to lipophilic (H-statins vs. L-statins). Taking H-statins was associated with significantly improved progression free survival compared with no statin (HR = 0.49).

Other in vitro and animal experiments reported positive effects such as increasing breast cancer apoptosis, preventing carcinogenesis, tumor growth inhibition, and inhibiting growth of triple negative breast cancer cells.[7–10]

Insignificant or No Benefit

Not all trials found benefit.

A large meta-analysis on statin use and the risk of breast cancer found no significant benefit. "A total of 24 (13 cohort and 11 case-control) studies involving more than 2.4 million participants, including 76,759 breast cancer cases contributed to this analysis. ... Statin use and long-term statin use did not significantly affect breast cancer risk (RR = 0.99 and RR = 1.03)."[11]

Another meta-analysis analyzed data drawn from 22 randomized, controlled trials with 66,582 patients receiving statins and 66,604 placebos. Five years of statin therapy had no effect on the risk of cancer-related death (RR 1.00).[12]

An experiment giving lovastatin (40 mg twice a day for 6 months) to women at high risk of breast cancer found no significant change in breast duct cytology or other biomarkers of breast cancer risk.[13]

Another study compared 565 breast cancer cases with 2260 controls and found no significant differences in breast cancer risk between women who took statins and those who did not.[14]

A large German study was also inconclusive. Data from 3189 patients with invasive breast cancer stage I–IV and 3024 patients with breast cancer stage I–III were analyzed for recurrence risk.

During a median 5.3 years follow-up, 404 of 3189 stage I–IV patients died, and 286 deaths were attributed to breast cancer. While statistically nonsignificant, use of lipid-lowering drugs was associated with an increase in non-breast cancer mortality (HR 1.49, 95% CI 0.88–2.52) and increased overall mortality (HR 1.21, 95% CI 0.87–1.69). Limiting data to only stage I–III breast cancer patients, lipid-lowering drug use was nonsignificantly associated with a reduced risk of recurrence (HR 0.83, 95% CI 0.54–1.24) and of reduced breast cancer-specific mortality (HR 0.89, 95% CI 0.52–1.49).[15]

We may want the Murtola study to be true, but, if we consider all the statin studies together, they " ... have not identified a strong relationship between statin use and reduced breast cancer incidence. These studies have several limitations and were not designed to detect modest effects in high-risk populations. Additional focused epidemiological and translational studies in high-risk populations are needed to justify and guide definitive large prospective trials."[16]

One of the largest prospective studies on this topic (Desai 2013), using Women's Health Initiative (WHI) data from 154,587 postmenopausal women, with 7430 confirmed breast cancer cases and of these 11,584 (7.5%) using statins at baseline, reported "no relationship between statins and breast cancer risk." "The annualized rate of breast cancer was 0.42% among statin users and 0.42% among nonusers."[17] Bottom line: It does not appear that statins lower breast cancer risk.

Bonovas writing in March 2014 sums it up: "As of today, the accumulated epidemiological evidence does not support the hypothesis that statin use affects the risk of developing breast cancer when taken at low doses for managing hypercholesterolemia. However, current evidence cannot exclude an increased risk of breast cancer with statin use in subsets of individuals, for example, the elderly."[18]

Statins May Still Cause Cancer

This increased risk that Bonovas writes about refers to one particular study (McDougall 2013).

Data from a case-control study of breast cancer in the Seattle-Puget Sound region allowed comparison of 916 invasive ductal carcinoma (IDC)

and 1068 invasive lobular carcinoma (ILC) cases with 902 controls. Women who used statins for 10 plus years had a 1.83-fold increased risk of IDC (95% CI) and a 1.97-fold increased risk of ILC (95% CI) compared with the women who had never used statins. Women diagnosed with hypercholesterolemia and who used statins for 10 years or longer had more than double the risk of both IDC (OR: 2.04) and ILC (OR: 2.43) compared with never users. [19]

This study brings us full circle, back to the old view that statins cause cancer.

Possible Explanations

There are several possible explanations, particularly for Nielsen's results.

Nielsen did not consider data on smoking. Patients may have stopped smoking when they started taking statins, perhaps inspired by a recent myocardial infarction. Smoking reduction or cessation by statin-takers could account for a lower mortality risk.

Another possibility is the concomitant use of other drugs that possess anticancer activity. In Nielsen's study, women taking statins were more likely to have cardiovascular disease (70% vs. 21%) and diabetes (18% vs. 3%) than non-statin users. This could have led to disproportionately higher use of aspirin and or metformin in the statin users. Both medications are associated with reduced cancer-related mortality. Nielsen did relook at the data with possible aspirin use in mind, and eliminated all participants with cardiovascular disease (the only indication in Denmark for routine aspirin use) and this second analysis yielded the same results.[20] (A meta-analysis of 51 random controlled trials reported that aspirin users were 15% less likely to die from cancer [OR = 0.85; 95% CI: 0.76–0.96].)[21]

Another explanation for the apparent positive statin effect goes back to the theory that high cholesterol may prevent cancer. Women in the statin cohorts prior to receiving statins had lived with elevated cholesterol for years. This period of elevated cholesterol may have provided residual protection. [22]

Statins do better in observational studies than in randomized controlled trials. Healthy-user bias in observational studies may explain this. Doctors may unconsciously underprescribe statins to obese patients or smokers because of their unhealthful lifestyles.[23] Healthier patients might take more statins.

Low cholesterol levels among statin users might also signal trouble. One study reported that among 47,294 patients with hypercholesterolemia who were treated with low-dose simvastatin for 7 years, the rate of cancer deaths in patients with a cholesterol level of less than 160 mg per deciliter was 3 times higher than in users with high or normal cholesterol values ($p < 0.001$).[24]

Women in the Cholesterol and Recurrent Events (CARE) trial, who received pravastatin, were 12 times as likely to have breast cancer as controls receiving placebos.[25]

HMG-CoA Reductase

Some tumors express HMG-CoA reductase (HMGCR), and these may be the tumors that really respond to statins.

In fact, Swedish data suggest that there may be a way to predict if cancers will respond to statin treatment. Tissue samples from 50 women diagnosed with invasive breast cancer and given high dose atorvastatin (80 mg/day) for 2 weeks before cancer surgery were compared between pre and post statin therapy. Ki-67 expression between paired samples decreased nonsignificantly by 7.6% after statin treatment ($p = 0.39$); but in tumors expressing HMG-CoA reductase (HMGCR), the rate-limiting enzyme of the mevalonate pathway, Ki-67, dropped a significant 24% ($p = 0.02$). Statins have the most antiproliferative effect in HMGCR ➤

positive tumors. Testing for HMGCR could provide one way to select cancer patients who will respond to statins.[26]

There may be other ways to discriminate between responsive and nonresponsive tumors. Treating 19 different breast cancer cell lines with a statin drug (fluvastatin) yielded a range of responses; cell death was triggered in only a subset of sensitive cell lines, and this response was associated with an estrogen receptor alpha (ERα)-negative, basallike tumor subtype. Using these data, researchers claim that they are developing a gene signature test that will predict statin sensitivity.[27]

Estrone-Sulfate

Researchers at Johns Hopkins conducted a novel prospective study seeking biomarkers; " ... the contralateral breast of women with a previous history of breast cancer was used. ..." Women " ... who had completed all planned treatment of a prior stage 0-III breast cancer received simvastatin 40 mg orally daily for 24-28 weeks." In the 50 women enrolled, total cholesterol, LDL cholesterol, triglyceride, and hsCRP fell significantly. Neither estradiol or estrone concentrations changed, but estrone sulfate concentrations decreased, particularly among postmenopausal participants.[28]

Estrone sulfate is the estrogen found in Premarin, also known as equine estrogen. Elevated levels are associated with greater breast density in menopausal women using hormone replacement therapy.[29] In breast cancer cell cultures, physiologic levels of estrone sulfate promote cancer cell replication.[30] Lowering levels might be good for women with a history of breast cancer.

H-Statins vs. L-Statins

The Ahern system for classifying statins divides them into two classes by whether they are hydrophilic or lipophilic. These classifications, H- vs. L-statins, predict their impact on the liver. The more hydrophilic, the greater impact; the more lipophilic, the greater impact on nonhepatic tissues. High hepatoselectivity (H-statins) is thought to reduce adverse drug effects.[31] Simvastatin is among the most lipophilic of the statins, while pravastatin is one of the least. Attention is now focused on which class is more useful for specific clinical conditions; for example, lipophilic statins may be more useful for acute myocardial infarctions.[32]

Harvard researchers reported that after analyzing data on all the women in Denmark diagnosed with invasive breast cancer between 1996 and 2003 (18,769), cancer rates varied by the type of statin that women took. Women who used simvastatin, a lipophilic statin, had approximately 10 fewer breast cancer recurrences per 100 after 10 years of follow-up compared with women who were not prescribed a statin. Women who took hydrophilic statins had about the same risk of breast cancer recurrence as women not taking statins. Thus the type of statin may matter; it is only the lipophilic ones that act.[33] This may explain the high frequency of breast cancer for women taking pravastatin in the CARE cohort, as this drug is an H-statin.

27-Hydroxycholesterol

We should consider the complex effect that cholesterol itself has on breast cancer. Several recent studies link cholesterol metabolism to breast cancer. Specific cholesterol metabolites may promote or suppress breast cancer.[34-36]

In recent months, one cholesterol metabolite, 27-hydroxycholesterol (27HC), has gained attention as it interacts with the estrogen receptor and increases breast cancer growth in animal models. It also promotes metastasis. Increased amounts of the enzyme that breaks down 27HC in human breast cancer samples are associated with improved patient survival. Increased amounts of the enzyme that converts cholesterol to 27HC are found in more aggressive breast tumors. There is more 27HC in breast tumors than in healthy breast tissue of the same patient and far more 27HC in patients with cancer than in patients without cancer. Some statin drugs may interfere with breast cancer because they prevent conversion of cholesterol to 27HC.[37] There is an awful lot about this that we still don't know.

Bottom Line

The initial data from the Nielsen and Murtola studies were exciting, but a year later, we must think twice about whether we act on their results. If true, we should be prescribing statins to women as breast cancer treatment. On the other hand, if the Puget Sound results are true, we should be counseling women to stop taking statins.

A March 2014 editorial sums up the current situation:

> As of today, the accumulated epidemiological evidence does not support the hypothesis that statin use affects the risk of developing breast cancer when taken at low doses for managing hypercholesterolemia. However, current evidence cannot exclude an increased risk of breast cancer with statin use in subsets of individuals, for example, the elderly. On the other hand, some studies show that statins might be useful to prevent recurrence and improve survival in patients already suffering from certain breast cancer types. They could also be combined with certain anticancer drugs and potentiate their effects, ameliorate their side effects or prevent the development of resistance.[38]

Information on statins is shifting quickly, and we need to keep our eyes open, watching for methods to predict which tumors will be inhibited. For now it makes sense to encourage lipophilic statins over the hydrophilic statins for treating hypercholesterolemia in women with

a history of breast cancer. Whether statins should be suggested to treat breast cancer alone is questionable. Testing tumors for HMG-CoA reductase (HMGCR) may someday prove useful. The developing knowledge on 27-hydroxycholesterol is fascinating and time will tell if it becomes clinically relevant.

Murtola's data in particular are compelling and hard to ignore. So are McDougall's results that statins might increase risk of breast cancer. Risk of doing a patient harm should outweigh unproven benefit.

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The Aging Brain Part 2: Calcium Homeostasis and a Theory Of Brain Aging

by Dan Moran

Over 20 years ago, the calcium hypothesis of brain aging was first proposed. Multiple theories of aging exist, but brain aging is always associated with dysregulation of the calcium ion (Ca2+). Despite differences in etiology, the deregulation of calcium homeostasis consistently appears as the underlying mechanism of neuronal loss and dysfunction in growing old and in age-related diseases such as Alzheimer's, Parkinson's, ALS, and other dementias.[1] In part 1 of this review, brain aging was defined and the role of the Ca2+ in normal brain function reviewed. In part 2, the mechanisms for calcium-induced brain aging are reviewed.

Biological systems depend on the Ca2+ through the intrinsic chemistry of protein molecules. Neurons have a specialized network of proteins that mediate calcium activation of biochemical events. Research into brain aging has revealed that the cumulative demise of the network of calcium-mediated systems of brain biology can be blamed for "normal" aging process and many age-related dementias. In the brain, these systems are networked by proteins through the Ca2+ making calcium dyshomeostasis the nexus of brain aging.[2,3] The loss of calcium regulation that results in brain aging is fundamental to age-related brain diseases such as Alzheimer's and other poorly diagnosed dementias.[2] Memory loss, slower movement, sluggish reflexes, changes in perception, reduction in analytical tasks, diminished response time, poorer judgment, and personality changes can be documented in the aging process. These age-related changes are associated with changes in the health of the cells of the nervous system.

