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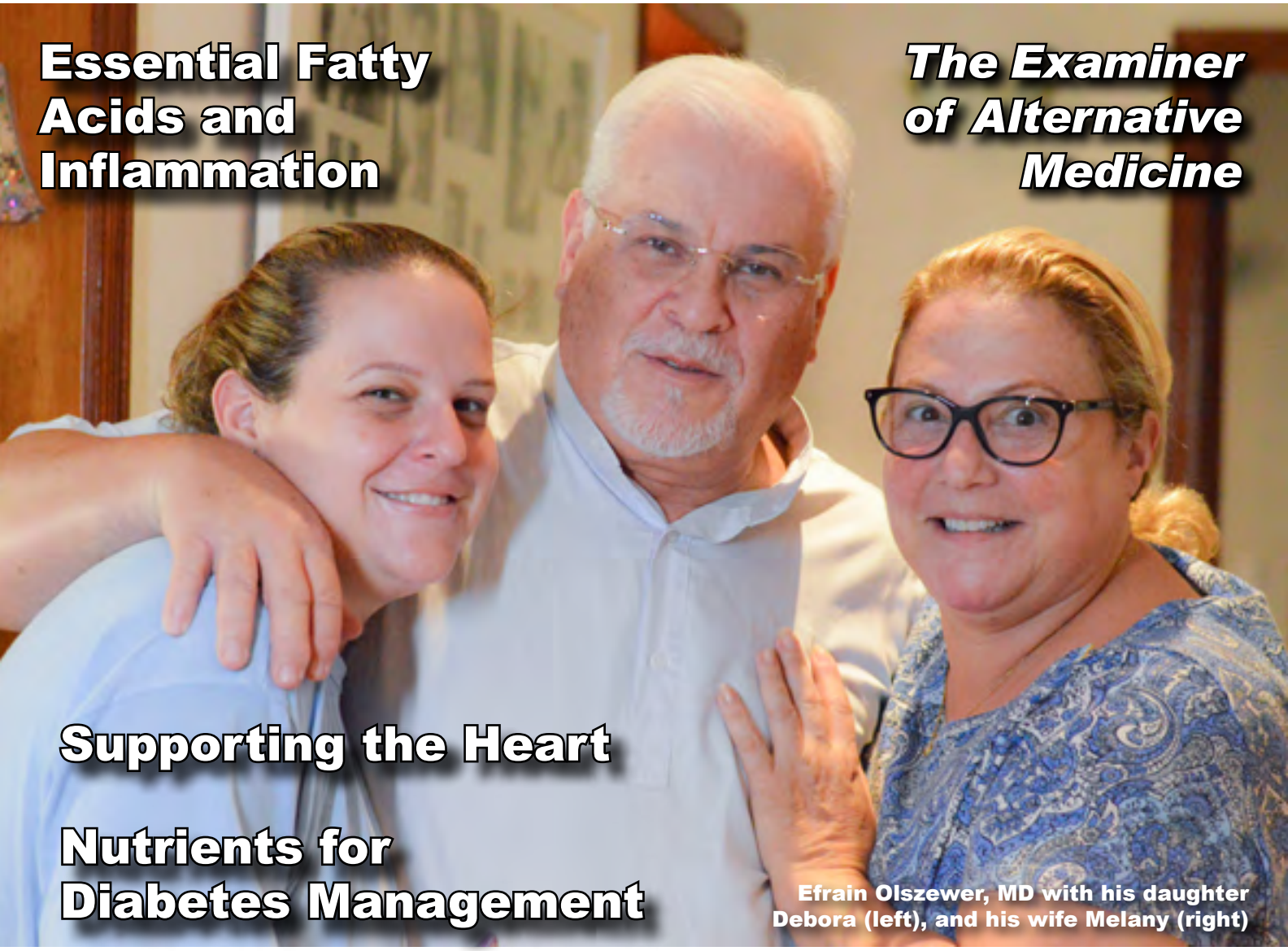

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The Examiner of Alternative Medicine

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Nutrients for Diabetes Management

Efrain Olszewer, MD with his daughter Debora (left), and his wife Melany (right)

May 2022
Issue #466
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Efrain Olszewer, MD

Omega-3 Fatty Acids and Cardiovascular Health

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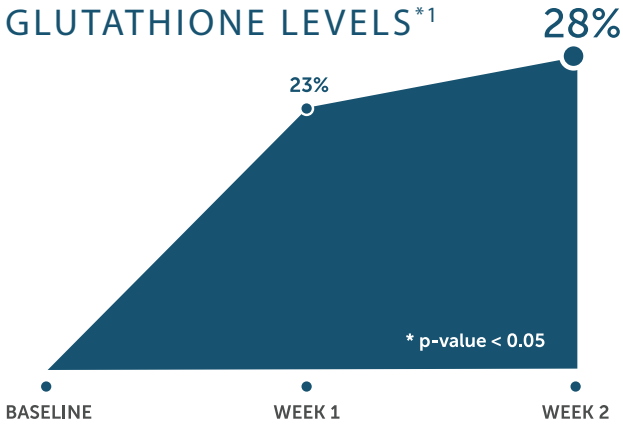

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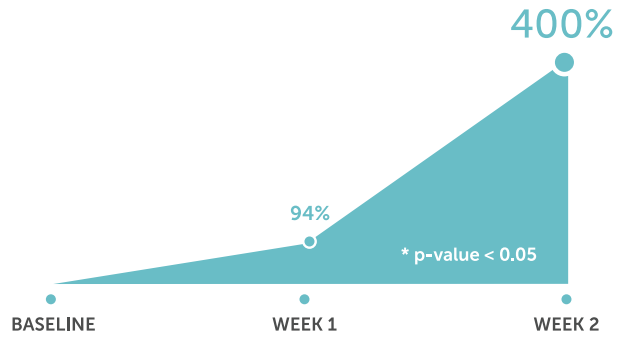

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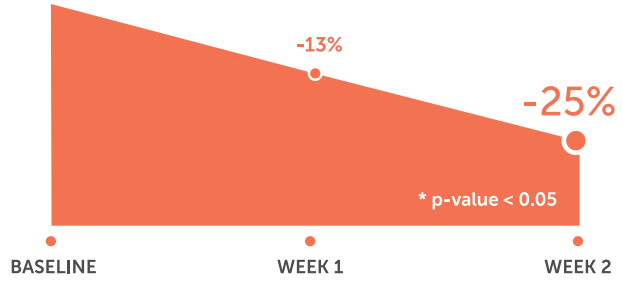

Learn more.

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

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From the Publisher

The Publisher Gets Egg on His Face

Over the first weekend in March, I was informed through an email that the FDA had lowered the guillotine and banned compounded bio-identical hormones. Well, it turns out, there was no formal announcement by the FDA although reliable sources strongly suggested that such a plan was in the works. Due to my spreading this incorrectly stated information, I caused quite a stir through the bio-identical hormone community. A colleague was booted from her FB group because of posting my information. Needless to say, I ashamedly informed one and all by email and social media that no such announcement had occurred. However, the battle we have with the FDA to stop their plan to ban compounding pharmacies from making hormones is hardly over.

Their scientific advisory group, NASEM, put out a very misleading report in 2021 that essentially condemned compounding of hormones as being adulterated, not properly

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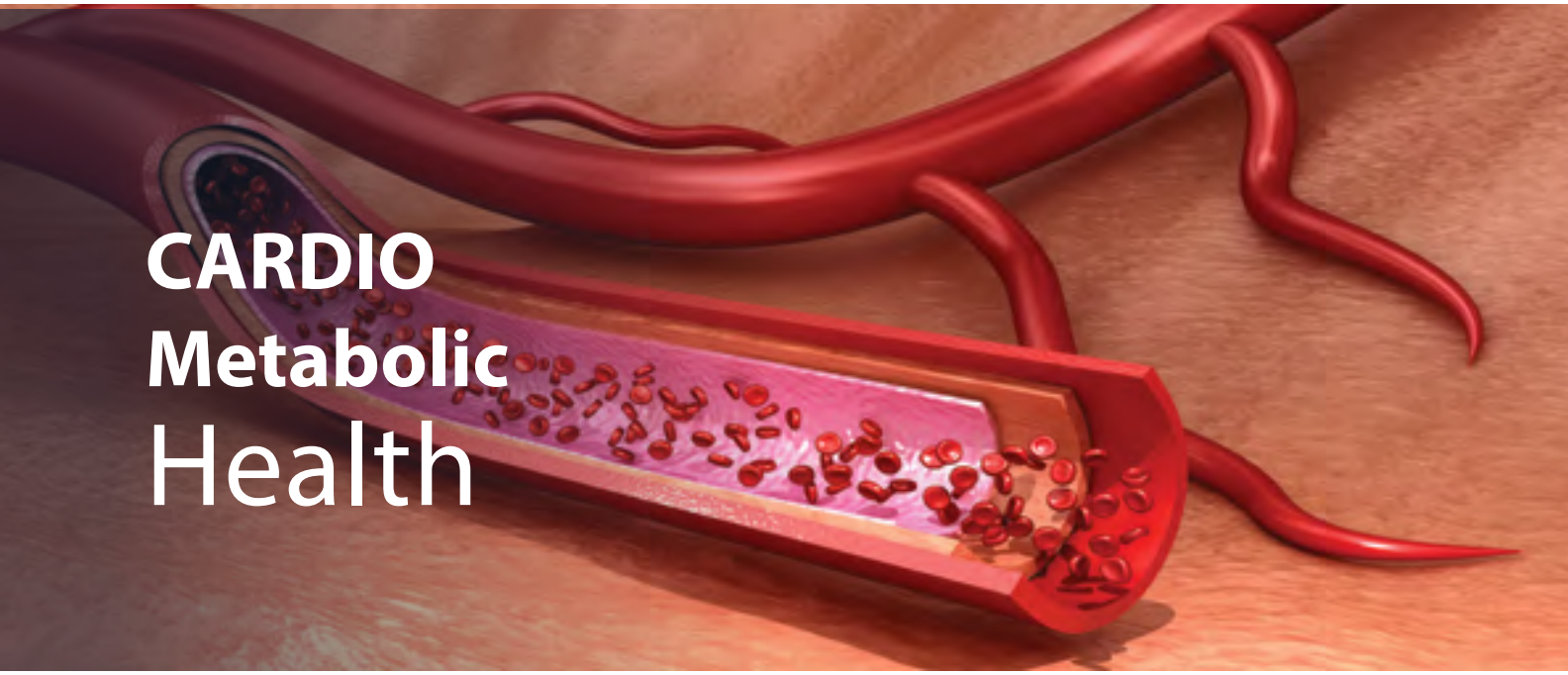

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Cardiometabolic health involves a group of interrelated factors and encompasses healthy blood lipid levels, circulatory and blood vessel function, optimal blood sugar levels and overall heart health. With a growing public concern for cardiometabolic health, Biotics Research Corporation, in conjunction with Dr. Mark Houston, Associate Clinical Professor of Medicine at Vanderbilt Medical School and Director of Hypertension Institute and Vascular Biology in Nashville, has developed a unique selection of "heart-healthy" nutritional formulas.

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Letter from the Publisher

➤ *continued from page 2*

dosed, and ridden with adverse effects. The NASEM only used 13 studies to draw their conclusion – and none of them looked at the evidence-based literature supporting the use of bio-identical hormones. There is a campaign underway in the conventional medical community and certain consumer groups to end the compounding of hormones. One Twitter posting in the past week from a gynecologist in the UK excitedly complained about a woman who developed uterine cancer while using compounded hormones. My response to that was would there have been any concern if the woman had been using Premarin? These self-proclaimed experts "know" that pharmaceuticals work and compounded hormones are dangerous.

We need to remember that drug companies pay the FDA about $370K yearly for the pleasure of being a pharmaceutical manufacturer partially financing the payroll of the FDA. The FDA, the drug companies, and the medical schools all interact and work together on a daily basis. Medical schools and academic hospitals need the latest and greatest drugs to "cure" disease. Pharmaceutical companies need to make the next blockbuster to bring in the bucks and provide for their shareholders. The FDA acts as a mediator for the MDs and the drug companies, obligated to make both happy. A compounding pharmacy is an insult to the drug company and a renegade to the chain drug store. Just like alternative docs are disdained by university docs, compounding pharmacies are despised by chain pharmacies and drug companies.

We do need to write our Congress people about this situation informing them of the great risk that our patients face if they lose their access to compounded hormones. Our patients need to write up their stories of how the hormone prescriptions have changed their lives; they should submit them to the coalition to protect access to bio-identical compounded hormones: https://cbhrtcoalition.org/. We need to think about acting legislatively to restrict FDA authority over compounding of hormones and medicine in general. On a state level, legislation could be enacted protecting the compounding of hormones superseding FDA oversight; however, this would not be helpful for the doc/patient getting their prescriptions filled out of state.

Compounding got a black eye in 2013 when a New England compounder prepared a bad batch of corticosteroids being used in pain clinics for back injections. Since that time the FDA has relentlessly sought to derail compounding pharmacies. A memorandum of understanding (MOU) enacted two years ago by the FDA places onerous requirements on compounding pharmacies causing many to cease compounding. A ban on compounding hormones would provide impetus for the FDA to limit compounding of injectables. Injectable supplies made by compounding pharmacies are the only means to access B vitamin, mineral, amino acid, and chelation supplies; the pharmaceutical companies no longer produce these injections. Even low dose naltrexone, a drug that has become widely popular in the treatment of autoimmune disease, may be threatened if compounding pharmacies are further limited by the FDA.

Please join the Alliance for Pharmacy Compounding, www.a4pc.org. Write your Congress people now and get your patients educated and involved!

Controlling High Blood Pressure **Book by Mark Houston, MD, and Lee Bell**

If you are like me, you have been taught that the vast majority of hypertension is essential hypertension. What this term means is that the hypertension is not due to some rare disorder such as a pheochromocytoma or renal artery stenosis. Essential or primary or genetic hypertension does not have a specific disease causing the high blood pressure. However, what Dr. Houston calls "infinite insults" of life manifest themselves in the cardiovascular system as either inflammation, oxidative stress, or vascular immune dysfunction. In conjunction with one's genetics, these "finite responses" to daily insults lead to damage to the artery endothelium, muscular media, and adventitial wall causing stiffness to these structures, and endothelial dysfunction, decreasing nitric oxide production necessary for the vessel to relax and dilate. The arterial insults, both biochemical and biomechanical, yield antigens binding to the arterial wall causing the trio of responses. Houston considers vascular disease to be a balance between injury and repair; nitric oxide and endothelial "progenitor" cells seek to repair the damage caused by inflammation, oxidative stress, and immune cell dysfunctioning. When vascular disease progresses, hypertension develops; but high blood pressure is asymptomatic – only diagnosed through blood pressure measurement.

Using this model Dr. Houston argues that hypertensive medication need not be the primary solution, although until the blood pressure is controlled by alternative means, the medication must be continued. Cardiology employs the Dash diets, a low sodium diet, as the primary nutritional management for hypertension. At his institute, the Hypertension Institute, it is assumed that one or more foods may be allergenic, sensitizing, or intolerant. Rather than doing a food allergy test, Houston asks patients to go on an elimination diet for two weeks avoiding gluten, dairy, eggs, corn, peanuts, soy, grains, legumes, nuts, seeds, nightshades as well as elimination of alcohol, caffeine, processed food, fast food, sugar, recreational drugs, and tobacco. (Of course, the latter two and alcohol will require special support.) What's left to eat? Actually quite a few foods do remain, and copious water drinking is obligatory. Reintroduction of foods one by one will enable one to determine food sensitivities.

Next, Houston employs a liver detox and 16/8 fasting, meaning fasting for sixteen hours, then eating only within an 8-hour window of time. A major do-over of one's eating is not something that can just be accomplished by giving the patient a booklet. The Hypertension Institute has all patients undergo cognitive behavioral therapy, at least to some degree, to relearn unhelpful ways of behavior and thinking.

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Letter from the Publisher

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It is critical that the patient understand why they are making these changes. Houston wants the patient to recreate the environment in which they eat; one can't make these changes if all kinds of processed and junk foods fill the refrigerator and pantry or if one heads to the food truck at lunch time.

Beyond what one eats, Houston discusses the literature supporting the use of each nutraceutical, vitamin, mineral, and EFA in the treatment of hypertension (despite the effort by conventional medicine to naysay supplements). Attempting to overcome one's need for anti-hypertension drugs without the use of supplements is a fool's mission. As you would expect, magnesium is number one on his list of supplements. However, he does want patients to use a wide range of hypertension-lowering nutraceuticals, including the use of CoQ10, garlic, and beetroot. He does offer some proprietary formulations that he favors (I will leave you to discover these on reading the book). One very fascinating chapter discusses the genetic aspects of hypertension; it turns out abnormal genetic SNPs do play a role in causing hypertension. Each SNP impacts the vasculature and renin-angiotensin system differently. Based on the abnormal SNP, a particular drug and nutraceutical is preferred to treating hypertension. For example, patients with the ACE I/D SNP would respond best to ACE inhibitor drugs and nutraceuticals pycnogenol, R-lipoic acid, garlic, and CoQ10.

The book originally published in 2021 by the CRC press is available now.

Cover Article: Is Fish Oil Effective Therapy for Cardiovascular Disease? by Efrain Olszewer, MD

Back in the day when we used to attend medical conferences, I was always impressed by doctors travelling great distances to give a presentation or just listen to the lectures. Probably I am among the minority, but it just didn't seem reasonable to travel 12 hours for 15-20 credit hours. I was always amazed to see Sao Paolo, Brazilian, Dr. Efrain Olszewer in attendance, not just for one but for a great many integrative medicine conventions in the US. Of course, Olszewer is a very renowned orthomolecular physician in South America, as president of the Associacao Medica Brasileira de Pratica Ortomolecular (AMBO). His speaking engagements in the orthomolecular societies not only had him traveling to the US but frequently to Spain and Portugal as well. Olszewer is the author of more than 80 books; he has written numerous journal articles, including this month's cover article.

I was particularly impressed with his authoring articles on the use of i.v. chelation therapy for cardiovascular disease. This was at a time years ago when the NIH chelation T.A.C.T. trial had not even been initiated. His work concluded that oral chelation failed to demonstrate effective changes in ASCHD compared to intravenous chelation. Before publication of the T.A.C.T. study, chelation therapy had a sullied reputation with the "quackbusters" frequently including it in their lists of fraudulent cures. It was heartening to have a Brazilian doctor publish articles countering the negative viewpoint American cardiologists held for EDTA chelation.[1]

In this issue Dr. Olszewer reviews and examines the literature on omega-3 fatty acids and cardiovascular prevention and treatment. Of course, we are not talking one or two studies. There are dozens and he analyzes a great many of them. As expected, many of the studies demonstrate an effective role for omega-3 fatty acids; however, there are more than a few that do not show such efficacy. For example, Olszewer discusses the meta-analysis compiled by Asmaa Abdelhamid for the Cochrane Database in 2018. Abdelhamid's conclusion was that there was insufficient evidence for the use of the omega-3s in cardiovascular disease. Yet, Olszewer's review of many other studies clearly demonstrates positive benefit. The REDUCE-IT trial published in December 2021 showed a purified form of EPA but not DHA called Icosapent Ethyl (IPE) had very positive cardiovascular benefit.[2] In the study, 2 grams of IPE (Vascepta®) not only reduced triglycerides but also reduced MIs, strokes, and stenting. (Vascepta is now an approved drug agent for reducing cardiovascular risk.) On the other hand, the STRENGTH study does not demonstrate a similar positive benefit for fish oil, which is not just EPA but also DHA. The 2020 study using a pharmaceutical form of fish oil, Epanova® failed to demonstrate improvement in triglyceride levels compared to a corn oil placebo; the study conducted by AstraZeneca was terminated before completion.[3] A logical question might be if the purified form of EPA yielded strong benefit, but a fish oil drug having both EPA and DHA failed, could it be that DHA has deleterious cardiovascular effects? Olszewer's review suggests that there very well could be concerns based on the type of omega-3 supplement that is being studied.

Conventional thinking has been that our large consumption of processed omega-6 oils as contained in the Standard American Diet (SAD) is a major cause of obesity, diabetes, heart disease, and more. Of course, we advise patients to lower their intake of trans-fats, fried foods, and processed foods containing omega-6 oils. So, omega-6 oil is the number one enemy for cardiovascular disease, right? Well, no. It depends on the exact nature of the omega-6 oil, how it is processed (or not processed), and how we consume it. Brian Peskin, an advocate for the use of unprocessed omega-6 oils, writes in this issue about the necessity of omega-6s in our diet and how such omega-6s are effective in reducing inflammation, especially in support of cardiovascular health. So, do we use omega-3s or omega-6s or a combination?

Jonathan Collin, MD

References

1. Olszewer, E, Carter, P. EDTA chelation therapy in chronic degenerative disease. *Med. Hypothesis.* 1988: 27(1); 41-49.
2. Bhatt, D, et al. Reduction of cardiovascular events with Icosapentyl Ethyl Intervention Trial – REDUCE-IT. *Amer Coll Card*. 2021: Dec. 20.
3. https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-phase-iii-strength-trial-for-epanova-in-mixed-dyslipidaemia-13012020.html#!

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Shorts

briefed by Jule Klotter
jule@townsendletter.com

Taurine, Mitochondria, and the Heart

Last month, "Shorts" looked at the possible benefits of using taurine, a sulfur-containing amino acid, to prevent vision loss in age-related macular degeneration – but it seems this amino acid also has a protective effect on mitochondria and the heart as well. In their 2021 review article for *Molecules*, Chian Ju Jong and colleagues report that taurine has a significant role in mitochondrial function.

Taurine, first isolated from ox bile in 1827, is made from methionine or cysteine in the liver. It is found in abundant amounts in the heart, brain, retina, and skeletal muscle. Some animals, such as cats, require high amounts of taurine in their diets (meat and seafood being primary sources). Without it, the animals develop cardiomyopathy and myocardial dysfunction, retinal degeneration leading to blindness, neurological problems, weakened immune response, and gastrointestinal problems. In research studies, taurine-supplemented diets protected the animals from cardiomyopathy, seizure, and retinopathy.

Taurine is known to have a significant role in maintaining mitochondrial function – though its mechanisms of action are not fully understood. It appears to modify mitochondrial tRNA and help synthesize mitochondrial proteins needed for efficient energy production; oxidative stress, created during mitochondria energy production (ATP), declines with taurine. Taurine also regulates intracellular calcium homeostasis necessary for modulating heart contractions as well as for regulating mitochondrial oxidative phosphorylation to produce ATP. In addition, taurine protects against glutamate-induced excitotoxity that can produce mitochondrial damage and neuron cell death.

Taurine has been an approved treatment for people with heart failure in Japan since 1985. More recently, it has also gained Japanese approval for the treatment of stroke-like episodes in people with the mitochondrial disease MELAS Syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes).

According to Japanese studies, taurine supplementation (2-3 grams/day for 4-8 weeks) increased cardiac output and stroke volume, ejection fraction, and mean velocity of circumferential fiber shortening in most patients with heart failure. Patients with NYHA class II or III heart failure showed improved exercise capacity after receiving 500 mg of taurine, three times/day for two weeks.

Taurine may also be helpful for patients with metabolic syndrome and type 2 diabetes: "When taurine is supplemented, glucose levels are restored, insulin secretion is enhanced and glucose and lipid metabolism in the mitochondria are stimulated." Several trials have indicated that taurine supplementation may reduce diabetic complications, such as nephropathy, retinopathy, and neuropathy – although a few have not found benefit.

Given its protective effects on mitochondrial function – and the growing list of disorders linked to mitochondrial dysfunction – taurine deserves more attention.

Chian Ju Jong, Sandal P, Schaffer SW. The Role of Taurine in Mitochondria Health: More Than Just an Antioxidant. *Molecules*. 2021;26:4913.

Strengthening Inspiratory Muscles to Reduce Blood Pressure

Researchers in Boulder, Colorado, are investigating a new type of exercise for reducing systolic blood pressure: inspiratory muscle strength training (IMST). IMST, originally developed in the 1980s to wean patients off ventilators, consists of breathing in through a hand-held device that provides resistance. "Imaging sucking hard through a straw which sucks back," writes Lisa Marshall.

In 2016, University of Arizona researchers found just 30 breaths/day with IMST helped people with obstructive sleep apnea rest better and strengthened the diaphragm and other inspiratory muscles; it also had the unexpected effect of lowering systolic blood pressure. The Boulder researchers decided to test the effectiveness of IMST on people with high blood pressure by conducting a six-week, double-blind, randomized, sham-controlled trial.

➤

Shorts

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Thirty-six healthy men and post-menopausal women (aged 50-70 years) were randomly assigned to the high-resistance IMST group (n=18) or the "sham" (control) group (n=18). All participants were instructed in using the POWERbreathe K3 inspiratory muscle training device and told to do "30 inspiratory maneuvers (5 sets of 6, 1-minute rest between sets), six days per week for six weeks." The device tracked adherence to the protocol.

The resistance provided by the device differed between the two groups and was determined by the individuals' maximum inspiratory pressure (PI_{MAX}). PI_{MAX} was assessed for each participant using a custom-built pressure transducer (Omega-Dyne). Resistance for people in the control group was set at 15% of their PI_{MAX} for the entire six weeks. In the intervention group, resistance was set higher and gradually increased: 55% of PI_{MAX} during week 1, 65% PI_{MAX} during week 2, and 75% PI_{MAX} for the final four weeks. Each participant's PI_{MAX} was re-assessed at the beginning of each week.

In addition to blood pressure, vasoendothelial function, arterial stiffness, plasma metabolomics, and blood biomarkers of systemic oxidative stress, antioxidant activity, inflammation, and sympathoadrenal activity as well as fasting serum lipids and plasma glucose were assessed. The researchers also conducted endothelial cell culture experiments using participants' serum to detect the effect on reactive oxygen species (ROS) production and on nitric oxide (NO) production. These measures were taken at baseline, at the study's end, and at an optional follow-up for IMST participants that occurred six weeks after the intervention concluded.

High-resistance IMST, which took less than 10 minutes/day, produced several positive effects after six weeks of the exercise; the control group showed no change from baseline in any of the measurements. Systolic blood pressure (SBP) decreased from 135±2 mmHg at baseline to 125±3 mmHg after six weeks of IMST ($p<0.01$). At the optional follow-up, SBP was 128±4 mmHg ($p<0.01$) in the 15 IMST participants who took part. This decline is greater than or equal to reductions observed with 150 minutes/week of moderate-intensity aerobic exercise. Moreover, the SBP reduction is associated with a 30%-40% lower risk of cardiovascular-related death.

Vascular endothelial function increased about 45% over baseline in the IMST group ($p<0.01$); but it returned to baseline in the follow-up.

For the most part, blood biomarkers showed no changes from baseline or between the two groups. C-reactive protein, a marker of systemic inflammation, was the exception. It decreased 30% after IMST: baseline 1.37±0.23 mg/L, end-intervention 0.96±0.17 mg/L; $P=0.05$.

The cell culture experiments showed that NO bioavailability (from increased endothelial NO synthase activation and decreased oxidative stress) was significantly greater after IMST training ($p=0.01$) and ROS bioactivity decreased ($p=0.01$).

No changes were observed in arterial stiffness measures, possibly due to the study's short length.

Neck muscle soreness (n=1) and lightheadedness (n=1) – both of minor severity – were the only treatment-related adverse effects. Adherence to the protocol was excellent: "The IMST group completed 94.4% of prescribed training sessions, whereas the sham group completed 90.0% of prescribed training sessions."

The authors write:

> The results from this pilot study will need to be confirmed in a larger trial, perhaps with a longer treatment duration. It is possible that a longer-term training stimulus would produce even greater improvements in cardiovascular function….
>
> Our results provide support for high-resistance IMST as a promising lifestyle intervention for improving cardiovascular function and possibly decreasing the risk of CVD and other clinical disorders, such as cognitive dysfunction and chronic kidney disease.

Craighead DH, et al. Time-Efficient Inspiratory Muscle Strength Training Lowers Blood Pressure and Improves Endothelial Function, NO Bioavailability, and Oxidative Stress in Midlife/Older Adults With Above-Normal Blood Pressure. *J Am Heart Assoc.* 2021;10:e020980.

Marshall L. Novel 5-minute workout improves blood pressure, may boost your brain. www.colorado.edu/today/. February 25, 2019.

Pfizer Whistleblower Lawsuit

In the January 2022 issue of *Townsend Letter,* publisher Jonathan Collin, MD, wrote about the *British Medical Journal* (*BMJ*) investigative report about methodological irregularities and data fraud that occurred at Ventavia, one of the test sites for Pfizer's COVID-19 vaccine. Brook Jackson, a trained clinical trial auditor with over 15 years' experience, worked as regional director at Ventavia Research Group for two weeks. She was fired in September 2020, after emailing a complaint to the US Food and Drug Administration when her superiors ignored the many data integrity issues that she had observed. Jackson provided investigative reporter Paul D. Thacker and *BMJ* with documentation (internal company documents, photos, audio recordings, and emails) that supported her allegations of falsified data, unblinded patients, inadequately trained vaccinators, and inadequate follow-up on adverse events in the Pfizer Phase III trial that led to its emergency use authorization.

In January 2021, a few months after being fired, Jackson filed a lawsuit against Pfizer, ICON PLC, (the Irish clinical research organization that was overseeing Pfizer's 160+ test sites), and Ventavia Research Group, LLC, under the Federal False Claims Act. The False Claims Act, passed during the US Civil War, allows whistleblowers to file lawsuits on behalf of the government against contractors who commit fraud; if fraud is proven and damages are recovered, the whistleblower(s) received a percentage of the money. According to the lawsuit, the US Department of Defense signed a contract with Pfizer to buy "100 million doses of the vaccine for $1.95 billion following FDA approval or Emergency Use Authorization ("EUA")."

Jackson's complaint remained under seal (available only to the judge, US attorney general and a few members of the Department of Justice) until February 10, 2022, at which time US District Court Judge Michael Truncale (Eastern District of Texas, Beaumont Division) allowed the lawsuit to be served on the defendants. The judge also released over 400 pages of exhibits to public view (posted in *The Epoch Times* article).

The US Department of Justice has declined to take part on her behalf at this point but may intervene later. Jackson told *The Epoch Times*, that even though her case may not succeed,"' [i]t's just a chance I have to take. I just feel like somebody has to be held accountable.'"

Stieber Z. Exclusive: Pfizer Trial Whistleblower Presses Forward With Lawsuit Without US Government's Help. *The Epoch Times.* February 14, 2022.
Thacker PD. Covid-19: Researcher blows the whistle on data integrity issues in Pfizer's vaccine trial. *BMJ.* November 2, 2021.

Thiamine Deficiency and Diabetes

Is thiamine (vitamin B1) an important, overlooked factor in diabetes? In a 2021 perspective paper, three Italian researchers report that thiamine has been linked to diabetes as far back as the 1940s and that addressing thiamine deficiency with supplementation improved symptoms of diabetic neuropathy in pilot studies. Thiamine is required for ATP production; it is an essential cofactor of glucose metabolism. It also modulates neuronal and neuro-muscular transmission. Severe thiamine deficiency results in beriberi and affects neurological function.

Beriberi and thiamine deficiency are believed to be rare in the US and other countries with food fortification programs (adding thiamine, niacin, riboflavin and other nutrients to flour). However, in an excellent 2021 article, Chandler Marrs and Derrick Lonsdale explain the biological effects of thiamine deficiency and why it is "hiding in plain sight."

Thiamine is found in many whole foods, including pork, salmon, trout, tuna, catfish, nuts (macadamia, pistachios), sunflower and flax seeds, navy and black beans, black-eyed peas, lentils, tofu, and brown rice; and the Recommended Dietary Allowance (RDA) to prevent beriberi is just 1.1 mg for adult females and 1.2 for adult males. But eating thiamine-rich foods is just one aspect of avoiding deficiency. Processed high-calorie foods, with increased sugars and chemical additives increase the need for more thiamine. The enzyme that catalyzes thiamine into its active form requires magnesium. Magnesium deficiency is common and can lead to "functional thiamine deficiency," even when plenty of thiamine is present. Chronic alcoholism contributes to thiamine deficiency, and nicotine in tobacco inhibits thiamine availability. Pharmaceuticals – including metformin, psychiatric medications, metronidazole, trimethoprim, anti-hypertensives, NSAIDS, proton pump inhibitors, and diuretics – can all contribute to a thiamine deficiency.