The Calcium Network of the Brain

Internal baseline concentrations of the Ca2+ are regulated by the cell through means of the energy-dependent plasma membrane Ca2+ pump (PMCA) and the sodium/calcium exchanger (NCX). The NCX removes Ca2+ through an ATP dependent electrochemical gradient. The NCXs are distributed generally throughout the cell membrane and are activated by the rise in calcium concentrations. The PMCAs have a high binding affinity for calcium and are localized in synaptic regions, and this localization is involved in priming the presynaptic junction for neurotransmitter release. PMCAs are regulated by calmodulin, a calcium-activated protein with multiple targets, as well as other mechanisms giving stringent local control to the activation of the PMCA.

Other cell membrane channels, the glutamate-regulated channels, are responsible for the majority of neurotransmissions of the brain. The channels are found as ionotropic receptors or G-protein coupled receptors. Three forms of the ionotropic receptors exist: the kainite (KA), the AMPA, and the NMDA receptors. Of these, the NMDA receptors have a higher conductance and are permeable to sodium and calcium ions. Depolarization of the membrane by activated KA/AMPA receptors stimulates activation of the NMDA receptors also by glutamate; the combination of controls for activation allows high increases in the calcium into the cell. This triggers key secondary messaging for various signal pathways. This localized control over NMDA receptor activation determines long-term potentiation and synaptic plasticity associated with learning and memory.[4]

The extensive endoplasmic reticulum (ER) found distributed throughout neurons store Ca2+ through a spectrum of channels, buffers, and sensors that are integrated for Ca2+ homeostasis. Ca2+s are released primarily through the ryanodine (RyR) and inositol 3-phosphate (InsP3) receptors. Each has three different subsets of receptors with different sensitivity to activation by the calcium ion. They are distributed both spatially and temporarily throughout the ER of cells and differentially in the brain tissues that reflect specialization of regions

in the brain. The release of Ca2+ by these calcium-activated receptors produces a wave of polarization across the ER. The organization of receptor placement creates different wave properties that are relevant to the formation of neuronal plasticity. Uptake of Ca2+ is by energy-dependent ER calcium ATPase pumps or SERCA, a family of pumps expressed in patterns relevant to the needs of the cell and brain region. The ER also contains calcium-binding buffering proteins, calreticulin and calsequestrin and others having low affinity for the calcium ion, adding to the fine control over calcium concentrations.

Mitochondria are organelles specialized to carry out the respiration of sugars and production of chemical energy for the cell. They are also an important Ca2+ buffer, sequestering the ion through a uniporter that creates an electrochemical potential to pull the ion into the cell. The enzymes of respiration are calcium regulated so that conductance of Ca2+ occurs when the concentration is high and ATP/ADP ration is low. The Ca2+ is exported from the mitochondria through a NCX or through a proton exchanger. Other means of calcium export involve the formation of a transient pore in the mitochondrial membrane, an event that appears to occur in pathological conditions of cell physiology.

A large family of calcium-binding proteins serve as sensors and buffers of the calcium ion. The sensing protein calmodulin is a calcium-activated protein that renders graded changes in the concentration of the calcium ion into graded responses through activation of various enzymatic pathways, including local changes in membrane proteins to modulation of genetic expression. Other calcium-activated sensor proteins switch compartmentalization of signal cascades or modify proteolytic processing of other proteins and regulate signal transduction systems.

Calcium-binding proteins have a few types of calcium-binding domains with each having a large repertoire of permutations with which to bind calcium.[5] Some permutations of the calcium-binding domain bind the ion strongly and others weakly. Certain proteins bind calcium with large conformational changes in their structure, and other calcium-binding associations cause subtle changes.[6] Proteins that bind the ion strongly with minor changes in conformation are buffers against calcium toxicity. Proteins that bind weakly and reversibly may undergo very large changes in conformation. These changes activate the protein to catalyze enzymatic reactions or to signal gene expression. The calcium-protein association permits cellular activity to proceed in a finely tuned orchestration of biochemical regulation that makes life possible. The signature motif for calcium-binding domains is the EF-hand structure. It has been found in over 1000 unique proteins in the animal kingdom, and several hundred proteins have been found in the human genome.[7,8] The brain cell has been engineered with extreme prejudice to perform small miracles from microsecond to microsecond, using calcium to orchestrate the power of control.

Other proteins such as calretinin, calbindin, and parvalbumin function as localized calcium buffers, especially in the pre- and postsynaptic regions, regulating Ca2+ densities to affect the sensitivity of the neuron to various stresses such as oxidative damage, ischemia, and depolarization. Furthermore, the expression and distribution of these proteins in critical locations of the neuron, including the internal membranes of the cell, contribute to a number of neuronal subtypes in tissues specialized for information flow and storage within the brain.

Neuronal Excitability and Synaptic Plasticity Affected

In essence, changes in synaptic plasticity and neuronal excitability result in cognitive decline typical of normal aging. The collective demise of calcium regulating systems of the neuron establishes a chronic elevation of intracellular Ca2+ concentration. This affects synaptic transmission. Long-term potentiation (LTP) increases synaptic activity, while long-term depression (LTD) reduces it. LTP strengthens the synapse, while LTD weakens synaptic connections. Both determine synaptic plasticity by high- or low-frequency stimulation, respectively. The imbalance of Ca2+ interferes with the sensitivity of these two forms of signal; the threshold for LTP is increased and the threshold for LTD is decreased. The overall effect is to reduce synaptic connectivity; LTP signals are down, LTD signals increase. Memories are being lost and new experiences difficult to record; learning and memory are impaired.

Age-Related Changes in Brain Cell Biology

Aged neurons show higher basal internal Ca2+ concentrations than younger neurons, and each of the calcium-dependent systems has shown abnormalities that contribute to calcium toxicity. The age-dependent changes in voltage-operated Ca2+ channels (VOCC) of the cell membrane, which regulate calcium entry upon neuronal depolarization, include two phenomena that lead to excess calcium entering the neuron. Some types of VOCC increase in their excitability, having lower thresholds to calcium entry.[9] Other calcium channels increase in number in aged neurons, increasing the entry points for Ca2+ upon activation.[10] Why the cell responds to age by increasing the presence of some channels when other channels are hypersensitive is unknown, but the result is excessive calcium entry into older brain cells with changes in depolarization and repolarization events (afterhyperpolarization).[10]

The NMDA receptors localized at the synapse activate upon the release of the neurotransmitter glutamate. The current thinking is that there is

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an age-related decline in the number of these receptors, but no change in glutamate affinity.[11] Different RNA editing has also been detected in a developmentally regulated way for the receptor protein in aged cells, resulting in electrophysiological changes in channel responsiveness and an increase in the peak current required for activation and its association with Ca2+ toxicity.[3] This would effectively reduce the neurotransmission signals while simultaneously increasing the electrical current demand for activation resulting in excess calcium entry to activate the channel, both of which establish adverse signaling, contributing to alteration in synaptic communications. In addition, gene-to-gene interactions of the NMDA receptor gene are magnified in age-related memory studies on carriers of certain genotypes.[12] This suggests that genetics plays a role in healthy aging when brain resources are at a premium.

Studies of the nerve endings of the cerebrocortex show that the activity of calcium extrusion by the NCX is reduced in the aged brain.[13,14] The transporter has a reduced affinity for the Ca2+.[15] In addition, the calcium-activated protease calpain inactivates certain but not all forms of the NCX of the neuron, contributing to the failure to maintain baseline Ca2+ concentrations.[16] Chronic increases in basal Ca2+ levels raise this aberrant protease activity, adding to Ca2+ dyshomeostasis.

Furthermore, impairments in the calcium sequestration and extrusion pumps of either the ER (SERCA pumps) or the plasma membrane energy-dependent calcium pumps (PMCA) have reduced activity in aged neurons. This raises the levels of intracellular calcium, resulting in a chronic overload of Ca2+ in the cytoplasm of neurons, reducing neuronal excitability and the dynamics of neuronal plasticity of aged cells.[17] Proteins that compose the calcium network undergo oxidative modification through time, resulting in conformational changes, aggregation, and internalization from the plasma membrane and proteolytic degradation by the calcium-activated calpains and caspases.[17] Additionally, genetic deterioration and reduced protein turnover in the cell add to the accumulation of defective proteins.[18]

Afterhyperpolarization events are calcium-dependent processes that increase in duration and decrease neuronal excitability in aged brain cells.[19] This is known to lead to difficulty in processing and storing new information, making learning difficult.[19,20] Increased afterhyperpolarization also increases the residence time of high calcium concentrations, adding to the chronic activation of calcium-sensitive messaging systems and inducing mitochondria into oxidative stress with concomitant damage to the mitochondria and the cell.[20]

In aging brain cells, the mitochondria show extensive oxidative damage to the internal membrane structures responsible for housing the proteins of the respiratory chain.[21,22] Chronic exposure of mitochondria to calcium overload leads to dysfunction and disruption of the organelle and programmed cell death of brain cells.[21,23] Damage to DNA, the internal lipid membrane, and to proteins occurs, reducing the efficiency of energy production and the availability of chemical energy to energize the calcium pumps of the cell.[24] Genetic damage by oxidative stress mutates proteins, destroying their antioxidative function and sensitizing the organelle to calcium overloads, toxic mechanisms, and dysfunction.[25] A cycle of chronic excessive Ca2+ in the cell is maintained. Over the years, this mitochondrial damage contributes to neurodegeneration and programmed cell death by the mitochondrial pathway.[24-26]

Calcium-binding proteins that function to buffer the Ca2+ are reduced in aged brain cells.[27,28] Calcium buffers modulate the short-lived burst of transient calcium increases in a manner that shapes and enhances the precise cellular impact of the Ca2+ on neuronal activity.[29,30] These proteins regulate the amplitude and duration of the transient calcium signal, fine-tuning the cell's response to the calcium signal and determining the extent of such processes as neuronal plasticity.[29,31] The short- and long-term potentiation of neuronal signals determines the extent of synaptic modulations that result in either short- or long-term memories.

Extensive studies on calcium buffering proteins in regions of the brain known to be vulnerable to age-related diseases such as Alzheimer's have shown huge losses of these proteins in such regions as the hippocampus, where memory is integrated, and the basal forebrain, where learning is regulated.[20,31-36] The reduction in calcium-buffering proteins appears to be due to a reduced level of gene expression as well as severe oxidative damage.[36,37] The damage to these proteins is from aggregation and an age-related decline in cellular repair and protein turnover mechanisms.[37,38] This loss of buffering capacity increases the oxidative load on the cell, resulting in corresponding increases in the concentrations of oxidized proteins.[38] Neuronal plasticity is weakened by the reduction in the fine-tuning of Ca2+ concentrations afforded by buffering proteins. These important changes are correlated to age-related deterioration in learning, memory

recall, and other measurements of cognitive function.

Collectively, the multiple defects in calcium homeostasis from the increased release of calcium from the ER, reduction in calcium extrusion through the cell membrane, the reduction in buffering capacity, and the impairment of calcium pumps, also the impairment of the mitochondrial sinks, result in changes to neuron function and cell viability.[39] Neurons become hypersensitive to innervation but sluggish in recovery. Synaptic response is reduced as well, interfering with synaptic communication and diminishing neuronal plasticity.[39] Learning and memory become impaired, and the demise of the calcium network of neuronal regulation imparts the sluggish response and behavior to the elderly. Cells may undergo a silencing of synaptic pathways (LTD) that weakens memory networks.[40,41] Furthermore, the compromise in the orchestration of the fine-tuning of the calcium-protein networks of the brain enhances vulnerability to damage and to disease conditions, leading to dementias such as Alzheimer's.[30]

With these considerations, the final section of this review (part 3) will examine preventative and potential therapeutic opportunities for intervening in the demise of cognition as an age-related phenomenon.

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Nine Research Areas That Need to Be Applied to or Expanded in the Study of Multiple Chemical Sensitivities

by Laurie Dennison Busby, BEd

In the majority of non-occupationally triggered multiple chemical sensitivities (MCS), MCS is a comorbidity of chronic fatigue syndrome (CFS) or fibromyalgia (FM).[1] Patients with MCS and sometimes CFS present with airway symptoms, especially upper airway nasal symptoms; sometimes cutaneous symptoms; and adverse drug reactions (ADR) to multiple medications.[2-6] In MCS and MCS-related disorders, "Preliminary data indicate the nasal pathology of these disorders is characterized by defects in tight junctions between cells, desquamation of the respiratory epithelium, glandular hyperplasia, lymphocytic infiltrates, and peripheral nerve fiber proliferation."[2]

Patients have sometimes used the term *allergies* to describe the reactions: "The CFS group tended to report more respiratory symptoms and drug allergies."[5] However, researchers have noted that total IgE levels are often not highly elevated when compared with symptoms being reported.[7,8] In an MCS cohort, "Total IgE values were relatively low, 32 patients (64%) showed the IgE value below 200 IU/ml."[7] In a CFS cohort, "78% had total IgE less than100 IU/ml."[8]

While mast cells have been found in the skin of patients with fibromyalgia in one cohort and in 20 patients with MCS, several research teams have concluded that IgE-mediated classic allergies are probably not responsible for the hypersensitivities in most patients with MCS and CFS.[7-11] "Inflammation and the consequent IgE-mediated activation of mast cells and eosinophils, as seen in asthma patients, is unlikely to be responsible for the presence of BHR in patients with CFS."[11]

One research team instead refers to patients with CFS as having a "high prevalence" of idiopathic nonallergic rhinopathy.[12] Patients with MCS, like nonallergic patients with other hypersensitivity conditions, have been described as being sicker than patients with allergies.[13] The hypersensitivities in patients with MCS and CFS may potentially share some of the same mechanisms seen in other hypersensitivity conditions. This article primarily focuses on non-IgE-mediated potential pathways and tests.