Marrs and Lonsdale say that early signs of thiamine deficiency are non-specific: uncharacteristic fatigue, hyper-irritability and mood lability, gastrointestinal discomfort and dysmotility, sleep disturbances, and loss of appetite. Several populations have a high incidence of thiamine deficiency, including those with diabetes, psychiatric illness, neurological disorders, and the obese. Late stages of deficiency result in high output cardiac failure and edema (wet beriberi), peripheral neuropathies, muscle pain, and weakness (dry beriberi), or mental confusion, ocular abnormalities and ataxia (Wernicke's). Because it is difficult to identify, the authors recommend testing for thiamine pyrophosphate (TPP), also called thiamine diphosphate.

Marrs and Lonsdale say, "Given the high rate of metabolic dysfunction observed in western countries, perhaps it is time to redress concepts associated with micronutrient sufficiency and deficiency and reassess diagnostic parameters associated with [thiamine deficiency]…."

Beltramo E, Mazzeo A, Porta M. Thiamine and diabetes: back to the future? *Acta Diabetologica.* 2021;58:1433-1439.
Marrs C, Lonsdale D. Hiding in Plain Sight: Modern Thiamine Deficiency. *Cells.* 2021; 10:2595.

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

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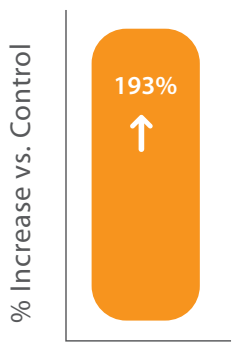
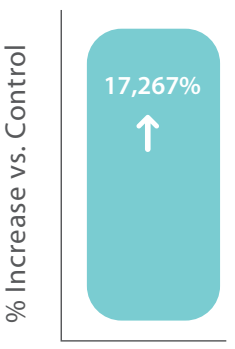


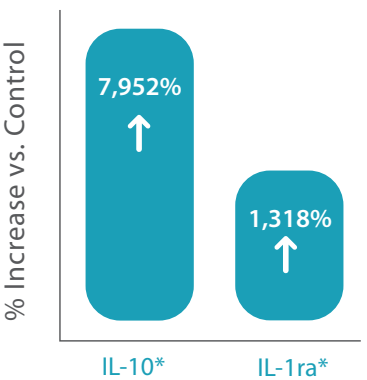
(*Mean fluorescent intensity for CD69 receptor on natural killer cells & CD69 / CD25 receptors for lymphocytes)

LYMPHOCYTE ACTIVATION*



(*Mean fluorescent intensity for CD69 receptor on natural killer cells & CD69 / CD25 receptors for B & T-cell lymphocytes)

IMMUNE MODULATION*



(* Mean fluorescent intensity on peripheral blood mononuclear cell cultures)

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In this Issue

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ON THE COVER: Efrain Olszewer, MD – Omega-3 Fatty Acids and Cardiovascular Health (pg. 30); Nutrients for Diabetes Management (pgs. 28, 39); Supporting the Heart (pgs. 7, 21); Essential Fatty Acids and Inflammation (pg. 48)

Literature Review & Commentary

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

Hesperidin for Hypertension?

One hundred fifty-nine Spanish adults (aged 18-65 years) with pre-hypertension or stage 1 hypertension were randomly assigned to receive, in double-blind fashion, 500 ml per day of orange juice (containing 345 mg of hesperidin), orange juice enriched with additional hesperidin (total, 600 mg per day), or a hesperidin-free control drink (contents not specified). At 2, 6, 10, and 12 weeks, compared with the control drink, mean systolic blood pressure was significantly lower with high-dose hesperidin and nonsignificantly lower with low-dose hesperidin. At all time-points, high-dose hesperidin was nonsignificantly more effective than low-dose hesperidin for decreasing systolic blood pressure.

Comment: Hesperidin is a flavonoid found mainly in oranges and other citrus fruits. In a previous double-blind trial, administration of 292 mg per day of hesperidin to overweight middle-aged and elderly men decreased mean diastolic blood pressure by 3.2 mm Hg compared with placebo ($p < 0.05$).[1] The results of the present study are also consistent with a modest antihypertensive effect of hesperidin, although the findings are not definitive. One possible interpretation of the results is that hesperidin has a dose-dependent blood pressure lowering effect, since the higher dose was more effective than the lower dose. However, another possible interpretation is that low-dose hesperidin was of little or no benefit (since the effect was not statistically significant), and that the greater effect with the higher dose was due at least in part to other components of orange juice (such as potassium and vitamin C).

continued on page 14 ➤

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Hesperidin is safe and inexpensive, so if a patient wishes to supplement with it as part of a comprehensive program to treat hypertension, I see no reason to discourage it. If hesperidin does not lower blood pressure, the patient will at least have stronger capillaries,[2] which may provide partial protection against some of the adverse effects of hypertension.

Valls RM, et al. Effects of hesperidin in orange juice on blood and pulse pressures in mildly hypertensive individuals: a randomized controlled trial (Citrus study). *Eur J Nutr*. 2021;60:1277-1288.

Do Omega-3 Fatty Acids Cause Atrial Fibrillation?

In this editorial, the author discussed four randomized trials conducted in the past four years that examined the effect of omega-3 fatty acids on risk of atrial fibrillation. The primary outcome in these trials was the incidence of a composite of cardiovascular endpoints or the incidence of cancer. The risk of atrial fibrillation was a secondary endpoint or the data were derived from an ancillary study of the original trial. Considered together, these trials suggest there may be a dose-related increase in risk of atrial fibrillation with omega-3 fatty acid intake. At a dose of 4 g per day, there was a highly significant increase in risk (nearly double). With an intermediate dose (1.8 g per day), there was an 84% increase in risk, which was of borderline statistical significance (p = 0.06). With a standard dose (840 mg per day, equivalent to about 2.8 g per day of fish oil), there was a nonsignificant 9% increase in risk.

Comment: This review of the evidence suggests that treatment with large doses of omega-3 fatty acids can increase the risk of developing atrial fibrillation. However, there is no clear evidence that there is an increased risk from the moderate doses of fish oil that are used by many people for cardiovascular disease prevention. High doses of fish oil or of eicosapentaenoic acid (EPA) are used in some cases to treat conditions such as rheumatoid arthritis, bipolar disorder, and hypertriglyceridemia. For patients with these conditions, the potential risk of atrial fibrillation should be balanced against the potential benefit of the treatment. For example, it may not be a good idea to recommend high-dose omega-3 fatty acids for people with certain risk factors for atrial fibrillation, such as excessive alcohol consumption, sleep apnea, or diabetes.

The studies described above pertain to fish oil and to the fatty acids present in fish oil (EPA and docosahexaenoic acid [DHA]). These studies do not imply that consumption of large amounts of alpha-linolenic acid (the omega-3 fatty acid present in plant foods) would have the same adverse effect as EPA and DHA. That is because humans have a limited capacity to convert alpha-linolenic acid to EPA and DHA.

Curfman G. Omega-3 fatty acids and atrial fibrillation. *JAMA*. 2021;325:1073.

Can Diet Help Prevent Heart Failure?

The association between adherence to the Dietary Approaches to Stop Hypertension (DASH) diet pattern and risk of developing heart failure was examined in a prospective cohort study of 18,856 US adults (mean age, 64 years) participating in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study who were free of suspected heart failure at baseline. The DASH diet score was calculated as the sum of eight component scores, as determined from a food-frequency questionnaire that assessed intakes of 1) fruits, 2) vegetables, 3) nuts and legumes, 4) low-fat dairy products, 5) whole grains, 6) sodium, 7) sweetened beverages, and 8) red and processed meats. For components 1 to 5, participants received a score of 5 if they were in the highest quintile and a score of 1 if they were in the lowest quintile. For components 6 to 8, participants received a score of 1 if they were in the highest quintile and a score of 5 if they were in the lowest quintile. The final DASH diet score ranged from 8 to 40, with 8 indicating the lowest adherence to the DASH diet and 40 indicating the highest adherence. Each participant was categorized into a quartile based on their score. During a median follow-up period of 10.1 years, compared with the lowest quartile of DASH diet score, individuals in the second to fourth quartiles had a lower risk for incident heart failure after adjustment for sociodemographic and health characteristics: quartile 2: hazard ratio [HR] = 0.69 (95% confidence interval [CI], 0.56-0.85); quartile 3: HR = 0.71 (95% CI, 0.58-0.87); and quartile 4: HR = 0.73 (95% CI, 0.58-0.92). However, there was no association between DASH diet score and risk of heart failure among participants aged 75 years or older at baseline.

Comment: The DASH diet was designed to provide abundant amounts of nutrients that play a role in blood pressure regulation, such as potassium, calcium, magnesium, vitamin C, and essential fatty acids. The diet is rich in fruits, vegetables, and low-fat dairy products; contains moderate amounts of nuts, seeds, and legumes; and is relatively low in saturated fat, total fat, and refined sugar. Randomized trials have found that adherence to this diet can lower both systolic and diastolic blood pressure in people with hypertension. The original DASH diet did not restrict sodium intake, but later research found that a sodium-restricted DASH diet was more effective than the original DASH diet for lowering blood pressure.

The results of the present study found that adherence to the DASH diet was associated with a reduced risk of developing heart failure among individuals younger than 75. Some of this reduced risk may be attributable to better blood pressure control. In addition, nutrients such as magnesium, potassium, and vitamin C may have a positive effect on myocardial function, independent of any effect they have on blood pressure.

Goyal P, et al. The Dietary Approaches to Stop Hypertension (DASH) diet pattern and incident heart failure. *J Card Fail*. 2021;27:512-521.

Vitamin K and Arterial Calcification

Forty-eight patients with chronic renal failure who were receiving maintenance dialysis were randomly assigned to receive, in double-blind fashion, 360 µg per day of menaquinone-7 (a form of vitamin K2) or placebo for two years. Thirty-seven patients completed year 1, and 21 completed year 2. Vitamin K status improved in the group assigned to receive vitamin K. The mean degree of coronary artery calcification increased in both groups. There was a nonsignificant trend toward greater increases in calcification in the vitamin K group than in the placebo group.

Comment: Arterial calcification is associated with an increased risk of cardiovascular disease-related mortality both in people with and without renal failure. Vitamin K is a cofactor for matrix Gla protein, which is an inhibitor of arterial calcification. Dialysis patients have accelerated vascular calcification and also tend to have low vitamin K status. It has therefore been suggested that vitamin K supplementation could decrease arterial calcification in people with end-stage renal disease. However, in the present study, vitamin K was not effective for that purpose, and it may have even accelerated arterial calcification. Similar findings were reported in an earlier study of patients with type 2 diabetes and cardiovascular disease. In that study, supplementation with 360 µg per day of menaquinone-7 for six months nonsignificantly increased calcification of the femoral artery compared with placebo.[3]

It is not clear why vitamin K was not beneficial in these studies. However, the results should remind us that we cannot always make assumptions about clinical efficacy from what we know about biochemistry.

Levy-Schousboe K, et al. Vitamin K supplementation and arterial calcification in dialysis: results of the double-blind, randomized, placebo-controlled RenaKvit trial. *Clin Kidney J*. 2021;14:2114-2123.

Magnesium and Heart Failure

Mice were fed for six weeks a diet that contained a normal amount of magnesium (600 mg per kg of diet) or a low-magnesium diet (15-30 mg per kg). The low-magnesium diet resulted in diastolic dysfunction (impaired cardiac relaxation), decreased left ventricular ejection fraction, and decreased myocardial ATP concentrations. All of these changes were reversed when the mice were fed a normal-magnesium diet for six weeks.

Comment: In this study, magnesium deficiency caused a reversible cardiomyopathy in mice. Magnesium deficiency is common in patients with heart failure. Factors that predispose to magnesium deficiency in these patients include anorexia, malabsorption secondary to bowel wall edema, and the use of magnesium-depleting drugs such as furosemide. Even when serum magnesium concentrations are normal, some heart failure patients have low magnesium levels in their heart tissue,[4] apparently because the diseased myocardium has an impaired capacity to take up magnesium against a concentration gradient. In my experience and according to uncontrolled trials, intravenous or intramuscular administration of magnesium often produces substantial clinical improvement in patients with heart failure. Oral magnesium supplementation is much less effective, presumably because oral administration does not raise serum magnesium levels enough to allow the diseased myocardium to extract magnesium from the serum.

Liu M, et al. Magnesium deficiency causes a reversible metabolic, diastolic cardiomyopathy. *J Am Heart Assoc*. 2021;10:e020205.

continued on page 17 ➤

Exciting Study Results for Post Covid Symptoms

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A single but promising case study revealed that in just two 5-minute anterior lung treatments with Firefly Light Therapy the patient, a 62 year old male struggling to recover from post-COVID lung symptoms, had remarkable results. Prior to treatment the patient noted 16 months of symptoms including shortness of breath, mild wheezing, and a feeling that he had to "push to breathe" and take a break after only 5 minutes of exertion.

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In my own personal COVID-19 experience I treated myself for loss of taste and smell and both returned after a series of treatments. This need is on the rise and as a fellow practitioner I'm very excited to share the possibilities with you.

Martin Bales
– Martin Bales L.Ac. DAOM

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➤ *continued from page 15*

Serious Side Effects from a Nutritional Supplement

An 81-year-old woman presented with pancytopenia (anemia, leukopenia/neutropenia, and thrombocytopenia). The serum zinc level was elevated (168 µg/dl; normal range, 60-130 µg/dl) and serum copper was very low (10 µ/L; normal range, 810-1,990 µ/L). The woman had been taking a multivitamin-multimineral (MVM) product for many years for the treatment of age-related macular degeneration. The product provided daily a relatively large amount of zinc (80 mg) and 2 mg of copper. The patient was advised to discontinue the MVM and she was started on 8 mg per day of copper. Within two weeks, white blood cell, neutrophil, and platelet counts became normal and the anemia improved markedly.

Comment: Zinc is known to inhibit copper absorption, and long-term use of large doses of zinc can cause copper deficiency. Reported manifestations of zinc-induced copper deficiency include anemia, neutropenia, and myelopathy (thrombocytopenia is uncommon). This case report did not mention the name of the MVM the patient was taking. One can assume it was PreserVision (marketed by Bausch and Lomb) or a similar product that contains the formula used in the Age-Related Eye Disease Study (i.e., the AREDS or AREDS 2 formula). PreserVision provides 80 mg per day of zinc and 2 mg of copper, which was the amount this patient was taking. Unfortunately, the copper in PreserVision is in the form of cupric oxide. Animal studies have shown that the bioavailability of orally administered cupric oxide "is not significantly different from zero,"[5] and it has been argued that cupric oxide should not be used as a copper supplement for either animals or humans. Zinc-induced copper deficiency can be prevented by supplementing with an adequate amount of copper, but a copper supplement that cannot be absorbed is likely to be ineffective.

Wahab A, et al. Zinc-induced hypocupremia and pancytopenia, from zinc supplementation to its toxicity, a case report. *J Community Hosp Intern Med Perspect*. 2021;11:843-846.

Gaby's Literature Review

Eggs and Cardiovascular Disease

A meta-analysis was conducted on 23 prospective studies, including a total of 1,415,839 participants, that examined the association between egg consumption and cardiovascular disease events. During a median follow-up period of 12.3 years, 157,324 cardiovascular disease events were documented. Compared with consumption of one egg per day or less, consumption of more than one per day was not associated with an increased risk of overall cardiovascular disease events (pooled hazard ratio = 0.99; 95% confidence interval [CI], 0.93-1.06). Higher egg consumption (more than 1 per day) was associated with a significantly decreased risk of coronary artery disease (pooled hazard ratio = 0.89; 95% CI, 0.86-0.93; $p < 0.001$), compared with consumption of one egg per day or less.

continued on page 19 ➤

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➤ *continued from page 17*

Comment: It has been suggested for many years that eating eggs can cause heart disease, because of the large amount of cholesterol present in egg yolks. In the present study, higher consumption of eggs was not associated with an increased risk of overall cardiovascular disease events, and was associated with a significant decrease in the incidence of coronary artery disease. These results conflict with a previous observational study, in which higher egg intake was associated with a modest but statistically significant increase in cardiovascular disease risk.[6]

It is difficult to draw conclusions from these conflicting studies, particularly since observational studies cannot prove causation. As I have noted before, the effect of egg consumption on cardiovascular disease risk might depend in large part on how the eggs are cooked. Cholesterol is an unstable molecule, and the cholesterol in food is susceptible to spontaneous oxidation, even in room air. Research in animals has shown that feeding pure cholesterol does not cause atherosclerosis, whereas oxidized cholesterol is highly atherogenic. Breaking the yolk of an egg during cooking exposes the cholesterol to high temperatures and oxygen (room air), which might accelerate the formation of cholesterol oxides. In contrast, the cholesterol in boiled or poached eggs, or fried eggs with an intact yolk, would be largely shielded from room air and might therefore be less susceptible to oxidation and less atherogenic. Future studies should examine whether the association between egg consumption and cardiovascular disease differs according to how the eggs are cooked.

Krittanawong C, et al. Association between egg consumption and risk of cardiovascular outcomes: a systematic review and meta-analysis. *Am J Med*. 2021;134:76-83.e2.

Oxygen Therapy for Acute Myocardial Infarction

Patients (n = 6,629) with a suspected acute myocardial infarction (MI), with oxygen saturation of 90% or higher were randomly assigned to receive supplemental oxygen (6 liters per minute for 6 to 12 hours, delivered through an open face mask) or room air. If it was deemed clinically necessary, particularly in cases of hypoxemia (oxygen saturation < 90%) caused by circulatory or respiratory failure, supplemental oxygen outside the protocol was provided. The primary endpoint of death from any cause within one year after randomization occurred in 5.0% of patients assigned to oxygen therapy and 5.1% of patients assigned to room air (p = 0.80). Re-hospitalization within one year for MI occurred in 3.8% of patients assigned to oxygen and 3.3% of those assigned to room air (p = 0.33). In the subgroup of patients with a confirmed MI, oxygen therapy had no significant effect on the composite endpoint of all-cause mortality, re-hospitalization for MI, or heart failure during long-term follow-up.

Comment: For more than a century, supplemental oxygen was used routinely in the treatment of suspected acute MI, and this treatment has been recommended in clinical guidelines (based on expert opinion). The rationale for using supplemental oxygen was to increase the oxygen supply to the ischemic myocardium and thereby limit infarct size and subsequent complications. However, above-normal oxygen concentrations in the blood can cause coronary vasoconstriction and increase the production of oxygen-derived free radicals, potentially contributing to reperfusion injury. A Cochrane review from 2016 did not show any evidence supporting the routine use of oxygen in patients with acute MI. Based on the results of the present study, clinical guidelines no longer recommend routine oxygen therapy in patients with acute MI who have normal oxygen saturation.

This is one of many examples of treatments that were considered "standard of care" in mainstream medicine, but ultimately turned out to be ineffective. Because of its own weaknesses, mainstream medicine is not in a position to criticize "alternative" medicine as being non-evidence based.

Alfredsson J, et al. Randomized comparison of early supplemental oxygen versus ambient air in patients with confirmed myocardial infarction: outcomes from DETO2X-AMI Sex-related. *Am Heart J*. 2021;237:13–24.

Hofmann R, et al. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med*. 2017;377:1240-1249.

Gaby's Literature Review

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4. Frustaci A, et al. Myocardial magnesium content, histology, and antiarrhythmic response to magnesium infusion. Lancet 1987;2:1019.
5. Baker DH. Cupric oxide should not be used as a copper supplement for either animals or humans. *J Nutr*. 1999;129:2278-2279.
6. Zhong VW, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. *JAMA*. 2019;321:1081-1095.

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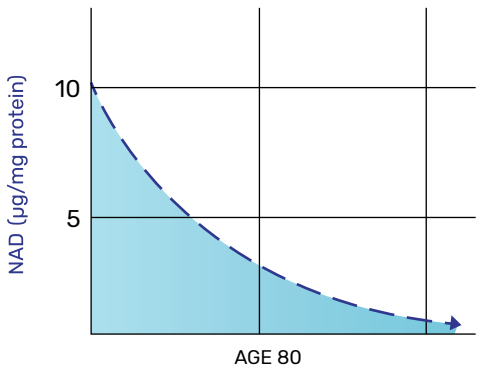

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Novel Ways to Support Cardiac Energetics

by Chris D. Meletis, ND

Aging is inevitable, yet we have some governance over our biological age versus our chronological age. Never is this more true than in regards to our heart health. For example, the prevalence of myocardial infarctions (heart attacks) roughly increases with mean age, but increased body mass index also plays a vital role in increased heart disease risk.[1] Other factors, many of which are under the control of patients, also impact heart health, such as exercise and diet. However, other factors are not as well recognized that play a role in the health of cardiovascular systems. In this article, I will address some of these lesser-known factors involved in heart health, particularly those often neglected when evaluating and treating patients with cardiovascular concerns.

Sleep Apnea and Heart Health

An individual can often live weeks without food, days without proper hydration, yet merely moments without air. Ensuring good oxygenation during exercise, rest, and sleep is a foundation to adequate energy production and recovery and consequently to heart health. Whether an individual seeks peak exercise performance goals or generalized wellness, quantifying sufficient pulmonary function and competency is of paramount importance.

Furthermore, simple pulse oximetry, spirometry, and home sleep apnea testing can save countless lives from cardiac events. There is a strong connection between obstructive sleep apnea, high blood pressure, and other cardiovascular problems. Organic acid profile (OAP) testing can detect the presence of sleep apnea by measuring analytes that may point to the presence of hypoxia, including lactate and pyruvate-lactate ratios, succinate, fumarate, malate, methylmalonate, and vanilmandelate.

Yet, despite the heart's need for oxygen, screening for sleep apnea often escapes even the savviest functional medicine provider. Functional medicine providers can suspect the presence of apnea by examining a patient's history. For example, does it include orthodontic work, mouth-breathing during early childhood, asthma, tongue-to-jaw ratio, soft and hard palate anatomy, and much more? It's also important to remember that not all patients with sleep apnea are obese or overweight.

The reality is that compromised energy production by myocardial tissue is a critical contributor to most forms of cardiac disease. An organic acid profile test can determine if this energy production by myocardial tissue is compromised.

Hydration and Heart Health

One factor not often considered in cardiovascular health is drinking plenty of water. Drinking less than ideal amounts of water or liquid or becoming dehydrated through exercise, heat stress, or diuretic use, known as hypohydration, has long been known to weaken mental and physical performance, but recent evidence has emerged that indicates low liquid intake may also harm the cardiovascular system.[2] Evidence suggests that the ideal amount of water intake may equal about a half-gallon within 24 hours, although this can vary from person to person.[3] Observational studies have associated habitual low water intake with an increased risk of adverse cardiovascular events.[2]

6 Ways to Improve Cardiac Energetics

Test for Sleep Apnea

Drink Enough Water

Support Mental Health

Test for Food Sensitivities (Linked to Circulatory System Inflammation)

Order an organic acid profile

Support healthy levels of NAD^+ (Levels Decrease with Aging and During Stress)

Hypohydration and cardiovascular disease are linked to impaired vascular function and blood pressure regulation.[2] Hypohydration may lead to reduced endothelial function, increased sympathetic nervous system activity, and a worsening of orthostatic tolerance,[2] the displacement of blood into appropriate vessels when arising from a lying to standing position. There's an indication that drinking water at night can reduce the nocturnal rise in blood viscosity and discourage a morning occurrence of cerebral infarction.[4]

The Heart Is Integrated with Other Bodily Systems

The human heart is an amazing organ. It pumps on average 103,680 times a day, with a sustained pulse of 72 beats per minute throughout a 24-hour period of time. The heart is perfusing the trillions of cells that comprise the human frame via approximately 60,000 miles of blood vessels. This process requires monumental quantities of ATP to sustain this level of repetitive contractility. Yet we must realize the heart is more than a mechanical wonder – its complexity and

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intricacies with other organs are highly integrated.

Indeed, a healthy gastrointestinal tract is essential for the assimilation of the biochemical substrates and nutritional co-factors to sustain this energetic demand of the heart. In turn, a healthy mind is critical as well to control deleterious cardiac impacts such as imbalanced sympathetic/parasympathetic pathways.

Happiness Is Linked to Heart Health

There is a definite link between cardiac health and mental health. Depression is a risk factor for the development of cardiovascular disease and points to a worse outcome in heart patients.[5]

Our ability to process and mindfully mitigate the impact of exogenous stressors that can burden the cardiovascular system depends on one's mindset and thoughts. In a world of stress, sorrow, and sadness, guarding one's heart literally and figuratively serves as a prime directive for longevity and happiness. As Emily Dickinson once said, "If I can stop one heart from breaking, I shall not live in vain." As documented in the scientific literature, there is a risk of dying of a broken heart. Takotsubo cardiomyopathy (broken heart syndrome) presents with the weakening of the left ventricle arising from severe emotional or physical stress.[6] Our mental health is therefore critical to our cardiovascular health.

Food Sensitivities and the Cardiac Inflammatory Response

It's often underrecognized the role that diet plays in our happiness. Yet, our mental health is linked to the food we eat and if the food we eat is sabotaging our mental health, then our cardiovascular system will suffer. Often, in regards to cardiac health, we only think about eating too much fat or sugar. But what about food sensitivities?

A 2018 article in the journal *Nutrients* discusses the role of IgG food reactivity and depression.[7] An inflamed brain impacts our ability to process life events and disrupts neurotransmitter production, sympathetic tone, and inflammation of the circulatory vasculature.[7] Exploring the contribution of food sensitivity and allergies relative to cardiac risk is paramount not only from a mental health impact but also the role of shifts in the complement pathway and innate immunity on pro-inflammatory status. Inflammation is a major contributor to heart disease[8] and anything that puts our bodies in a state of inflammation – including food sensitivities – can harm the vascular system.

Furthermore, patients who tested positive for food intolerances to fructose, sugar cane, and sugar beet had an increased incidence of insulin resistance,[9] a condition that is an important component of metabolic syndrome, which is associated with an increased risk of heart disease. A gene that promotes insulin resistance was common in these sugar-intolerant subjects.[9]

Ensuring that the foods patients eat are not causing an inflammatory response that can harm the cardiovascular system is critical to promoting vascular health. Testing patients for food sensitivities, food allergies, and gluten reactivity is essential to empower them to eat right for their unique biochemistry and immunology to promote cardiovascular and whole-body health.

Is Your Heart Getting Enough Energy?

Without continuous energy production, it is estimated that the cardiac muscles will run out of ATP in 2 to 10 seconds.[10] So, how can we measure cardiac energy metabolism? In clinical practice, employing an organic acid profile (OAP), a simple urine test, can offer significant clinical insights for those seeking to gain perspective into cardiac energy metabolism, including fatty acids, glucose, lactate, ketones (β-hydroxybutyrate), pyruvate, and amino acid utilization.[10]

Quantifying the metabolic energy pathways that fuel the heart and other life-sustaining functions throughout the body would seem to embody the very foundation of functional medicine testing. Any and all tissues within the body – including the heart – can only manifest their full genetic potential with optimal energy production and reserves. This very point leads me as a clinician to perform OAP testing on a variety of patients with a wide array of presenting maladies.

The adult heart harnesses energy production via mitochondrial oxidative phosphorylation (95%) and glycolysis (5%). Forty to sixty percent of mitochondrial ATP production is generated from the oxidation of fatty acids, with the remainder arising from the oxidation of pyruvate from glucose and lactate, ketone bodies, and amino acids.[10] Among the numerous organic acid profile analytes that offer insights relative to cardiac energetics include beta-hydroxybutyrate, adipate, suberate, ethylmalonate, methylsuccinate, succinate, alpha-ketoisocaproate, alpha-ketoisovalerate, alpha-keto-beta-methylvalerate, and methylmalonate. Analyzing each of these analytes on an organic acid profile can indicate whether the heart is getting enough energy. The levels and ratios will vary depending on each analyte, related analyte, and dietary habits.

All of the analytes of an organic acid profile test must be looked at through a clinical lens of diet, lifestyle, exercise, and other individual factors. If levels of analytes are high or low relative to the classical bell-shaped curve on these analytes on an organic acid profile test, there is either an under-fueling via substrate in the case of low levels or insufficient metabolic processing of organic acid analytes.

Diet and some other factors can affect some of these analytes. For example, a keto diet or high-fat diet or diabetes can alter the analyte beta-hydroxybutyrate. In the case of other analytes such as adipate, suberate, and other fatty acid analytes, they can be shifted due to excess fueling of a pathway or insufficient co-factors to allow for proper metabolism, and in the case of this discussion, the fueling of the citric acid cycle or electron transport chain.

Furthermore, analytes can be abnormal either due to overt mitochondriopathy or subclinical mitochondrial dysregulation, which will directly or indirectly place sufficient cardiac energetics in peril.

Specific analytes may also potentially identify hypoxia. The organic acid profile analytes that may point to the presence of hypoxia include the following:

- Lactate and pyruvate-lactate ratio
- Succinate
- Fumarate
- Malate
- Methylmalonate
- Vanilmandelate (a metabolite of norepinephrine)

Fueling the Heart for Optimal Performance

I have developed a deep appreciation for the role of nicotinamide adenine dinucleotide (NAD^+) in various aspects of health, including heart health. NAD^+ is an essential coenzyme involved in multiple metabolic pathways. More than 500 enzymes are created, sustained, and uniquely maintained by NAD^+ and are therefore NAD^+ dependent. Boosting NAD^+ levels is an effective way to treat a wide variety of pathophysiological conditions. I have found that the best way to enhance levels of NAD+ is to supplement with nicotinamide riboside (NR), one of the most studied NAD^+ precursors. Mounting scientific evidence from animal and human studies has validated NR's health benefits in several cardiovascular, neurodegenerative, and metabolic disorders.[11]

Functional medicine providers must not become myopic and focus on just one condition or organ system. Instead, it is the entirety of patients that is important. If a nutrient can support biochemistry, healthy aging, and cellular performance in all the trillions of cells in the human body, is that not the perfect fit? Such is the case with NR. I tell my patients it's like the saying, "A rising tide lifts all boats." So, too, NR improves all aspects of health.

Nevertheless, having acknowledged the importance of NR's role in the body as a whole, we will zoom in on its role in cardiovascular health and related conditions. Mitochondrial dysfunction disrupts NAD^+ homeostasis, which leads to the development of cardiac hypertrophy and heart failure.[11]

NAD exists in its oxidized form (NAD^+) and its reduced form (NADH). The NAD^+/NADH ratio is important as this is what dictates how well the cell can make adenosine triphosphate (ATP), the fuel our cells use to produce energy. The heart has a high energy demand and requires the ongoing production of large amounts of ATP.[10] In heart failure, the NAD^+/NADH ratio shifts,[12] which affects cardiac vulnerability to stress.[11] Supplementation with NR normalizes the NAD^+/NADH ratio and protects the heart from adverse cardiac remodeling while also triggering antioxidant gene expression.[13] By improving NAD^+ homeostasis, NR can stop the decline in cardiac function and therefore protect against heart failure.[11]

There is an association between cardiovascular problems, and inflammation, and NR may have a role to play in reducing this inflammatory response. In humans with stage D heart failure, NR supplementation protected the mitochondria of peripheral blood mononucleated cells, leading to a lower inflammatory response.[14] Another human study in 12 aged men found that NR lowered levels of circulating inflammatory cytokines and exhibited anti-inflammatory effects.[15]

Animal research indicates that increasing NAD^+ levels also improve metabolic disorders linked to cardiovascular diseases such as type-2 diabetes and metabolic syndrome.[11,16] Furthermore, increasing NAD^+ levels is important in non-alcoholic fatty liver disease (NAFLD),[11] a condition associated with increased cardiomyopathy, atherosclerosis, and arrhythmias.[17]

Conclusion

There are often several factors that are neglected when evaluating the heart health of patients. I tell my patients in regard to the heart, "There is no single organ that is more tangibly physical and yet metaphysical at the very same moment." Ignoring this fact is why mental health aspects of cardiovascular problems are often under appreciated.

Other neglected factors include determining if a patient has sleep apnea, proper hydration, the role of food sensitivities in inflammation of the circulatory vasculature, and the use of an organic acid profile test to evaluate whether the heart is getting enough energy. Finally, increasing levels of NAD^+ through supplementation with nicotinamide riboside is critical for cardiovascular health and cardiac energy metabolism.