Infectious Agents: Potential Role as Trigger and In Maintaining Reactions

In CFS, viruses including cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV-6) are often cited as triggers, with EBV and HHV-6 often cited as coinfections.[14,15] In one CFS cohort, 47% had increased HHV-6 antibody titers.[14] Some patients with CFS due to an infectious trigger are left with crimson crescents on their pharyngeal pillars. "This appearance is most closely associated with elevated HHV-6 titers in our patients."[15]

Viruses can be found in nasal mucosa and other tissues in close proximity in normals without signs of systemic infection upon autopsy.[16] Reservoirs of CMV have been found in nasal mucosa, trachea, and thyroid; EBV in nasal mucosa, tonsils, and lymph nodes; and HHV-6 in salivary glands and thyroid.[16] In a similar study, "Using autopsy specimens, we found that the frequency of HHV-6 DNA in the olfactory bulb/ tract region was among the highest in the brain regions examined."[17] Interestingly, "EBV was detected in all eight cases ... but in only two of six whole-blood specimens."[16]

"Viruses injected into the nasal cavity have been found to enter olfactory neurons, replicate, travel into the olfactory bulb and then into the central nervous system (CNS)," due to "the close proximity and the synaptic connections between the nasal cavity and the CNS. ... In addition, viruses in circulation can also cross from capillaries in the lamina propria into olfactory neurons."[18]

Enzymes

Xenobiotic-metabolizing enzymes (XMEs) are found in the liver, kidney, skin, olfactory epithelia, and bronchiolar epithelium. XMEs are highly expressed in the mammal olfactory mucosa, and for several compounds tested, the rate of olfactory mucosa metabolism from parent compound to subsequent compound was 3- to 65-fold higher

than hepatic. Inhibitors of these enzymes, increased the electro-olfactogram (EOG) response. "This increase in EOG amplitude provoked by XME inhibitors is likely due to enhanced olfactory sensory neuron activation in response to odorant accumulation. ... In addition to protecting against inhaled toxic compounds, these enzymes could also metabolize odorant molecules, and thus modify their stimulating properties or inactivate them. ... They may also protect the brain because the olfactory nerve can carry viruses, bacteria and chemicals into the brain."[19]

Viruses are known to affect enzymes. Could an ongoing virus also affect olfactory mucosa enzymes thus inhibiting attenuation of olfactory signals in patients with an infectious trigger? Odorant inhalation tests to detect odorant metabolites in exhaled air may have the capacity to help differentiate respiratory xenobiotic-metabolizing enzyme capacity in patients with MCS versus controls.

Enzyme polymorphisms have been found in the blood in MCS and have been able to differentiate MCS, suspected MCS, CFS, and FM, and healthy controls.[20,21] Genotyping for these variants could be a reliable and cost-effective test to help diagnose these illnesses, according to these researchers.[21]

Neuropeptides and Neurogenic Inflammation

In addition to XMEs, the respiratory tract also contains neuropeptide-degrading enzymes. While some neuropeptides have been associated with inducing or augmenting the effects of histamine in respiratory conditions, some have also been associated with neurogenic inflammation and angioedema, which may have the potential to play a role in MCS and CFS respectively.[14,22]

When compared with asthmatics, patients with MCS and asthma-like symptoms were found to be more sensitive to inhaled capsaicin. Lidocaine, which effects sensory nerves and reduced the symptoms indicating the mechanisms behind chemical sensitivity, "may originate in the sensory nervous system."[23]

In the nose, chemical irritants, such as capsaicin, stimulate irritant receptors on sensory nerve C-fibers, which leads to the release of substance P (SP) and other mediators.[22] Some of the same substances that induce SP inhibit neutral endopeptidase (NEP), the enzyme that breaks down SP.[22] Common respiratory viruses can also reduce NEP.[24]

In an MCS cohort, "Plasma levels of substance P, vasoactive intestinal peptide and nerve growth factor, but not histamine, were elevated. ... Exposure to VOCs increased plasma levels of all parameters," and "enhanced skin wheel responses induced by histamine. ... These results indicate that exposure to VOCs may enhance neurogenic inflammation with concomitant enhancement of histamine-induced responses."[25] Exposure to VOCs did not have these effects in normal subjects or patients with atopic eczema/dermatitis syndrome (AEDS).

The C1 Esterase Inhibitor, Complement C4, and Angioedema

Other neuropeptides such as neuropeptide Y (NPY) or bradykinin may be elevated in CFS.[14,26] This is important since bradykinin has the potential to account for laryngeal swelling not necessarily accompanied by high IgE levels.

Some patients in one CFS cohort were found to have decreased C1 esterase inhibitor and complement C4.[14] In patients with C1 esterase inhibitor deficiency or dysfunction, complement C4 decreases, due to a consumptive process, and bradykinin increases. This can result in swelling, or angioedema (abdominal, facial, laryngeal).

In addition, activation of bradykinin B2 receptors, expressed in sensory nerves, "results in excitation and sensitization of sensory neurons," and bradykinin can lead to the release of SP.[27]

ASST As A Marker of Autoreactivity in Hypersensitivity Conditions

In a CFS cohort, "Patients with bronchial hyperresponsiveness presented significantly more often with fatigue that was made worse by physical exercise, recurrent flu-like illness, thyroid inflammation, and painful lymph nodes."[11] In an asthma cohort, findings and recommendations included that people with thyroid diseases seem to present more signs of asthma and that asthmatics should be checked for thyroid diseases.[28]

One thing that nonallergic bronchial hyperactivity, Hashimoto's thyroiditis, and CFS have in common, beyond their potential to be triggered or exacerbated by viruses, is that they are all theorized to have an autoimmune component, and it is possible that MCS may have as well. CFS and MCS have a female predominance and an increased incidence of Hashimoto's thyroiditis (HT) and/or positive antinuclear antibodies (ANA).[13,14] Some other hypersensitivity conditions (nonallergic asthma, chronic autoimmune urticaria) are thought to have an autoimmune component with a female predominance, an increased frequency of positive ANA and HT-related autoantibodies, and a positive autologous serum skin test (ASST).[28-30]

A positive ASST is thought to be a marker of "self reactivity" in hypersensitivity conditions, and when compared, ASST positive nonallergic patients have often been found to have more severe cases than their allergic counterparts with the same hypersensitivity condition.

A positive ASST has been seen in 53% of nonallergic asthma. By contrast, it is seldom positive in allergic asthma and allergic rhinitis.[29] "Asthma patients with ASST-positive results as compared with patients with ASST-negative results exhibited a significant increased airway hyperresponsiveness (PC(20) methacholine)."[31]

In chronic urticaria (CU), "patients with a history of rhinitis and food

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allergy and positive skin prick tests results for pollens and dog ... had attacks of shorter duration," while ASST positive patients had "frequent involvement of more body sites ... presence of throat angioedema and general constitutional, respiratory or gastrointestinal symptoms in comparison with the ASST-negative patients."[32,33] Researchers concluded, "Apparently, ASST-positive patients have more severe clinical manifestations of chronic urticaria."[33]

In multiple drug hypersensitivity (MDH), also known as multiple drug intolerance or multiple drug "allergy" syndrome, most multiple drug reactors (94%) had a positive ASST.[34] In single drug reactors and atopics, who never had an ADR, a positive ASST was seen in 40% and 0 respectively.[34] By contrast, single drug reactors were more likely and multiple drug reactors were less likely to have IgE to beta lactam antibiotics, 36% and 9% (1 patient) respectively. "Skin reactions were generally more intense in the (MDH) patient group."[34]

ASST has the potential to be positive in some patients with MCS, particularly in females, who have HT or a positive ANA and have had multiple ADR.

High Affinity IgE Receptor (Fc Epsilon RI) Autoantibodies and Basophil Histamine Release Assays or Basophil Activation Tests

High affinity IgE receptors (Fc epsilon RI) have been found in nasal mucosa, oral mucosa, airway smooth muscle, and skin. Fc epsilon RI autoantibodies (anti-FceRI) are thought to play a role in some cases of nonallergic asthma and CAU and are sometimes seen in ASST positive patients, whereas they are almost never seen in ASST negative patients. In some patients with hypersensitivities, anti-FceRI or autoantibodies to IgE (anti-IgE), or another unidentified factor are capable of causing histamine release from basophils. These types of tests are known as the basophil histamine release assay (BHR) or basophil activation test (BAT).

In one study of nonallergic asthmatics, "findings indicate that ASST is positive in about half of patients with nonallergic asthma and that a proportion of patients (16%) has functional evidence of circulating histamine-releasing factors."[29] In another asthma study, 37.2% of asthmatics had a positive BAT.[35] In multiple drug reactors, 23% had sera capable of inducing significant histamine release from basophils, while no single drug reactors did.[34]

Other Potential Autoantibodies

There are multiple other potential autoantibody candidates, many of which should be explored but are too numerous to be listed here. Based on findings in other hypersensitivity conditions, among the standouts are autoantibodies to cytokeratin. Anti-cytokeratin (CK) 18 and anti-CK 19 have been associated with nonallergic asthma and/or chemically (toluene diisocyanate)-induced asthma.[36,37] In asthmatics, "Significant correlations were found between positives for the anti-CK18 and anti-CK19 autoantibodies and the PC(20) methacholine values. ... "[38]

MCP-1 and the MCP-1 Stimulation Test

Monocyte chemotactic protein-1 (MCP-1) acts as a chemoattractant, promoting infiltration of immune cells, and as a basophil agonist, which leads to histamine release. MCP-1 is elevated in postviral CFS, MCS, HT, lupus, CU, some types of asthma, and during infections (EBV, HHV-6).[39-46]

In a study of patients with allergic rhinitis, submucosa had increased MCAF/MCP-1 and associated histamine release from basophils, suggesting that MCP-1 "is stored in human nasal mucosa, possibly participates in protracted histamine release from basophils and in the pathogenesis of perennial allergic rhinitis."[47]

While in one study of atopic asthmatics, who had increased total IgE and eosinophils, a significant association with MCP-1 was not found in all patients; in a different study of asthmatics, MCP-1 was elevated in the serum during asymptomatic periods and further elevated during acute attacks.[44] In addition, when testing patients with chemically (dissocyanate)-induced asthma, one team found that MCP-1 stimulation assays (MSA) with dissocyanate-human serum albumin (DIISO-HSA) were more sensitive than DIISO-HSA antibody tests in identifying patients.[48]

Potentially, MSA might be positive in those who developed MCS from sick building syndrome or another lengthy exposure.

Other Potential Non-IgE-Mediated Immune Mechanisms

T cells or inflammatory cytokines may play a role in some patients. T cells have been associated with non-IgE-mediated delayed-type hypersensitivity reactions and with ADR. In one CFS study, in response to intradermal administration of common antigens such as *Candida albicans* and in vitro T cell activation tests, patients had a delayed-type hypersensitive (DTH) response, and "the intensity of the DTH response correlated with the number of T-cells activated in vitro."[49]

Increased inflammatory cytokines have been found in the blood in several CFS cohorts and an MCS cohort. However, preliminary tests did not find increased cytokines in nasal fluid in one CFS cohort with rhinitis.[39,50,51]

While the exact mechanisms in MCS and CFS have yet to be elucidated, research on these diseases is getting closer to answers and the above pathways have the potential to play a role.

As researchers begin to gain more understanding of non-IgE-mediated hypersensitivity pathways, doctors may eventually be able to more readily recognize patients with nonallergic hypersensitivity reactions. Once doctors become familiar with some of the associations in these diseases, including the increased frequency of

HT-related autoantibodies in patients with hypersensitivities, maybe someday patients, especially female patients with concurrent Hashimoto's thyroiditis, will be able go to their doctors and say, "I have a hard time taking medicine because I tend to react to everything," and doctors will no longer tell them, as they have told me, "That's impossible!"