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The Third Line of Defense for Cardioprotection: Hormetins, Sirtuins, and Sestrins

by Fraser Smith

Cardiovascular disease (CVD) is the number one cause of mortality in the United States,[1] and globally. Although substantial resources have been devoted to reducing the impact of CVD, from primary prevention to intensive stating therapy, it remains a major problem. Looking under the surface of aggregated data about LDL levels and mortality, which does shift slightly with medical therapy, it is simple enough to see a number of driving factors of CVD that are on the rise.

In a natural medicine, whole health approach, we want to maximize the body's adaptive responses, at the same time that we work with the patient to reduce the factors that disturb health. That often means examining the patient's mode of living and identifying what determining factors of health are not addressed. Or it can mean active avoidance of harms such as environmental toxins or food additives.

One of the exciting aspects of working in the natural medicine field these days is that the mechanisms of how the body restores balance are becoming more clearly mapped out. For example small doses of substances, including some that are known to be toxins at higher doses can turn on pro-survival responses. An area of pharmacology known as hormesis[2,3] has grown substantially in the size of its research body in the last 25 years. The roots of hormesis, a term which is from the Greek word "to excite" stretch back centuries. The idea of using very small amounts of something that can be harmful in large amounts, to stimulate healing, might seem like a paradox. Paracelsus alluded to this when he wrote that the dose determines the poisonous *or* the medicinal effect. In the early 20th century this concept was expressed by the Ardnt-Schultz principle – that small doses stimulate, and large doses inhibit. For a time, this nonlinear dose-response model was on its way to becoming the dominant paradigm in pharmacologic research. The contemporary competing paradigm to the "biphasic" responses implied by Ardnt-Schultz, was a paradigm that was championed by some of the leading British pharmacologists of the day. It focused on the linear dose response curve with clearly demarcated thresholds between no observed effect and the beginning of possible adverse effects. It's clear which model triumphed.[4] And for 100 years, only a linear model of dose-response curves in pharmacology that, while very productive for predicting drug potency and efficacy, more or less relegated the body's inherent defenses and responses to a relatively unimportant "X Factor."

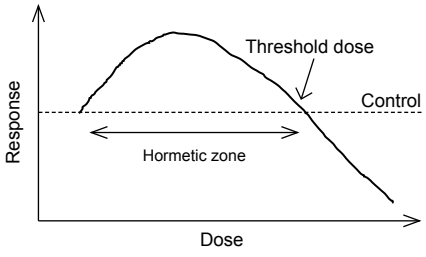
Hormesis, An Exciting Topic

In the 1990s, a brilliant pharmacologist, Dr Edward Calabrese, started to create bioassay methods that could much more accurately determine what responses were happening at very low doses, particularly those doses between 0 and what is typically thought of as the classic pharmacologic dose where both drug effects and adverse effects are presumed to begin. In this model, which Calabrese continued to use the term "hormesis" for, there were different types of biological responses for many drugs, or plant extracts, and two different dosing zones: the very low dose and the classic higher dose. Calabrese not surprisingly encountered skepticism in his initial attempts to publish his work and recruit other pharmacologists to pursue this research, yet he persisted. Eventually he had his early research pushed in respected peer reviewed pharmacology journals. Through dialogue with likeminded researchers and critics, he not only refined his research methodology but helped to bring hormesis research into a much higher state of acceptance and productivity. Now many hundreds of publications on hormesis have been made and thousands of bioassays conducted.

Calabrese defines hormesis as a stimulation in the low dose zone.[2,3] That stimulation effect, when measured, is of a reasonably modest magnitude – about 150% above control. It typically happens midway between 0 dose and what is considered the usual pharmacologic dose of a drug. In many cases, that stimulatory effect can bring out health-creating and pro-survival responses at the cellular and genetic level. These responses are highly conserved among different organisms and could be described as a biologically fundamental response to stressors on the organism. In a pharmacologic sense, the dose response curve for hormetic substances is shaped like a U or a J instead of a straight line.

This is of importance in natural medicine because what we often do involves using sub-toxic doses and often low doses of plant-derived or food-derived molecules to turn on adaptive

responses in the body.[5] One example is phytonutrients from the Cruciferae family of vegetables. Sulforaphane, which can be found in broccoli, for example, switches on defenses in the cell that normally serve to shield the



From Wikimedia commons

cell from oxidative stress. This sulfur-containing compound from broccoli (and other Cruciferae family vegetables) finds its way to the cytoplasm. There it encounters a complex called NRF 2 (Nuclear factor-erythroid factor 2-related factor 2). This protein is bound to another protein called KEAP1 (Kelch-like ECH-associated protein 1).[6] When oxidative stress rises in the cell, NRF2 dissociates from KEAP1 and is free to translocate to the nucleus. Once there, it binds to the antioxidant response element (ARE). This control center, once activated, allows for transcription of downstream suites of genes that are responsible for antioxidant enzymes, such as glutathione synthase.

When the ARE is activated, this in turn switches on a suite of genes responsible for expressing what we call Phase Two enzymes. For example, glutathione synthase, is upregulated. Although sulphoraphane at dietary levels is not harmful, it is perceived by the cell "as if" oxidative stress has increased, and in turn, a thermostat of sorts detects this and turns on the production of more antioxidant/detoxification proteins.

It turns out that many substances can act hormetically. They act through different pathways and induce expression of different responses and gene expression. All living organisms seem to respond to a low dose challenge of some chemicals or physical stressors, by making a modest "overcompensation response" which ultimately is to the organism's benefit. In this case, the aphorism stated by both the philosopher Frederick Nietzsche and the singer Kelly Clarkson holds true – "what doesn't kill me makes me stronger," with the caveat that the stimulus should not be overly taxing on the organism.

Interestingly, NRF2 overactivation can be deleterious in heart disease with regards to heart remodeling.[7] So, a deficiency of these plant-derived compounds might lose us an opportunity to increase our defenses. Too many of these compounds may have downsides. The low dose (which is what we would get from diet) is probably best. This is a reminder that when supplementing, more is not always better.

Hormesis is stimulation of pro-survival responses at the cellular level, caused by very low doses.

What hormetic responses could improve cardiovascular health and reduce the risk of disease? Exercise has hormetic effects on the heart. This is of a form of pre-conditioning. The proteins that allow a myocardial cell to better tolerate ischemic stresses will increase due to exercise. Exercise, of course, creates collateral circulation in the heart as the muscle gets more and more conditioned. It also can help the heart muscle become stronger. But the hormetic aspect of exercise is the way in which exercise can make oxygen demands that the heart struggles to meet. The heart is an enormous consumer of energy, ripping through it's own supply of ATP every few seconds. This muscle must perform a tremendous amount of beta-oxidation in the mitochondria. The challenging dose of exercise prepare mitochondria for this task and helps us express genes that allow us to tolerate mild ischemia.

Sestrins and Response to Stress

The benefits of exercise also work with a class of proteins known as sestrins.[8] Sestrin was originally discovered in research looking for targets for the tumor suppressor p53. Further research showed that DNA damage elicited more sestrin production. Later, it was shown that sestrin expression was strongly induced upon DNA damage. As mentioned above exercise can mildly create ischemia. But those with coronary artery disease and myocardial disease, or angina pectoris, experience ischemia frequently. Sestrin expression, particularly Sestrin2, is increased after cardiac ischemia, coinciding with activation of adenosine 5' monophosphate-activated protein kinase (AMPK) – an important signal that allows for more energy production when the cell needs it most. Loss of Sestrin2 can reduce the needed ischemic activation of AMPK, and this makes a heart more vulnerable to damage from bouts of ischemia. These episodes can come from overwork in a heart patient, or simply the partial blockage due to stenosis and platelet aggregation, even if a total infarct doesn't develop.

Sestrin2 expression in the heart declines upon aging in mice, and its role in the activation of protective proteins is well understood. What about human studies involving those with heart disease? Sestrin levels are higher in those with heart disease who are going through a very disease-active state. Although much still remains to be learned about sestrins, it appears that these higher levels in those with heart disease are a response, not the cause, of the disease. As strain on the heart increases, so does sestrin production. When the heart cells are under attack from oxidative stress, or suffering from ischemia, sestrin production is an attempt to increase the survivability of those beleaguered cells.

This defense mechanism could be useful for long-term health maintenance. Sestrins suppress the mechanistic target of rapamycin complex 1 (mTORC1) activity during feeding; and conversely, they sensitize insulin action via activation of the mTORC2 signaling. That kind of sensitization is helpful because dysfunction of the insulin receptor and insulin resistance can lead to metabolic syndrome and higher risk for cardiovascular disease. Caloric restriction and exercise are ways to increase sestrin levels.

Sirtuins and the Power of NO

Sirtuins are proteins that are integral to the intima of the artery, particularly the endothelium. This single cell layer governs the ingress and egress of substances into the artery way, most notably LDL particles.[9] The endothelium produces nitric oxide, a substance critical

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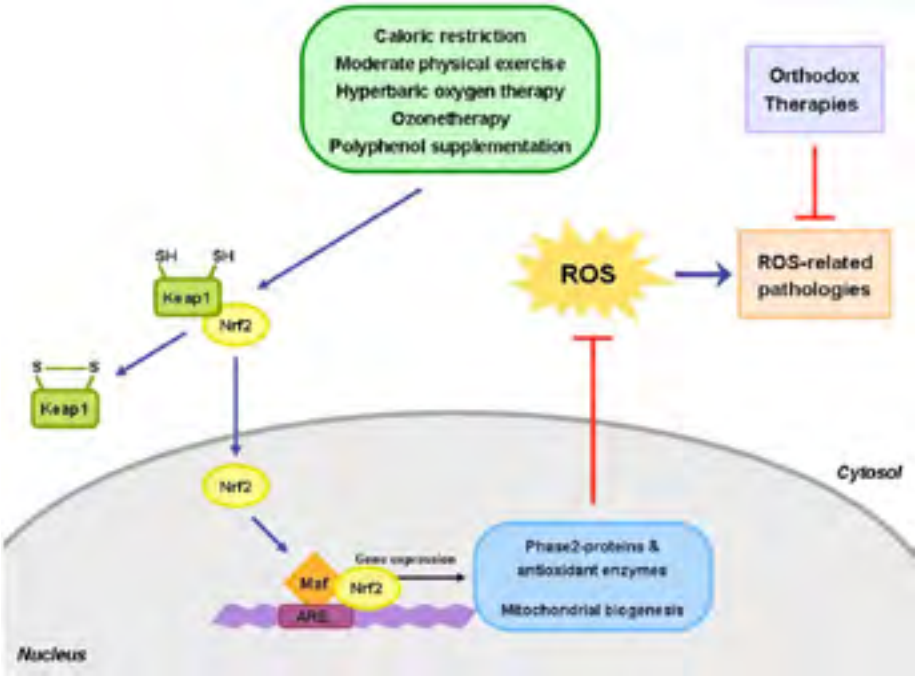
for vasodilation. Nitric oxide also reduces inflammation local to the artery, and this leads to less oxidation of LDL particles, and less inflammation. Without adequate nitric oxide, there is vasoconstriction, and increased inflammation, including the damage of oxidized LDL.

expression of endothelial NO synthase (eNOS), stimulating eNOS enzymatic activity, and preventing eNOS uncoupling. At the same time, resveratrol inhibits the synthesis of endothelin-1 and reduces oxidative stress in both endothelial cells and smooth muscle cells.

Some of the hallmarks of a heart that is reacting pathologically to stressors such as cholesterol deposition and



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Resveratrol is a polyphenol of the stilbenoid group, possessing two phenol rings linked to each other by an ethylene bridge. It is found in many plant foods, and red wine (a component of many Mediterranean diet plans) has a lot of it.[10,11] Resveratrol is a well-known dietary supplement for antioxidant and cancer prevention uses. Resveratrol causes more sirtuin activation and therefore, more production of nitric oxide (NO) in endothelial cells by upregulating the oxidative stress include smooth muscle cell proliferation, vascular remodeling, and arterial stiffness. This can be, to an extent, ameliorated by resveratrol as well. "In addition, resveratrol also modulates immune cell function, inhibition of immune cell infiltration into the vascular wall, and improves the function of perivascular adipose tissue. All these mechanisms contribute to the protective effects of resveratrol on vascular function and blood pressure in vivo. Sirtuin 1, AMP-activated protein kinase, and estrogen receptors represent the major molecules mediating the vascular effects of resveratrol."[12]

As we learn the molecular language of the healing power of nature, it sheds light on why some of the treatments and substances we know help patients actually work. It also helps us to consider new ways to use existing treatments. And it opens the door to add to our treatment inventory. The science of how to increase human resilience in ways that are financially and physiological low cost is very exciting.

Primary prevention, such as smoking cessation is of course important for prevent cardiovascular disease. Secondary prevention that works to repair or change something in physiology – such as lowering LDL – can bring benefits. The third line of defense is the activation of pro-survival genes. This can be done with substances that are hormetic in nature, or at the very least can in a linear dose dependent fashion raise the levels of sestrins, surtuins, NRF 2 and many other adaptive proteins in our body. For the time being, safely conducted caloric restriction under medical supervision, consumption of pro-antioxidants such as Cruciferae family vegetables (and curcuminoids from turmeric – *Curcuma longa*), exercise to tolerance, and resveratrol from foods or from supplements, are a good start to increasing resilience.

Fraser Smith, ND, is a naturopathic doctor who trained at Canadian College of Naturopathic Medicine in Toronto, Ontario completing a residency with Dr. Paul Saunders. In 2006 he helped National University of Health Sciences in Lombard, Illinois launch their new Doctor of Naturopathic Medicine degree program, which is now a fully-accredited program. He is currently the chief academic officer for the ND program serving as Assistant Dean for Naturopathic Medicine in NUHS' College of Professionals Studies. He is an associate professor, and author of the textbook *Introduction to Principles and Practices of Naturopathic Medicine* and several nutritionally focused books for the public. He teaches botanical medicine at NUHS and is licensed as a naturopathic physician in Vermont. He is currently president of the Association of Accredited Naturopathic Medical Colleges.

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Nutraceutical Approaches to Diabetes Management

by Meagan Purdy, ND

Recently, I've noticed a trend in my clinical practice. I'm seeing far more instances of blood sugar dysregulation on screening labs, even in patients I wouldn't otherwise suspect of metabolic issues. Many patients have joked that it's due to quarantine weight or lifestyle changes that they know are less than ideal. Cultural changes that have taken place over the past two years have no doubt brought about changes to our overall health. Many people have opted for less nutritious foods and decreased their activity levels during times of quarantine, which can disrupt metabolic health.

Herbs and nutraceuticals may offer better results than diet and exercise alone.

Markers of metabolic health and signs of early metabolic syndrome should be at the forefront of any integrative practitioner's mind right now. Not only is healthy glucose metabolism a significant predictor of overall health and mortality, but we know that COVID-19 infections may have more devastating effects in those with elevated blood glucose levels.[1] With that knowledge, it's almost more important now to intervene when a patient presents with markers indicating early or advanced glycemic dysregulation. Many of these patients may be resistant to medications or present in the early, pre-diabetic stage, yet in desperate need of intervention beyond just diet and lifestyle management for effective results. In these cases, it's essential to look to alternative options, such as herbs and nutraceuticals, that may offer better results than diet and exercise alone.[2]

Chromium

Chromium is a trace mineral that's often overlooked but of utmost importance for proper blood sugar regulation. Low chromium levels are associated with impaired glucose and insulin function, and subsequently, type II diabetes.[3] Physicians first noticed the importance of chromium for glucose tolerance with patients receiving long-term total parenteral nutrition (TPN). TPN patients developed symptoms of diabetes, yet their symptoms would not respond to insulin administration. However, they improved when supplemented with chromium, suggesting that the chromium deficiency may be a source for symptoms of glucose dysregulation, which spurred a much-needed area of study for diabetic patients.[2]

More recent research has shed light on chromium's mechanisms as an integral piece of blood sugar regulation. Chromium increases insulin receptor numbers and affinity, allowing for increased insulin binding to cells.[4] Chromium also activates intracellular signaling pathways involved in glucose transporter 4 (GLUT4) translocation, increasing glucose transport and enhancing insulin sensitivity.[5] Long-term chromium supplementation leads to improved glucose tolerance because it potentiates insulin in the cell.

Chromium has also been shown to have acute effects clinically, with multiple studies documenting improved postprandial glucose levels when supplemental chromium was ingested with the meal.[3] In clinical trials, it appears that levels above 200 mcg daily have been shown effective for improving glucose profiles and that chromium picolinate or polynicotinate are the most efficacious forms.[2]

Biotin

Biotin can act as an important adjunct vitamin to chromium in blood sugar regulation. It has been shown to increase the efficacy of chromium when used to address blood glucose levels.[3] Pairing biotin with chromium in clinical trials has resulted in improved HbA1c, fasting glucose levels, and decreases in current prescription medications for diabetic patients.[3] These results may be due to biotin's essential role in carbohydrate metabolism.[3]

Biotin functions as a gene modulator, as it alters gene expression. Proposed mechanisms for biotin's hypoglycemic qualities include upregulation of hepatic and pancreatic glucokinase expression.[6] Glucokinase is a critical enzyme that regulates glucose uptake by the liver and regulates insulin secretion in response to changes in blood glucose concentration. Biotin upregulates insulin production through these mechanisms in the presence of elevated glucose.[7]

Biotin deficiencies have been linked to impaired glucose tolerance tests and decreased glucose utilization, while supplemental biotin, particularly when paired with chromium, is linked to better glucose regulation. One RCT involving 447 subjects with poorly controlled type 2 diabetes were given 600 mcg of chromium picolinate paired with 2 mg of biotin or a placebo. Changes in HbA1c and fasting glucose levels were

significantly different in the treatment group vs. placebo.[7] Multiple studies have revealed similar results, suggesting that biotin and chromium can be used in concert to enhance their properties of glucose regulation.[8]

***Fraxinus excelsior* L.**
(European Ash, Ash)

Many American physicians might not readily recognize this botanical. Still, it has a long history of traditional use as a hypoglycemic agent, particularly in North Africa, where the tree that bears the seed is native. Locals know of the seeds as a health-promoting food and consume them regularly in the diet.[9] While the exact mechanisms of European Ash remain unknown, some researchers suggest that the glycoside flavonoids present in it partially inhibit intestinal glucose uptake.[10]

In clinical studies, it has performed quite remarkably. One study looked at the effects of a liquid extract of *F. excelsior* L. seed on glucose-induced postprandial hyperglycemia in healthy, non-diabetic volunteers. The glycemic curve for the treatment group showed a gradual improvement over the first two hours following glucose ingestion compared to the placebo group.[9] Another randomized, crossover, double-blind, placebo-controlled study utilized Glucevia®, a branded standardized extract of *Fraxinus excelsior*, to observe its effects on insulin sensitivity and glycemic homeostasis for a group of overweight individuals aged 50-80 years old, a cohort with a high risk of diabetes development. Researchers observed that Glucevia® administration resulted in a remarkable reduction (28%) in glucose area under the curve (AUC) values compared to the placebo group.[11] There were no changes to insulin levels in each of the studies mentioned above, suggesting that Ash inhibits glucose uptake without impacting insulin sensitivity. Likely due to this mechanism of action, Ash has a very high safety profile while effectively moderating postprandial glucose levels, positioning it as both a preventative and an effective interventional agent.

Berberine

Berberine is well-known as a metabolic gem in integrative medicine. Its mechanism for lowering blood glucose rests in its ability to increase insulin receptor expression.[12] Research also suggests that berberine increases AMP-activated protein kinase activity, stimulating glucose uptake in the muscles and reducing glucose reproduction in the liver.[13] There is also some evidence that berberine increases glucagon-like-peptide-1 secretion in animal models.[14]

Berberine's multiple mechanisms of glycemic control are consistent with its results in clinical trials. One clinical trial found berberine to be comparable to metformin in individuals with newly diagnosed type 2 diabetes mellitus. The measured parameters included HbA1c, fasting blood glucose, postprandial blood glucose, and plasma triglycerides, each significantly improved in the berberine group as well as the metformin group.[15] Multiple clinical studies have repeated these results, with berberine consistently showing a reduction in both blood glucose and lipid profiles.[16] Berberine is well-worth considering as a supplemental agent for patients struggling with impaired blood glucose regulation.

Conclusion

Insulin resistance and blood sugar dysregulation can each be a dangerous and deadly process. Unfortunately, we often see this process progress rather than regress once it has begun unless interventions are made. It is well-documented that diet and lifestyle play a significant part in the onset and also the progression of diabetes and metabolic syndrome. Those interventions should always be discussed and implemented, as they are of utmost importance, particularly for the truly integrative approach. However, some patients might find these challenging and need supportive options while they are incorporating new lifestyle changes that may take time to become second nature. This is where natural interventions can really shine. When working with a patient who desires a natural approach to diabetes or blood sugar dysregulation but could use some speedy results, consider integrating one or all of these options. In doing so, you could support healthy insulin levels, postprandial glucose levels, fasting glucose levels, and a healthier HbA1c.

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On the Cover

Systematic Review – Cardiovascular Prevention with Omega-3 Fatty Acids

by Efrain Olszewer, MD

Abstract

This systematic review involves studies and meta-analyses that looked at the intake of omega-3 polyunsaturated fatty acids (PUFAs) and their role in cardiovascular prevention and CVD pathologies. We identified and analyzed the benefits of different doses. The studies use varied dosages, which is why, we believe, the studies and meta-analyses have varied, and sometimes controversial, results.

We concluded that there is an inverse relationship between consuming omega-3s and cardiovascular pathologies; the higher the dose of omega-3, the better the results seem to be.

The authors recommend more studies with adequate doses of omega-3 to establish an ideal dosage with a strong inverse relationship between omega-3 consumption and cardiovascular disease.

Understanding Omega-3s

Omega-3 polyunsaturated fats consist of carbon atoms and double bonds; the first double bond is three carbon atoms from the omega end. The omega-3 alpha-linolenic acid (ALA) has 18 carbon atoms with three double bonds. When the enzyme elongase is activated, linolenic acid incorporates two more carbon atoms for a total of 20 and is converted to EPA (eicosapentaenoic acid); and the addition of two more carbon atoms turns EPA into another omega-3, DHA (docasahexaenoic acid). EPA is also metabolized into prostaglandin E3 (PGE3), which has the following effects: anti-inflammatory, vasodilatation, platelet anti- aggregation, and anti-thrombotic.[1-2]

EPA and, to a lesser extent, DHA have been shown to affect endothelial function, dyslipidemia, hypertension, atherosclerosis, and arteriosclerosis.[4]

The nutritional pharmacological activity of linolenic acid and its derivatives EPA and DHA is based on the presence of three important molecules: protectins, resolvins, and lipoxins. These three molecules modulate the anti-inflammatory pathway of PGE3, which has a modulation-inhibitory effect over the pro-inflammatory activity of PGE2, and modulate the lipoxygenase pathway and pro-inflammatory alternative mechanism related to the buildup of the leukotrienes family.[3]

The pro-inflammatory pathway includes the formation of arachidonic acid (AA) by cytokines activated from white blood cells and visceral fats, converting linoleic acid (AA precursor) by use of the phospholipase A enzyme, stimulating the cyclooxygenase enzyme, and building up the last molecule PGE2,[4] that has the following properties: vasoconstrictor, pro-inflammatory, platelet aggregation, and pro-thrombotic.[5]

Asmaa Abdelhamid, published in 2018, a negative meta-analysis between omega-3 and cardiovascular diseases in the Cochrane Database Systemic Review. From this study, we decided to randomly choose five studies from the 70 cited to see if we found the same relationship; none of the five cited this relationship. Instead, we found the following:

- Culp, 1980: it found beneficial effects of omega-3 in cardiovascular diseases.
- Proudman, 2015: all the studies involved rheumatoid arthritis.
- Erdogan, 2007: the study was only related to atrial fibrillation.
- Welcome, 2015: only looked at non-fatty liver disease.
- Sofa, 2006: the study was on tachyarrhythmia and implantable defibrillator.

The DOT study included different studies one showing benefit in endothelial markers and controlling interleukin. Identifying this controversial use of medical studies, we decide to study only those research papers that have a direct relationship between omega-3 and cardiovascular disease.

In 2020 Abdelhamid et al added updated evidence suggesting that increasing LCn3 [long chain omega 3] slightly reduces coronary heart disease events and mortality

(previously the evidence suggested little or no effect). Our understanding of effects of LCn3 on other outcomes, and of ALA on all outcomes, has not been altered.[6]

Based on the physiological and nutria-pharmacological action of omega-3, we reviewed studies in order to see the relationship between the ingestion as nutrients and the cardiovascular risks.

Omega-3 and Cardiovascular Disease

An study published in 2020 showed that the omega-3 (n-3) fatty acids, EPA and DHA, in long-term prospective cohort studies, consistently demonstrate an association between higher intakes of fish, fatty fish, and marine n-3 fatty acids (EPA + DHA) or higher levels of EPA and DHA in the body and lower risk of developing cardiovascular disease (CVD), especially coronary heart disease (CHD) and myocardial infarction (MI), and lower cardiovascular mortality in the general population. This cardioprotective effect of EPA and DHA is most likely due to the beneficial modulation of a number of known risk factors for CVD, such as blood lipids, blood pressure, heart rate and heart rate variability, platelet aggregation, endothelial function, and inflammation.[7]

Zhang et al made a long study involving a total of 240,729 men and 180,580 women from NIH-AARP Diet and Health Study who were prospectively followed-up for 16 years. Dietary intakes were assessed using a validated NIH Diet History Questionnaire. A total of 54,230 men and 30,882 women died during 6.07 million person-years of follow-up. Higher fish and LCn-3 PUFAs intakes were significantly associated with lower total mortality ($P < 0.0001$). Comparing the highest with lowest quintiles of fish intake, men had 9% (95% confidence interval, 6-11%) lower total mortality, 10% (6-15%) lower cardiovascular disease (CVD) mortality, 6% (1-10%) lower cancer mortality, 20% (11-28%) lower respiratory disease mortality, and 37% (17-53%) lower chronic liver disease mortality; women had 8% (5-12%) lower total mortality, 10% (3-17%) lower CVD mortality, and 38% (20-52%) lower Alzheimer's disease mortality.[8]

For men whose intake of omega-3 fatty acids placed them among the highest **20%**, the risk of mortality from any cause was **11%** lower than the risk experienced by men whose intake was among the lowest **20%**. Similarly, women who were among the top **20%** of omega-3 consumers had a **10%** lower risk.

When the risk of death from specific diseases was analyzed, men who had the highest intake of omega-3s experienced a **15%** lower risk of dying from cardiovascular disease, and for women in the top group, the risk was **18%** lower. Another interesting finding was that the greater omega-3 fatty acid intake was significantly associated with a lower risk of mortality due to respiratory disease and Alzheimer's disease in men and women, and with a lower risk of chronic liver disease and cancer in men.[8]

The Netherlands Heart Foundation showed that low-dose supplementation with EPA–DHA or ALA did not significantly reduce the rate of major cardiovascular events among patients who had a myocardial infarction and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy, showing clearly that low doses of omega-3 have no influence on cardiovascular disease.[9]

Another study done at Harvard University researched the benefits of vitamin D and omega-3 in cardiovascular disease; it included 25,871 people, with mean age of 50 years, using 1 gram of omega-3 daily. Though the authors' conclusions established there was no effect on cardioprotective pathologies by either vitamin D or omega 3, the second end point was extremely relevant.

This study strongly suggests that supplementation with omega 3 is an important prevention measure in cardiovascular risk.

Upon closer examination, the results showed a reduction in heart attacks without a reduction in strokes. Specifically, the omega-3 fatty acid intervention lowered the risk of heart attack by 28% and the risk of fatal heart attack by 50% but had no benefit on stroke or cardiovascular deaths not related to heart disease. Additionally, omega-3 fatty acids reduced the rate of angioplasty procedures by 22%. In the same study African Americans had a remarkable 77% reduction in heart attacks compared to the placebo.[10]

The most compelling evidence for CV benefits of omega -3 PUFA comes from four controlled trials of nearly 40,000 participants randomized to receive eicosapentaenoic acid (EPA) with or without docosahexaenoic acid (DHA) in studies of patients in primary prevention, after myocardial infarction, and most recently, with heart failure (HF).

The evidence from retrospective epidemiologic studies and from large randomized controlled trials show the benefits of omega-3 PUFA, specifically EPA and DHA, in primary and secondary CV prevention and provide insight into potential mechanisms of these observed benefits. An important aspect was that the target EPA-DHA consumption should be at least 500 mg/day for individuals without underlying overt CV disease and at least 800 to 1,000 mg/day for individuals with known coronary heart disease and HF.[11]

Randomized controlled trials (RCTs) assessing use of long-chain omega-3 polyunsaturated fatty acids (LC-OM3), primarily eicosapentaenoic acid and/or docosahexaenoic acid, have shown mixed results. A study included fourteen RCTs (randomized controlled studies) for the primary analysis (71,899 subjects). In the long chain omega-3 (LC-OM3) arms, 1613 cardiac deaths were recorded (4.48% of subjects), compared with 1746 cardiac deaths in the control groups (4.87% of subjects). The pooled relative risk estimate showed an 8.0% (95% confidence interval 1.6%, 13.9%, $P = .015$) lower risk in the LC-OM3 arms vs controls. Subset analyses showed numerically larger effects (12.9%-29.1% lower risks, all $P < .05$) in subsets of RCTs with eicosapentaenoic acid plus docosahexaenoic acid with dosages >1 g/day. Also, larger effects were seen with patient groups with higher risks, including baseline mean or median triglycerides ≥150 mg/dL; low-density lipoprotein cholesterol ≥130 mg/dL; and statin use <40% of subjects.[12]

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Statistically significant protective effects were observed for cardiac death (RR, 0.68; 95% CI, 0.56 to 0.83), sudden death (RR, 0.67; 95% CI, 0.52 to 0.87), and myocardial infarction (RR, 0.75; 95% CI, 0.63 to 0.88) in a meta-analysis done by Yun-Tao Zhao et al.

Eight trials were identified, comprising 20,997 patients. In patients with prior myocardial infarction (MI), omega-3 fatty acids reduced relative risk (RR) of SCD (RR = 0.43; 95% CI: 0.20-0.91). In patients with angina, omega-3 fatty acids increased RR of SCD (RR = 1.39; 95% CI: 1.01-1.92). Relative risk for cardiac death and all-cause mortality were 0.71 (95% CI: 0.50-1.00) and 0.77 (95% CI: 0.58-1.01), respectively. Overall, their results supply evidence that long-term effect of high-dose omega-3 fatty acid supplementation may be beneficial for decreasing the risk of cardiac death, sudden death, and myocardial infarction among patients with a history of cardiovascular disease.[13]

Dietary supplementation with omega-3 fatty acids reduces the incidence of sudden cardiac death in patients with MI but may have adverse effects in angina patients, and this should be studied.[13]

Omega-3 and Vascular Diseases, Inflammation, and Atherosclerosis

"Vascular inflammation is a key component involved in the process of arthrosclerosis, which in turn increases the risk for cardiovascular injury. In the last 10 years, there have been many trials that looked at omega-3 fatty acids to reduce cardiovascular risk."[14] Omega-3s have decreased triglyceride levels in several studies and increased increased LDL and HDL levels, "likely because omega-3 fatty acids promote triglyceride conversion into HDL/LDL."[14]

In their review article, Sarabjeet Singh et al looked at the effects of omega-3 fatty acids DHA and EPA on triglycerides, LDL-cholesterol and HDL-cholesterol in seven clinical studies. In a second data search, Singh et al looked at vascular biomarkers and cardiovascular risk in articles that focused on high-sensitivity C-reactive protein and oxidized low-density lipoprotein.[14] Two of the more recent trials, MARINE and ANCHOR, looked at omega-3 effects on vascular inflammatory markers as well as triglycerides, LDL, and HDL.

"The results of two of these trials not only showed reduction in cardiovascular risk because of reduction in vascular inflammation and reduction in the lipid panel but also showed that one of the MARINE-derived omega-3 fatty acids is superior to the other."[14]

Although both EPA and DHA decreased triglyceride level and increased HDL-C in earlier studies, those studies also showed that DHA "has more undesirable effects on LDL." EPA does not have the same effect on LDL. "Furthermore, the MARINE and ANCHOR trials have both shown that not only does EPA improve the lipid panel but also helps to decrease the levels of the vascular inflammatory biomarkers, thus further helping to decrease cardiovascular risk."[14]

Biochemical studies have shown the PUFAS pathway's role in inflammation resolution. Omega-3 fatty acids serve as the substrate for the formation of a group of lipid mediators that mediate the resolution of inflammation. The cardiovascular inflammatory response in atherosclerosis and vascular injury is characterized by a failure in the resolution of inflammation, resulting in a chronic inflammatory response.[15]

Importantly, the resolution of cardiovascular inflammation is an active, multifactorial process that involves modulation of the immune response, direct actions on the vascular wall, as well as close interactions between macrophages and vascular smooth muscle cells. Promoting anti-atherogenic signaling through the stimulation of endogenous resolution of inflammation pathways may provide a novel therapeutic strategy in cardiovascular prevention.[15]

EPA and DHA have proven effective at inhibiting calcification in vivo.[16,17] Specifically, EPA inhibit warfarin-induced vascular calcification in rats and spontaneous vascular calcification in klotho mutant mice.[18]

Mechanically, some work trying to elucidate the mechanism of action of DHA and EPA has been carried out using calcifying vascular cells (CVCs), a subpopulation of bovine aortic medial cells that undergo spontaneous osteoblast differentiation and calcification.[15]

DHA promotes the phosphorylation of p38 mitogen-activated protein kinase (MAPK), alongside the activation of the peroxisome proliferator-activated receptor-γ (PPAR-γ). In line with these results, EPA prevents the β-catenin-induced VSMC trans-differentiation towards osteoblast-like cells through the activation of PPAR- γ.[15]

In another study the author established that there is a vast disagreement in relation to the possible beneficial effects of omega-3 polyunsaturated fatty acids (omega-3 PUFA) supplementation in patients with diabetes and cardiovascular disease.[19] The conflicting results between the various original studies and meta-analyses could be partially explained as a result of variable supplementation dosage and duration, either of which may modify the effects of omega-3 PUFA on cardio-metabolic biomarkers. Meta-analyses are limited usually by the inability to draw inferences regarding dosage, duration and the interaction of dosage and duration of omega-3 PUFA intake. Even so, almost all endpoints in the so-called "negative" meta-analyses leaned toward a trend for benefit with a near 10% reduction in cardiovascular outcomes and a borderline statistical significance. Many trials included in these meta-analyses tested an insufficient daily dose of omega-3 PUFA of less than 1000 mg. Other studies clearly indicate that, probably, the consistent cardiovascular effects of omega-3 PUFA supplements could be expected only with daily doses above 2000 mg.[20,21]

In the Diet and Reinfarction Trial, 2033 men who had recovered from MI were advised to increase fatty fish intake, to increase dietary fiber, to decrease saturated fat. This study done by MRC Epidemiology Unit, Cardiff, where subjects were given a fatty fish diet/week (~350 mg of EPA/d) had a 29% reduction in all-cause mortality over two years.[22]

In a follow-up study, the researchers looked at blood pressure in the men who were told to eat two portions of fatty fish/week or take EPA (330 mg/d) and compared that group to the men who did not receive that advice. They found that the fish group (when adjusted for age and BP at baseline) showed at difference of -0.61mm Hg at 6 months and 0.40 mm Hg at two years. The difference in diastolic BP was -0.50 mm Hg at 6 months and 0.19 mm Hg at two years.[23]

In a GISSI-Prevenzione trial, conducted between 1993-1995, 2836 men and women who had survived a recent MI (≤3 months) MI received EPA/DHA (1 g/day) for 3.5 years. Results showed 30% reduction of CV death, 20% reduction in major fatal events and 45% reduction from sudden cardiovascular death (SCD). However, no significant beneficial effect was obtained in patients with stroke or non-fatal MI. The beneficial protective effect from SCD was four times higher in patients with left ventricular systolic dysfunction.[24,25]

In the JELIS trial, between 1996-1999, 18,645 hypercholesterolemic (≥6.5 mmol/L) patients on statin therapy, with or without CHD, in Japan were given 1800 mg EPA/day. At the 5-year follow up, the EPA group had 19% reduction in major CV events and 25% reduction in LDL cholesterol.[26]

The GISSI-HF randomized, placebo-controlled trial, between 2002-2008, enrolled 6975 CHF patients (New York Heart Association class II-IV) irrespective of cause and left ventricular ejection fraction >40%. The treatment group received 1 g daily EPA/DHA. At median 3.9 years follow up, there was a 6% reduction in CV death or hospitalization.[27]

A decreased mortality rate from CHD was evidenced in a Japanese population when they consumed three or more servings of not fried seafood. Furthermore, when compared to the subjects with little or no seafood intake, the protection is better for moderate consumers of one to two servings/week.[28-30]

A strong review done in 2019 briefly describes why some studies may have shown no benefits and reviewed three very recent major clinical trials that did show CVD benefits for omega-3 fatty acids. These studies included healthy individuals, patients with diabetes, and patients with mildly elevated triglycerides taking statin drugs.[31]

They also describe possible mechanisms that explain the cardiovascular benefits of omega-3 fatty acids, define current long-chain omega-3 fatty acid intakes, and advise clinicians about what can be done in practice to first determine and then optimize the omega-3 fatty acid intake for their patients.

- Clinical trial results released in the past 12 months have demonstrated clear benefits of omega-3 fatty acid intake for cardiovascular disease risk, with significant reductions in risk of heart attacks, other major cardiovascular events, and cardiovascular disease death.
- The mixed results regarding the effects of omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on the primary and secondary prevention of cardiovascular disease from previous studies may be due in part to methodological limitations, such as using composite end points, a short intervention duration, low omega-3 fatty acid supplementation dose, and high background fish intake.
- Based on results from REDUCE-IT, the addition of 4 g/d of EPA should be considered for statin-treated patients who have cardiovascular disease or diabetes and elevated triglycerides.
- For clinical practice, evidence from the most recent clinical trials supports the recommendation to consume at least one to two servings of fish/seafood per week, with additional primary prevention benefits conferred by consuming ~1 g/d of EPA and DHA.[31]

Kathy Musa-Veloso et al reached in their study the following conclusions: "Prospective observational and intervention data from Japan, where intake of fish is very high, suggest that n-3 LCFA intakes of 900 to 1000 mg/d and greater may confer protection against non-fatal myocardial infarction. Thus, the intake of 250 mg n-3 LCFA per d may, indeed, be a minimum target to be achieved by the general population for the promotion of cardiovascular health."[32]

A meta-analysis of 13 randomized controlled trials, one of which was REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), looked at myocardial infarction, coronary heart disease (CHD) death, total CHD, total stroke, CVD death, total CVD, and major vascular events. This current updated meta-analysis incorporating data from 13 RCTs, including three recent large trials, suggests that marine omega-3 supplementation is associated with lower risk of MI, total CHD, total CVD, and death from CHD or CVD causes. Such inverse associations may be particularly evident at higher doses of marine omega-3 supplementation:

> Inverse associations for all outcomes were strengthened after including REDUCE-IT while introducing statistically significant heterogeneity. Statistically significant linear dose-response relationships were found for total CVD and major vascular events in the analyses with and without including REDUCE-IT.... Marine omega-3 supplementation lowers risk for myocardial infarction, CHD death, total CHD, CVD death, and total CVD, even after exclusion of REDUCE-IT. Risk reductions appeared to be linearly related to marine omega-3 dose.[33]

Atheroma's Instability

Tetsuya Aman et al found: "A lower serum content of ω3 PUFAs (especially of EPA and DPA) was significantly associated with lipid-rich plaques, suggesting the contribution to the incidence of acute coronary syndrome."[34]

> Patients with low EPA levels, low DPA levels, and low DHA levels had a significantly higher % lipid volume (p = 0.048, p = 0.008, and p = 0.036, respectively) and a significantly lower % fibrous volume (p = 0.035, p = 0.008, and p = 0.034, respectively) than those with high levels of these fatty acids. Even after adjustment for confounders, the presence of both low EPA and low DPA levels proved to be an independent predictor for lipid-rich plaques in any of the two categories.[34]

Results from cross-sectional studies,[35] cohort studies,[36] and RCTs[37,38] on the associations of consumption of fish or fish oil with the progression of atherosclerosis are mixed. Our

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observed HRs, which were close to 1.00 for the association between n-3 LCPUFAs and the progression of atherosclerosis, including both native disease and restenosis, support previous studies observing no or modest effects.[35,37] In contrast, Erkkila et al observed reduced progression of atherosclerosis among diabetic women with existing CAD consuming two servings of fish per week compared with women with lower intakes.[36] However, the EPA+DHA intakes in the reference group in that study were much lower than in our study, and this may be an explanation in populations with lower intakes than ours.

In a population with established and well-treated CAD and with a relatively high intake of n23 LCPUFAs, we observed no significant association between intakes of n-3 LCPUFAs or fish and risks of coronary events or mortality. Only patients with very low intakes of these fatty acids may reduce their risk of coronary events by increasing their intakes.[38]

Epidemiological and clinical evidence suggests that an increased intake of long-chain n-3 fatty acids protects against mortality from coronary artery disease.

A five-year Japanese study recruited 18,645 patients with high cholesterol (6.5 mmol/L or more) between 1996 and 1999. They were randomized into two groups: 1800 mg of EPA/day with statin (n=9326) or statin only (control, n=9319). Any major coronary event was the primary endpoint: sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting.

> In patients with a history of coronary artery disease who were given EPA treatment, major coronary events were reduced by 19% (secondary prevention subgroup: 158 [8.7%] in the EPA group *vs* 197 [10.7%] in the control group; p=0.048). In patients with no history of coronary artery disease, EPA treatment reduced major coronary events by 18%, but this finding was not significant (104 [1.4%] in the EPA group *vs* 127 [1.7%] in the control group; p=.132).
>
> EPA is a promising treatment for prevention of major coronary events, and especially non-fatal coronary events, in Japanese hypercholesterolemia patients.[39]

The results of the Omacor Carotid Endarterectomy Intervention (OCEAN) study showed that advanced atherosclerotic plaques incorporated omega-3 fatty acids when available; "and this results in lower numbers of macrophages, foam cells, and T cells, as well as the lower expression of inflammatory markers."[40] Histologically, the plaque appears to be less inflamed and more stable. This may contribute to reduced mortality in patients consuming omega-3 fatty acids, for example, in the GISSI-Prevenzione trial.

In his 2012 article, Phillip C. Calder explained:

> Eicosanoids produced from arachidonic acid have roles in inflammation. EPA also gives rise to eicosanoids and the products are usually biological weak. EPA and DHA give rise to resolvins, which are anti-inflammatory and inflammation resolving. EPA and DHA also affect production of peptide mediators of inflammation (adhesion molecules, cytokines, etc.). Thus, the fatty acid composition of human inflammatory cells influences their function; the contents of arachidonic acid, EPA and DHA aperture especially important. The anti-inflammatory effects of marine n-3polyunsaturated fatty acids (PUFAs) may contribute to their protective actions towards atherosclerosis and plaque rupture.[41]

A clinical trial published in *The Lancet* (February 8, 2003) found that omega-3 fatty acids enhanced the stability of atherosclerotic plaques. The researchers randomized 162 patients awaiting carotid endarterectomy into three groups. They received six capsules of either fish oil (1.4 grams omega-3 fatty acids), sunflower oil (3.6 grams of the omega-6 fatty acid linoleic acid), or an oil blend designed to provide the intake of the average adult diet (control) before surgery. Median treatment time was 42 days. They found:

> Atherosclerotic plaques readily incorporate n-3 PUFAs from fish-oil supplementation, inducing changes that can enhance stability of atherosclerotic plaques. By contrast, increased consumption of n-6 PUFAs does not affect carotid plaque fatty-acid composition or stability over the time course studied here. Stability of plaques could explain reductions in non-fatal and fatal cardiovascular events associated with increased n-3 PUFA intake.[42]

Omega-3 and Hypertension

Lawrence J. Appel and colleagues conducted a meta-analysis of controlled clinical trials that looked at the effect of omega-3 on blood pressure.

> In the 11 trials that enrolled normotensive individuals (n=728), ω-3 PUFA supplementation led to significant reductions of systolic BP (SBP) and diastolic BP (DBP) in two and one trials, respectively. In the six studies that enrolled untreated hypertensives (n=291), significant reductions of SBP and DBP were present in two and four trials, respectively….
>
> Doses of ω-3 PUFA tended to be high (average dose >3 g/d in 11 trials). The magnitude of BP reduction was greatest at high BP but was not significantly associated with dose of ω-3 PUFA….
>
> Our analyses indicate that diet supplementation with a relatively high dose of ω-3 PUFA, generally more than 3 g/d, can lead to clinically relevant BP reductions in individuals with untreated hypertension.[43]

In their investigation of EPA, DHA, and blood pressure, Paige E. Miller and colleagues used random-effects meta-analyses to generate weighted group mean differences and 95% confidence intervals (CIs) between the EPA+DHA group and the placebo group: "Modification of the blood pressure effects by age, gender, blood pressure, and body mass index was examined."[44]

Their meta-analyses of seventy RCTs showed that EPA+DHA provision reduced systolic blood pressure (−1.52 mm Hg; 95% confidence interval (CI) = −2.25 to −0.79) and diastolic blood

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pressure (−0.99mm Hg; 95% CI = −1.54 to −0.44) compared to control. "Overall, available evidence from RCTs indicates that provision of EPA+DHA reduces systolic blood pressure, while provision of ≥2 grams reduces diastolic blood pressure."[44]

Johanna M. Geleijnse et al conducted a meta regression analysis of 90 randomized trials (1966-March 2001) involving fish oil and blood pressure. "Intake of fish oil was high in most trials (median dose: 3.7 g/day). Fish oil reduced systolic BP by 2.1 mmHg [95% confidence interval (CI): 1.0, 3.2; P<0.01] and diastolic BP by 1.6 mmHg (95% CI: 1.0. 2.2; P<0.01)."[45]

They concluded: "High intake of fish oil may lower BP, especially in older and hypertensive subjects. The antihypertensive effect of lower doses of fish oil (< 0.5 g/day) however, remains to be established."[45]

Toshinori Hoshi et al describe a mechanism that helps explain the health-promoting effects of long-chain polyunsaturated omega-3 fatty acids. They report:

> …DHA with an EC_{50} of ~500 nM rapidly and reversibly activates BK channels composed of the pore-forming Slo1 subunit and the auxiliary subunit β1, increasing currents by up to ~20-fold. The DHA action is observed in cell-free patches and does not require voltage-sensor activation or Ca^{2+} binding but involves destabilization of the closed conformation of the ion conduction gate. DHA lowers blood pressure in anesthetized wild type but not in Slo1 knockout mice. DHA ethyl ester, contained in dietary supplements, fails to activate BK channels and antagonizes the stimulatory effect of DHA. Slo1 BK channels are thus receptors for long-chain omega-3 fatty acids, and these fatty acids – unlike their ethyl ester derivatives – activate the channels and lower blood pressure. This finding has practical implications for the use of omega-3 fatty acids as nutraceuticals for the general public and also for the critically ill receiving omega-3-enriched formulas.[46]

Omega-3 Endothelial Rigidity

Matthew P. Pace and colleagues conducted a meta-analysis with 10 trials to assess the effect of omega-3 supplementation on arterial stiffness. Four trials used pulse wave velocity (PWV), and six used arterial compliance, measured as capacitive compliance or systemic arterial compliance, as outcome measures.

> Meta-analysis revealed that n-3 was statistically significant in effectively improving both PWV (g = 0.33; 95% CI 0.12, 0.56; P<0.01) and arterial compliance (g = 0.48; 95% CI 0.24, 0.72; P<0.001). The findings of the present study reveal that supplementation with n-3 offers a scientifically supported means of reducing arterial stiffness. Reduction in arterial stiffness by n-3 may account for some of its purported cardioprotective effects.[47]

Gerasimos Siasos et al conducted a double blind, placebo-controlled cross-over study with 20 healthy smokers to see if supplementation with omega-3 polyunsaturated fatty acids had an effect on endothelial function or arterial stiffness. In the 12-week study, 2 grams/day of omega-3s resulted in significant improvement in pSm values of flow-mediated dilation (FMD; endothelial function; p<0.05), augmentation index (AIx; arterial wave reflections; p<0.001) and pulse wave velocity (PWV; aortic stiffness; p<0.01). Even though smoking caused a decrease in FMD and increases in Aix and PWV, omega-3 treatment "blunted the acute smoking-induced impairment of FMD (p<0.001), AIx (p<0.05) and PWV (p<0.05) and significantly decreased levels of TNFα (p<0.05) and IL-6 (p=0.01) and increased levels of PAI-1 (p=0.05)."[48] In conclusion, healthy smokers who took omega-3 polyunsaturated fatty acids showed improved endothelial function, more elasticity in the arteries, and less inflammation.[48]

Marcela A. Casanova et al conducted a study to compare omega-3 and ciprofibrate effects on vascular structure and function in hypertensive patients with hypertriglyceridemia: "Association between hypertriglyceridemia and cardiovascular (CV) disease is still controversial."[49] The 29 adults with high triglycerides (150-499 mg/dL) were randomly assigned to receive omega-3 fatty acids (1800 mg/day) or ciprofibrate (100 mg/day) for 12 weeks. After an eight-week washout period, the treatment was switched.

> Clinical evaluation and vascular tests were assessed at baseline and after intervention. Peripheral (131±3 to 125±3 mmHg, P<0.05) and aortic (124±3 to 118±2 mg/dL, P<0.05) systolic blood pressures were decreased by ciprofibrate in low-risk patients (CV risk<7.5%). In high-risk patients (CV risk≥7.5%), pulse wave velocity was reduced (10.4±0.4 to 9.4±0.3 m/s, P< 0.05) and flow-mediated dilation was increased (11.1±1.6 to 13.5±1.2%, P<0.05) by omega-3. In conclusion, omega-3 improved arterial stiffness and endothelial function, pointing out the beneficial effect of this therapy on vascular aging, in high-risk patients.[49]

Conclusion

Marine omega-3 fatty acids are effective in preventing cardiovascular and coronary events and cardiac deaths, especially in persons with high cardiovascular risk. In this systematic review, we found an overall decreased risk of cardiovascular event, a decreased risk of cardiac death, and a decrease of coronary events.

It seems also that there is an inverse relationship between the doses of omega-3 and the cardiovascular risk.

This study strongly suggests that supplementation with omega 3 is an important prevention measure in cardiovascular risk. "Most of the studies analyzed included persons with high cardiovascular risk."[50]

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References are available online at www.townsendletter.com.

Niacin and Hypertension

by Jacob Schor, ND

The term "early adopter" used today to describe people that start using a new technology as soon as it becomes available applies to only about 13.5% of the population. I suspect that among naturopathic doctors, the percentage is higher. Everett Rogers introduced the term back in 1962 in his book, *Diffusion of Innovations*. In describing how new ideas spread through a population, Rogers introduced a now classic graph that divides people into five categories by how they respond to innovation (Figure 1). These categories are innovators, early adopters, early majority, late majority, and laggards.

Early Adopters vs. Tenacious Laggards

My impression is that naturopathic doctors adopt new ideas in medicine and translate them into practice quicker than other professionals do often before they are proven or widely accepted. As we read papers, we ignore caveats that larger and longer clinical trials are necessary to confirm the early results seen in "this small trial." We often jump in and try to mimic whatever the experimental protocol used hoping that our patients will see similar results to those of the study participants. Since our therapies are generally safe and well tolerated, we can get away with such a 'might help, won't hurt' attitude most of the time.

The problem with being an early adopter is that we will find ourselves utilizing therapies that turn out not to be helpful and need to be abandoned. It can be hard to let go of once promising therapies, especially once patients buy into them. This is especially true because many naturopathic doctors sell supplements from their clinics and profit from those sales.

Rethinking Niacin Dosing

I'm thinking about these ideas today after reading a recent study by Zhuxian Zhang et al that examined dietary niacin intake and the risk of being later diagnosed with high blood pressure.[1]

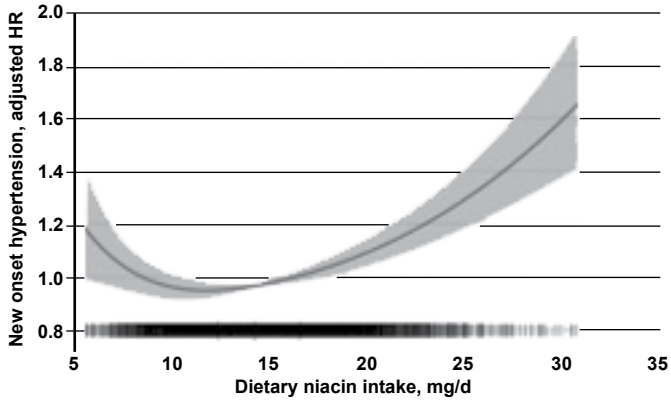
Zhang and colleagues conducted their study using data from the China Health and Nutrition Survey (CHNS), which is an ongoing multipurpose longitudinal open cohort established in 1989.

Dietary intake of niacin was calculated and compared with whether participants were eventually diagnosed with high blood pressure. Mean dietary niacin intake among participants was 14.8 mg/day. This sounds pretty good as the US Recommended Dietary Allowance (RDA) for adults is 16 mg NE for men, and 14 mg NE for women.[2]

Of the study's 12,243 participants, 4306 developed new-onset hypertension over the half dozen years of followup. The risk of this occurring was directly associated with their niacin intake. The association, however, was not a straight line, but rather a J-shaped curve dipping down to an inflection point where risk was lowest at 15.6 mg/d. The lowest risk of hypertension was found in participants consuming 14.3 to 16.7 mg/d (HR, 0.83 compared with those who consumed <12.4 mg/d). In those with niacin intakes less than 15.6 mg/day, for every 1 mg/d increase in dietary niacin, there was a 2% decrease in hypertension risk (adjusted HR, 0.98), but a 3% increase in new-onset hypertension (HR, 1.03) for participants with niacin intakes of 15.6 mg/d or greater. A graph of these results will make this easier to comprehend (Figure 2). These results suggest daily niacin intake based on risk of hypertension should ideally be between 14.3 to 16.7

Figure 1. Everett Roger's Graph

Figure 2



https://pubmed.ncbi.nlm.nih.gov/33404619/#&gid=article-figures&pid=figure-1-uid-0

mg/d. Once above 15.6 mg/day, risk increases with intake. At 30 mg/day, risk of developing hypertension was 60% higher than for those in the ideal range of 14.3 to 16.7 mg/d.

Any change in risk is clinically important when we consider how common hypertension is. Hypertension is a leading cause of disease, mortality, and disability worldwide.[3] In China, an estimated third of the adult population, approximately 300 million people, have elevated blood pressure.[4] In the United States, nearly half of adults, about 116 million, have hypertension.[5] Finding ways to prevent, reduce, or reverse risk of this disease is a relevant clinical goal. The data in this study suggest that even slight shifts in niacin consumption might improve the health of millions of people.

Niacin (also known as nicotinic acid or vitamin B3) is a precursor to nicotinamide adenine dinucleotide (NAD) and is essential for energy metabolism and redox reactions in the body.[6] Tryptophan in the body can be converted into niacin. Niacin acts as a coenzyme: more than 400 enzymes have been identified that depend on niacin to catalyze their reactions. As a result, niacin participates in a wide range of reactions that include conversion of nutrients into energy, creating cholesterol and fats, building and repairing DNA, and acting as antioxidants.

Niacin was once called the 'anti-black tongue factor' because deficiency caused this symptom in dogs.[7] In humans, niacin deficiency leads to another distinct condition called pellagra, which was first reported in Spain in 1735 by Casal and then in Italy in 1771. The disease's name derives from Frapolli's description during this Italian outbreak. In Italian, "pella" means skin, and "agra" rough, or rough skin.[8] Rough skin, appearing as if sunburnt, is characteristic, probably pathognomonic, of niacin deficiency.[9]

Pellagra was first reported in the US in 1902. Over the next twenty years, the disease spread across the southern states as if it were an infectious epidemic. Risks for catching the disease seemed to be a combination of poverty and corn consumption.[10] As etiology remained unclear, "pellagraphobia" caused the public to shun patients and ostracize them. Joseph Goldberger, MD, of the United States Public Health Service eventually solved the pellagra puzzle.[11] If you are not familiar with his fascinating story, the history is worth reading about: https://history.nih.gov/pages/viewpage.action?pageId=8883184.

Niacin was first isolated by Elvehjem and colleagues who showed that it could reverse both black tongue and pellagra in 1937.[12] Niacin deficiency is now quite rare in developed countries.

More is not necessarily better when it comes to dosing nutritional supplements.

Niacin is measured in milligrams (mg) or niacin equivalents (NE). One NE equals 1 milligram of niacin or 60 mg of tryptophan.* The Recommended Dietary Allowance (RDA) for adults is 16 mg NE for men, 14 mg NE for women, 18 mg NE for pregnant women, and 17 mg NE for lactating women.[13]

Dietary niacin comes from cereals, meat, and vegetables.[14] However, much of the niacin in flour along with other B vitamins and nutrients is lost when the germ and bran are removed during refining. To prevent deficiencies, white flour in the US is 'enriched' (since 1938). Current FDA requirements specify that 24 milligrams of niacin be added to each pound of white enriched flour. Corn first arrived in Europe in 1492 and was rapidly adopted as a major food stuff in Spain and then Italy. Niacin present in corn is often chemically bound in a macromolecular complex called niacytin, from which the niacin is not released during digestion. Heat and alkali treatment are required, a process called nixtamalization, to make niacin bioavailable.[15] However, this practice of nixtamalization was not introduced in Europe along with the corn.

Niacin for Dyslipidemia

Niacin supplementation acutely decreases plasma concentration of free fatty acids by inhibiting mobilization from adipose tissue.[16] As a result niacin can be used to treat dyslipidemia and to lower cholesterol. In the past, we used niacin at high doses, in the range of 1,000 to 2,000 mg/day, for this purpose. Hesitation to do so began only when it became apparent that excessive niacin was linked to insulin resistance and elevated homocysteine.[17]

High-dose niacin supplementation also creates side effects that many patients found intolerable. Skin flushing is probably the most reported, but high-dose niacin also caused stomach upset and diarrhea. Early clinical trials suggested that high dose niacin was associated with reduced CVD events and death, so we encouraged patients to take these high doses in spite of these side effects. However, two large clinical trials published in 2011 and 2014, failed to confirm any real benefit to taking niacin for dyslipidemia.[18,19] These were large, randomized placebo-controlled trials that followed participants for four years. Niacin supplements were given (1,500-2,000 mg daily), alone in one trial and with a statin in the other. Both trials concluded that taking niacin supplements brought no benefit: no reduction in strokes, heart attack, or CVD deaths even though blood lipids improved. The 2014 study, the niacin supplement-only trial, reported a significant increase in adverse reactions compared to the placebo group, including increased incidence of type 2 diabetes, gastrointestinal bleeding and ulcers, and diarrhea. Additionally, a Cochrane review conducted by Stefan Schandelmaier et al, which analyzed 23 randomized controlled trials on niacin supplements to prevent CVD, reported that supplementation did not reduce overall deaths, CVD deaths, heart attacks, or strokes, but was associated with negative side effects.[20] Such results led to the US Food and Drug Administration (FDA) to change their minds about the efficacy of niacin for CVD protection issuing a statement that the "scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-cholesterol levels in statin-treated patients results in a reduction in the risk of cardiovascular events."[21] That was in 2016 so I assume this is no longer news to any readers.

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High-dose niacin has also been used in a detoxification protocol first suggested by L. Ron Hubbard, the founder of the Church of Scientology. The process involves daily heat exposure for extended periods accompanied by increasing doses of niacin working up to a dose of 5,000 mg/day. The process has been promoted as a way to treat drug addiction and other toxic exposures. While Hubbard's protocol has been employed by well-known colleagues, published evidence is scant to support the idea that the process, at least the high dose niacin, reduces toxic burden.

This past niacin research focused on the high dose niacin in high-risk populations and not dietary niacin in the general population. This recent study by Zhuxian Zhang turns our attention to slight variations in dietary doses of niacin and suggest an unsuspected impact on CVD risk. While Zhang's work examined only risk of new onset hypertension, we can extrapolate and worry that increasing risk of hypertension will lead to an increase in CVD. Notably Zhang's data provide a target for daily intake. Their data demonstrates a textbook hormetic response: risk of subsequent hypertension is lowest in study participants who consumed 15.6 mg/d of niacin but it goes up for those consuming either lower or higher amounts.

Many other examples of the J-shaped dose response curves have come to light in recent years so that we should now be familiar with the concept of hormesis and the Goldilocks' need for getting dosing 'just right.' Plant-derived substances such as curcumin, ginseng, *Ginkgo biloba*, resveratrol, and green tea, all induce a broad spectrum of desired effects via hormesis in which higher or lower doses are less effective than an ideal target dose.[22] In September 2021, vitamin B-12 levels were also reported to have a J-shaped dose response associated with mortality.[23] An August 2021 trial suggests that vitamin D's protection against preeclampsia also varies, following a hormetic pattern.[24]

In September 2020 we read that red blood cell folate is associated with cardiovascular disease risk and that this relationship also follows a J-shaped hormetic curve. Using data from 2,986 NHANES participants, Twum et al reported that participants with intermediate folate levels were at lower risk of death from CVD and acute MIs. After adjustment for age, sex and other factors, the data revealed that those with higher levels of RBC folate were more than twice as likely to die of acute MIs than those with intermediate folate levels. In Twum's data, intermediate RBC folate levels for men were defined as 137 ng/mL to 256 ng/mL.[25] MedScape however still lists a normal range for RBC folate as 140 to 628 ng/mL.[26]

Zhang's study at this point stands alone. It is the first to suggest this connection and all the caveats apply to believing early results like this from a single study. If the results are confirmed, they will shift much of our thinking about niacin and possible other vitamins.

These studies are a timely reminder that more is not necessarily better when it comes to dosing nutritional supplements, be they herbs or vitamins. We reflexively fall back on history and past paradigms; we want to blame illness on nutrient deficiencies. The modern food supply however is now one of superabundance, and our current problems may result from overconsumption and excess rather than deficiency.

Zhang's results suggest we might need to reconsider the way we think about niacin. Our longstanding assumption has been that because niacin is water soluble any excess will be urinated out. Thus, we considered high-dose niacin relatively safe to consume. This might not be true. Our use of mega-dose niacin supplements to treat dyslipidemia was proven ineffective. Now even lower doses should be viewed cautiously. The daily multi-vitamin that I took until yesterday, supplied 80 mg niacin per day. Zhang suggests a daily dose of only 14.3 to 16.7 mg. Any more, and hypertension risk increases. If Zhang's results hold true, they should have serious implications to our practices.

We naturopaths are often early adopters. That's true. Sadly, we can be tenacious at believing in what we do and hesitate to abandon beliefs and practices that are no longer accepted by medical science. We are adept at finding fault in studies so we might ignore their results and continue practicing the way we do. We need to learn to be 'early ditchers.'

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Can Your Body Make Niacinamide? If Not, It Must Be Taken Every Day

by Jonathan V. Wright, MD

Jonathan V. Wright, MD's "Green Medicine Newsletter", Volume 6, Issue 9, September 2021
(www.GreenMedicineNewsletter.com)

Why should our bodies make niacinamide? Niacinamide and niacin are both "B vitamins"; our bodies aren't designed to make vitamins, that's why they're in foods and all the "health food stores", so we can buy them in foods and take them as supplements as part of our efforts to stay as healthy as we can for as long as we can! So, what's this about our own bodies making niacinamide, one of the B vitamins?

When vitamins were first discovered years ago, niacinamide and niacin were two vitamins very clearly identified as being not made in human bodies but also identified as essential to human health and longevity. However, there have been changes published since then: for example, Professor Gregory Oxenkrug at Tufts University[1] Medical Center in Boston, "Taxachusetts" (that's a local native's alternative name for "Massachusetts") wrote us about Chapter 8 in a book titled *Tryptophan Metabolism: Implications for Biological Processes Health and Disease,* in which he told us that the amino acid tryptophan, if digested and absorbed well (which is more likely before age 50 and less likely after that age[2]), can be metabolized with the help of pyridoxal-5-phosphate (the "active" form of "vitamin B6" into niacinamide adenine dinucleotide ("NAD"), which also helps "power" any cell in the body that needs more energy into making more ATP (adenosine triphosphate, human bodies' so-called "energy molecules").