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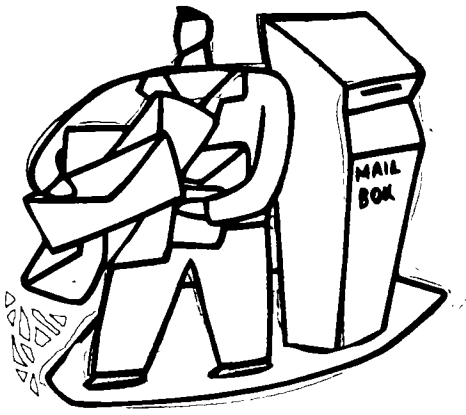
Laurie Busby received a BEd from the University of Missouri. At age 30, she developed chronic fatigue syndrome and the hypersensitivities that sometimes accompany it. Shortly thereafter, her aunt, a nurse anesthetist, handed her a huge medical dictionary and some studies, insisting that Laurie learn 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.



Letter to the Editor

Another Look at 'Adrenal Fatigue' Question

I feel that some additional edification is needed in response to the column by my friend and fellow U of MD alum Alan Gaby, "Is It Really 'Adrenal Fatigue'?" in the August/September 2014 issue. It appears that some recontextualization, and possible change in language, is needed to more completely understand what is taking place. I agree that true glandular failure is actually quite uncommon.

What is becoming more and more ubiquitous, in a world where Alvin Toffler's prediction of "future shock" is becoming a reality, however, is hypothalamic-pituitary-adrenal (HPA) axis dysfunction resulting in disturbed circadian rhythm and resultant functionally low daytime cortisol levels, frequently associated with elevated nocturnal cortisol, the latter resulting in disturbed sleep, dysinsulinemia, muscle wasting, etc. While it is certainly true that these patients will respond to a combination of adrenal adapotogens/glandulars, stress reduction, meditation/tai chi, etc., the patients whom I have been seeing for the past 14 years, who can only afford what their insurance will cover (a major cause of their stress) and whose lives are literally falling apart in front of their eyes because they are depressed, exhausted, and cannot mentally function, do not have the months and longer for those therapies to work. These are also patients who not uncommonly have lifelong themes and belief systems surrounding feeling trapped and/or victimized to begin with so that dramatic changes are needed to give them hope that they can actually get better.

It is here that I have found the use of low-dose hydrocortisone, as initially described by Dr. Jeffries and further expounded on by Jacob Teitelbaum, MD, to be truly a life- and game-changer. This has been especially true in patients with a.m. cortisol levels below 10, but frequently even higher. It appears that, while the adrenal glands may not be the primary source of dysfunction, proper levels of cortisol are needed to heal the HPA axis; otherwise, a vicious cycle is set up. In the overwhelming majority of these patients, provided that they have properly attended to the life situations that have contributed to their deterioration in the first place, the hydrocortisone can be gradually withdrawn, now using adaptogens, glandulars, etc., after they have been consistently doing well for 6 to 12 months or so. I did have one young mother on hydrocortisone for 5 years, due to the fact that she had 3 special-needs children and an unemployed husband, but even she was finally able to come off once she was able to get out from underneath the worst of her burdens.

So, whether or not it is actual "adrenal fatigue," something is clearly going on in the HPA axis that needs to be addressed in many patients. This situation seems to be exacerbated by any form of excessive stress, whether mental/emotional or physical. After using Dr. Teitelbaum's protocol for past 14 years, my experience is that, while many patients with fatigue can be found to have a single primary source, such as those described in Dr. Gaby's column, a large and growing number have multisystem disruptions in which HPA axis dysfunction is usually one, if not the main, culprit and that they do not truly become well without this being addressed.

Joel B. Klein, MD
Ventana Wellness
www.ventanawellness.com

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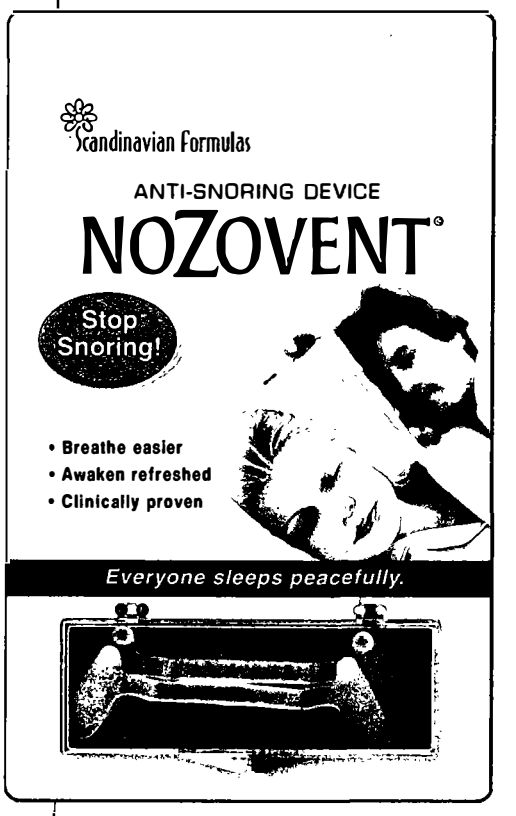

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An Anti-Aging Perspective on the Restorative Potential of Sleep

A survey by the National Sleep Foundation reports that about 15% of adults experience chronic pain. Among older adults, that number rises sharply to over 50%. The most common problem is the inability to achieve refreshing sleep. The major causes of sleep loss due to pain are back pain, headaches, facial pain caused by temporomandibular joint (TMJ) syndrome, and muscoloskeletal pain, which includes arthritis and fibromyalgia.

Restorative sleep can be particularly elusive, among women. Paivi Polo-Kantola and colleagues from the University of Turku (Finland) surveyed 850 mothers about their sleep when they were 42 years old, on average. Sixty percent of the study subjects reported waking up frequently at night, and 42% experienced morning sleepiness, with 32% plagued by daytime sleepiness. The team observed that postmenopausal hot flashes and night sweats further increased the difficulties with sleep. Noting, "Chronic diseases and use of medications was associated with various sleep disturbances," the study authors observe: "Almost one-quarter of middle-aged women is dissatisfied with their quality of sleep."

In this column, we review recent scientific literature reminding us of the restorative potential of sleep.

Pain and sleep [Web page]. National Sleep Foundation. http://sleepfoundation.org/sleep-disorders-problems/pain-and-sleep. Accessed 21 July 2014.

Polo-Kantola P, Laine A, Aromaa M, et al. A population-based survey of sleep disturbances in middle-aged women – Associations with health health related quality of life and health behavior. *Maturitas*. 4 December 2013.

Insomnia Raises Death Risk

Men who experience difficulty falling asleep, and sleep that is not restorative, are at increased risk of death – particularly due to cardiovascular disease. Xiang Gao and colleagues from Brigham and Women's Hospital (Massachusetts, US) followed 23,447 men enrolled in the Health Professionals Follow-Up Study who self-reported insomnia symptoms for a period of 6 years. Beginning in 2004 through 2010, researchers documented 2025 deaths using information from government and family sources. After adjusting for lifestyle factors, age, and other chronic conditions, researchers found that men who reported difficulty initiating sleep and nonrestorative sleep had a 55% and 32% increased risk of cardiovascular–disease related mortality over the 6-year follow-up, respectively, as compared with men who did not report these insomnia-related symptoms.

Li Y, Zhang X, Winkelman JW, et al. The association between insomnia symptoms and mortality: a prospective study of US men. *Circulation*. November 13, 2013.

Less Sleep May Age the Brain

The less time that older men and women sleep, the faster their brains may age. June Lo and colleagues from Duke-NUS Graduate Medical School Singapore (Singapore) examined the data on 66 older Chinese adults, from

the Singapore-Longitudinal Aging Brain Study. Participants underwent structural MRI brain scans measuring brain volume and neuropsychological assessments testing cognitive function every 2 years. Additionally, their sleep duration was recorded through a questionnaire. Those who slept fewer hours showed evidence of faster ventricle enlargement – a marker for cognitive decline and the development of neurodegenerative diseases such as Alzheimer's, as well as a decline in cognitive performance. Concluding, "In healthy older adults, short sleep duration is associated with greater age-related brain atrophy and cognitive decline," the study authors note: "These associations are not associated with elevated inflammatory responses among short sleepers."

Lo JC, Loh KK, Zheng H, Sim SKY, Chee MWL. Duration and age-related changes in brain structure and cognitive performance. *Sleep*. 37(07):1171–1178.

Quality Sleep a Cognitive Essential

A study from the University of Oregon finds that middle-aged or older men and women who get 6 to 9 hours of sleep a night think better than those sleeping fewer or more hours. Theresa E. Gildner and colleagues leveraged data collected in the first wave of the Study on global AGEing and adult health (SAGE), focusing on 30,000 subjects ages 50 years and older, residing in China, Ghana, India, Mexico, the Russian Federation, and South Africa. Data analysis revealed that men reported higher sleep quality than women in all six nations, with men and women in Mexico reporting the highest. Women reported longer sleep durations than men in all countries except Russia and Mexico. Men and women in South Africa slept longer than in any other country. The fewest sleep hours for both sexes occurred in India. Individuals sleeping less than 6 hours and more than 9 hours had significantly lower cognitive scores compared with those in the intermediate group. Writing, "This study documented positive correlations between cognitive scores and sleep quality, and between cognitive ... scores and intermediate sleep duration," the study authors submit: "These findings are clinically important given the growing rates of dementia and aging populations globally."

Gildner TE, Liebert MA, Kowal P, Chatterji S, Snodgrass JJ. Associations between sleep duration, sleep quality, and cognitive test performance among older adults from six middle income countries: results from the Study on global ageing and adult health (SAGE). *J Clin Sleep Med*. 2014;10(6):613–621.

Poor Sleep Raises Alzheimer's Biomarker

Shorter sleep duration and poorer sleep quality may raise a person's levels of beta-amyloid, an Alzheimer's disease biomarker. Adam Spira and colleagues from Johns Hopkins Bloomberg School of Public Health (Maryland, US) completed a cross-sectional study of adults from the neuroimagining substudy of the Baltimore Longitudinal Study of Aging, average age of 76 years. The researchers examined the association between self-reported sleep variables and beta-amyloid deposition. Study participants reported sleep that ranged from more than 7 hours to no more than 5 hours. Reports of shorter sleep duration and lower sleep quality were both associated with greater beta-amyloid buildup. The lead author observes: "To the degree that poor sleep promotes the development of Alzheimer's disease, treatments for poor sleep or efforts to maintain healthy sleep patterns may help prevent or slow the progression of Alzheimer disease."

Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and [beta]-amyloid deposition in community-dwelling older adults. *JAMA Neurol*. 2013 Oct 21.

Consistent Sleep Habits Promote More Healthful Weight

Women who go to sleep and wake up at same time every day have lower body fat. Bruce W. Bailey and colleagues from Brigham Young University (Utah, US) enrolled 330 university-aged women, in a study to ascertain sleep patterns and their effect on weight. At the study's start, the participants were first assessed for body composition and given an activity tracker to record their movements during the day and the sleep patterns at night. The researchers tracked sleep patterns of the participants for one week. The team found that those participants who went to bed and woke up at or around the same time each day had lower body fat. Those with more than 90 minutes of variation in sleep and wake time during the week had higher body fat, as compared with those with less than 60 minutes of variation. Specifically, wake time was most particularly linked to body

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fat. Those who woke up at the same time each morning had lower body fat. Observing, "Inconsistent sleep patterns and poor sleep efficiency are related to adiposity," the study authors conclude: "Consistent sleep patterns that include sufficient sleep may be important in modifying risk of excess body fat in young adult women."

Bailey BW, Allen MD, LeCheminant JD, et al. Objectively measured sleep patterns in young adult women and the relationship to adiposity. *Am J Health Promot.* 7 Nov. 2013.

Consistent Habits Are Key

Two recent studies suggest key approaches to achieving a good night's sleep:

1. **Consistent daily routine**: Natalie D. Dautovich and colleagues from the University of Alabama (US) completed an observational study design involving 14 consecutive days of diaries kept by 100 community-dwelling adults. Fifty participants between ages 18 and 30 years and another 50 between ages 60 and 95 years recorded their patterns of daily activities and sleep. The researchers analyzed 3 activities (going outside, starting work, and eating dinner) and 5 sleep variables (sleep onset latency, wake time after sleep onset, number of awakenings, total sleep time, and sleep quality rating). The team found that maintaining a consistent daily routine was associated with better-quality sleep. Young adults who went to work and ate dinner at the same time every day typically slept better and woke up fewer times during the night; they also fell asleep more quickly at that time. Interestingly, the researchers observe that among older adults, inconsistent daily schedules were sometimes linked with better sleep: older subjects whose dinnertime varied tended to sleep longer at night, and those who started home activities or began work at different times each day fell asleep more quickly.

Dautovich ND, Shoji KD, McCrae CS. Variety is the spice of life: a microlongitudinal study examining age differences in intraindividual variability in daily activities in relation to sleep outcomes. *J Gerontol B Psychol Sci Soc Sci.* December 10, 2013.