Professor Oxenkrug also writes that "Aging, obesity, depression, Parkinson's disease and schizophrenia" and treatment with anti-psychotic drugs are "highly associated with insulin resistance" ("IR") and type 2 diabetes mellitus ("T2D"). If you or any member at all of your family has had type 2 diabetes, you (unfortunately) are much less likely to internally synthesize niacinamide from tryptophan, even if digestion and assimilation of nutrients appear to be functioning well! Chapter 7 of this same book is titled "Diabetes and Tryptophan Metabolism" (written by Ugur Unluturk and Tomis Erbas).

Dementia Prevention with Niacinamide

If not the greatest risk, dementia is among the greatest risks to those of us who cannot or no longer can internally synthesize niacinamide.

Researchers at the University of California in Irvine genetically engineered experimental animals to develop dementia identical to human Alzheimer's. How could the researchers detect signs of early Alzheimer's in "experimental animals"? When these "experimental animals" could no longer "run the maze" to find their food, the researchers biopsied their brains and (no surprise) they identified "beta-amyloid," "tau protein," and "neurofibrillary tangle," all early signs of Alzheimer's dementia in both humans and "experimental animals."

The animals were then given relatively large quantities of niacinamide equivalent to 3 grams per day in humans. Took a little time, however, but the "experimental animals" all regained the ability to "run the maze" and find food. At the next brain biopsy, most of the (literal) garbage mentioned before that accumulates in Alzheimer's disease had very significantly diminished.

This is extremely important if you or an older family member have had type 2 diabetes, as humans with that genetic heritage CANNOT internally synthesize niacinamide at all, according to Professor Oxenkrug. If you have this family tendency towards type 2 diabetes, it's not only important to take your total of 3 grams of niacinamide (perhaps 1 gram thrice daily) to lessen your "down-the-road" chances of diabetes, but it's also very important to check with your physician about any signs of pre-diabetes type 2 you may not know about!

Self-Testing for Pre-Diabetes and Gestational Diabetes

One of the potential ways to self-test is with a 24-hour urine collection test. Nearly everyone knows that this is one of the best ways to test for "BHRT" (bio-identical hormone replacement therapy), but not everyone knows that this test can be used for early detection of type 2 diabetes using the category "metabolic disorders" (which is just a polite way to say "on the road to type 2 diabetes"). If one is indeed "on the road" to type 2 diabetes, what appears in the "metabolic disorders" part of the 24-hour urine test are very often "xanthurenic acid" and "kynurenic acid."

- Xanthurenic acid (XA) – a tryptophan metabolite is high in serum (and urine) in gestational diabetes.
- Xanthurenic acid binds insulin, impeding its action.

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- Vitamin B6 (most effective as "P5P" also termed pyridoxal-5-phosphate) lowers xanthurenic acid.
- In two 1970s research studies, 86% and 100% of women with gestational diabetes normalized their blood sugar in two weeks.
- Gestational diabetes increases autism risk for the unborn child; vitamin B6 eliminates that extra risk.

Dementia is among the greatest risks to those who cannot internally synthesize niacinamide.

No, not kidding! If you're a pregnant woman who never had any sort of diabetes before you became pregnant and developed high blood sugar only after becoming pregnant (gestational diabetes), you can safely eliminate it all by yourself within two to three weeks. You might have the remedy at home already! If not, a trip to your favorite natural food store, compounding pharmacy, or maybe even an online order from the Tahoma Clinic Dispensary or other online source will equip you to eliminate gestational diabetes almost every time! And of course, speak with your physician skilled and knowledgeable in Nature's approach to health care.

Of course, if you're a man, you'll never have this problem. However, your wife, sister, or daughter might, so keep this information in mind in case it's ever needed.

One of many reasons gestational diabetes should be eliminated as rapidly as possible was discovered recently and published in the *Journal of the American Medical Association* just last year. What is this reason? Autism! Here's what the researchers wrote: "…exposure to maternal gestational diabetes mellitus diagnosed by 26 weeks' gestation was associated with risk of autism spectrum disorder in offspring."[3] Yes, that's extra risk for the child of developing autism!

But even though in gestational diabetes blood and urine sugar is higher than normal, *gestational diabetes is not type 2 or even type 1 diabetes mellitus!* To make this point clear to everyone, gestational diabetes should be re-named *diabetes mellitus xanthurenica* to clearly identify its cause: excess serum xanthurenic acid. When this re-naming occurs, even conventional medicine might quit treating gestational diabetes with "diabetic diet" and insulin, and actually *treat the cause!*

Here's what WebMD says is the cause of gestational diabetes[4]:

> During pregnancy, the placenta… releases hormones that help your baby grow. Some of these make it harder for your body to make or use insulin. This is called insulin resistance….To keep your blood sugar levels steady, your pancreas has to make…as much as three times more [insulin] than usual. If it can't make enough extra insulin, your blood sugar will rise and you'll get gestational diabetes.

And here's what the American Diabetes Association tells women[5]: "Treatment for gestational diabetes always includes *special meal plans and scheduled physical activity.* It may also include daily blood glucose testing and insulin injections."

Let's send a note to WebMD and the ADA: "Read the medical research!" What actually causes gestational diabetes was well researched between the 1940s and 1975, when a report[6] summarized the earlier research and then explained that gestational diabetes is caused by excessive amounts of xanthurenic acid, usually present in blood in very low levels. All this xanthurenic acid combines with insulin molecules and blocks its activity. The "xanthurenic acid-insulin complex" can't activate insulin receptors nearly as well as insulin alone does, and blood sugar rises.

Type 2 Diabetes, Type 1 Diabetes, Gestational Diabetes

Back to the causes of diabetes mellitus type 2 and type 1. In "type 2," the cause is overproduction of insulin in response to carbohydrates (and dairy, but an explanation for that at another time). As a prior issue of *Green Medicine* explained, overproduced, chronically high insulin causes insulin resistance, which in turn leads to even more insulin secretion to overcome that resistance, which leads to even more insulin secretion.

This back and forth upward trending interplay (more insulin, more resistance, even more insulin, even more resistance, and so on) goes on and on (unless "carbs" – and dairy – are significantly restricted) until the insulin resistance is so strong it can't be completely overcome, no matter how much insulin there may be. Blood sugar then goes too high – and it's diagnosed as "type 2" diabetes. This known cause of type 2 diabetes is very different than the cause of *diabetes mellitus xanthurenica!*

The cause of type 1 diabetes is much simpler. For a variety of reasons, the insulin-producing cells ("islet cells") become weak and die. When that happens, insulin levels go lower and lower, until there's very little insulin, or even none – that's type 1 diabetes. Again, a very different cause from *diabetes mellitus xanthurenica.*

But doesn't everyone's body chemistry make xanthurenic acid? (It's a metabolite of tryptophan.) Indeed, 100% of us have this body chemistry. So why don't we all have gestational diabetes even if we're not pregnant? The reason is that levels of xanthurenic acid are relatively low in most of us (unless we're deficient in a certain B-vitamin named pyridoxal-5-phosphate or "P5P") so there's not very much "xanthurenic acid-insulin complex" formed.

What's different during pregnancy? Among other things, it's a combination of "genetic" causes and those really-high-estrogen levels that women's bodies make when pregnant – way, way more than when not pregnant. But why does all that extra estrogen cause only a minority of women's bodies to make lots more xanthurenic acid and develop gestational diabetes, when most women's bodies don't do that?

That's the "genetic" part: Women who develop gestational diabetes have "weakness" in the enzymes that metabolize tryptophan into serotonin and melatonin, but no weakness in the enzymes that metabolize tryptophan into xanthurenic acid. Without the pregnancy levels of estrogen "putting pressure" on these weak enzymes, they can perform as they do in most women – metabolizing tryptophan much less into xanthurenic acid and much more into many other

molecules we've all heard about, including serotonin and melatonin.

With the high pregnancy levels of estrogen, the weak enzymes falter, and metabolize much more tryptophan than usual into xanthurenic acid, and much less into melatonin, serotonin, and related molecules. If there's much more xanthurenic acid, there's much more "insulin-xanthurenic acid complex" formed, and impairment of insulin activity. With enough insulin impaired, diabetes – gestational – is the result.

But a woman can't stop being pregnant (for many months, anyway), and she definitely can't change her genetics, so she can't really rid herself of gestational diabetes, returning to normal blood sugar levels (while reducing her baby's risk of autism, too) within two to three weeks? Can she?

Yes, she can! To understand how, a refresher about what many of us learned in high school and college chemistry about how enzymes change one molecule into another. The key is that enzymes never work alone. They're always aided by co-factors, which are almost always "essential" (necessary to life) vitamins and minerals! Without those co-factors, the enzymes can't function; and ultimately, we die. That's why they're defined as "essential" nutrients!

"Weak" enzyme function can frequently be strengthened by adding in more co-factors! A key co-factor for the enzymes that metabolize tryptophan into serotonin and melatonin is vitamin B6. Next, the results that women with gestational diabetes achieved by taking extra vitamin B6 to strengthen their genetically "weak" enzymes.

In 1975, fourteen pregnant women were diagnosed with gestational diabetes by the standard glucose tolerance test. All the women took vitamin B6 (as pyridoxine) 100 milligrams daily for two weeks, after which repeat testing found that twelve of the fourteen (86%) no longer had the problem![7] In 1977, different researchers reported almost identical results in the same length of time for thirteen women.[8] All took vitamin B6 (as pyridoxine) 100 milligrams daily. Glucose tolerance tests were done before and after. All fourteen women (100%) had "statistically significant" improvements in their glucose tolerance tests. The researchers wrote: "…low vitamin B6 levels appear to alter metabolic pathways which result in a lowering of the biologic activity of endogenous insulin." In English: vitamin B6 strengthened specific weak enzymes so that less xanthurenic acid was available to "complex" with insulin, blocking its activity. Better blood sugar control was regained.

The 1975 and 1977 research was actually done more than two decades *after* several groups of researchers[9,10,11,12] had confirmed in the *early 1950s* that vitamin B6 returned levels of xanthurenic acid to normal. For the technically inclined, all the 1950s research and much more was reviewed in a 1960 publication titled "The Effect of Vitamin Supplementation on the Urinary Excretion of Tryptophan Metabolites by Pregnant Women."[13] This last publication confirmed that pyridoxine lowered xanthurenic acid!

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And a last fact: Textbooks of laboratory medicine *in the 1940s* told us that higher than usual xanthurenic acid in urine is *diagnostic* for vitamin B6 deficiency! It's 2016, yet despite all this forty- to seventy-year-old basic science and clinical research *demonstrating the cause and cure of gestational diabetes, it's still rarely being applied!*

But you – yes that's you, if you want to prevent gestational diabetes or cure yourself of it – can apply this extensive science, safely prevent or cure gestational diabetes yourself, and at the same time reduce your child's risk of autism!

To eliminate gestational diabetes, use pyridoxal phosphate – not pyridoxine! Don't use the "pyridoxine" form of vitamin B6. That's actually the "inactive" form of vitamin B6 which actually does not "activate" the "receptors" for this vitamin. Most – but not all – humans can "activate" pyridoxine, but we have no way (without testing) to know if you are in the pyridoxine activating group, or not. (It's quite possible that the 14% whose gestational diabetes didn't disappear in the 1975 research summarized above were "poor activators" of pyridoxine.)

To make sure the pyridoxine actually "does its job" it's best to use the "active" form, pyridoxal-5-phosphate ("P5P"), fortunately available nearly everywhere supplements are sold, usually in a 50-milligram size. Don't stop using your "pregnancy multiple vitamin-mineral" as it contains the rest of the B-complex vitamins, which "back up" the pyridoxal-5-phosphate.

Check with your "natural medicine" doctor:

1. If you have any doubts at all about doing this!
2. Towards the anticipated delivery date. Vitamin B6 in both forms can inhibit the production of prolactin,[14] the hormone necessary for normal lactation and nursing. Work with a physician skilled and knowledgeable in natural and nutritional medicine to help you determine (possibly while checking your own blood sugar) a P5P "tapering schedule" so you can nurse your child normally. This physician will also be able to tell you about botanicals used for centuries to improve lactation should they be needed.

A kind testimonial from a reader of *Green Medicine Newsletter:*

> I wanted to say thank you as I found your article on P5P and gestational diabetes a while back and have had blood sugar numbers 85-115 this pregnancy (31 weeks) versus my last pregnancy (120-180). I only have had to take 20 mg daily at this point. But thank you times a thousand and giving me a chance to have a natural birth this time around. Thank you!

Niacinamide for Prevention and Treatment of Osteoarthritis, Glaucoma, and Energizing Every Cell in Our Bodies (Not Kidding!)

Decades ago, William Kaufman, MD, published a book titled *The Common Form of Joint Dysfunction,* which was all about the successful elimination of joint pain in all but four of three hundred fifty-four osteoarthritis sufferers. All but four had complete elimination of all joint pain by taking a total of 3 grams of niacinamide daily. Took a nearly a month to notice much pain relief at all; after four months, nearly everyone's osteoarthritis pain was eliminated and did not return if the niacinamide was continued.

In the last few years "stem cell therapy" for osteoarthritis has become the preferred treatment by many surgeons, but of course it's partially a "surgical procedure" which (fortunately) uses one's own stem cells instead of un-natural treatment material and is of course considerably more costly.

How does the niacinamide do this? Very likely by promoting the formation of ATP (adenosine triphosphate) a major "energy molecule" in every cell in our bodies. Since all of our joint cartilage cells "take much more beating" than most cells do every day, it's very likely that the "re-energization" of cartilage cells is more important to good "joint cartilage cell maintenance" than it is to many other cells in our bodies!

I have had no need to refer anyone for joint replacement surgery, as everyone has reported (as noted above) disappearance of all osteoarthritis pain within the four months specified by Dr. Kaufman.

Niacinamide protects against glaucoma. A title from a recent research publication: "*Nicotinamide* [which is the same molecule as niacinamide but contains no nicotine] *provides neuroprotection in glaucoma by protecting against mitochondrial and metabolic dysfunction.*" How does it do that? As noted repeatedly (sorry about that), by causing the formation of ATP (adenosine triphosphate, "the energy molecules" needed by every cell in our bodies, in this case in our eyeball cells), which – as many, many cells do – need maximum possible energy production.

Niacinamide extends longevity. Greater longevity might be expected with any natural molecular substance that promotes production of ATP energy in every cell in our bodies! Bit of a surprise: A Harvard professor – David Sinclair – somehow managed to "patent" niacinamide (even though it's been present in Nature for as long as Nature has existed)! The patent was even "assigned to Harvard University"! Here is the patent title and a few details: "Methods and Compositions for extending the lifespan and increasing the stress resistance of Cells and Organisms." Inventors: David A. Sinclair, West Roxbury Massachusetts; Kevin J. Bitterman, Boston, Massachusetts. Assignee: President and fellows of Harvard University, Cambridge, Massachusetts.

It should be apparent to all how important niacinamide is to optimal potential good health and longevity, particularly as we all get older! And it's important to all of us at all ages if we're hoping for maximal possible ATP energy in our brains, eyes, hearts, and anywhere else in our bodies. Remember, it's very, very likely our bodies make less and less niacinamide as we age.

Final Word: Yes, It's Possible to Take Too Much Niacinamine!

I really likely working with engineers with their health concerns, as engineers are usually very meticulous. Over three decades ago, I told an engineer suffering from osteoarthritis about Dr. Kaufman's work, advised him to follow Dr. Kaufman's recommendation about taking one gram of niacinamide thrice daily.

He asked if Dr. Kaufman every reported adverse or overdose effects; told him that Dr. Kaufman said that "low-grade nausea" was and is an indicator of too much niacinamide for that person. Didn't see him again for several months when he came in about another health concern, but first reported that his joint pain had been completely gone for several months. However, after three weeks he started having a little "low-grade" nausea, so he

decided to continue since his pain was much less. However, he also reported that the low-grade nausea got a bit worse and cause him to "barf into the toilet" twice before he cut the dose back to a total of 2500 milligrams a day, which was not associated with any nausea, so he decided to stay at that quantity, particularly as he reported his over-all energy levels were much improved from what they were before he first started the niacinamide. He has continued the lower quantity with no other problems; the osteoarthritis pain remains gone.

Other Niacinamide Functions

In 1979, an article titled "Nicotinamide is a brain constituent with benzodiazepine like actions" was published[15] by the pharmaceutical research department of F. Hoffman-La Roche & Company, Ltd. "Benzodiazapines" is the fancy pharmaceutical company word for the patented medicines Librium, Valium, and other "tranquilizers."

Of course, being pharmaceutical company employees, they got it exactly backward. As niacinamide has been present in humans and animals for as long as humans and animals have been on planet Earth, a more accurate title would have been "Benzodiapines are patented artificial molecules with niacinamide-mimetic activity." "Mimetic" ("mimicking" but not exactly duplicating) is the most accurate description for the activity of these un-natural molecules.

As soon as this 1979 article was published, any physician who really is striving for the best health effects (with of course minimal if any adverse effects) should have switched all of his or her "Librium," "Valium" or other un-natural patent medicine medication treatments to Nature's original molecular substance: nicotinamide! Even in 2021, these un-Natural patent medications are still recommended by some physicians instead of Nature's molecule, niacinamide.

Comments About Niacinamide

"My husband has been noticeably less grumpy – especially with the grandkids – since he's been taking his niacinamide every day."

"My wife has been much less nervous and anxious since been taking her niacinamide every day."

"We're both sleeping a lot better at night with not only 'time-release' niacinamide (tradename Enduramide) but also 'time-release' melatonin. Not only that, we both have notably more energy during the day when we take our niacinamide totaling 3000 milligrams per 24 hours." (Remember, niacinamide promotes cellular energy by formation of ATP, the energy molecules needed by every cell in our bodies.)

Remember, too much niacinamide for any one person results in low-grade nausea, which always means cut back the dose to the 24-hour total that does not cause any nausea.

Niacinamide and Aging

As you've likely assumed already, the older we are, the more we need to take the maximum daily 24-hour quantity of niacinamide we can energize our bodies as much we can every day, without causing low-grade nausea, of course. Some (but not all) of us can make enough niacinamide in our own bodies when we're younger; but as we grow older, we're actually likely to internally synthesize less and less niacinamide with time. I have seen reports of zero, and near zero in "older" individuals. No, I'm not at all writing that niacinamide is a "longevity" molecule (there's so far no research reporting that) but it definitely is an energizing molecule at all ages, particularly as we all get older.

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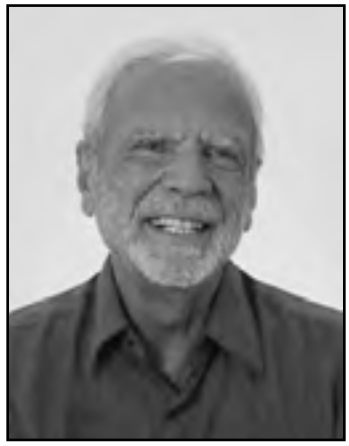

Dr. Jonathan Wright established Tahoma Clinic (www.TahomaClinic.com) in 1973 in Washington State to offer nutritional and other proven natural therapies for common health conditions. A long-time researcher, author, speaker, and clinician, he has educated physicians in his techniques since 1983.

Dubbed the "Father of Bio-Identical Hormones" by his peers, Dr. Wright was the first physician in the United States to prescribe comprehensive hormone replacement therapy (in the early 1980s) with hormones identical to those found in Nature. This therapy (shortened to "BHRT") is now used nationwide by millions.

Also an author, he has written 13 books (with two texts achieving best-selling status), numerous medical articles, monthly magazine columns from 1976 to 2000, and since 1994 has written a popular monthly newsletter on natural health topics (www.GreenMedicineNewsletter.com).

Rapamycin: A Quantum Leap in Life Extension

Rapamycin, mTOR, Autophagy, and Treating mTOR Syndrome

by Ross Pelton

Rapamycin is an FDA-approved drug that is ushering in a new era of life extension. However, to be clear, rapamycin is not approved by the FDA as a life extension drug. In September 1999, rapamycin received FDA approval as an immunosuppressant drug to prevent organ transplant rejection.[1] Unfortunately, rapamycin's ability to suppress the immune system has given it a 'reputation' that has inhibited its acceptance by mainstream physicians as a life extension drug.

Treatment with rapamycin has resulted in significant increases in lifespan in animal models, including yeast, worms, fruit flies, and mice.[2] Animals get many of the same diseases that humans develop. Results from animal studies reveal that rapamycin slows down the onset of many age-related diseases. In addition to improving animals' health, treatment with rapamycin has produced life extensions ranging from 25-60%.[3]

Rapamycin is not approved as a life extension drug. However, many life extension enthusiasts have begun taking rapamycin based on the improvements in health and lifespan in animal trials and initial human studies. My new book titled ***Rapamycin, mTOR, Autophagy and Treating mTOR Syndrome*** reviews the history and scientific studies that explain why rapamycin is so effective at delaying the onset of age-related diseases and increasing both healthspan and lifespan. My book can be ordered from www.LifeExtension.com/rapa.

Discovery of Rapamycin

Rapamycin is a compound that is produced by a strain of bacteria named *Streptomyces hygroscopicus*. This bacterium was discovered from a soil sample taken during a scientific expedition to Easter Island in 1964.[4] The purpose of that expedition was to search for new compounds that might express antifungal and/or antibiotic properties. Rapamycin expressed strong antifungal activity. However, efforts to develop rapamycin as an antifungal drug were discontinued when it was discovered to have potent immunosuppressive activity.

Rapamycin also exhibited anti-proliferative properties, which prompted scientists to send samples of rapamycin to the National Cancer Institute (NCI). Tests conducted there revealed two remarkable findings. The first revelation was that rapamycin suppressed growth in a variety of solid tumors.

The second finding was the discovery that rapamycin appeared to be a totally new type of anticancer drug because it functioned by inhibiting cancer growth (cytostatic) rather than by killing cancer cells (cytotoxic). Cytotoxic chemotherapy drugs cause a wide range of side effects because they damage other rapidly dividing cells in the body. Rapamycin's activity against solid tumors plus its cytostatic mechanism of action motivated the NCI to elevate rapamycin to "priority drug" status in order to accelerate additional research.[5]

Rapamycin's Mechanism of Action

Over the past 25 years, research into rapamycin's mechanism of action has resulted in the discovery of a new understanding of cellular biology and the aging process. This research has revealed that two mechanisms named mTOR and autophagy, which are found inside every cell, are critical regulators of cellular metabolism.

mTOR and autophagy are counter-balancing mechanisms that regulate the health and aging process of all living organisms. In my mind, the mTOR/autophagy story is even more important than the story about rapamycin. The discovery and understanding of mTOR and autophagy are revealing how we can delay the onset of age-related diseases and achieve significant increases in lifespan and healthspan.

When rapamycin crosses a cellular membrane and enters a cell, it binds with an enzyme that was named mTOR, which stands for the *mechanistic target of rapamycin (mTOR)*. mTOR is a key regulator of cellular metabolism that has stimulated a great deal of scientific interest.

Now, 25 years after its discovery, over 12,000 papers have been published on mTOR. When nutrients are available to a cell, mTOR sends cellular signals that activate cellular metabolism, telling the cell to use the available nutrients to build new proteins, new enzymes, and other cellular components. mTOR activates cellular anabolic (building) processes of growth and proliferation.

Counterbalancing mTOR is the cellular process known as autophagy. In 2016, Japanese scientist Yoshinori Ohsumi was awarded the Nobel Prize in physiology and medicine for discovering the mechanism of autophagy.[6] PubMed now contains over 30,000 citations with the term autophagy in the title, which gives an indication of the scientific interest in this topic.

Autophagy has been referred to as the cellular housekeeping process or cellular trash removal. Over time, various cellular components become damaged, break down, and become dysfunctional. If these waste products continue to accumulate, cellular functions would decline, and the cell(s) would eventually die.[7] When autophagy is activated, damaged and dysfunctional cellular components are broken down for reuse and recycling or for removal. Autophagy can also be thought of as cellular detoxification.

Animals get many of the same age-related diseases that humans get. Rapamycin gained prominence as a life extension drug based on its ability to treat a variety of age-related diseases and increase the lifespan in numerous species of animals. However, human trials were lacking because ethical issues, costs, and time constraints make it virtually impossible to conduct life extension trials in humans.

Breakthrough: Rapamycin's Use in Humans

'Twas the night before Christmas… on Dec. 24, 2014, a groundbreaking study titled "mTOR inhibition improves immune function in the elderly"[8] was published that ushered in the era of rapamycin use in humans. The study was conducted by Joan Mannick, MD, who was a senior scientist at Novartis. In addition to being a human clinical trial, Mannick's study is important because it sheds light on **why** and **how** rapamycin can be used safely and effectively in humans to slow down the onset of age-related diseases and increase lifespan and healthspan.

In this trial, elderly adults were treated with RAD001, which is a synthetic version of rapamycin (a rapalog) whose effects are virtually the same as rapamycin. Dr. Mannick's wanted to evaluate the effects of mTOR inhibition on human aging-related conditions and she chose the immune system, which normally declines with age, as the target for her study.

In this six-week placebo-controlled trial, 218 volunteers who were 65 years of age or older were divided into four groups. The doses administered were 0.5 mg daily, 5.0 mg once weekly, 20 mg once weekly, or placebo. Following six weeks of therapy, there was a two-week drug-free interval followed by administration of the seasonal flu vaccine.

The hemagglutination inhibition (HI) assay, which measures the concentration of antibodies to the hemagglutinin protein of the influenza virus, was used to measure the subject's response to the influenza vaccine. The HI titer correlates with protection against influenza illness.[9]

The results from the Mannick study reported significant increases in antibody titer at all three doses of everolimus (RAD001) for at least one of the three influenza strains they looked at. At the 0.5 mg daily and 5 mg/weekly dosing, two of the strains were statistically significant and the third was trending in the positive direction. At the 20 mg/week dose the data are less convincing as antibody titers were slightly reduced for two of the strains. Also, individuals taking 20 mg dose experienced a higher incidence of adverse effects, which suggests that the 20 mg dose is probably too high.

The immune system of the elderly adults who received a 5 mg dose of RAD001 once weekly exhibited a 20% enhanced response to the influenza vaccine with virtually no side effects. The results of this clinical trial suggested that the ability of rapamycin or similar rapalogs to enhance immune function in elderly adults might be able to delay the onset of age-related diseases in humans.[10]

Joan Mannick's study helps us understand that rapamycin's initial classification as an immunosuppressant drug was incorrect. Rapamycin is not an immunosuppression it is an immunomodulator.

The mTOR/Autophagy Ratio

Life…it's all about balance. This is especially true regarding the mTOR/autophagy ratio. Extreme suppression of mTOR (hypo-functioning) results in suppression of the immune system. This is what happens when rapamycin is administered daily to prevent organ rejection following organ transplant surgeries.

Rapamycin is the name of the compound that is naturally produced by the soil bacteria *Streptomyces hygroscopicus*.

When mTOR is hyper-functioning, the immune system gets exhausted, which also results in immunosuppression. I believe most people alive today suffer from an under-functioning immune system, which is due to the over-activation of mTOR. I call this condition *mTOR Syndrome.*

Dysregulated mTOR/Autophagy Ratio

The majority of Americans are not well. We are literally experiencing an epidemic of epidemics. We have an epidemic of cancer, heart disease, diabetes, obesity, osteoporosis, Alzheimer's disease, ADD/ADHD, autism, opioid addiction, to name a few. The over-expression of mTOR (mTOR Syndrome) is increasingly being recognized as a fundamental mechanism that is present in many of our common diseases such as cancer,[11] diabetes,[12] cardiovascular disease,[13] and Alzheimer's disease.[14]

I believe most people living today are suffering to some degree from mTOR Syndrome. Understanding why the mTOR/autophagy ratio has become so universally unbalanced will help explain our epidemic of chronic degenerative diseases and also explain why rapamycin appears to be effective (in animal studies) in the treatment of such a wide range of diseases.

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Rapamycin

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Within the past 300 years, humans have managed to get the mTOR/autophagy ratio severely out of balance. Two categories of technological advancement have played a large role in the development of mTOR Syndrome.

The first technological advancement was the invention and development of refrigeration, which greatly improved the ability to store and preserve foods and make them easily available. Artificial refrigeration began in the mid-1750s. The first home refrigerators were invented in 1913. Fast forward to today and the refrigerator has become the most popular home appliance. According to government data, nearly 100% of American households have a refrigerator and approximately 25% of homes have two (or more) fridges and/or freezers.[15]

The second technological advancement that played a major role in dysregulating the mTOR/autophagy balance was the rapid development of the industries of food processing and packaging. The rapid development of refrigeration, food processing, and the widespread production and distribution of convenience foods means that food is now easily available ALL the time for most people. As a result, modern humans spend much more time eating every day compared to our ancestors.

Throughout 99.9% of mankind's evolution, people had to hunt or forage for their food. Consequently, our ancient ancestors did not eat three meals per day. I estimate that our ancestors often only ate one meal a day. This means they spent about four hours digesting their meal and 20 hours without food intake (fasting). There were also probably periods when people went one or two days without eating. Compared to modern humans, our prehistoric ancestors spent much less time eating and during hundreds of thousands of years of evolution, mTOR and autophagy were in balance.

Since mTOR initiates anabolic processes when nutrients are available, the easy access to food 24/7 has resulted in mTOR being constantly overexpressed coupled with a serious under-expression of autophagy. This results in what I've chosen to call mTOR Syndrome.

Partial Inhibition of mTOR

It has been estimated that there may be up to one thousand mTOR sites within cells. When rapamycin is taken, it enters cells and binds to some of the mTOR sites, which results in partial inhibition of mTOR. The degree of mTOR inhibition is dose-dependent. This is a critically important point. If the rapamycin dose is too large, or if it is given too frequently, suppression of the immune system develops. However, episodic dosing once weekly or every other week partially inhibits mTOR, which results in a wide range of health benefits.

Benefits of Taking Rapamycin

Rapamycin is not a 'miracle drug'; it is not going to 'fix' everything. However, rapamycin will enable most people to gain significant improvements in their health. By inhibiting mTOR and activating autophagy, all cells in the body begin to detoxify more effectively and undergo revitalization and renewal. Results from animal models suggest that rapamycin will help improve symptoms for virtually all chronic degenerative diseases. This includes metabolic syndrome and type 2 diabetes, neurological diseases such as Parkinson's disease and multiple sclerosis, inflammatory conditions like rheumatoid arthritis and systemic lupus erythematosus, macular degeneration, glaucoma, obesity, hearing loss, periodontal disease, cognitive decline, and Alzheimer's disease.

Dose Recommendations

Rapamycin's use in humans is so new that studies to determine the optimal dose and frequency have not yet been conducted. I believe that biochemical individuality will play a big role. We will probably learn that the optimal dose will be different for different people. For now, 5 mg once weekly seems to be the dose that most people take, based on the results of the Joan Mannick human clinical trial.

Because mTOR is the master regulator of the growth activities in cells, rapamycin should not be given to children, adolescents, and young adults because these are periods of rapid growth. Although there is no agreed-upon age for people to start taking rapamycin, I don't think people younger than thirty should be taking it.

Results from animal studies suggest that rapamycin can even benefit the elderly. When rapamycin therapy was initiated in elderly (600-day old) male and female mice (roughly the equivalent of 60-year-old humans), female mice achieved a 14% increase in lifespan while males achieved a 9% increase in lifespan.[16] This equates to an increase in more than seven years of human life. The expectation (hope) is that even elderly humans may gain significant improvements in health and increases in lifespan by taking rapamycin.

Rapamycin is the name of the compound that is naturally produced by the soil bacteria *Streptomyces hygroscopicus*. Pfizer is the drug company that holds the patent on rapamycin under the brand name Rapamune. The generic name for Rapamune/rapamycin is sirolimus.

Obstacles to Taking Rapamycin

Rapamycin is a prescription drug. However, most physicians will initially not be aware of it, and many physicians who have heard of it only know of it as an immunosuppressant agent or a cancer chemotherapy drug. Thus, physicians will need to be educated about the safety and potential benefits of rapamycin with episodic dosing to achieve partial inhibition of mTOR. This was one of my goals in writing my new book ***Rapamycin, mTOR, Autophagy, and Treating mTOR Syndrome.*** Also, many physicians now work in group practices that have "standard of practice" guidelines that limit what medications can be prescribed.

The cost could be another obstacle as even the generic version, sirolimus, is relatively expensive. The wholesale price to pharmacies for a bottle of 100 2-mg sirolimus tablets is over $3,000. Some people report being able to have their prescription covered by their

insurance. I personally take 6 mg of rapamycin/sirolimus weekly (3 of the 2 mg tablets), and I get my monthly prescription of 12 tablets for a $20 copay.

Natural Methods to Inhibit mTOR and Activate Autophagy

Exercise at moderate- to high-intensity levels is known to inhibit mTOR and activate autophagy.[17] This has been documented in animal and human clinical trials.[18]

Intermittent fasting and/or time-restricted eating are dietary trends that have recently increased in popularity. These programs recommend consuming all your daily food/caloric intake within a shorter time period. The 16:8 protocol is the most popular regime where food is consumed within an eight-hour period, which leaves 16 hours without food, or fasting.

Rapamycin: Risks and Side Effects

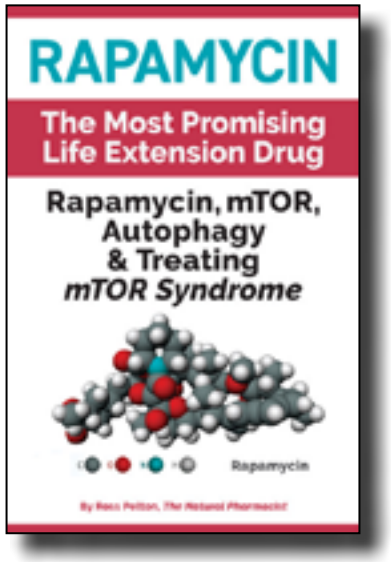
There is a long list of *potential* side effects, but they are associated with daily and/or high dose administration. Rapamycin is very safe when taken intermittently (e.g. once a week) as opposed to daily. Potential side effects include stomatitis and mycositis (ulceration of the mucous membranes of the mouth and the digestive tract), low platelet count, low iron levels and anemia, and leukopenia (low white blood cell count). But, these side effects seldom occur when rapamycin is taken intermittently.

In a recent placebo-controlled trial, *healthy elderly volunteers* (70-95 years old) took either 1 mg of rapamycin or a placebo daily. At the end of the eight-week trial, no significant side effects occurred.[19]

I am a strong advocate of laboratory testing. I recommend getting lab tests before starting rapamycin and then rechecking your labs on a periodic basis. This enables you to track your progress and determine which dose and frequency work best for you.

I recommend the following lab tests: CBC with Differential, Comprehensive metabolic panel, coronary risk panel, and iron total iron-binding capacity (TIBC). These tests enable you to track your hemoglobin, white and red blood cell count, iron levels, triglycerides, blood sugar, and blood insulin levels.

Rapamycin has been an FDA-approved drug for decades (taken daily) to prevent organ transplant rejection. However, newer research is revealing that when rapamycin is taken at lower



doses (once weekly rather than daily), autophagy is activated, which results in significant health benefits. In fact, rapamycin is ushering in a new era of life extension.

Although long-term human clinical trials have not yet been conducted, results from studies on various species of animals consistently reveal that rapamycin therapy slows down the onset of a wide range of age-related diseases. Two trials to look for: The TRIAD Trial and the PEARL Trial.

The TRIAD Trial. The TRIAD trial, which is part of the larger Dog Aging Project, is a double-blind, placebo-controlled clinical trial of the drug rapamycin. Dogs get many of the same age-related diseases that humans get, such as cancer, arthritis, and heart disease. The goal of the Test of Rapamycin in Aging Dogs (TRIAD) trial is to confirm, in a double-blind, placebo-controlled clinical trial, that treatment with rapamycin improves health and slows down the onset of age-related diseases.

The PEARL Trial. PEARL stands for the Participatory Evaluation of Aging with Rapamycin for Longevity. AgelessRx, in affiliation with the University of California, has succeeded in raising $183,000 in crowdfunding donations, which will enable the launch of this double-blind, randomized, placebo-controlled human clinical trial to evaluate the safety and effectiveness of rapamycin in healthy adults for longevity. The PEARL trial is also revolutionary because it is the first nationwide telemedicine trial and the first large-scale human intervention trial on longevity.

My new book titled ***Rapamycin, mTOR, Autophagy & Treating mTOR Syndrome*** can be ordered at www.LifeExtension.com/rapa.

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EZTREK™ Medical Food* – A New Era in Combatting Chronic and Acute Inflammation

by Brian Scott Peskin

Peskin Pharmaceuticals®

The recent pandemic has made all levels of physicians' lives even more stressful than before, especially with respect to dealing with an ongoing increase in conditions of general systemic inflammation. We hope this information can help your patients – if they wish to take action – under your guidance.*

Peskin Pharmaceuticals® follows the new medicament paradigm. Instead of treating diseases/disorders by blocking/impeding and "managing" the illness' progression, our focus is reversing and optimizing the resolution of the underlying disease/disorder. Once inflammation is reduced, healing accelerates naturally. Until now, there has not been a medicament designed to naturally and safely resolve inflammation by maximizing the production of prostaglandin PGE1. **EZTREK**™ is the new adjuvant medical food – compensating for an impaired delta-6 desaturase metabolic pathway – the medical profession has been lacking.

Systemic inflammation is a part of many intractable diseases, including cancer, CVD, diabetes, arthritis – to name a few. Compensating for an impaired delta-6 desaturase metabolic pathway is fundamental and required to successfully reverse the underlying etiology of these diseases/disorders. Once inflammation is reduced, healing accelerates naturally. EZTREK™ is the clinical culmination of this groundbreaking science.

Our unique focus is compensating for an impaired delta-6 desaturase (D6D) metabolic pathway – maximizing PGE1 production to decrease inflammation. No modality of patient treatment can be maximized without also optimizing patients' EFA-based metabolic pathways; in particular, D6D and PGE1.

*Per FDA Regulations, *unlike a Nutritional Supplement* – to **purchase a Medical Food, the patient *must* be under the continuing care of a licensed medical practitioner who can prescribe medications.**

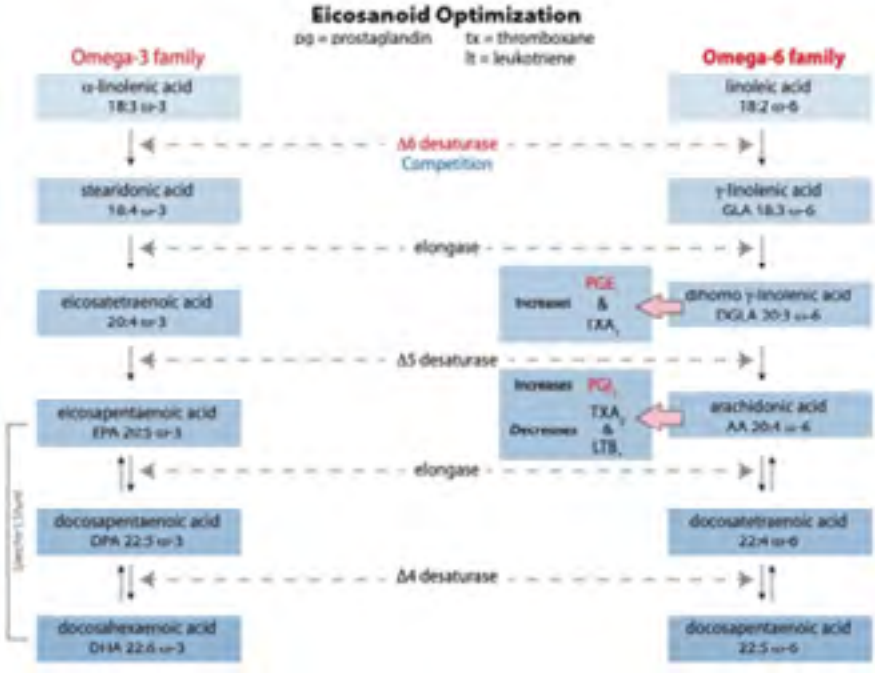
Introduction

Unfortunately, many physicians and healthcare professionals have not been exposed to EFA-based science. Although extremely important, the field is mischaracterized by many as simply an exploration of fish oil. It is so much more than that. Because the field of eicosanoid physiology and its strong link to pathophysiology of disease is technically complex, this article is limited to an overview focusing on impaired delta-6 and a direct consequence of that impairment – decrease in production of the anti-inflammatory PGE1. Compensating for this impaired pathway has not been fully exploited until now. Because this field is so underpublicized, this article's purpose is to provide significant insights – that most physicians have not yet seen.

While treating patients for a particular disease/disorder, the patient may also be suffering from an essential fatty acid (EFA) impairment of the delta-6 desaturase pathway (D6D). This impairment is increasing rapidly in the general population and in younger select patient populations. The increase in disease can be explained from a biologic, chemical, and pathophysiologic viewpoint. **The body's initial modulator of inflammation is PGE1**, which **requires fully functional linoleic acid** (LA). This is accomplished via the delta-6 desaturase pathway (*See* Figure 1). **PGE1 is a potent anti-inflammatory, a systemic vasodilator – regulating the cellular transport system – and an immune system regulator.**

Importantly, PGE1 can exert both immunosuppressive and immuno-

Figure 1



enhancing activities in *vivo* – by the body on an "as needed" basis.[1] PGE1 modulates critical T-cell activation from dysregulated release of interleukin (IL)-6, IL-17, and other cytokines.

As you know, understanding a disease's etiology is crucial. If the D6D pathway is impaired or inhibited, all subsequent long-chain derivatives (gamma-linolenic acid (GLA), dihomo-γ-linolenic acid (DGLA), arachidonic acid (AA), eicosapentaenoic acid, (EPA), docosahexaenoic acid, (DHA), etc.) made via successive desaturase pathways are also impaired – causing a down-the-line "cascade of impairment." (See Figure 1)

Autoimmune diseases/disorders have become epidemic. A physiologic explanation is because an impaired D6D pathway significantly decreases PGE1 output. **PGE1 "throttles down" the inflammation cascade**. [Technically, PGE1 raises levels of cyclic adenosine monophosphate (cyclic AMP), 15(OH)DGLA, inhibits conversion of free arachidonic acid to leukotrienes and other metabolites of 5- and 12-lipoxygenases, and initiates T lymphocyte suppressor cells.]

Important note: Pharmaceutical "anti-inflammatory" drugs (i.e., steroids/corticosteroids/NASIDs) work by blocking or impeding critical pathways (e.g., cyclooxygenase – COX-1 and COX-2, lipoxygenase, etc.). Long-term, these drugs inhibit the D6D enzymatic pathway and decrease critical PGE1 and PGI2 (prostacyclin) signaling molecules – leading to serious side-effects. Short-term, they "treat/minimize the symptoms" but inadvertently "feed the cause" – resulting in long-term negative effects.

To the contrary, optimizing PGE1 output via a properly calibrated EFA formulation will *not cause* harmful or unintended side-effects (e.g., addiction).

NSAIDs *block* the COX enzymes and reduce production of critically important prostaglandins. *Steroids* are even more *disruptive to EFA metabolism*, and long-term drug intolerance occurs. Tumor necrosis factor (TNF) inhibitors carry their own black box warnings.

As the following journal article details, there are a multitude of factors causing impairment of the D6D pathway:[2] "…Other factors which **inhibit D6D** activity are **diabetes**, **alcohol** and **radiation**, all of which may be associated with accelerated aging. **PGE1 activates T lymphocytes**, inhibits smooth muscle proliferation and thrombosis [blood clotting], which is important in gonadal function and raises cyclic AMP levels in many tissues."

An additional and often overlooked significant cause of D6D impairment is because *patients (unknowingly) consume adulterated cooking oils*; often over decades – laying the foundation for this metabolic impairment.[3] As Land's important, yet underpublicized experiment using radioisotopes clearly shows: *The amount of adulterated/highly processed and nonfunctional EFAs that are incorporated into the cell/tissue/organ, is in direct proportion to the amount of their consumption*.[4] This result was confirmed.[5]

Of course, an impairment in the functioning of one organ/tissue system, can lead to impairment of another organ/tissue system. This aggravates chronic inflammation which will start a chain reaction. If anti-inflammatory pathways are not activated, the results can be disastrous, as we have seen with the Covid pandemic.

I find an illustration may be helpful. Picture a house in Houston, Texas, in late February 2021. The ambient temperature dropped dramatically even though the exterior structure was sound. Many people had to abandon their homes because utilities (electricity, heat, and water) were not properly functioning.

This house/utilities analogy is applicable to what is required for a patient's EFA metabolism to be fully functional (*See* Figure 2). There are three main classes of EFA-related function:

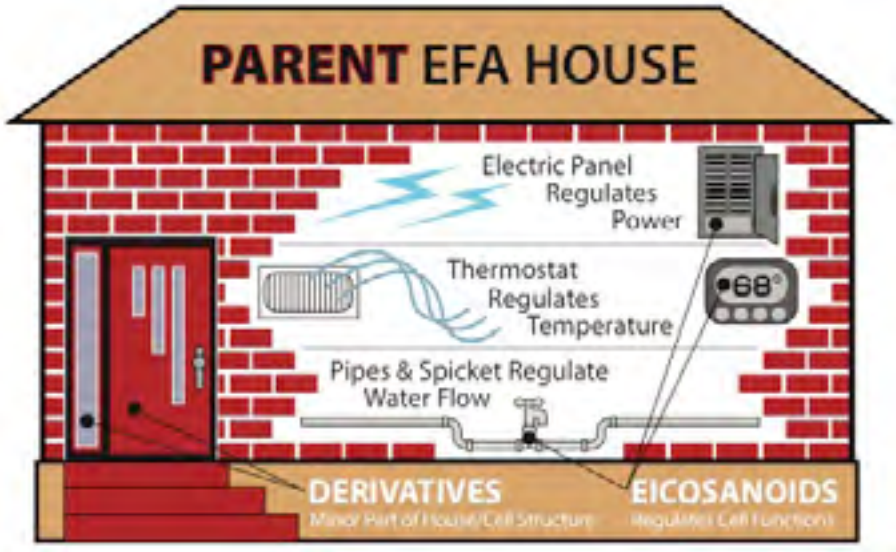
1) **Parents (Parent Essential Oils)**: The "brick and mortar" of each cell membrane (Parent omega-6/-3; LA (linoleic acid) and ALA (alpha-linolenic acid)) – high quantities, 100 trillion cell membranes with 25% -33% of "Parents" incorporated into each cell's lipid bilayer.[6]
2) **Derivatives**: Made from both "Parents" in small quantities (e.g., GLA, DGLA, AA, EPA, DHA, etc.).
3) **Eicosanoids (such as PGE1)**: The complex signaling molecules. Made from the derivatives in even smaller quantities. They may not even enter the bloodstream and can be extremely short-acting.

A home with broken/crumbling walls and great heat and water is insufficient for living, just as a home with great structure (lots of Parent EFAs only) and no electricity, heat, or water in winter is insufficient for living.

Prescribing a precise combination of both quantities and ratios of all three classes of EFA-related components rewards the physician with improved patient outcomes.

Note: Quoted passages are used extensively. I want you seeing the scientist's/researcher's direct statements. Following is a brief, significantly referenced sampling of substantial patient populations ➤

Figure 2



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with diseases and disorders caused/associated with a delta-6 desaturase impairment. There are many others.

Type I and Type II Diabetic Patients

Your diabetic patients often suffer from numerous issues such as retinopathy, neuropathy, nephropathy, and foot ulcers. It is well documented that diabetic patients have impaired D6D metabolic pathways from impaired insulin production.[7,8,9] In particular, this metabolic defect causes a poor anti-inflammatory response in Type I patients. Even with insulin therapy, the D6D pathway remains deficient: "Diabetes, even when controlled by regular insulin injections, reduces the metabolism of linoleic acid, but the effect [of insulin use] is less than previously published. The fatty acid compositions of plasma and liver microsomal lipids are *not reliable indices of the delta-6 desaturase activity in diabetes*."[10] In this enormous patient population, the inaccuracy of this marker is underpublicized.

Type II patients also suffer significant impairment of D6D activity:[11]

- "The effect of *prostaglandin E1 on the increased binding* of the insulin was found to be reversible…. *Binding capacity increased 2-fold*."[12]
- "Levels of PGE1 in the serum of IDDs [insulin dependent diabetics] were significantly lower than those of the healthy volunteers p<0.002 at all sampling times."[13]
- "…These results demonstrated that PGE1 maintained the phenotype of VSMCs [vascular smooth muscle cells] via the AKT/mTOR-dependent autophagy, which prevented diabetes-induced vascular complications."[14]

Insulin sensitivity increases with PGE1 output.[12] Because of the reversibility of insulin binding, the impaired pathway must be compensated for on a daily basis. With EZTREK™ your patients may require less insulin and will certainly suffer fewer complications.

Frustrating for physicians is that diabetic patients frequently consume an overabundance of p*rocessed foods containing adulterated oils*.[3] They are at great risk for chronic low-grade cellular inflammation – triggering long-term cellular stress. The team, led by Professor Ernst, described how the cell's UPR [unfolded protein response] senses nonfunctional/adulterated membrane lipids and responds accordingly, triggering chronic inflammation:[15]

> According to this new mechanism, the UPR is activated not only by misfolded proteins, but also by anomalous membrane lipid compositions. Secretory cells [e.g., the pancreas] are particularly sensitive to these changes, because they have already activated their UPR to produce more proteins and therefore at risk of 'overheating' [inflamed]. The study provides a new perspective on the active role of biological membranes may be a game changer for the understanding of a great variety diseases.[15]

This is highly underpublicized, yet important information.

Wound Healing

Fat cells, if fully functional, help to heal a wound. They can be motile and not exclusively stationary:[16]

> After arriving at the site of a wound, fat body cells perform several useful functions [including minimizing infections]…. The fat cells crowd into the wound and waft debris to the edges of it, where the debris can be consumed by the immune cells. The fat cells are large enough that anywhere from one to four cells can plug the wound, playing a role similar to a clot or scab in vertebrates. The cells physically keep bacteria out of the wound while it heals, while helping increase the production of antimicrobial peptides to quell any infections. The fat cells stay at the wound site until it is healed. 'Then they detach and just swim off, as though their job is done,' Martin says.

With processed/adulterated cooking oil consumption, their healing capability is impaired. Does this effect translate to humans? It likely does.

Lipid-Enveloped Viruses, Including Covid/SARS

For a multitude of reasons, Covid has been devastating to physicians. Following is important, yet underpublicized lipid science: The majority of viruses are enveloped with lipids. Fatty acids of the 16-20 carbon atom range inactivate viruses. In particular, fatty acids of the omega-6 series are known to inactivate (lipid) enveloped viruses.[17] "PUFAs (polyunsaturated fatty acids) have anti-bacterial, anti-viral, anti-fungal, anti-parasitic actions. LA, ALA, and AA have bacteriostatic effect on both gram-positive and gram-negative bacteria. Both LA and AA can inactivate animal herpes, influenza, Sendai, and Sind-bis virus within minutes of contact."[18] "There are millions or billions of these viruses out there. The immune system fights back and attacks the virus; this is what causes inflammation and fever. But in extreme cases, the immune system goes berserk; particularly in the 'Coronavirus' (SARS-CoV-2); [causing a cytokine explosion], causing more damage than the actual virus."[19]

The physician is now presented with a new class of patient (with unique challenges) – the Covid "long-hauler." Fortunately, there is help and these harmful effects can be mitigated: "Essential fatty acids are natural anti-inflammatory agents and therefore decrease the production of cytokines and histamine, which can contribute to neurotransmitter imbalance."[20] PGE1 activates (Cytotoxic) T Lymphocytes – the body's powerful "killer cells" of intruders/infections/bacteria/viruses, etc. (British Society for Immunology).

Research suggests a direct structural link between LA, COVID-19 pathology, and the virus itself and suggest that both the LA-binding pocket within the S protein and the multi-nodal LA (Parent omega-6) signaling axis, represent excellent therapeutic intervention points against SARS-CoV-2 infections.[21] PGE1 "puts the brake" on "cytokine storm." Cytokines, proteins, peptides, and proteoglycans that modulate the body's immune response are elevated in patients with mild-to-moderate disease severity.[22]

Massive oxidative damage to the lungs has been observed in areas of consolidation documented on lung radiographs and CT scans in patients with COVID-19. Because disseminated virus can attach itself to cells containing an ACE-2 (angiotensin-converting enzyme

Sample Clinical Results

C-reactive protein (in a cancer patient) – 12/06/2021
"…3 high-sensitivity *CRP tests* conducted since June [2021]. June value was 1.4, mid-September was 1.8, and late June was 0.7. The 0.7 value [*61% decrease*] represents approximately 3½ weeks of EZTREK™ use."

Hip fracture (in pre-treated female) – 02/07/2022
"92-year-old female fell – 3 fractures of hip; similar event 10 years prior. She had been taking EZTREK™ for 6 months prior to falling. After 10 days skilled nursing, projected time to home using walker, was 6-8 weeks. She started walker after 1 week using walker as before, normally, with *full recovery* at home in 4 weeks. *PT no longer required*."

Pain – 02/08/2022
"I injured my back mid-2021. I rehabbed using exercising and stretching. I did not take drugs. I felt better but with any sudden movements, 'I really felt it.' I started using EZTREK™ and within 7 days the muscle *inflammation in my back subsided to the point that I moved freely without concern*."

Rheumatoid arthritis
(in a breast cancer patient using EZTREK™ precursor)
"55 y/o woman with bilateral breast cancer treated with PEOs postoperatively after mastectomies to optimize her chest wall healing with reconstructive implants. The patient did well and *after approximately 5 weeks* also reported that the *moderately severe long-term pain of arthritis in both feet had resolved to the point* that she was *able to d/c her arthritis medication permanently."*

Cardiovascular disease (with EZTREK™ precursor)
"One of my patients, a 68-year-old male, smoker, I have followed on yearly basis beginning in 2005. In spite of all routine conventional treatment that included blood pressure medication, a "statin" drug, high-dose niacin, co-enzyme Q-10, and a daily aspirin, his coronary plaque volume continued to progress, although an acceptable slow rate. As you can see, for the first time from 2007 to 2008, the volume of plaque decreased from 39 to 30, which is a decrease of 22% when annualized on a yearly basis. *I have never seen a decrease of coronary artery plaque volume by more than 5% in one year*.

"I have important news regarding our study. Patient zero, who brought PEOs to my attention, came back for heart scan. Last April he had a Cardiac calcium score that went down by 20% and the only thing it could be attributed to was the PEOs he started taking for cancer prevention. Well, his score now went up by slightly more than 100% when calculated on an annual basis. My first question was when *did you stop taking the PEOs?* Sure enough, he stopped the end of August. [Note: This proves a direct cause/effect relationship of the medicament's effectiveness.]"

Neuropathy (in a cancer patient) – 02/28/2022
"52-yr-old Hispanic female. History of Her 2 positive *stage 4 breast cancer for 17 years*. Mets to bone and liver. Spine, clavicle, rt femur. *Chemo-induced neuropathy plus 3 years*. She has been on EZTREK™ for *3 weeks and is having less problems with pain from neuropathy*. She reports *more energy and feels stronger*. *This is an exciting case as the scars underneath both arms are already getting softer*. Will be having scans in 2 months. She is *limited on remaining options for treatment*, so EZTREK™ is the only thing she is doing at moment, as she finished radiation one month ago."

Lung cancer (with an EZ precursor)
"In a patient of mine, *this tumor is no longer visible on the chest x-ray*, which surprised the pulmonologist. 'He stated that he never or rarely experienced this.' After a chest X-ray was made, he went through the CT scan and then he had a pathologic tissue diagnosis. The tumor was 4.6 cm long. According to the oncologist, the tumor is coarse cell and slow growing." [Note: A thoracic surgeon – cancer specialty – stated, "*Impressive and unheard of*."]

COPD (Case #1) – 01/15/2022
"I was diagnosed with *COPD over 10 years ago*. Mine is from lupus and chronic bronchitis. I'm a stage 2. I also have a history of pneumonia over the years. *I have been taking Albuterol for 10 years now plus Symbicort and Prednisone.* The doses go up when I am having flares. Over the past few months, I have struggled with shortness of breath, wheezing, and coughing. When I started EZTREK™, within an hour, I could actually feel my lungs opening. Over the first week *I could feel myself able to take a deeper breath* and expand my lungs. *Over the past 2 plus weeks I have reduced my prednisone from 10 mg to 2.5 mg a day. I am no longer using my Albuterol*. I am still on Symbicort. *I have more energy and am able to walk without being winded*. My *blood pressure is normal* now and *pain has reduced completely*."

COPD (Case #2) – 02/28/2022
"54-yr-old female. History of smoking less than 1 pack a day for 20 years. Diagnosed with *COPD 3 years ago*. Put on several medications. History of Covid-19 which caused *damage to lungs*. Pneumothorax with collapsed lung that required hospitalization. *Ct showed significant scarring*. Pulmonologist was guarded on any improvement, stating, 'Your case is grim.' She has labored breathing and *required 24-hour oxygen*. On Feb 28, 2022, she saw pulmonologist and had a *CT and PFT evaluation of lungs that showed obvious positive changes*. (She has only been on EZTREK™ for one month.) Her *pulmonologist was pleasantly surprised*. She *no longer requires oxygen* and *can now speak and move about without being winded*. Nothing else changed other than adding EZTREK™.

Lyme/tick-related – 02/10/2022
"I have a patient taking EZTREK™ for 1 month and she says her *brain fog and mental clarity have greatly improved* (a result of decreased inflammation of the brain). She has a number of problems such as Epstein-Barr, hypothyroid, Lyme, and post-Covid fatigue. Nothing else changed other than adding EZTREK™."

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2) receptor, the disease can spread and damage organs and soft tissues throughout the body, including the lungs, heart, intestines, kidneys, blood vessels, fat, testes, and ovaries, etc. The disease can increase systemic inflammation and induce a hypercoagulable state. Without anticoagulation, intravascular blood clots can be devastating. However, *PGE1 increases blood flow (vasodilation) and inhibits platelet aggregation.*[23,24]

Dermatology: Epithelial/Epidermis Tissue/Atopic Dermatitis

There is an increasing epidemic of dermatologic diseases. An understanding of EFA metabolism can help physicians combat this rise in cases: "Atopic dermatitis (AD) has been related to a deficiency of D-6 desaturase…."[25] Furthermore, there is identification of a fatty acid delta-6 desaturase deficiency in human skin fibroblasts.[26] [*Fibroblasts* are in the dermis underneath the outer layer of skin. Fibroblasts also allow skin to generate connective tissue to recover from injury.]

Alzheimer's Disease

With a defective cellular lipid membrane, membrane-based proteins may leak out. This is likely why the beta-amyloid hypothesis as the cause of Alzheimer's has failed and pharmaceutical success in the area remains largely ineffective. *Alzheimer's is now known as a cardiovascular disease* caused by cellular impairment in the (at least 40 million) capillaries in the brain (Capillary's EFA structure is comprised of exclusively Parent omega-6). The following extraordinary journal article published in 1990 "hits the nail on the head":

> The findings strongly indicate abnormalities in D-6 desaturation. Alteration in PUFA desaturation/elongation processes and resultant membrane abnormalities may play a key role in the pathogenesis of Alzheimer's disease. Membrane phospholipids are not only actual membrane constituents, but also determine membrane function. … [T]he findings strongly indicate abnormalities of D-6 desaturase in Alzheimer's disease. The decrease in 22:6 (n-3) further supports altered D-6 desaturase activities. Abnormalities in the destruction/elongation process [initiating with D-6 desaturase] of PUFA (polyunsaturated fatty acid) and resultant membrane dysfunction may play a key role in the pathogenesis of Alzheimer's disease.[27]

"Evidence is fast accumulating which indicates that Alzheimer's disease is a vascular disorder with neurodegenerative consequences rather than a neurodegenerative disorder with vascular consequences."[28]

Furthermore, as the 2011 *Nature Reviews Neuroscience* article makes clear:[29] "Patients with Alzheimer's disease or other dementia-causing diseases frequently show focal changes in brain microcirculation…consistent with the *chronic* cerebral hypo-perfusion and hypoxia that were observed in these individuals."

"In a series of 300 autopsy cases of AD, Kalaria and Ballard reported 98% CAA [cerebral amyloid angiopathy], *100% microvascular degeneration*...."[30] By compensating for an impaired D6D metabolic pathway, EZTREK™ has great promise in helping these patients.

Cardiovascular Disease

The EFA content of the lining of arteries (intima) and structure of the capillaries is comprised entirely of Parent omega-6 (LA).[31,32] If this omega-6 is adulterated/nonfunctional from patients consuming processed foods/processed cooking oils, then the arteries/capillaries/veins will suffer chronic inflammation, resulting in initiation of plaque, occlusions, and disfunction.[3]

Staprãns' groundbreaking insights make clear it is *the exogenous, consumed, and already adulterated LA from processed foods* – not in *vivo oxidation* – that are the cause of the deleterious CVD-related and other systemic damage from "oxidized cholesterol."[33] The renowned German biochemist Spiteller (University of Bayreuth) independently confirmed this, adding significant insights.[34]

A 1997 study published in the journal *Arteriosclerosis, Thrombosis, and Vascular Biology*, reported: "Cholesterol esters [cholesteryl esterized with EFAs] are the predominant lipid fraction in all plaque types…" It also stated that, "Intimal [innermost arterial lining] macrophages contain substantial amounts of cholesterol *esters*, which are *rich in PUFAs* [*including substantial amounts from commonly consumed foods containing already oxidized (exogenous) Parent omega-6*].[35]

The brilliant pathologist, Vladimir Subbotin, demonstrated to me via high resolution images that the endothelium intima (inner lining of the artery), is actually multi-layer – up to 30 layers in an adult – significantly increasing the potential for CVD, because of significantly increased surface area allowing potential for significantly more inflammatory damage.[36]

Intimal hypoxia (lack of oxygen) is also an initiating cause of CVD, and fully functional Parent omega-6 significantly improves cellular oxygenation. Dr. Campbell's seminal article, "Abnormal fatty acid composition and impaired oxygen supply in cystic fibrosis patients," demonstrates that the Parent omega-6's oxygen in the cell membrane can (reversibly) disassociate (release) oxygen – at physiologic pressure – increasing the tissue cellular oxygenation. *In addition to the bloodstream, oxygen can come from the cell membrane itself.*[37] Chronic low-grade inflammation plays a role in cardiac hypertrophy and heart failure.[8,38] Both microcirculation and macrocirculation of the heart are improved with the strong anti-platelet aggregation effect of PGE1.[39] Increased cellular oxygenation/decreased hypoxia also occurs with increased PGE1.[40] Increased blood flow and cardiovascular support also occur.[41]

Furthermore, and most importantly, *LA is not inflammatory*; it is the *adulterating/chemical processing – for long shelf-life – by food processors that turns LA inflammatory*. As the 2009 American Heart Association article makes clear: "This current systematic review and meta-analysis of prospective cohort studies of LA consumption *provides robust evidence that higher LA intake is associated with lower risk of CHD in a dose-response manner*." [42]

continued on page 55 ➤

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Dr. Iichiroh Ohhira: A Pioneering Genius in Probiotic Science


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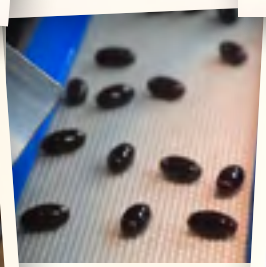
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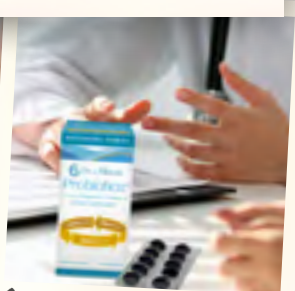
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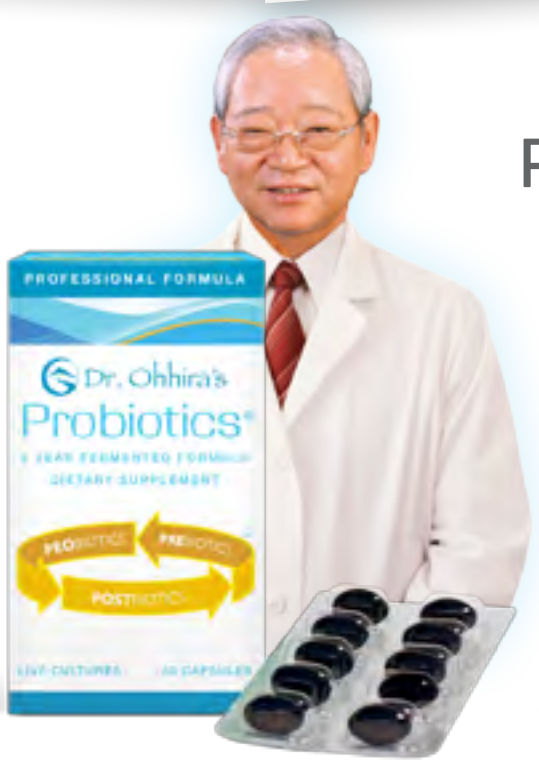

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➤ *continued from page 52*

Harris, lead author for the AHA writing group, makes clear: "… [O]mega-6 PUFAs also have powerful anti-inflammatory properties that counteract any proinflammatory activity….It's incorrect to view the omega-6 fatty acids as 'proinflammatory.'" Harris spells out in an AHA press release, "Eating less linoleic acid will not lower tissue levels of arachidonic acid because the body tightly regulates the synthesis of AA [arachidonic acid] from LA [linoleic acid]." According to Harris, one of the ideas promulgated by diet and nutrition books is the idea of an optimal omega-6:3 ratio [advocated by nutritionists], something he says is based on a "*misinterpretation of the science*."[43]

"Microcirculation and macrovascular circulation of the heart are improved with the strong anti-platelet aggregation effect of PGE1."[32] "Prostaglandins are capable of limiting thrombosis."[44] EZTREK™ is a new tool for you and your patients in the cardiovascular space.