2. **Daily exercise regimen**: The National Sleep Foundation (Virginia, US) completed 1000 surveys comprising a representative sample stratified by age and area of the country (Northeast, Midwest, West, and South). Self-described exercisers reported better sleep than self-described nonexercisers, even though they said that they slept the same amount each night (6 hours and 51 minutes average on weeknights). Vigorous, moderate, and light exercisers were significantly more likely to say "I had a good night's sleep" every night or almost every night on work nights than nonexercisers (67%–56% vs. 39%). Also, more than three-fourths of exercisers (76%–83%) said that their sleep quality was very good or fairly good in the past 2 weeks, compared with slightly more than one half of nonexercisers (56%). Further "vigorous exercisers" were almost twice as likely as nonexercisers to report "I had a good night's sleep" every night or almost every night during the week. They also are the least likely to report sleep problems. The Task Force urges: "Exercise is beneficial to sleep. It's time to revise global recommendations for improving sleep and put exercise at the top of our list for healthy sleep habits."

2013 Exercise and Sleep: Sleep in America Poll. National Sleep Foundation, March 4, 2013.

To learn the latest breakthroughs in natural approaches for achieving restorative sleep that may offset disease and improve your quality of life, 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. ◆

Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, DHANP, LCSW, and Robert Ullman, ND

www.healthyhomeopathy.com

Homeopathy for Asperger Syndrome: Remarkable Long-Term Transformation

Asperger Syndrome Needs No Introduction

Twenty years ago the term *Asperger syndrome* was virtually unknown outside the pediatric psychiatric community. When we first published *A Drug-Free Approach to Autism Syndrome and Asperger's* in 2005, the syndrome was not as familiar as it is now. Perhaps the average American might have been familiar with the concept of savant, having seen *The Rainmaker,* but there was little differentiation between Asperger's and other autism spectrum diagnoses. Now approximately 1 in 88 children in the US is diagnosed as being on the autism spectrum and 1 in 250 with Asperger syndrome. The constellation of communication difficulties; repetitive, stereotyped behavior patterns; and social communication problems, in combination with quirky behaviors; fascination to the point of obsession with specific subjects (commonly trains, fans, electrical items); and rapid-fire speech makes these individuals highly unusual. Uniqueness is what allows the homeopath to find the best match for the patient, so we have found these individuals to be some of the most rewarding to work with in our practice.

Ricardo, from the beginning, was highly unusual, even among our many Asperger patients. We began treating him 13 years ago and his mother has been faithful to homeopathic care throughout all of this time. The family has had phone appointments consistently every 6 weeks and has only met with us in person once. Ricardo benefited from various medicines over the first 5 years. Though he continued to improve gradually, we found it challenging to find his *simillimum* – the one best homeopathic medicine for *all* of his symptoms. As happens, typically, when we have not yet fully understood our patients or discovered that simillimum, we prescribed medicines from all three kingdoms (animal, plant, and mineral), as well as nosodes. It was in summer 2006 that we found the medicine that would benefit him for the next 7 years. It is not surprising that it took a number of years before finding this medicine, because it is rarely prescribed, especially for patients on the autism spectrum. Ricardo's case was so inspiring that Judyth presented it at the Mental Health Congress in Bad Krozingen, Germany, in March 2012. Since then, we have changed the medicine and he has progressed much further.

Ricardo, Age 5

To appreciate the virtually miraculous change that Ricardo has undergone, we really need to give a picture of this child when we first saw him. In the initial interview, Ricardo's mom, Carol, described him as follows:

> He never really had any playmates. When he was 14 months old, he developed a fascination with oscillating fans. At the age of 3 he told us he could see inside his body. Ricardo talked about killing himself with a saw and asked his mom whether she killed people or animals or whether she ate intestines. The child had strange ideas such as a dislike of cones on the street, shoes on the Mervyn's rack that were not perfectly lined up, and cereal boxes hanging off the top of the fridge. Ricardo didn't like to look at his dad's navel because of the cracks. Nor did he appreciate holes. The child talked about cutting off his head, writing on his eye with a pen. On and on. ...

His mother summed it up as "bizarre, bizarre thinking." He told his dad, "Kill mommy," threatened to poison God. Recurrent themes were dying and hatred. Ricardo feared the dark, and being around other children. He was fascinated with fire and talked about digging up people in the cemetery, blowing up cars, eating poison, shooting trees, eating electricity, and putting batteries in fire. There was a family history of obsessive-compulsive disorder. Ricardo exhibited periodic compulsive hand washing, touching one side of his body and then the other, and found much in his environment to pose danger: mushrooms growing in his back yard and berries on holly bushes. Other obsessions included matches, lighters, electrical outlets, flags, construction work signs,

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torches, lanterns, matches, the skull and crossbones symbol, sprinklers, speedometers, old record players, steering wheel covers. Ricardo exhibited no interest in riding bikes, though he did enjoy playing with cars. He spent his days screwing on outlet covers and, when scolded, replied that his outlet was broken. Rather than wanting toys, he preferred new outlet covers from the electrical department of the local hardware store. There were more ordinary symptoms such as clumsiness, an inability to get a grip on his pen to write, dislike of touching dirty socks or underwear, repetitive questions about the same topic, toe walking and flapping. He had a recurrent tendency to personalize inanimate objects such as pretending that his shirt was daddy or kissing the outlets. He was also averse to bathing.

Ricardo had a tendency to allergies and had suffered recurrent strep throat.

He had taken Prozac, Risperdal, Klonopin, Paxil, Luvox, and other psychotropic medications with no satisfactory results, and some made him aggressive. His mother was so distraught during the first interview that she cried. She had given him several homeopathic medicines without success.

The Next Five Years

A variety of homeopathic medicines were prescribed with slow, yet steady results. We were able to meet once in person at an airport 5 years later during our travels. Eight months later, in August 2006, we restudied Ricardo's case, hoping to find a better match. Around this time, the personalization of telephones, laptops, stuffed animals, and other objects was a common topic of conversation. Ricardo often described theses as "cute." He began to develop a concern with environmental sustainability. "People are wasting our natural resources ... ruining our world. ... I've always wanted to recycle." His fears of chemicals, poisons, gasoline, and dying were more apparent. We were continually struck by Ricardo's overall sensitivity to the world around him.

A New Look at the Case

We were not satisfied with the improvement and took another look at Ricardo's case. The prominent features were pacing, spitting out germs, obsession with poison and filthy, messiness, lack of concern about hygiene, and disorganization. Often, when there are indications for more than one homeopathic mineral, a mineral salt is required. In this case, we had previously prescribed *Arsenicum album* and, briefly, *Sulphur*. We came upon a new prescription: *Arsenicum sulphuratum flavum*, which we had never before used in our practice. Looking at the material medica for the medicine, it was not so much its unique features that led us to prescribe it, but rather the combination of the *Arsenicum album* and *Sulphur* symptoms. We gave it in an LM1 potency and only needed to gradually increase the potency to LM4 nearly 7 years later.

The first follow-up, a month later, was impressive. "He is much improved. He adjusted remarkably quickly to the beginning of the school year." He is less anxious, not worried about germs, and was washing his hands much less often. Carol described the improvement as 75%. We noticed a significant change in his speech – much more easeful and less high-pitched – which was permanent.

Over the next 7 years, Ricardo continued to become happier and more relaxed, maturing in a surprisingly natural fashion. He was better able to adapt to school, talking less and less about his previous obsessions. His mother was relieved and pleased with his development. We were not once inclined to change Ricardo's prescription. No longer was he so self-focused. He steadily developed a growing fascination with television, especially news anchoring, and dreamed of working in the field. And, most of all, he began to be concerned about friendships. We cannot begin to describe how much Ricardo changed over the years. Our conversations with him became much more personal, feeling-related, and deep. We genuinely looked forward to each of our interviews with Ricardo, and he continued to amaze us with his depth of caring, writing talent, and determination and dedication to his envisioned television career. Also impressive was his strong desire for independence and self-expression.

A New Medicine 7 Years Later

No matter how long we have treated a patient with a particular medicine with good results, we try to be fresh and open to the possibility of changing the prescription if the need arises. And so it did. We did the retake when Ricardo was 17.

> I have trouble getting along with my friends. We are supposed to be working together on a film. I want to have them as my friends forever. They are what make me happy. I want to be the producer of the film. I no longer feel so shy. ... Being in television is what I live for. To be on my own and be able to give what I want to give. Not just have a nice house or car, but to be able to share what I have with others. It's about being a leader in ideas. If I can't give to the group, it is a terrible feeling. I don't want to just be alone. That is no fun. Being alone I would feel despair, sadness, loneliness. ... The material things aren't worth anything unless you have someone to share them with. It is our life together. What you see on television is kind of fake. Just working to get your ratings up. Be number one. It is the people who make it special.

We gave a medicine with which we did not have much clinical experience but had heard a number of teaching cases with various themes. It is *Lac humanum* (human milk), which is made from the human milk of one donor; it is different from but more commonly prescribed than *Lac maternum* (mother's milk), which is made from a mixture of human milk from nine donors at different stages of lactation, including colostrum. One main indication of this medicine is being helpful to others so that you receive acceptance and do not feel alone. The "I" needs to be sacrificed for the good of the "we." In our homeopathic training, we have

seen only a handful of cases of these two milk medicines, and the themes of *Lac humanum* are varied. Besides those mentioned above, the following are additional features of those needing this medicine from the homeopathic literature: conflict between one's higher (spiritual) and lower (animal) natures; issues of community; the polarity between simple human living/needs and values and the quest for materialism; individuality versus group conformity; the need for control and to put the world close to home in order; detachment or isolation from the world. We find this to be one of the most complex homeopathic medicines to understand, and this is our only case needing it to date.

After deciding on the prescription, we checked with Carol to see if she had breast-fed Ricardo. Her reply: "I tried. I pumped to the point of exhaustion. He was on a soy formula and would get very upset. He just couldn't get enough milk. I also had the problem of being on medication following the C-section with him."

Three-month follow-up: Carol reported that Ricardo was doing "great." He eagerly ate lunch with friends, compared with the previous year when he didn't have any and was relegated to eating alone. Ricardo was volunteering to do community service and was working on a design project. We have only given Ricardo the LM1 potency once a day. Eight months later, he shared his excitement about the school prom and about beginning driver's education. Most recently: Ricardo had just graduated from high school, thoroughly enjoyed the graduation party, and was planning to attend a local community college. Having completed driver's training, he was proud to have obtained his driver's permit. Though he was sad to leave his friends, Ricardo was looking forward to his future. "Everything is good. I'm at the crossroads." Neither we nor Carol would have ever believed, 13 years ago, that Ricardo would be where he is today – a talented, caring young man who will undoubtedly make a positive contribution to the world, likely in the field of television, his dream. This is our reward for being homeopaths!

Judyth Reichenberg-Ullman and Robert Ullman are licensed naturopathic physicians, board certified in homeopathy. New, revised editions of *Ritalin-Free Kids, Homeopathic Self-Care*, and *Whole Woman Homeopathy* are available. Their other books include *Treatment of Depression, Anxiety and Bipolar Disorder, A Drug-Free Approach to Asperger Syndrome and Autism, Rage-Free Kids, The Patient's Guide to Homeopathic Medicine*, and *Mystics, Masters, Saints and Sages: Stories of Enlightenment*. Kindle and EPUB versions of all of the books have just been released. 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 at 425-774-5599, drreichenberg@gmail.com, or drbobullman@gmail.com. Their website is www.healthyhomeopathy.com.

Healing with Homeopathy

Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

White Spacing: A New Approach to Breaking the Allergen-Dysmetabolism Cycle

Introduction

Allergens in the indoor environment are metabolically mischievous. They sap energy, disrupt sleep, and sabotage weight reduction plans. Allergen-imposed corporal stress manifests itself in ways similar to less-avoidable forms of stress. Consequently, indoor allergens often remain unrecognized and unmitigated. This *Townsend Letter* column identifies meritorious yet little-known ways to break the allergen-dysmetabolism cycle.

Background

White spacing is a trendy name for scheduling unscheduled time. Since most of us are busier than we wish to be or should be, it's not surprising that white spacing is increasingly used for personal and corporate Day-Timers.

In my opinion, white spacing is a great name because it's a fitting entendre. White spacing makes it easier for me to visit my favorite white space – the beach. More often than the beach, I visit my second best white space – my room. That's why, with resourceful endeavor, I've found five ways to transform my bedroom to a "beach."

Fresh White Air

Hours after leaving the beach, my white T-shirt still beckons my olfactory system to the fresh-air moment. Olfaction is a chance to marvel – and is probably our most underutilized sense. I drink in the freshness and think, "I want my clothes and linens to smell like this."