Fatty Liver Disease, Including NAFLD

Fatty liver disease consists of a variety of pathological states ranging from simple buildup of fat in the liver (hepatic steatosis) to nonalcoholic steatohepatitis, cirrhosis, and ultimately liver failure. This disease has reached epidemic proportions with up to 30% of Americans having some level of NAFLD. Reductions in hepatic insulin sensitivity are also documented:

> NAFLD is a low-grade systemic inflammatory condition. …Thus, release and timely formation of *anti-inflammatory bioactive lipids is necessary* to prevent NAFLD and/or resolution of inflammation seen in NAFLD…. Nonalcoholic fatty liver disease (NAFLD) is associated with decreased levels of AA, EPA and DHA and their anti-inflammatory products PGE1, PGD2, LXs, resolvins and protectins with a concomitant increase in pro-inflammatory cytokines, IL-6 and TNF-alpha and bioactive lipids PGE2, LTs and TXs. The low levels of AA, EPA and DHA can be a result of decreased activities of D6 and D5 desaturases.[45]

"An important aspect is the pathological process that occurs in nonalcoholic fatty liver disease (NAFLD), a condition in which *oxidative stress of nutritional origin* (fat and carbohydrates overload), in association with obesity, produces a significant and *drastic decrease in the activity* of the delta-5 and delta-6-desaturase enzymes in the liver."[46]

Multiple Sclerosis (MS)

"Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) of an unknown origin."[47] MS affects approximately 200,000 patients per year. An impaired D6D metabolic pathway decreases PGE1. A shortage of EFAs is a risk factor. *EFAs are important in the active phase of myelin synthesis.* Numerous conditions in addition to impaired myelin synthesis occur, such as impaired learning, motor, vision, and auditory abnormalities. Both the central and peripheral nervous systems are comprised of significant amounts of Parent EFAs (PEOs).[48,49] The myelin sheath contains 70-85% lipids.[50]

Cancer and Radiation Therapy

Chronic inflammation, which contributes to heart disease, may be a key to unlocking the mysteries of cancer. *Scientific America's* feature article delivered a shocker in the July 2007 issue, pages 60-61. The article states that cancer researchers have "changed focus." The eminent cancer researcher Robert Weinberg of MIT states: "The connection between inflammation and cancer *has moved to center stage* in the research arena. … [I]nflammation is the fuel that feeds it [the malignant cancer]… In this rewriting of the textbook…"[51]

"Misoprostol, a [injectable] prostaglandin (PG) E1 analogue, is one of the most effective radiation protectors of the PGs [prostaglandins] investigated to date."[52] "Wound healing was significantly delayed because of X-irradiation, but PGE1 administration prior to irradiation led to a significantly shorter delay in wound healing compared with controls. It has been indicated that experiments in the utilization of EFA in cancer modulation exist regarding intake and effect on cell structure and biochemical interactions within the cell in the prevention of cancer development."[26]

"A lower level of D6D was seen in breast tumors compared to normal tissues."[53] "Chronic inflammation is a major causative factor in human malignances. Pro-inflammatory cytokines influence tumor microenvironment and promote cell growth and survival and angiogenesis such that tumor cell growth is facilitated."[54]

COPD

COPD is also associated with systemic inflammation. Furthermore, there is a markedly increased risk of cardiovascular disease (particularly coronary artery disease) and lung cancer in patients with COPD. Also, there is strong associative evidence that the inflammatory cells/mediators in COPD are also relevant to the development of cardiovascular disease and lung cancer.

"[Current] pharmaceutical therapy for the treatment of inflammatory process in COPD is relatively ineffective. Corticosteroids remain the cornerstone of asthma treatment but are generally relatively ineffective in COPD."[55] EZTREK™ offers new hope to patients of COPD.

Special thanks to both Canadian EFA / Eicosanoid consultant, Paul Beatty, BA, BPHE, MBA (email: efapaul@yahoo.ca) for his technical assistance, and Geoffrey L. Robb, MD, FACS Professor / Past Chairman (1998-2013) Department of Plastic Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, for his invaluable assistance.

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References are available online at www.townsendletter.com.

Brian Peskin is a theoretical research scientist at Peskin Pharmaceuticals® specializing in lipids-based pharmacognosy. Peskin Pharmaceuticals® follows the new medicament paradigm. Instead of treating diseases/disorders by blocking/impeding and "managing" the illness' progression, our focus is reversing the underlying disease/disorder. Peskin's focus is the modulation of physiologically targeted essential fatty acids (EFAs) and their eicosanoid metabolites. He is the formulator of the Medical Food, **EZTREK**™ – to heal and minimize/prevent inflammation in diverse patient populations by compensating for an impairment in the delta-6 desaturase metabolic pathway. Once inflammation is reduced, healing accelerates, naturally. Peskin Pharmaceuticals® is at the forefront of this groundbreaking science.

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Regenerative Orthopedics: Avoiding Surgery with Stem Cell/PRP/Prolotherapy

by Peter A. Fields, MD, DC

The regeneration of the joints and spine may seem like a thing of the future, but it's not. It is happening today.

For patients who have been told they need to have a joint replacement because they have severe arthritis, a degenerated joint, bone-on-bone, or worn away cartilage...there is now another option...stem cells! Stem cells are an exciting field because they have the potential to regenerate cartilage and repair the damaged joint. It's no wonder regenerative therapies are growing in popularity in the medical world!

Stem cell is a type of non-surgical therapy called regenerative orthopedics, which include treatments like stem cells, PRP, and prolotherapy. These treatments are so effective, they can be used as an alternative to joint replacement. It is a very exciting time in the field of regenerative medicine.

With Regenerative Orthopedics, You Can Avoid the Problems That Come with Surgery

I am not against surgery. But I am concerned about excessive orthopedic surgeries. Many times, they have little or no effect. And sometimes they have disastrous results. The rush to "cut first and ask questions later" approach should be avoided, especially when there are alternatives that people are demanding. Regenerative orthopedics, like stem cells, PRP, and prolotherapy are effective options to avoid joint replacement. *Remember that once surgery is done, it cannot be undone.*

There is more good news! Following a regenerative orthopedics procedure, patients are not only able to continue with exercise, but movement is encouraged. Sure, there are a few days of rest, but motion is encouraged. Slowly returning to normal activities is expected.

With regenerative stem cell treatments, there is no down time, no wound infection, no antibiotics, no multiple doses of prescription narcotics, and no physical therapy for rehabilitation necessary.

These treatments allow the body to heal itself. There are none of the problems associated with total joint replacement such as the wound not healing, device failure, bleeding into the wound, and none of the worst post-surgical problems – more pain!

Did you know that joint replacements only last 8 to 12 years? That means many patients will need to have the procedure done several times during their lifetime. On the other hand, with stem cell therapy, in the majority of the cases, the treatment only has to be done once if properly performed.

The Gold Standard in Stem Cell Therapy

In our practice, we use The Gold Standard in Stem Cell Therapy, which combines several different regenerative treatments to effectively repair joints. We treat the entire joint! Besides stem cells from bone marrow, we use stem cells from fat (lipoaspirate), along with PRP (platelet rich plasma), which provides growth factors to help the stem cells grow. In addition, we treat the outside of the joint with the above as well as apply dextrose prolotherapy to the soft tissue areas where many of the problems originated.

That means we treat the cause and the effect; not just the effect as many others do. We repair the source of the problem, so you have the results you are looking for! These regenerative treatments, along with dextrose prolotherapy in and around the involved joint, offer the benefits of pain relief, regenerative results, and cartilage repair.

Stem Cells from Bone Marrow. Bone marrow is a rich source of stem cells in the body. These stem cells are also termed mesenchymal stem cells and progenitor cells, among other names. Harvesting them from one's own body eliminates the possibility of cross reaction or rejection. These autologous (obtained from oneself) stem cells can regenerate and repair tissue such as cartilage, tendon, meniscus, and ligament.

After extraction and concentration, the stem cells are then injected straight to the area that has a cellular deficiency. Stem cells aid in fibroblastic proliferation where cell growth, proteosynthesis, reparation, the remodeling of tissues, and chondrocyte proliferation occurs.

Studies show stem cells from bone marrow are very effective in the treatment of osteoarthritis. Slovenian researchers compared bone marrow aspirate to other treatments and found bone marrow to be more effective in the treatment of symptomatic knee osteoarthritis, especially in the patients with more severe degenerative changes.[1]

Although studies have shown great results with stem cells alone, in our experience we have discovered that the combination of solutions used in The Gold Standard of Stem Cell Therapy provides the best results.

Adipose Stem Cells. Adipose tissue is also a rich, but different, source of adult stem cells. These cells, harvested from one's own fat, have an extensive

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proliferative capacity. And they too can regenerate ligaments, cartilage, muscle, and other tissue. Adipose stem cells are now being used in musculoskeletal medicine to not only regenerate tissue but also to provide a scaffold to hold stem cells in place and allow them to grow.

The Gold Standard in Stem Cell Therapy uses stem cells in combination with platelet rich plasma and prolotherapy.

Platelet Rich Plasma (PRP). Not all injuries require stem cells to heal. Studies show the effectiveness of PRP in soft tissue injuries, such as moderate to severe ligament and tendon damage, as well as tears in a meniscus or labrum. In a study in the *Journal of Orthopedic Surgery and Research*, the authors concluded that "PRP renders similar results to that of corticosteroids in most clinical aspects among patients with rotator cuff tendinopathies; however, pain and range of motion may show more significant improvement with the use of PRP." This is especially important to point out "considering that the use of corticosteroids may be contraindicated in some patients and may be associated with the risk of tendon rupture." The researchers suggested the use of PRP in place of corticosteroid-based injections among patients with rotator cuff tendinopathy.[2]

Dextrose Prolotherapy. Dextrose prolotherapy is a technique that is used to aid the body in healing by promoting growth of soft tissue like ligaments and tendons that have mild to moderate damage. Various trials and studies have shown the effectiveness of dextrose prolotherapy in treating osteoarthritis, as well as ligament and tendon injuries.[3-5] Since these regenerative treatments are effective at repairing ligaments and tendons, treatment earlier on in the arthritic process has the potential to prevent damage and help to avoid the lifestyle adjustments that often transpire with the disease. In many cases, prolotherapy alone is sufficient to bring the pain relief and repair needed.

Dextrose prolotherapy involves the injection of a hyperosmolar dextrose solution into an injury site to elicit localized inflammation, which is the first step in healing the damaged area. The dextrose solution acts as a proliferant via the induction of local inflammatory and wound healing cascades, including fibroblast cells that make collagen.

What Is the Expected Outcome?

The success rate with traditional prolotherapy, alone or with PRP, is very good for most patients. However, for those cases of advanced arthritis or aggressive injuries, stem cell treatment may be needed to regenerate the defective joint.

In our clinic, patients are treated with The Gold Standard in Stem Cell Therapy, which is using stem cells in combination with PRP and prolotherapy, as well as treating the outside of the joint to accelerate healing and to strengthen and stabilize the surrounding joint structures. These patients report significantly decreased pain, remarkable gains in function and quality of life, boosted exercise ability, increased range of motion, as well as losses in stiffness and crepitus. These regenerative therapies are safe and effective treatment options with the potential to slow down the progression of degeneration while promoting the regeneration of articular cartilage. The treatment is essentially a new paradigm in the treatment of osteoarthritis, and one that decreases the need for surgical joint repair and replacement.

Adult Stem Cell Injections, NOT Embryonic Stem Cell Injections

The stem cell therapy done at OrthoRegen® has nothing to do with embryonic stem cell therapy. Most research and studies have shown that cord blood does NOT have many, if any, stem cells. We only use the patient's own adult stem cells. We take the bone marrow from the patient's own tibia or iliac crest bones and use fat from the abdominal or buttock areas so that the stem cells are the freshest. Additionally, there is no cross contamination this way! After concentrating these cells, we then inject them into the defective joint.

Stem Cell Therapy at OrthoRegen®. When degeneration is advanced, which in most cases means bone on bone, cartilage degeneration, or a recommendation to have the joint replaced, or any combination of these, we use The Gold Standard in Stem Cell Therapy and integrate the regenerative components of blood, fat, and bone marrow, while also treating the outside of the joint. Many clinics use only one or two of these procedures, but we have discovered that this combination acts as an amazing regenerative solution to reverse the damage of a degenerated joint.

Our goal with The Gold Standard in Stem Cell Therapy is to give the patient's joint the best possible chance of repairing itself and to improve treatment outcomes in patients with advanced degenerative conditions. All solutions are centrifuged and concentrated to get a solution with the most concentration of stem cells.

The Gold Standard in Stem Cell Therapy is a great solution for regeneration that addresses the whole joint. Regenerate First; Surgery Last!

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

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

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

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Regulatory Capture on Steroids

review by Jule Klotter

The Real Anthony Fauci – Bill Gates, Big Pharma, and the Global War on Democracy and Public Health
by Robert F. Kennedy, Jr.
Skyhorse Publishing; www.skyhorsepublishing.com
Hardback and Kindle; 449 pp; c 2021; $32.50 (US; print edition)

Since November 2, 1984, Anthony Fauci has directed the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health (NIH). He joined the agency in 1968, after completing medical training, as an alternative to joining one of the armed forces during the Vietnam War. *The Real Anthony* Fauci by Robert Kennedy, Jr., documents how Fauci has used the billions of dollars in NIAID's budget, corporate media, and his influence with powerful allies to capture public health agencies for pharmaceutical interests.

During his tenure, Anthony Fauci – enabled by unquestioning journalists and fawning media support – has created a complex system that ensures pharmaceutical profits with little regard for public health. That path began with the AIDS pandemic in the 1980s. His fearmongering predictions that the general population was at risk from HIV ("the AIDS virus") and that the virus could spread with casual contact increased federal funding for research at NIAID. All attention was on finding vaccines and treatments to combat HIV, declared to be the cause of AIDS at a press conference without peer-reviewed research to support that claim. Possible alternative causes of AIDS such as HHV-6, mycoplasma, and the recreational use of amyl nitrate were ignored. By 1992, Luc Montagnier, co-founder of HIV, was admitting that the virus, by itself, was not enough to destroy the immune system.[1] Yet, scientists who questioned the HIV hypothesis, like molecular biologist Peter Duesberg, were ostracized, censored, lost jobs, and saw their research funding disappear.

With the increased funding from the AIDS pandemic, Fauci provided federal grants to principle investigators (PIs) – academic physicians and researchers who have contracts with pharmaceutical companies and, thereby, wield tremendous influence with their universities and the research hospitals where clinical trials are conducted. Not only do PIs receive federal funding for research, they and their academic institutions collect royalties on any product they help develop when it reaches the marketplace. These same PI researchers act as lobbyists, spokespersons, and serve on FDA and CDC advisory panels that approve drugs and vaccines. The influence of these principal investigators cannot be over-stressed. As Kennedy explains:

> [PIs] use their seats on medical boards and chairmanships of university departments to propagate dogma and root out heresy….They populate the Data and Safety Monitoring Boards (DSMBs) that influence the design of clinical trial protocols and guide the interpretation of clinical trial outcomes and conclusions; the external advisory FDA panel, Vaccines and Related Biological Products Advisory Committee (VRBPAC), that guides determination of whether new vaccines are 'safe and effective' and merit licensure (marketing); and the CDC panel, The Advisory Committee on Immunization Practices (ACIP), that essentially mandates vaccines to children. They are the credentialed and trusted medical experts who prognosticate on television networks – now helplessly reliant on pharmaceutical ad revenue – to push out Pharma content. (p 136).

Despite the need for effective AIDS treatments in those early years, Fauci refused to approve the off-label use of already approved (and often inexpensive) drugs successfully used by frontline doctors, such as the anti-viral AL 721, without randomized placebo-controlled studies. Nor would he fund clinical trials for these treatments until senators, urged on by activists, forced him to change his tune and speed up approval for treatment in 1989 (p 159). FDA, stacked with scientists and doctors from his PI system. had already given Emergency Use Approval for Burroughs Wellcome's drug AZT in March 1987. AZT, a DNA chain terminator, was originally developed in 1964 as a possible chemotherapy drug but deemed too toxic for use. Despite its known toxicity, FDA and NIH bypassed primate studies that would have identified toxic effects (p159), and Fauci ended the study used to approved AZT two months early (at four months instead of six) before long-term adverse effects were evident. "Even more importantly for Burroughs Wellcome shareholders," Kennedy writes, "Dr. Fauci cleared AZT for use on healthy HIV-positive people, meaning people with no symptoms" (p161). That approval expanded the market for AZT, which cost the manufacturer pennies per dose to make yet cost patients $10,000/year (p148).

When Fauci finally agreed to test the less-toxic antiviral Al 721, the clinical studies were sabatoged. When the AL721 NIAID study actually showed signs that the drug stopped viral replication, "Dr. Fauci and his PIs cancelled the trial, making sure that AL721 never went to Phase 2. Dr. Fauci told skeptical activists that he could not get any volunteers to enroll in the study." (p.160). That same excuse was used to stop NIAID trials for ivermectin early in the COVID-19 pandemic, when news stations were reporting hundreds of new cases each day.

Meanwhile, other new drugs to treat AIDS – like NIH-developed didanosine (ddl), which can cause non-cirrhotic portal hypertension (a fatal liver disease) and manufactured by Bristol Myers Squibb – were tested in small studies without placebo controls. In some cases, the test subjects were foster children at NYC's Incarnation Children's Center and similar facilities. These children were forced to take the drugs that often made them very sick and, in some cases, led to their deaths; no adult was looking out for their welfare. Another AIDS drug with known toxicity, Nevirapine, was tested on African mothers and their children – without informed consent.

Jonathan M. Fishbein, MD, was in charge of monitoring and enforcing federal research and ethical policies in NAIDS-sponsored AIDS studies for a short time. He was fired after unearthing problems with Nevirapine and Proleukin trials and then gained whistleblower protection. Dr. Fishbein told Kennedy:

> "I couldn't get a job in public health for five years," Dr. Fishbein says of Dr. Fauci's vendetta. "Everyone in science is terrified of crossing him. He's like a mafia kingpin. He controls everything and everyone in public health." Dr. Fishbein added, "He spreads so much money around and everyone knows he is vindictive. I had one friend tell me, 'I can't risk hiring you because I can't afford to anger Fauci.' Says Dr. Fishbein, "This was my first exposure to the cancel culture."

In 2000, Bill Gates and Fauci formed a partnership. Two years before, Gates, via the William H. Gates Foundation, had announced a $500 million plan to fund AIDS vaccine development. Although the foundation "gives away" money, the "charitable" giving is done in a way that ends up boosting Gates' investments in multinational food, agriculture, pharmaceutical, energy, telecom, and tech companies. "Federal tax laws require the [Bill and Melinda Gates Foundation] to give away 7 percent of its foundation assets annually to qualify for tax exemption," Kennedy explains. "Gates strategically targets agencies and the media, allowing him to dictate global health and food policies so as to increase profitability of the large multinationals in which he and his foundation hold large investment positions" (p 291). Gates added $23 billion to his wealth during the 2020 COVID-19 lockdowns that he and Fauci promoted in corporate media that year.

Gates is also the largest funder of the World Health Organization (p 301). Instead of focusing on improved nutrition and water quality and on reducing poverty, Gates has pushed vaccine development – some of which have had little or no benefit on health but have greatly increased pharmaceutical profits. GAVI, the Vaccine Alliance, is a public-private global health organization launched by Gates in 1999 with a $700 million donation. "GAVI is the most tangible outcome of the partnership Gates sealed with Fauci in early 2000," Kennedy writes. "Under the terms of the partnership, Dr. Fauci greenhouses a pipeline of new vaccines in NIAID labs and farms them out for cultivation in clinical trials by his university PIs and the pharmaceutical multinationals in which Gates holds high investment stakes. Gates then builds out supply chains and creates innovative financial devices for guaranteeing those companies markets in Third World countries" (p. 302-303).

Concerns about biowarfare, raised by the anthrax mailings after 9/11, ushered in fears about new infectious threats, calls for vaccine development, and more. Gates and Fauci with NIH have partnered with military and intelligence to prepare for new pandemics by funding gain-of-function research (increasing microbes' disease-making function) in the name of creating new vaccines. Gates has also directed simulations for global health ministries that "war-game" a bioterrorist attack:

> …the simulations war-gamed how to use police powers to detain and quarantine citizens, how to impose martial law, how to control messaging by deploying propaganda, how to employ censorship to silence dissent, and how to mandate masks, lockdowns, and coercive vaccinations and conduct track-and-trace surveillance among potentially reluctant populations. (p 382)

These simulations emphasize autocratic control and have little to do with effective treatment and public health. And their tactics have been used throughout the COVID-19 pandemic in several countries.

Governments' response to the COVID-19 pandemic is built upon the corrupt foundations initiated by Anthony Fauci during the AIDS epidemic and extended by Bill Gates and his industrial and military partners. Individual researchers caught up in this web, like Andrew Hill who was asked by WHO to evaluate ivermectin's effectiveness early in 2021, succumbed to fears of being cut off from research funding or losing one's job for not going with the program (pp 44-52). For me, this combination of forces explains why early treatments were disparaged, why US academic research institutions sat back and waited for a vaccine instead of searching for off-label treatments (even though out-patient treatment and vaccination are pillars of public health), and why knowledge gained from previous respiratory pandemics about masking and lockdowns were ignored.

During his 40 years as an environmental lawyer, Kennedy has litigated against oil, coal, chemical and agricultural polluters and the "illegal concessions" made by federal agencies on their behalf. But the collusion between Pharma and federal agencies is beyond anything he had seen before: "From the moment of my reluctant entrance into the vaccine debate in 2005, I was astonished to realize that the pervasive web of deep financial entanglements between Pharma and the government health agencies had put regulatory capture on steroids" (p. xv).

Despite years of reading Dr. Alan Gaby's editorials on FDA's Pharma bias and about clinical trials purposely designed to disprove alternative treatments (e.g., Nicholas Gonzalez's cancer protocol and Pauling's use of vitamin C), I was not prepared for the weight of collusion and corruption that has ensnared public health agencies worldwide. Every chapter has hundreds of citations to back up the information. In an interview with Catherine Austin Fitts, Kennedy said the book was heavily vetted by doctors and lawyers before publication; and he and the publisher welcome the chance to correct any identified errors.[2,3]

While corporate media continue to attack Kennedy's credibility, they have not attacked the veracity of the book's contents. In fact, they have totally ignored its publication and instead focus on *ad hominin* attacks. Corporate media's smears against Kennedy have prevented my own library from buying a copy for its shelves. Despite the censorship and lack of publicity in mainstream media, over 800,000 copies had been sold within the first nine weeks. The book has acquired a 5-star rating with over 12,000 reviews (as of February 22, 2022) on Amazon. A new edition, released in March, includes a new chapter on the Wuhan lab and gain-of-function research funded by Fauci. The book has also been translated into other languages.

The Real Anthony Fauci is a detailed examination of the regulatory capture governing public health. It is an important, eye-opening book and provides vital information that we need; we can't fix what we don't face.

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3. Lyons T. Publisher of 'The Real Anthony Fauci' Challenges Critics to Find Factual Errors in Book, Calls for Open Debate. Children's Health Defense. December 10, 2021.

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CALENDAR

APRIL 28-30: A4M SPRING CONGRESS – Eat, Fuel, Health: Nurturing the Second Brain in Hollywood, Florida. CONTACT: https://www.a4m.com/

APRIL 28-30: A4M/MMI MODULE – Advanced Endocrinology: The Hormonal Symphony in Hollywood, Florida. CONTACT: https://www.a4m.com/module-i-a4m-2022.html

APRIL 28-30: A4M/MMI MODULE – Triads: A Systems Biology Approach in Hollywood, Florida. CONTACT: https://www.a4m.com/module-v-a4m-2022.html

APRIL 29-30: CONNECTING THE DOTS IN CARDIOMETABOLIC MEDICINE Integrative Approaches to Improve Patient Care in Hollywood, Florida. CONTACT: https://www.cardiometabolichealth.org/

APRIL 29-30: 12th WORLD CONGRESS ON DRUG ADDICTION AND REHABILITATION THERAPY in Las Vegas, Nevada. CONTACT: https://addiction.healthconferences.org/

MAY 6-8: INTERNATIONAL CONSORTIUM ON MANUAL THERAPIES CONFERENCE 2022 in Phoenix, Arizona and online. https://www.icmtconference.org/

MAY 12-14: ASSOCIATION FOR THE ADVANCEMENT OF RESTORATIVE MEDICINE SPRING HERB SEMINAR online. CONTACT: https://restorativemedicine.org/conferences/2022-spring-herb-seminar/

MAY 13-14: 51st ANNUAL INTERNATIONAL ORTHOMOLECULAR MEDICINE TODAY CONFERENCE online. Leading orthomolecular clinicians and researchers on the topics of detoxification, immunology, pain medicine, and nutritional intervention. CONTACT: https://isom.ca/event/51st-conference/

MAY 20-22: 11th INTERNATIONAL ADVANCED APPLICATIONS IN MEDICAL PRACTICE (AAMP) CONFERENCE -Advanced Chronic Neurological Disorders in Scottsdale, Arizona, and online. Topics: Neurological Autoimmunity, Addiction, Trauma, TBI and Neurotransmitter balance. CMEs. CONTACT: https://aampconferences.com/spring-conference-2022/

MAY 21-22: 2nd ANNUAL EPIC FUNCTIONAL MEDICINE CONFERENCE in Charlotte, North Carolina. CONTACT: https://epicfmconference.com/

MAY 23-26: INTERNATIONAL CONGRESS ON INTEGRATIVE MEDICINE AND HEALTH in Phoenix, Arizona. CONTACT: https://www.consortiumcongress.org/

JUNE 2-4: IFM ANNUAL INTERNATIONAL CONFERENCE in Dallas, Texas. CONTACT: https://www.ifm.org/learning-center/

JUNE 3-6: MEDICINES FROM THE EARTH HERB SYMPOSIUM in Black Mountain, North Carolina. Botanicals for resetting circadian rhythm, targeting VEGF in cancer treatment, geriatric mental health, long-term drug use, and more. CEUs. CONTACT: www.botanicalmedicine.org

JUNE 10-12: GPL MASTER PRACTITIONER WORKSHOPS live online. CONTACT: https://www.gplworkshops.com/

JUNE 25: KEY COLLABORATIONS IN HOMEOPATHY RESEARCH online. CONTACT: https://www.hri2022.org/

JULY 8-10: IFM IN-PERSON CLINICAL SKILLS TRAINING in Chicago, Illinois. CONTACT: https://www.ifm.org/learning-center/

JULY 21-23: AANP 2022 CONFERENCE in Spokane, Washington. CONTACT: https://naturopathic.org/

JULY 22-24: FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULES – Hormones live stream online. CONTACT: https://www.ifm.org/learning-center/

AUGUST 4-7: 13th ANNUAL INTEGRATIVE MEDICINE FOR MENTAL HEALTH CONFERENCE in Chicago, Illinois. CONTACT: https://www.immh.org/

AUGUST 19-22: FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULES – Bioenergetics live stream online. CONTACT: https://www.ifm.org/learning-center/

AUGUST 25-28: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING for Doctors, Dentists, & Health Professionals with Simon Yu, MD, in St. Louis, Missouri. Detecting Parasites, Dental & Fungal. CONTACT: 314-432-7802; https://preventionandhealing.com/training

SEPTEMBER 24-25: OZONE THERAPY CERTIFICATION COURSE with Dr. Bryan Rade, ND, in Halifax, Nova Scotia. Learn intravenous and intraarticular ozone therapy. Space limited to eight attendees. CONTACT: www.eastcoastnaturopathic.com.

OCTOBER 14-16: 12th INTERNATIONAL ADVANCED APPLICATIONS IN MEDICAL PRACTICE (AAMP) CONFERENCE – Endocrine Assessment and Treatment in Scottsdale, Arizona, and online. CMEs available. CONTACT: https://aampconferences.com/spring-conference-2022/

OCTOBER 28-29: INTERNATIONAL CONFERENCE ON PREVENTIVE MEDICINE AND INTEGRATIVE MEDICINE in Los Angeles, California. CONTACT: https://waset.org/preventive-medicine-and-integrative-medicine-conference-in-october-2022-in-los-angeles

OCTOBER 28-30: ACADEMY OF INTEGRATIVE HEALTH & MEDICINE CONFERENCE – People. Planet. Purpose in San Diego, California. CONTACT: https://www.aihm.org/conference/

OCTOBER 28-30: AzNMA NATUROPATHIC MEDICINE EDUCATION CONFERENCE in Scottsdale, Arizona. CONTACT: https://www.aznma.org/

NOVEMBER 4-5: NEW HAMPSHIRE ASSOCIATION OF NATUROPATHIC DOCTORS CONFERENCE in Newcastle, New Hampshire. CONTACT: https://www.nhand.org/

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Chew on This…But Don't Swallow – Exposing the Truth About Common Dental Procedures: It's Not What You Have Been Told

by Blanche D. Grube, DMD, and Anita Vazquez Tibau

Dr. Blanche D. Grube and Anita Vazquez Tibau have released their debut book, titled *Chew on This…But Don't Swallow* – exposing the truth about common dental procedures: It's not what you have been told. Dr. Blanche D. Grube has taken her 40-plus years of research, continuing education, and clinical practice to reveal what she has learned and observed about conventional dental procedures, including "the safe, the harmful, and the outright dangerous"! She explains how whole-body health begins in the mouth and how common dental procedures such as dental mercury amalgams, metal crowns, root canals, implants, and even braces, have been found to be a causative factor in many diseases that people around the globe are facing today from depression to cancer**.** She includes her personal experiences, actual case studies, and hundreds of peer-reviewed scientific references on the many facets of dentistry. Dr. Blanche stated, "These scientific references are for the sake of the professionals who, in the face of even compelling evidence, will continue to object, 'but there is no scientific proof!'"

Chew on This…But Don't Swallow was written not only for the layperson but also for any healthcare professional interested in getting to the "root cause" of a disease rather than just treating symptoms. Dr. Blanche had been trained by and worked with Dr. Hal Huggins (Author of *It's All in Your Head*) for decades, and together they developed the Huggins-Grube Protocol, which includes doing a "Full Dental Revision."

Dr. Blanche D. Grube is the past president of the International Academy of Biological Dentistry and Medicine. She has published scientific papers, including presenting research at the prestigious International Conference on Mercury as a Global Pollutant. She continues to lecture worldwide, training dentists on the Huggins-Grube Protocol and "Full Dental Revisions."