Fresh air in one's home or office is to a large extent the absence of indoor air pollutant. That is why an effective air filter helps retain freshness. This may be the most advantageous time of year to use an air filter in the northern continental US. November is when people tend to make their homes more airtight and insulated and consequently concentrate indoor chemicals. People and their pets concentrate indoors, too. Pets, uninvited animals, plants, and lawn furniture relocate indoors, each with its distinct signature on indoor air. Blankets, sweaters, and holiday decorations emerge from their summer storage with a waft of naphthalene or rosemary-clove moth deterrents, and forced-air heating ducts, painted radiators, and fireplaces are back in use.

I run air filters in my home and my office and feel rewarded by "beachy" freshness. There is a wide selection of air filters available, some more effective than others, and my research led me to choose from a company that offers five different filters for different purposes. Interestingly, all their models look pretty much the same from the outside, but the filtration package on the inside is designed to meet varying specific allergen/pollutant needs. Apart from its casing needing occasional vacuuming, the filter component has a 5-year life expectancy before a new cartridge is needed. Filters come simply in two sizes, either standard or small for not-so-large rooms. See www.AustinAir.com to peruse customized filters.

Why so much emphasis on air filters? A longstanding challenge for environmental health researchers is measuring chemical exposures. While attending an environmental health sciences symposium at Johns Hopkins, I learned about a new source of data: silicone wristbands. Yes, I'm talking about the colorful trendy bracelets with monikers like "Life's a beach." For example, let's suppose that you and a friend wore identical "Kiss me I'm Irish" wristbands that you nimbly caught at the St Patrick's Day parade. After the parade, your friend drank green beer at a smoky pub, and you as the designated driver drank coffee at the char grill burger joint across the street. Environmental researchers could distinguish your bracelets based on exposures of cigarette smoke, alcohol, caffeine, and heterocyclic amines passively absorbed from ambient air and dermal contact.

Rooms may or may not have silicone, but they have various surfaces that absorb "fresh-deterring" chemicals. Utilizing an air filter set to run steadily on low speed reduces the toxins that would become part of other surfaces. I'm not aware of such a study, but it might prove enlightening to see if silicone wristbands are less distinguishable when air filters are used.

In sum, even if you don't want to wear a green silicone bracelet, bring some Irish blessing to your home. "May the wind be always at your back. ..."

White Noise

> The silence between the notes is as important as the notes themselves.
>
> – Wolfgang A. Mozart

Sleep studies published in the scientific literature now fully apply the composer's statement to human health. Only with silence during sleep can the human body fully refresh itself. Removing silence disrupts and measurably alters sleep stages.

Second only to silence is the sound of surf. I recently had a multisensory surf experience while waiting in a medical office. During what would otherwise have been an anxious moment as the family member of a patient, I relaxed to an oceanscape projected on the wall accompanied by surf and an air-conditioned breeze. The entire office atmosphere seemed pleasantly different. Surf's salutary effects can be recreated by a sound machine, or some patients enjoy the air-flow white-noise sound effect of a home air filter. Air filters produce white noise as a byproduct of the filtering process. With a turn of a knob, the surf's up.

White Light

Small frequent doses of full-spectrum light, like an early morning jog on the beach, have among their benefits a vitamin D boost and melatonin signal. Unfortunately, various indoor lights perform poorly if at all in this regard. I have field-tested various full spectrum lights, including during my sojourn as Antarctic station doctor at Palmer and McMurdo Stations, and recommend them when sunlight isn't an option.

White Salt

My intrigue with salt was piqued in 2002 when I read Mark Kurlansky's book *Salt: A World History*. I initially picked it up out of surprise that the topic could make the *New York Times* best-seller list.

Since then, sea salts such as those that reside on my cheeks following a morning jog on the beach are another component of my indoor white space. An open bag of Epsom salts can add magnesium and sulfur to the air, and a rock of Himalayan sea salt set on a porcelain plate disperses its minerals. Some people get elaborate and make lamps, foot warmers, and tea-light holders, using warmth to help distribute the salt. Caution should be taken, since salt corrodes. Handheld plastic salt air inhalers are also available.

White Sand

Recent scientific publications about geomagnetic storms highlight another benefit of the beach. Bare feet in white sand may help us weather geomagnetic storms, the way that people have for millennia before the advent of modern living.

Geomagnetic storms increase the earth's magnetic field and are most familiar to us in the context of aurora in high-latitude regions of earth and for disrupting satellite communication. The same geomagnetic storms influence human health. The magnitude to which geomagnetic storms are temporally linked to stroke, heart attacks, suicides, and acute psychiatric admissions is surprising researchers. For example, epidemiologic data suggest that geomagnetic storms impose the same risk of stroke as postmenopausal hormone therapy.

The following scenario offers a broad risk comparison. During a solar storm, one man is standing on the beach fishing with his bamboo rod the way that he does each morning. His daily sun exposure is moderate and he never gets a burn. His diet is mineral replete and rich in nutrients that discourage the accumulation of magnetizing heavy metals. During the same storm, another man has an office job that seldom allows him to see the light of day. That evening, he takes work home with him. He is slumped on an inner-spring mattress containing metal coils and frame, which

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can act like antennae, potentially intensifying EMFs. He's working on his laptop encircled by Wi-Fi, remote controls, high EMF-emitting transformers in multiplug outlets, and a digital clock radio. He answers his cell phone between bites of his carry-out dinner.

A clinically relevant question is to apply the Peter Principle: What is the 20% effort that could make the second man's risk 80% similar to the first man's? This question is not as informed by science as would be useful, and that's part of the challenge in sorting through the numerous Internet claims.

For indoor space as close to white sand as possible, I interviewed Scot Appert, a degreed building biologist and environmental consultant who founded Biohealthyhomes.com.

Scot begins consults by avoiding EMF exposure where possible. Since EMFs are invisible, people are often unaware of hazards that they would not be inconvenienced at all to eliminate or reduce, if they only knew about them. He says that finding these exposures often takes a site visit.

Metals to which one can hold a magnet amplify EMFs and should be substituted where possible. This can get pricy if it means getting a new mattress and bed, so simple interventions such as covering the metal with aluminum foil may be the practical interim solution. Instead of in your lap, or staying in physical contact with your notebook computer day after day, using your laptop with a detached keyboard and a monitor can reduce EMF exposure. Experts also suggest getting an extension cord to move the multiplug transformers far enough away from your workspace to drop the EMFs substantially. A few feet of space away from high sources such as these notebook computers and electric device transformers can actually make a noteworthy exposure difference.

Where removal or reduction of EMFs is not possible, neutralizer stickers and plug-ins offered by Aulterra may be of potential benefit. That said, for the time that they have been available, I found comparably little scientific research. Eastern medicine such as Tibetan singing bowls, magnets, yoga, and relaxation techniques may similarly dissipate untoward effects of EMFs and have centuries of history. My favorite approach remains a hug.

Conclusions

Why white space? Those who bring the beach with them into their homes are helping break the allergy-dysmetabolism cycle by clearing the air; restoring sleep; replenishing immune-regulating vitamin D; delivering immune-regulating salts to inflamed linings; and avoiding energy-dissipating, unhealthful electromagnetic forces.

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Executive Director, NutriBee National Nutrition Competition Inc.
Editor, *Advancing Medicine with Food and Nutrients* (CRC Press; 2013)

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JUNE 5-7: HOMEOPATHY RESEARCH INSTITUTE 2015 CONFERENCE – Cutting Edge Research in Homeopathy in Rome, Italy. CONTACT: www.HRIRome2015.org

AUGUST 28-30: NATURAL ADDICTION CONFERENCE in Myrtle Beach, South Carolina. CONTACT: Sharon Phillips, 954-540-1896; Sharon@fmi-marketing.com

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Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Valerian/Lemon Balm in Menopausal Sleep Problems

The purpose of this study was to determine whether a combination of valerian/lemon balm could improve sleep problems in menopausal women. A total of 100 postmenopausal women aged 50 to 60 years with sleep disorders were studied. Women were selected randomly after fulfilling the entrance criteria. The Pittsburgh Sleep Quality Index (PSQI) questionnaire was completed to assess the status of their sleep disorder in the month prior. The PSQI consists of various measurements, including general description of individual sleep quality and patterns, delay in the onset of sleep, sleep duration and pattern as well as waking in the night, use of tranquilizers, and daily performance problems due to lack of sleep. A score of 5 or greater constitutes a sleep disorder and the 100 women selected were those with a scoring above 5. Women were randomly divided into two groups, with 50 in the herbal treatment group, which received two capsules containing 160 mg of valerian and 80 mg of lemon balm, and 50 in the control group, which received capsules containing starch. Participants and investigators and the statistician were all blinded. The duration of the intervention was one month and then followed by another PSQI questionnaire.

One month following use of the valerian/lemon balm supplement, 36% of the treatment group and 8% of the placebo group showed an improvement in the quality of their sleep. Sleep disorder scores decreased by 5 points, which was statistically significant.

Comment: Perimenopausal and menopausal women are faced with hormonal changes that can result in not only nighttime hot flashes that can disrupt sleep, but lengthened time it takes to fall asleep, frequent awakenings, waking and poor return to sleep, early morning waking, and nonrestorative sleep. Botanical options that can improve any or all aspects of sleep disruption are an important part of a comprehensive approach to treating this. However, addressing sleep disorders in this population usually also involves strategies that target the fundamental issue, which is hormonal changes and the impact on neurotransmitters, cortisol, stress adaptation, and sleep cycle physiology.

In 2011, another study of valerian and insomnia was published. The participants were generally healthy women aged 50 to 60 years who were menopausal for at least 1 year, not using hormone therapy, and experiencing insomnia. One group was given capsules containing 530 mg of concentrated valerian extract twice per day and the other group placebo, twice per day, for 4 weeks. A statistically significant change was reported in the quality of the sleep in the valerian group when compared with the placebo group. The average score on the sleep scale before valerian was 9.8 and after valerian it was 6.02. The placebo group had an initial average sleep scale score of 11.1 and after placebo, 9.4. Overall, 30% of the women taking valerian and 4% taking placebo reported an improvement in their sleep quality.

Although not all research on valerian and insomnia has shown positive results, these two studies bring more focus to using valerian in menopausal women for sleep disorders.

Taavoni S, Ekbatani N, Kashaniyan M, Haghani H. Effect of valerian on sleep quality in postmenopausal women: a randomized placebo-controlled clinical trial. *Menopause*. 2011;18(9):951–955.

Taavoni S, Nazem ekbatani N, Haghani H. Valerian/lemon balm use for sleep disorders during menopause. *Complement Ther Clin Pract*. 2013;19:193–196.

Valerian and Hot Flashes

Hot flashes and/or night sweats are the most common symptoms that perimenopausal/menopausal women seek relief for. They can be mild, moderate, or severe; occur infrequently or daily, even many times a day if not several times per hour; and last an unpredictable number of months/years. Some women are affected greatly and symptoms can affect mood, sleep, social encounters, work, and general quality of life. About 70% to 80% of women who go through normal natural menopause have hot flashes/night sweats, and 90% to 100% of women with surgical menopause (both ovaries removed) experience them.

In this double-blind clinical trial, 76 menopausal women with the chief symptom of hot flashes were enrolled with the treatment group receiving a 225 mg valerian capsule 3 times per day and the other group, placebo, for 8 weeks. Five women from the placebo and 3 from the valerian groups were excluded due to irregular use, inaccurate

recording, mild side effects, or taking other medications that affect hot flashes. A total of 68 women completed the study. Questionnaire and information forms were filled out 2 weeks before and 4 and 8 weeks after treatment, and recorded the severity and frequency of hot flashes. After 4 and 8 weeks of treatment, the evaluation of results showed a meaningful difference between the valerian group and the placebo group.

At week 4 and week 8 posttreatment, the valerian group had significantly fewer severe hot flashes (9.82 ± 1.87 pretreatment and 5.23 ± 1.52 after 8 weeks) compared with the placebo group (9.96 ± 1.84 pretreatment and 9.86 ± 1.95 after 8 weeks). There was no significant change in severity of hot flashes in the placebo group compared with baseline. In addition, at week 4 and week 8 posttreatment, the valerian group had significantly fewer hot flashes compared with the placebo group. Valerian pretreatment was a mean frequency of 7.91 ± 30.0 and 4.83 ± 0.52 after 8 weeks vs. placebo pretreatment 7.73 ± 42.0 and after 8 weeks 7.75 ± 0.32. There was no significant change in frequency of hot flashes in the placebo group compared with baseline.

Comment: The purpose of this randomized, double-blind, placebo-controlled study was to evaluate the effect of valerian treatment for 8 weeks on hot flashes. Valerian is an interesting choice, but it does contain some flavonoids, which are phytoestrogenic components, and therefore it is a reasonable hypothesis that it may reduce menopause symptoms.

Currently available conventional treatments include various regimens of hormone therapy, conventional nonhormonal options such as an SNRI or SSRI, gabapentin, clonidine, and possibly an antihistamine. Efficacy of the nonhormonal treatments is less than with adequate doses of estrogen. However, all of these have a benefit and risk profile that needs to be considered by patient and menopause practitioner. Natural treatments that have scientific support span all kinds of plants and nutraceuticals. Some of the plants are phytoestrogen-containing plants such as soy, red clover, kudzu, and hops. Some of the plants that do not contain phytoestrogens include black cohosh, maca, Siberian rhubarb, St. John's wort, pine bark, and kava kava. Even fish oils have shown some efficacy in treating hot flashes. These herbal/nutraceutical treatments can be quite effective in reducing severity and frequency of hot flashes but are also sometimes not effective. Having more options to help women with hot flashes and/or night sweats provides is extremely helpful in addressing the diverse array of clinical situations and individual needs/choices based on benefits and risks.

Mirabi P, Mojab F. The effects of valerian root on hot flashes in menopausal women. *Iran J Pharm Res.* 2013;12(1):217–222.

NSAIDs and Reduced Breast Cancer Risk in Overweight Women

The Nashville Breast Health Study (NBHS) is a population-based, case-control study of the incidence of breast cancer in the Nashville, Tennessee, area. Women were eligible if they were between 25 and 75 years old, were newly diagnosed with primary breast cancer (an average of 10.4 months prior to study entrance), and had no previous history of other cancers unless it was a nonmelanoma skin cancer. For a little over 10 years, the study recruited 2694 women with breast cancer. A similar number of women were identified as controls.

Women were asked to report prescription and over-the-counter use of all nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin at least 3 days per week, over a period of at least 2 months in the previous 15 years. Regular users were women who took NSAIDs 3 or more times a week for a minimum of 1 one year.

Breast cancer subtypes were classified based on estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) status of the breast cancer tumors. Women were also stratified by body mass index (BMI). Underweight or normal weight was defined as BMI <25 kg/m^2 and overweight as BMI ≥ 25 kg/m^2.

In this large, population-based, case-control study, regular use of any NSAID, including 81 mg/day of baby aspirin, was associated with an overall reduced risk of breast cancer of approximately 20%. This risk reduction existed for all subtypes of breast cancer regardless of estrogen or progesterone receptor or HER2 receptor status, and primarily in overweight women.

Comment: The results of this study are not surprising in that there have been other studies that have demonstrated approximately a 20% reduction in risk of breast cancer. The Women's Health Initiative Study (WHIS) reported a 21% decrease in breast cancer risk among women who used any NSAID for 5 or more years compared with no or minimal use. It also showed a protective effect more evident in women with a BMI ≥ 27 kg/m2 However, not all previous findings have been consistent and have varied based on receptor types. Some recent analysis from the Nurses' Health Study (NHS) reported no significant association of use of aspirin, other NSAIDs, or total NSAIDs with the incidence of breast cancer. It is not clear why these different studies are finding different results. The protective association for NSAIDs, primarily in overweight women in the current study, is consistent with the fact that obesity is a known risk factor for breast cancer in postmenopausal women. Breast cancer is also associated with chronic low-grade inflammation. NSAIDs may reduce the inflammatory influence of obesity and as a result reduce the risk of breast cancer.

Cui Y, Deming-Halverson S, Shrubsole M, et al. Use of nonsteroidal anti-inflammatory drugs and reduced breast cancer risk among overweight women. *Breast Cancer Res Treat.* 2014;146:439–446.

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. ◆

Cognitive-Enhancing Cognizin Citicoline Found to Improve Motor Speed and Attention in Adolescents

Recently unveiled at the annual American Society of Clinical Psychopharmacology conference in Hollywood, Florida, a new randomized, double-blind, placebo-controlled human clinical trial conducted by the Brain Institute, at the University of Utah, found that adolescent males experienced increased motor speed and attention after supplementation of Cognizin brand citicoline (CDP-Choline). The trial involved 75 adolescent males over a 28-day period in which the citicoline, a known cognition-enhancing nutrient, was administered. The research reported that the individuals who were administered citicoline showed multiple improved cognitive domains, which includes measures of attention and motor speed.

Although Cognizin has been the subject of previous trials in healthy subjects, the nutrient has undergone limited research dedicated to healthy adolescent populations.[1-3] Lead researcher Dr. Deborah Yurgelun-Todd, professor of psychiatry at the University of Utah, said, "The study finally sheds a light on the cognitive-enhancing effects of citicoline in healthy, adolescent individuals, which is something we at the Brain Institute have never done before." (Typically, research on citicoline involves adults with neurological deficits.) Furthermore, the research found that self-reported side effects of administration were not greater as compared with participants in the placebo-controlled group.

Participants included 75 healthy adolescent males divided into treatment (n = 51) and placebo groups (n = 24) after completing a screening visit including a medical exam and clinical measures.

Individuals were then randomly assigned to a 250 mg or 500 mg Cognizin citicoline treatment group or placebo group. To test the group, researchers conducted the "finger tap test," a motor function assessment during which participants are required to press a lever attached to a mechanical counter as many times as possible during discrete time periods. Additionally, the "Ruff 2 & 7 Selective Attention Test" was also administered, which tests a timed cancellation task in which participants cross out 2's and 7's embedded in blocks of distractor numbers or letters. Those who were given the citicoline scored higher in both tests after the 28-day period.

"The work that Dr. Yurgelun-Todd and the Brain Institute has done with citicoline and adolescent males is outstanding," said Danielle Citrolo, PharmD, Kyowa Hakko USA. "We're continuing to learn amazing things about the positive effects that Cognizin citicoline has on the human brain."

About the Study

- Participants included 75 healthy adolescent males divided into treatment (n = 51) and placebo groups (n = 24).
- Participants completed a screening visit including a medical exam and clinical measures.
- Individuals were then randomly assigned to a 250 mg or 500 mg Cognizin citicoline treatment group or placebo group.
- Between group differences, after 28 days of citicoline supplementation, individuals in the treatment group exhibited increased motor speed compared with individuals in the placebo group ($p = 0.03$; treatment group FTDH* Baseline mean = 479.96, SD = 69.39; treatment group FTDH Day 28 mean = 518.05, SD = 49.86; placebo group FTDH Baseline mean = 504.90, SD = 81.08; placebo group FTDH Day 28 mean = 513.43, SD = 64.03).
- Individuals in the treatment group exhibited improved attention compared with the placebo group (Ruff 2 & 7 Speed $p = 0.02$; treatment group Ruff Speed Baseline mean = 86.98, SD = 22.62; treatment group Ruff Speed Day 28 mean = 104.90, SD = 21.31; placebo group Ruff Speed Baseline mean = 84.04, SD = 16.93; placebo group Ruff Speed Day 28 mean = 96.79, SD = 19.56).

Cognizin is grandfathered as a dietary ingredient in the US and is the only form of citicoline allowed as a dietary ingredient for use in dietary supplements or functional food/beverages. Cognizin is self-affirmed GRAS and has Novel Food registration in Europe. Cognizin citicoline can be found in a variety of dietary supplement and beverage formulations. For more information, visit www.cognizin.com.

This study was supported by Kyowa Hakko USA Inc. and Kyowa Hakko Bio. Ltd.
A copy of the poster is available upon request.

* Refers to Finger Tap Total Dominant Hand test.

About Cognizin Citicoline

Cognizin is a branded form of citicoline, a natural substance found in every cell of the body and especially vital to brain health. Citicoline is broken down during intestinal absorption and, after passing through the blood–brain barrier, is reconstituted in the brain as citicoline. Citicoline is a water-soluble compound that supplies precursors for the synthesis of phospholipids, including phosphatidyl-choline, a major constituent of brain tissue; helps maintain normal levels of acetylcholine, a chemical that regulates memory and cognitive function; enhances communication between neurons; supports visual function; protects neural structures from free-radical damage; enhances metabolism and healthy brain activity; and helps sustain healthy cellular mitochondria for sustained energy. Cognizin is also highly stable, GRAS, ultrapure, and allergen free. For more information on Cognizin, visit http://www.cognizin.com.

About Kyowa Hakko USA

Kyowa Hakko USA is the North American sales office for KYOWA HAKKO BIO CO. LTD. (Kyowa), an international health ingredients manufacturer and world leader in the development, manufacturing, and marketing of pharmaceuticals, nutraceuticals, and food products. Kyowa is the maker of branded ingredients including Cognizin Citicoline, Pantesin Pantethine, Setria Glutathione, as well as Sustamine L-Alanyl-L-Glutamine. For more information, visit www.kyowa-usa.com.

Notes

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◆

Electromedical Products International Inc. Hails Reclassification of CES Devices

Electromedical Products International Inc., the manufacturer of Alpha-Stim AID and Alpha-Stim M, welcomed the announcement in the Federal Register of June 12, 2014, by the Food and Drug Administration (FDA) of the agency's intention to reclassify cranial electrotherapy stimulation (CES) devices from a class III to a class II designation in Dockets No. FDA-2011-N-0504 and FDA 2013-N-0195.

"We welcome the action taken by the FDA, which reflects the overwhelming evidence of absolute safety and effectiveness of CES treatment for anxiety, depression and insomnia," stated Daniel L. Kirsch, PhD, FAIS, chairman of the board for Electromedical Products International. "This is a battle we have fought with the FDA for the past 22 years, and are pleased that we can now move forward with the proper classification."

It has been the position of Electromedical Products International that such devices never should have been designated as class III, which is reserved for life-sustaining or life-support devices, such as surgical implants.

In its statement, the FDA announced that it was withdrawing the proposed rule and proposed order to call for premarket approval applications (PMA) for CES devices and would be establishing special controls in addition to general controls, but did not specify what those controls would be. According to the FDA statement, the committee received more than 300 comments to the docket in response to the proposed rule and proposed order, which were "usually in favor of a class II designation." In addition, the FDA received four separate submissions to request a change in the classification of CES from a class III to class II. This, combined with information submitted at previous hearings was considered, and the agency decided in favor of reclassification.

Kirsch noted that the reclassification of CES devices to class II will greatly improve health-care providers' ability to treat such conditions as anxiety and depression with an effective alternative to drug therapy and open the door to broader insurance compensation.

Alpha-Stim's CES therapy has been in use since 2005 by the US Army and the Veterans Affairs Medical Centers (VAMC) as treatment for depressive disorders, anxiety disorders, sleep disorders, and both chronic and posttraumatic pain.

"This reclassification is exceptional news for the many military and veteran patients whose war trauma and postwar symptomatology respond exceedingly well to Alpha-Stim therapy," said clinical psychologist and retired Army Reserve COL Kathy Platoni, PsyD. "CES frequently permits the reduction and/or elimination of mood-altering medications, many of which have the potential to result in dangerous side effects and to impair service members in the performance of their duties in the combat theater. My experience, without exception, is that the effectiveness of CES treatment far exceeds the benefits of long-term drug therapy, whether in the wartime theater of operations, during the reintegration process, or in any case, as this applies to mental health treatment in general."

About Alpha-Stim M and Alpha-Stim AID

Alpha-Stim uses cranial electrotherapy stimulation (CES) for anxiety, depression, and insomnia and microcurrent electrical therapy (MET) for people suffering from acute, chronic, or posttraumatic pain. The patented microcurrent waveform unique to Alpha-Stim is what makes it such a safe and effective medical device. With more than 95 research studies and published reports as well as ongoing research and patient follow-up, there is more research supporting Alpha-Stim than any other therapeutic device in its class. Most people feel better from the very first treatment and improve more than 50% in just a few weeks.

About Electromedical Products International Inc.

Electromedical Products International Inc. (EPI) was founded in 1981 by Dr. Daniel L. Kirsch, a world-renowned neuroscientist who developed Alpha-Stim technology as a safe and effective solution for the treatment of pain, mood, and sleep disorders. With headquarters in Mineral Wells, Texas, EPI is a global enterprise with representatives throughout the world. EPI is an FDA-registered establishment with operations certified by an independent third party to the International Standards Organization (ISO) 13485:2003 standards for quality in medical devices. Alpha-Stim products earned and maintain the CE mark through compliance with the European Medical Device Directives and is approved for over-the-counter use in China, Japan, and Korea as well as many other countries.

◆

Low-Disaccharide Diet Effective Against Crohn's Disease

Nowadays the airways are being bombarded by commercials for Humira, a drug that has been approved by the FDA for the treatment of Crohn's disease. This drug costs about $19,000 per year, and can cause serious side effects, including life-threatening infections, neurologic disorders, and cancer. With sales of $10.7 billion last year (it is also approved for several other autoimmune diseases), Humira is the largest-selling drug in the world. It is one of the latest examples of obscenely expensive, frightfully dangerous drugs being advertised to desperate patients with serious diseases.

Fortunately, a safe and effective dietary treatment for Crohn's disease – the Specific Carbohydrate Diet – has been available for more than 20 years. Although it has not been as widely publicized as drug treatments, a growing number of Crohn's-disease sufferers have experienced dramatic improvements, and in many cases apparent cures, from this diet. It is called the Specific Carbohydrate Diet because it only allows foods that are free of or contain negligible amounts of disaccharides (a specific type of dietary carbohydrates) or disaccharide precursors.

Low-Disaccharide Diet

Lactose, sucrose, maltose, and isomaltose are the major disaccharides present in the human diet. These nonabsorbable disaccharides are hydrolyzed to absorbable monosaccharides by disaccharidase enzymes present in the small-intestinal mucosa: lactase, sucrase, maltase, and isomaltose, respectively.

Lactase deficiency has been observed in 30% to 40% of patients with Crohn's disease.[1] In addition, a significant reduction in total disaccharidase activity was found in the jejunum of patients with Crohn's disease who had no radiologic evidence of small-bowel involvement.[2] It is well known that malabsorbed lactose is fermented by intestinal bacteria, which leads to the production of gases that can cause various gastrointestinal symptoms. Patients with lactose intolerance complicating Crohn's disease often experience an improvement in their intestinal symptoms when they avoid cow's milk and other lactose-containing foods. Similarly, patients with congenital sucrase deficiency experience an improvement in gastrointestinal symptoms when they avoid sucrose-containing foods.[3]

Elaine Gottschall, in her 1994 book, *Breaking the Vicious Cycle*, hypothesized that the consumption of disaccharide-containing foods not only exacerbates symptoms in many patients with Crohn's disease but also plays an important role in the pathogenesis of the disease.[4] According to this hypothesis, the presence of undigested disaccharides encourages bacterial proliferation in the normally sterile small bowel. The byproducts of bacterial fermentation, in addition to triggering gastrointestinal symptoms, further damage the small-intestinal mucosa and further decrease disaccharidase activity, which leads to a vicious cycle of more bacterial overgrowth and more pronounced intestinal damage. This vicious cycle can be broken by avoiding all foods that contain either disaccharides or starches that are metabolized to disaccharides (such as amylopectin).

Gottschall reported that consumption of a low-disaccharide diet frequently results in marked clinical improvement or complete remission in patients with Crohn's disease. Moreover, many patients who strictly adhere to the diet for 2 years or more are apparently "cured," in that they are able to relax the

dietary restrictions without experiencing a recurrence of the disease.

The Specific Carbohydrate Diet excludes all grains (including wheat, oats, barley, rye, corn, rice, millet, buckwheat, spelt, and triticale), milk and other lactose-containing foods, potatoes, soybeans and certain other beans, corn syrup, foods that contain sucrose, and a number of other foods. It is described in detail in Gottschall's book. In my experience, the Specific Carbohydrate Diet has been highly beneficial for several patients with Crohn's disease.

Other investigators have recently confirmed Gottschall's observations. In a new report, researchers reviewed the medical record of 7 children (aged 7–16 years) with Crohn's disease who had followed the Specific Carbohydrate Diet and had not received immunosuppressive medication. The mean duration of dietary therapy was 14.6 months (range, 5–30 months). All symptoms were resolved in all cases at a follow-up visit 3 months after the start of the diet. Each patient's laboratory tests, including serum albumin, C-reactive protein, hematocrit, and stool calprotectin (an indicator of intestinal inflammation), either became normal or improved significantly. All patients had an increase in height and weight.[5]

Many of the foods prohibited on this diet (such as wheat, corn, and milk) are among the most frequently allergenic foods, so it is not clear how much of the improvement is due to allergen avoidance and how much to the avoidance of disaccharides. In addition, it is not clear how the proposed vicious cycle of small-bowel bacterial overgrowth and disaccharidase deficiency begins. Studies in infants recovering from enteritis have shown that ingestion of cow's milk protein can cause a marked reduction in lactase, sucrase, and maltase activity (isomaltase activity was not measured), accompanied by histologic changes in jejunal mucosa.[6] That finding suggests that consumption of allergenic foods may in some cases be the initial insult that leads to disaccharide intolerance. In other cases, the initial insult might be disruption of the intestinal flora secondary to antibiotic therapy.[7]

Alan R. Gaby, MD

Notes

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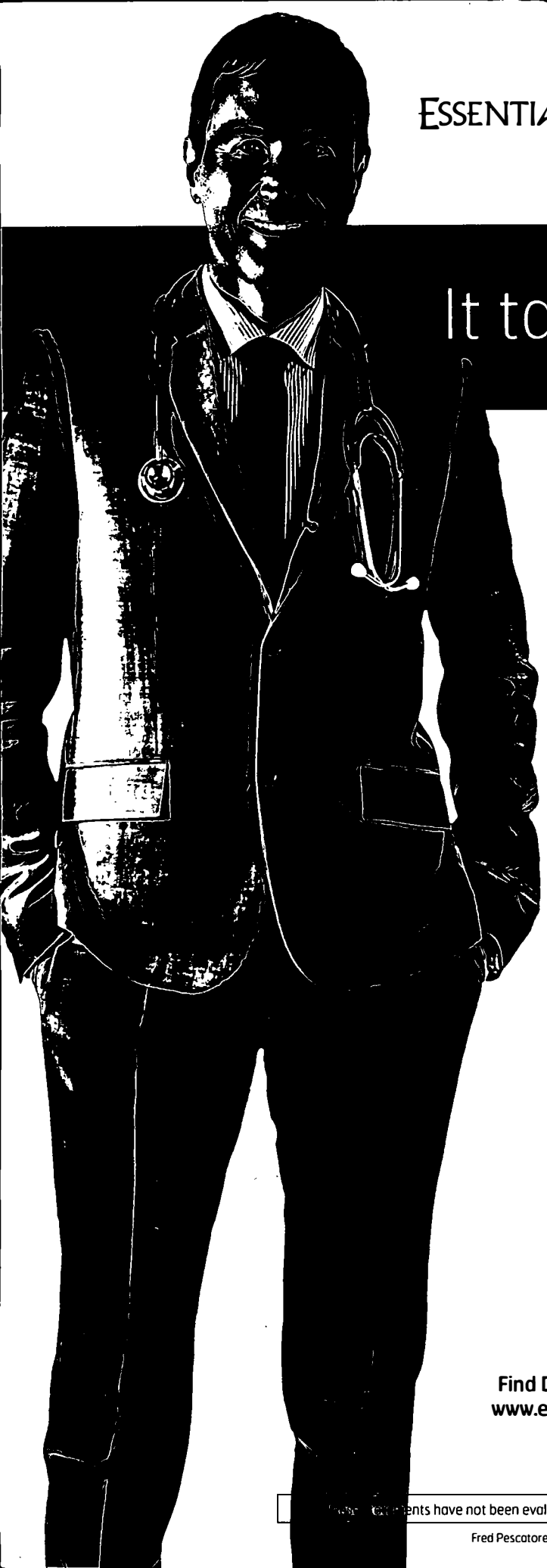

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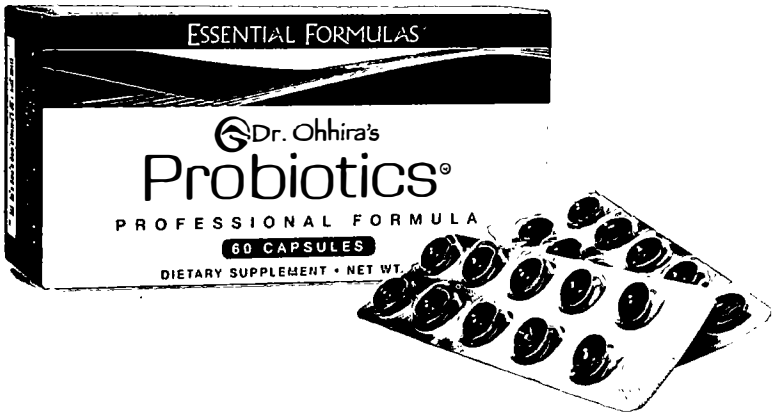

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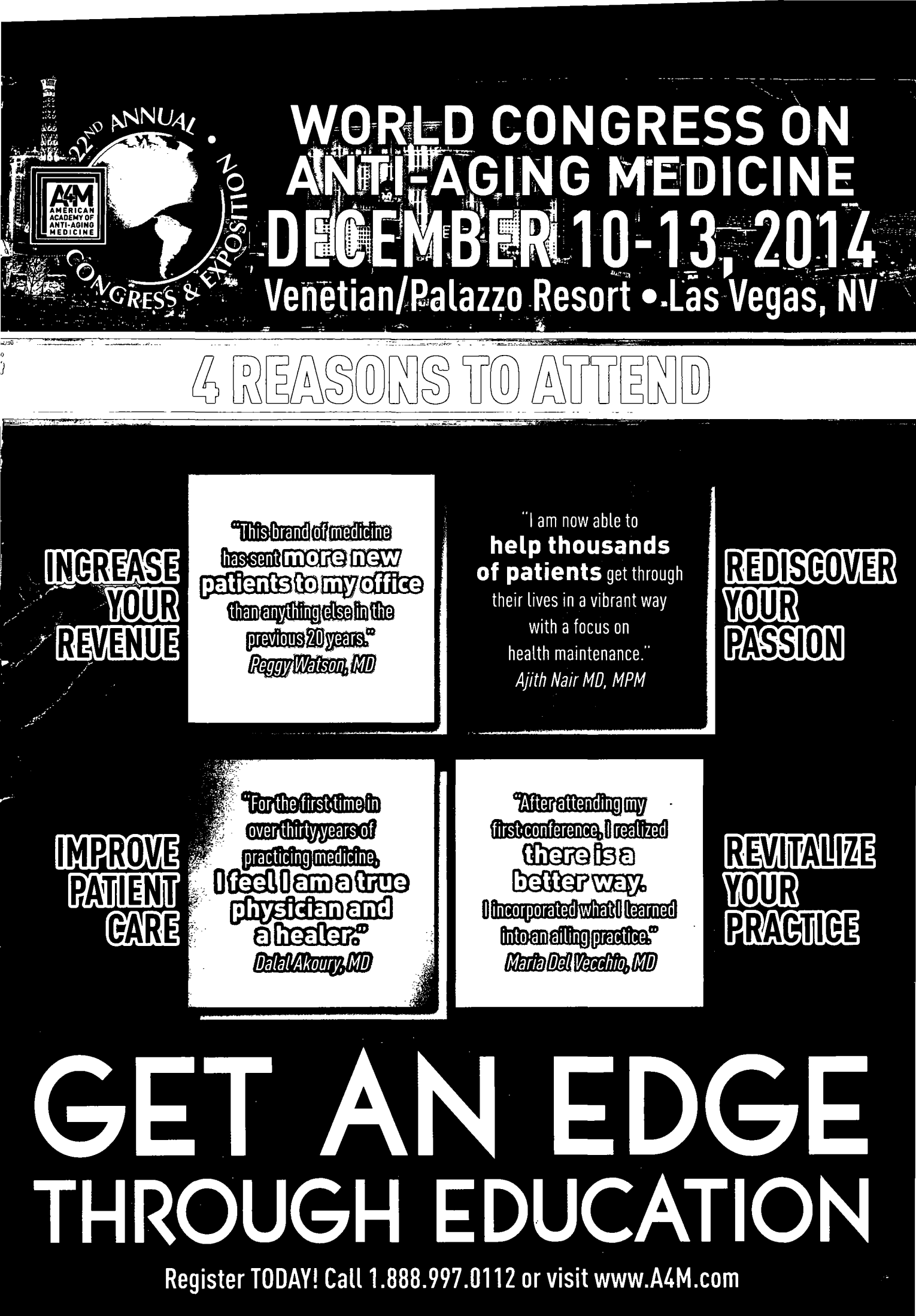
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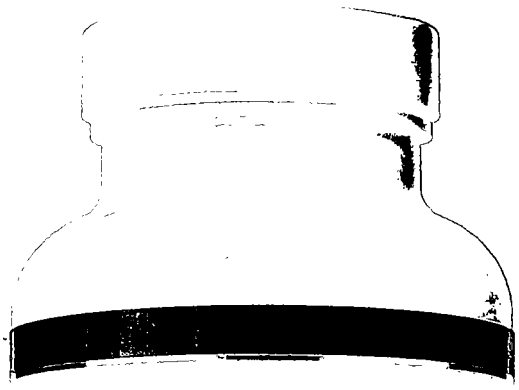

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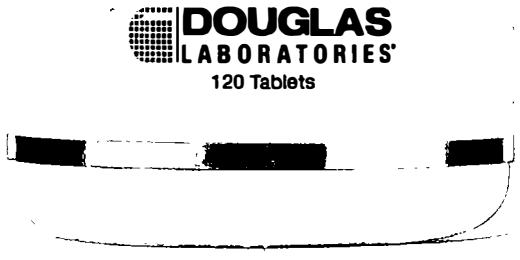

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