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COVID-19 Health Care Policy: Behind the Scenes with Scott Atlas, MD

Interview by Karina Gordin

Scott W. Atlas, MD, is the Robert Wesson Senior Fellow in health care policy at Hoover Institution and founding scholar at the Academy for Science and Freedom, in Washington, DC. In 2020, Dr. Atlas served the nation as Special Advisor to the President on the White House Coronavirus Task Force, and today aims to continue advocating for safe, reliable, and effective public health policies in both government and academia.

Dr. Atlas is the author of numerous books, including *Magnetic Resonance Imaging of the Brain and Spine*, *Reforming America's Health Care System*, and most recently *A Plague Upon Our House: My Fight at the Trump White House to Stop COVID from Destroying America*.

Karina Gordin (KG): How has your background in the medical science field prepared you for the role of Special Advisor on the White House Coronavirus Task Force?

Scott Atlas (SA): For the past ten plus years I have been at the Hoover Institution as a senior fellow working one hundred percent of the time in health care policy. I took that position after being in academic medicine for more than 20 years at Stanford University and formerly at institutions like University of Pennsylvania and Mount Sinai Medical Center. At Stanford, as Chief of Neuroradiology, I presided over a diagnostic field that integrates information over many medical subspecialties, and I was directly involved in patient care, research, and education.

I was added as Special Advisor to the White House Coronavirus Task because I am a health care policy expert, and we had the biggest health care policy crisis in a century. I had been doing research full time on the pandemic since the end of February 2020. I put everything aside and focused exclusively on the pandemic in a health care policy capacity when I saw that our policy was misguided and failing.

KG: Who did you work closely with on the Task Force?

SA: No one. Firstly, I was the only health policy scholar on the Task Force. Yes, there were other doctors, namely, Dr. Anthony Fauci, Dr. Deborah Birx, and Dr. Robert Redfield. Those were the three main medical doctors. But more than that, they are government bureaucrats. Fauci and Birx have been in their government positions for more than three decades.

I came out of a totally different background – a world of research science, practical policy work, and clinical medicine. I served a different function from other members on the Task Force. When addressing a certain issue, I would arrive prepared with a stack full of publications from scientific journals and give my analysis of the data – citing literature, going through studies, critiquing the data. In response, I was often met with either silence or accusations that I am an outlier. I was never refuted with data; I never saw any of the other doctors bring in a single publication from medical literature or so much as cite and critique the data. I never heard Birx, Fauci, or Redfield disagree with one another, which in and of itself can be a red flag because medical sciences necessarily bring forward debate and discussion points that not everyone agrees with.

"I cannot emphasize this enough: we must be critical thinkers."

KG: What was the mission of the White House Coronavirus Task Force?

SA: The mission of the medical doctors was misguided – it was to stop COVID-19 at all costs and didn't take into account the impact of the policy itself. Remember, I joined the Task Force as an expert in health care policy – analyzing public health issues and applying data to determine a course of action. Solely focusing on stopping COVID-19 at all costs is not how appropriate, ethical health care policy and public health guidance is done.

My advice took into account all public health impacts, *including the impact of the policy itself*. That's how public health policy is formulated. I was the only one that focused on the impact of the policy. I was the only one that considered long-term health harms of the Fauci-Birx lockdowns – from missed medical care to the mental health toll. In the end, stopping COVID-19 at all costs not only failed to stop the infection from spreading,[1] but it failed to stop the vulnerable populations from dying,[2] and caused tremendous harm such as food insecurity,[3] school closures,[4] and contributed to unnecessary deaths.[5]

KG: As a health care policy expert, how did your view of public policies, such as universal masking, differ from other members on the Task Force?

SA: Our views varied, particularly when it came to widespread forced masking of school-aged children – contrary to science and logic. Take Sweden for instance, the Swedish Public Health Agency reported that throughout the 2020 spring wave, daycare and schools remained open for every one of its 1.8 million children – ages one to sixteen. That is to say, all the schools in Sweden were open without subjecting children to testing, masking, physical barriers, or social distancing. What was the outcome? Zero COVID deaths in kids, while the teachers had a COVID risk similar to the average of other professions.

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Our school closures are on the verge of destroying an entire younger generation, and its unique to the US. It's a heinous abuse of public health policy. As adults, we have a responsibility to protect our children, and instead we are harming them by keeping them in masks and afraid, and making them think they're dangerous to others. This is anti-science, and it really is immoral and violates all ethical standards of medical care.

Keep in mind, I supported the use of masks to protect our most vulnerable populations, such as those in nursing homes. As I wrote in my book, *A Plague Upon Our House*, Fauci was inconsistent and erratic about mask efficacy and Dr. Birx cited severely flawed research such as the "hair salon study," to prove the efficacy of population masking. If you ask me, that is low-level scholarship.

KG: What does the preponderance of evidence suggest regarding masking? For instance, a recent large, randomized study led by researchers at Stanford Medicine and Yale University found that widespread adoption of masks effectively reduces the spread of COVID-19 in community settings.

SA: One of the most important randomized controlled trials is from around the end of 2020 from Denmark. More than 6,000 participants were randomized to follow public health measures with or without the additional recommendation of a surgical mask. Participants were tested for virus by PCR and the study found no statistically significant protection from masks in the prevention of respiratory infections. Ultimately, the difference in infection rate between the masked and unmasked groups was not statistically significant in the community setting.

Another study by University of Louisville (2021) reviewed COVID-19 case growth rate in states that imposed statewide mask mandates. The study authors found that the case growth was not significantly different between mandate and non-mandate states and the findings did not support the premise that population mask wearing (not just mandates) plays a significant role in COVID-19 transmission rates.

The Bangladesh study that you referenced was very different. In Bangladesh, "treatment villages" were instructed to use masks while "control villages" were not (approximately 340,000 participants total). The research team found that the number of symptomatic cases was lower in treatment villages compared to control. Specifically, treatment villages that wore surgical masks demonstrated eleven percent fewer COVID-19 cases than villages where masks were not worn.

This was not a study that was designed to talk about people that actually wore the masks. They were not specifically examined. And eleven percent is not a massive reduction. Also, that reduction was not visible in the data in people under 50. Now why would that be you have to wonder? Either masks work or they don't work. To me, that means there was a behavioral difference in people over 50, among other reasons.

By the way, the study had many flaws, including the fact that the study did not test people to see if they newly developed the infection. There's no evidence that any of them got the infection during the time of the study. From what I read, the people in the study were not tested beforehand and then verified that they later got the infection. So, to claim that the study proves masks work is false and in fact once that study was published, the journal has been discredited. The data do not show that widespread population masks are effective, that's completely false, and we need to read the available data critically.

I cannot emphasize this enough: we must be critical thinkers. We can listen all day to people who say, "I am following the science," but oftentimes these people don't know the science and act contrary to the science. The time of listening to the so-called experts – and assuming they're correct – is over. Sure, they may be in a position of authority and have a degree after their name, but as thinking adults, we must make a greater effort to critically evaluate what we hear and read. Frankly, that critical thinking was also completely missing from what I saw on the Task Force. That's the biggest shock of all, the complete ignorance and absence of critical thinking from people who were deemed scientific experts.

KG: Would you say it's more a lack of critical thinking or perhaps an agenda, or both?

SA: I don't assign motives, I can only say what I saw, and what I saw were health care professionals that were not rigorous in their thinking. They were not prepared with the publications and the data, and there was no scientific discourse that I'm used to hearing at Stanford University and where I worked for the last thirty years in medical centers. There was no level of sophisticated analysis whatsoever; rather, there were sophomoric conclusions made on the most naïve level. For instance, claiming if two things occurred at the same time – correlation – there must be causation. That is simply not the way scientists think. So, I don't know about motives. I, as an advisor to the President, brought in as much information as I could. I was advising. I wasn't in charge, if anything, I was advising the best I could because infection was spreading. People were dying. The policy was failing. That's why I was called.

As I mentioned earlier, I came in doing the best I could giving my advice and supplying data. In fact, I brought in some of the nation's top medical scientists not only in virology but in specialties like pediatric disease, vaccines, and public health, from institutions like UCLA, Tufts Medical Center, Harvard University, Stanford University. I brought in the experts to speak with the President. By the way, that meeting was scheduled so that Dr. Birx can specifically attend. Right before the meeting, one day before, she refused to attend. So, motive? I don't know. I will let people judge the motive.

My motive was to get the information and get research to the President of the United States. People should be thrilled to hear that President Trump had input from more outside pandemic experts. That's what I tried to do here. Instead, we had someone say they're not coming, and then comment to the media that she was concerned that there were "parallel streams of information" coming into the President and it didn't go through her. My goal wasn't to be a funnel or a filter of information – that's not what you do as an advisor.

KG: During your meetings at the White House, did topics such as repurposed drugs or gain-of-function research come up?

SA: No, I never heard any discussion or mention in the meetings during the time I was there. Everything has come to light after I left at the end of November 2020. But during the time I was there, that was never discussed in my presence.

KG: A lot has come to light since your time on the Task Force. If you were to write a sequel to *A Plague Upon Our House*, what would the next book focus on?

SA: The most important information that can be talked about now is what has been exposed by the pandemic and its management. It's not just about the pandemic. It's about the big issues this country is now facing. What has been exposed is a tremendous bias that we all knew sort of existed in the media and on university campuses and in the scientific community. But now we clearly see politicization of science – a massive campaign to stop information and the free exchange of ideas from occurring on campuses and even in scientific journals. So, to me, the crisis is well beyond this pandemic. The crisis that needs to be written and talked about is the inhibition, the smearing, the censure, the censorship of the scientific views not accepted by the mainstream.

We see the most powerful people colluding with big tech and literally taking down and blocking information. If the American public, if the world does not have the capacity to even hear the arguments, how are we going to arrive at scientific truths that are so desperately needed to solve this and other crises? That would be the issue that I report on next.

KG: How much of a role did politicization of science play in the COVID-19 vaccine rollout?

SA: I will say this: the US is uniquely off the rails in mandating vaccines and aggressively pushing vaccines for people who don't necessarily need them, including recovered people and healthy children. That has undermined the trust in vaccines for people who do need them. When I say, "uniquely off the rails," I am talking compared to European nations. We are one of the only countries among our Western peer nations that has failed to acknowledge immunological protection following COVID infection recovery. Data are clear from Israel and elsewhere that longer lasting, stronger protection is conferred following infection, compared to vaccine-induced immunity but never having had the infection.[6] That's not opinion at this point, and yet the public health leaders never discuss that.

Several countries in Scandinavian regions have suspended vaccines for populations under 20. When you look at the UK advisory body, they do not recommend vaccines for healthy children aged 12 to 15 years. Why is that? There are two reasons. First, healthy young people do not have significant risk from COVID.[7] That's proven. That's factual. That's inarguable. Second, there is an incidence of side effects like myocarditis from the vaccine particularly in those same young people. So, there is a risk-benefit equation that people should consider. It's an individual decision.

I am for vaccines being offered to everybody, and based on what we know so far, I think it's smart to take vaccine if you have serious risk of death from COVID. But to insist that everyone get vaccinated – and now everyone get a booster – is not following the science. Remember, most vaccines take five years to get safety data on. We got an emergency use authorization granted on a relatively small set of subjects in the clinical trials for the vaccines, because it was specifically an emergency.

Trust in American institutions and public health leaders and research scientists has been damaged severely, and for good reason. Now what? The solution is transparency. The solution

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to regaining trust in these institutions is more transparency of information, more open discussion, and far less restriction by self-proclaimed authorities on the dissemination of information.

KG: Would the same apply to the PCR testing? In *A Plague Upon Our House*, you note that mass testing was a response to political pressure.

SA: There are problems with PCR tests. Firstly, PCR tests are super sensitive and the way they're done typically during this pandemic is they detect either extremely minute quantities of virus that are not really relevant or they detect pieces of virus – dead virus, fragments of virus. So, in terms of the sensitivity setting, or a high cycle threshold, 97 percent of the time you're not detecting contagious or live virus, you're detecting either dead or irrelevant virus.

So, the first problem is that it's too sensitive. The second problem with mass PCR testing is that when people are infected, they can remain positive on a PCR test for months. You're only contagious for maximum of around nine days, not months. That's what the literature shows. As such, the testing is giving us potentially misleading information and unfortunately that was a problem during the entire pandemic. Unsurprisingly, that was never recognized even though I outlined the problems inside the Task Force. I distributed articles about the problems of PCR, but it was never acknowledged during the time I was there. It was ignored. I was the only one that brought it up during my three-and-a-half months of sitting in on the meetings. That's just another example of how we didn't have the right people in charge. That's the bottom line. This is a problem that can never be repeated.

KG: If President Trump had been re-elected for a second term and you were still on the Task Force, what direction might the country be heading in now?

SA: Severe restrictions and the Birx-Fauci lockdowns were instituted before I walked in the door of the White House. I didn't arrive until the beginning of August 2020. So, the six months before I arrived the wrong policies were in place, and they remained in place the entire time I was there, and they remained in place after I left.

The wrong policies were implemented, and why were the wrong policies implemented by the way? I just want to clarify something. Dr. Birx was the one in charge of the medical side of the Task Force. She functioned as the so-called coordinator on the Task Force. Dr. Birx wrote and disseminated all the written advice of the federal policy to the governors who oversaw implementing their own state's policies. Dr. Birx visited dozens of states and met all the public health officials. During the months I was there, I visited one single state – Florida.

If people have a problem with what happened during 2020, throughout the Trump presidency, keep in mind that the policies implemented were that of doctors Birx and Fauci. If anyone has a problem with the results, they may want to speak with Dr. Birx and Fauci. In terms of what would happen, well, I was on a temporary position, I was a special government employee. I had a 130-day appointment, and I was leaving no matter what. And when I left, I left at the end of that appointment.

So, I was not staying on no matter who won. I was not there for political reasons. By the time I had left, which was the end of November, the emergency use authorization was already granted for the vaccines. Whether or not Trump remained the President, the goal should be targeted protection – increasing protection of high-risk populations and minimizing the societal harm of COVID-19 restrictions.

KG: Since leaving the Task Force, have you remained active in COVID-19 research and advocating for positive public policy changes?

SA: Dr. Jay Bhattacharya of Stanford School of Medicine, Dr. Martin Kulldorff of Harvard University, and I have begun a collaborative project – The Academy for Science and Freedom at Hillsdale College. Our mission is to address current issues such as dissemination of information in pursuit of truth and the furtherance of the free exchange of ideas. That is really the only way that science is conducted, and that's been missing, so we believe that there is a tremendous amount of reform to be done within the scientific community.

For instance, there's a stranglehold on the funding of research that is done by the same people who are conducting public policy and editing the journals. So, it's not in the public interest to have a single cartel of people who control all the research funding, all the careers of academic scientists, all the publications, and now the public health policy advice. This is very detrimental to scientific debate – a key factor in arriving at scientific truth. When you have former NIH director Dr. Francis Collins colluding with Fauci and the corporate media to discredit scientists with dissenting views, the need for transparency and civil discourse is even greater.

Science depends on the free exchange of ideas without intimidation. Since leaving the Task Force, I have been working to make those problems visible as well as propose and explore solutions so we can benefit as a society from the brainpower and resources that we devote as a country to science.

Scott Atlas, MD, investigates the impact of the government and the private sector on access, quality, and pricing in health care as well as global trends in health care innovation. He is a frequent policy advisor to policymakers and government officials in the United States and other countries. He has served as Senior Advisor for Health Care to several candidates for president, as well as counseled members of the US Congress on health care, testified before Congress, and briefed directors of key federal agencies. From July to December 2020, he served as a Special Advisor to President Trump and as a member of the White House Coronavirus Task Force.

He is the author of numerous books, including *In Excellent Health: Setting the Record Straight on America's Health Car*e, and most recently *Restoring Quality Health Care: A Six-Point Plan for Comprehensive Reform at Lower Cost***.** He is also the editor of *Magnetic Resonance Imaging of the Brain and Spine*, the leading textbook in the field.

Katrina Gordin is a medical journalist and currently writes for a variety of commercial and peer-reviewed health publications. She would like to thank her father, Dr. Leonid Gordin, for advocating the importance of meditation and mindfulness, which has informed her writing and research. Karina can be reached at Write@HealthWright.org.

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Ask Dr. J

by Jim Cross, ND, LAc
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The Clot Thickens

In Scottish MD Malcolm Kendrick's new book, *The Clot Thickens*, prepare to belly laugh and dramatically improve your cardiac and cognitive dexterity. Dr. Kendrick interjects humor in a manner analogous to Alan McDaniel. His humor facilitates the ease of reading without taking away from the subject matter. He is the author of other books, notably *Doctoring Data*, which is similarly an educational and humorous book about modern, medical data manipulation. In his present book, he proposes a new clinical explanation for the origin of cardiovascular disease (CVD). Just as the plot thickened in the wonderful movie, *Knives Out*, the clot will most definitely thicken in his unique take on CVD.

This topic will most undoubtedly ruffle some scientific feathers. Dr. Kendrick has a wonderful quote by Leo Tolstoy that is very relevant to the topic and science in general: "The most difficult subjects can be explained to the most slow-witted man if he has not formed any idea of them already, but the simplest thing cannot be made clear to the most intelligent man if he is firmly persuaded that he knows already, without a shadow of a doubt, what is laid before him."

To further add to this idea about open-ended science, Dr. Kendrick considers himself both an ABCD or an evidence-based conspiracy discoverer plus an ABCDEF or an evidence-based conspiracy discoverer using established facts. For him, as it should be for all scientists and doctors, science needs to always be a journey but never a destination. All any of us can do is try to move our understanding of the world and human bodies a few steps further down the road.

He also puts forth a new paradigm in the never-ending quest for the cause(s) of diseases. He thinks we need to stop searching for the actual cause or causes and consider CVD to be a process where we must fully understand the mechanism causing the arterial damage before we jump to any premature conclusions as to what actually causes it and then back fill a theory around it. In other words, understand first not what causes CVD but how it is caused!

He defines this as process thinking, which allows one to connect all the CVD risk factors. Once you sleuth this out, you can ascertain how different risk factors can cause CVD in the same manner and establish an efficient treatment and prevention protocol. To summarize: do not focus on individual causes. Focus on process, then see if the actors fit into the process. If they don't, your process is wrong.

For him, the cholesterol hypothesis came, it saw, and it conquered! Dr. Kendrick claims that statin lowering drugs have now passed from a billion-dollar industry to a trillion dollar industry. In successive chapters he debunks Ancel Keys' diet/heart hypothesis and has an excellent review on the various types of cholesterol and their effects on the body for those of us whose biochemistry has unfortunately lapsed.

He also wishes to traverse a new trajectory. For him, heart disease and CVD are misnomer titles. Atherosclerosis doesn't affect veins or arterioles. It is only an arterial disease and even that has limitations as it doesn't affect the pulmonary arteries. He titles his theory: the Thrombogenic Hypothesis. He shows that atherosclerotic plaques are the result of blood clots that are formed on top of the endothelium of arteries in response to local damage to the endothelium.

A cardiologist I played basketball with at UC Davis told me recently that he wanted all his patients to have a healthy endothelium lining all arteries of the body. Dr. Kendrick theorizes that the atherosclerotic process begins when the endothelium is damaged in any myriad of ways. This leads to a clot which covers the area like a scab. A new layer of arterial lining then grows over the top of the thrombus which effectively draws the scab into the arterial wall. In many cases, the remnant thrombus is fully broken down and reabsorbed into the body. When there is excessive damage, bigger or tougher blood clots form and the body's repair systems are overwhelmed, which leads to repeated clotting at the same spot with the plaques enlarging and eventually causing a severe constriction.

He also considers the endothelium to be a separate organ, as the endothelium acts as an absolute barrier to movement of substances from the bloodstream into the subendothelial layer.

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Ask Dr. J

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Could plaques in arterial walls really be the remains of blood clots? He contends that end stage plaques contain 87% fibrous tissue and notes that there is the presence of fibrin in all plaques. Fibrin is an extremely difficult protein to dissolve, so it could remain under the scab. Also, fibrin and fibrin degradation products have mitogenic activity, which encourages smooth cell proliferation in the tunica media layer and eventual movement into the clot. Fibrin also acts as a chemical attractant for leukocytes. Finally, fibrin binds to red blood cells, which provide free cholesterol that is used as a building block for cholesterol crystals found in the plaque.

He also introduced me to a new term: endothelial progenitor cells (EPCs). After damage to the endothelium, EPCs form on top of the clot. They are manufactured in the bone marrow and float free in the bloodstream and are attracted to areas of endothelial damage. They are also similar to monocytes, as both turn into macrophages once they leave the bloodstream. Inside the clot, these macrophages then attempt to clean up the residual blood clot. Finally, EPCs also form a continuous barrier to prevent emboli from breaking free of the clot.

Dr. Kendrick also shows evidence that people with CVD tend to exhibit reduced EPC number and function. In addition, he claims that diabetes, chronic kidney disease, and steroids all decrease the number of EPCs in the bloodstream. Having a decreased EPC count would definitely hamper the endothelial repair system and make certain individuals more prone to developing CVD.

His plan to optimize endothelial health encompasses two directions: protect and sustain the glycocalyx and increase nitric oxide/NO synthesis.

Unfortunately, the vast majority of health care practitioners have probably never heard of the glycocalyx. It is a layer of proteins and sugars that lies just underneath the endothelium and looks like a miniature meadow under a microscope. It is basically the super Teflon of the human body. It has many functions. I will list a couple here:

- Protects the endothelium with enzymes and chemicals;
- Secretes substances like tissue factor inhibitor and nitric oxide that act as anticoagulants;
- Forms an interface/exclusion zone between the endothelium and moving blood;
- Modulates adhesion of inflammatory cells and platelets to the endothelium.

NO used to be called endothelium-derived relaxation factor (EDRF). It dilates arteries, thus lowering blood pressure, stimulates production of new EPCs, and is a powerful anticoagulant. Another reason to spend more time in the sun is that sunlight increases NO synthesis. Dr. Kendrick also claims that inhaling through the nose stimulates NO manufacture in the nasal passages, which is then transmitted to the alveoli and into the blood stream. He has an incredible idea for a T-shirt: "Say YES TO NO!"

To end, this is a quote that many attribute to Aleksandr Isayevich Solzhenitsyn:

> We know they are lying
> They know they are lying
> They know we know they are lying
> We know they know we know they are lying
> But they are still lying.

Most practitioners and patients, who have done their due diligence in searching for the cause(s) of CVD, will have come to the conclusion that fat and cholesterol are not the main culprits. Dr. Kendrick's wonderfully written and researched book will arm them with more solid, scientific ammunition to convince their patients and other doctors that the truth is out there. One must just expend a little bit more energy than normal to ascertain it!

Sometimes I feel a kinship with certain authors. Dr. Kendrick is one of them. Here is a small snippet from his "About the Author": "Malcolm would like more people to challenge the status quo and never just accept the party line. He likes to ski, golf, sail, play squash, walk in the hills, and drink…not necessarily in that order!" ◆

Pediatric Pearls

by Michelle Perro, MD

Ditch the Itch: An Approach to Eczema in Children

Nothing will send more shivers down the spine of my husband, an emergency physician with over three decades of experience, than an infant with a rash! "Pediatric Pearls" has visited the integrative approach to common rashes (November 2020) in the past, but the topic of pediatric eczema requires its own space and place. So, why do bumps on a little one's skin make a grown man cry like a baby?

The very term "eczema," encompasses many other varieties of dermatidities, promoting confusion from its nomenclature. The historical naming of this disorder is attributed to ancient physicians, said to have given the name to "any fiery pustule on the skin."[1] The word likely derives from the Greek word, *ekzema*, meaning "something thrown out by heat,"[2] which creates a strong visual image of the appearance of an eczematous eruption. The actual term "eczema" refers to a group of inflammatory skin conditions in the same family, including nummular eczema, atopic/contact/dyshidrotic/seborrheic dermatitis, and lichen simplex. The most commonly used term in pediatrics is atopic dermatitis (AD), which is also the most common inflammatory skin condition of childhood. It is defined as an often chronic and relapsing disease, usually beginning in infancy or childhood, and can be the beginning of the 'atopic march' (followed by allergic rhinitis and allergic asthma).[3]

Of concern, the prevalence of AD has risen three-fold over the past few decades, now encompassing 30% of children of all skin types and ethnicities. Notably, one-third of children with AD will experience moderate to severe disease, with children of African American and Latino descent experiencing more severe AD.[4] One in four adults report adult-onset of initial symptoms, so AD is not age-dependent. Eighty percent of individuals affected with AD experience disease onset prior to six years of age, and many will "outgrow" AD by adolescence or adulthood.[5]

The clinical impact on children, particularly infants from this disorder is the "itch," followed by dryness and a predisposition to skin infection. A profound sequelae from the relentless itch is sleep disturbance which can occur in approximately 60% of children with AD.[6] The occurrence of sleep issues is what will create desperate parental measures bombarding the office with calls and emails. The scratching of the lesions by the child creates the thickening and plaques of the skin as well as the potential risk of secondary infection. Although superficial bacterial and fungal infections are common, the prevalence of even more serious systemic infections are higher in adults with AD as compared to those without AD.[7]

If not managed early, children with AD can go on to develop food allergy, allergic rhinitis, and asthma as mentioned above, which can persist for years. There are other additional co-morbid conditions associated with AD, including autoimmune, cardiac, ocular and neuropsychiatric conditions.[8] Children with AD are more likely to experience ADHD, depression, anxiety, and suicide.[8] The rash can be particularly upsetting to parents since the skin involvement can be extensive and some children can look reptilian from the scaly lesions.

Another way to approach thinking about AD is analyzing the various endogenous and exogenous factors that can contribute to the pathogenesis. Endogenous factors include immunologic and genetic abnormalities (mutations in genes coding for skin proteins such as filaggrin), foods, and even emotional stressors. Additionally, children with AD may demonstrate reduced ceramide content in the stratum corneum of their skin. This reduction in lipids affects water retention and barrier protection function.[9]

The range of exogenous factors is extensive, including phthalates, cosmetics, dyes, chemicals, detergents, and pathogens. Phthalates may induce changes with increases of inflammatory cytokines secreted by barrier-defective skin cells via the production of a thymic stomal lymphopoietin.[10] These mediators of immune regulators are important considerations in understanding the impact of environmental toxicants on immune function, particularly in vulnerable populations.

There is a misconception that eczema is a benign rash likely due to the fact that it is so common and can be managed with the slathering of various topical steroids. There could be nothing further from the truth. The action of steroids is suppressive and while they may give temporary relief, they rarely fix it by addressing the root cause. When they are discontinued, the skin resumes its job of being the child's largest organ of detoxification trying to clear whatever insult the child is facing. It becomes a vicious cycle of expression, suppression, and expression of symptoms while the body tries to correct itself. Additionally,

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steroids can cause subsequent immune suppression as well as local thinning of the skin. There have been innumerable cases of parents dutifully applying steroid creams to the diaper area only to have to deal with raging secondary fungal infections causing further itching, pain, and overall discomfort.

The Case of an Itchy Baby

There are so many patients to discuss with AD, however, one particular baby comes to mind. Six-month-old Camille was born to healthy parents, had a normal vaginal birth, and has a healthy two-year-old sister. She was exclusively breast fed when she presented with AD literally from head to toe. The parents consulted her regular pediatrician who first prescribed a topical steroid. When she didn't improve, a pediatric dermatologist was consulted, and she was given a topical anti-fungal with the steroid which seemed to further exacerbate her skin. The parents reported that the baby rarely had a decent night's sleep since she was up scratching most of the night. Baby mittens and using diphenhydramine as a sleep aid offered minimal relief. The parents were exhausted.

However, an interesting event occurred during the evaluation and treatment of Camille. Mom developed COVID-19 during the initial stages of treatment, as well as the rest of the family, experiencing only a brief course of mild respiratory symptoms. The baby never developed symptoms and tested negative. I found this to be interesting and noodled around looking for why this might be. Research at the University of Florida showed that a combination of diphenhydramine paired with lactoferrin (a protein in human milk) impaired CoV-2 virus in monkey and human lung cells.[11] While this is preliminary research, this combination could have possibly protected baby Camille!

A Clinical Approach to AD

The bandwidth and the purse of each family must be taken into consideration when creating a treatment plan. I laid out a simple and doable program to tired parents:

- Discover and reduce/eliminate the offending agent(s)
- Soothe the inflamed skin
- Heal any potential contributing factors (intestinal permeability, dysbiosis, etc.)

Reduce/eliminate the offending agents. Food allergens are often the biggest contributing factor in my clinical experience as well as being documented in the literature.[12] For ease, cost and practical considerations, I first try an elimination diet, with cow's milk, wheat, egg and soy being the most common offenders in infants. A careful environmental health review ensues, with a keen eye on the identification and removal of phthalates, artificial dyes and household chemicals.

Soothe the inflamed skin. While my focus is on treating the gut and resolving possible intestinal permeability and dysbiosis while trying to rebalance the activated TH2 pathway (which is responsible for the avoidable atopic march), an important initial goal is giving the baby and parents much needed relief. The skin is a large absorptive organ, so considerations in using the least toxic, most effective treatments are a priority in children. I use a concoction of homeopathic calendula (which has both anti-inflammatory and antiseptic properties), with added aloe vera gel, vitamin E, shea butter or coconut oil. Colloidal oatmeal in the bath (which contains starches and beta glucans [containing avenanthramides]) can help the itch from its anti-inflammatory and water absorptive functions.[13]

The homeopathic treatment of AD requires some experience, but learnable for integrative practitioners. I recommend buying a copy of *The Homeopathic Treatment of Eczema* by Robin Logan, which will greatly aid both clinician and patient.[14] I initially prescribed *Sulfur*, which should be in every parent's toolbox, known as the best skin remedy. It is also overprescribed and it should be used with care in cases where there is a history of suppression (e.g., from steroids). I used a 30c potency twice a day for a week and then reevaluated. While there was some clinical improvement, I knew we were close and reassessed the situation since there was just a minor clinical change. I opted for *Calcarea sulfurica* 30c, same prescription, based on the yellow crusts and scales as well as the cracks and desquamation noted on her skin. At the follow up visit, the baby was 80% better. I switched to a 200c once a week for four weeks and then held treatment. At that point, the AD completely cleared. Another miracle for homeopathy!

Heal any potential contributing factors. In this particular baby, I didn't have to work on the possibility of intestinal permeability and dysbiosis. This may have been secondary to the young age of this baby as well as her having been exclusively breast fed, with Mom eating only organic foods. In an older child, I would have definitely assessed for gut issues, possibly tested using both food antibody and comprehensive stool analyses and treated either with homeopathics, herbal remedies, and nutraceuticals. I did begin the mom on a *Lactobacilli/Bifidobacteria* probiotic, omega 3s (1000 mg EPA and 600 mg DHA) and flaxseed oil since treating a breast-feeding mom is a great way to treat a sensitive baby. There are many herbal strategies for managing AD, including immune modifiers (e.g., echinacea root), anti-inflammatory herbs (e.g., licorice) and antiseptics such as goldenseal. However, care must be administered in treating infants with potent herbals, and because they respond so well to gentle, but effective homeopathics, this is the cornerstone of my treatment to *ditch the itch*.

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Environmental Medicine Update

by Marianne Marchese, ND
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Cardiovascular Health and Mercury

Introduction

Every year the American Heart Association releases the most up-to-date statistics related to heart disease, stroke, and cardiovascular risk factors. These typically include data on smoking, physical activity, diet, and weight in relation to cardiovascular disease as well as links to uncontrolled cholesterol, blood pressure, and glucose and heart disease. What they seem to leave out is the link between toxicants found in air pollution, food, water and personal care products and cardiovascular disease and, in particular, hypertension. This article will present some basic information on mercury and its role in hypertension and how to address patient care from an environmental health and medicine approach.

Mercury Basics

Mercury is a toxic metal that affects human health. There are several forms of mercury.[1-3]

Elemental mercury (also called metallic mercury) is found in old thermometers, thermostats, fluorescent bulbs, dental amalgam fillings, and latex paints. It is lipophilic, accumulates in the brain and the kidney. Exposure sources are dental amalgams, inhalation of mercury vapors in ambient air, latex paint (prior to 1991), and living in proximity to former mercury industries. Other sources of exposure are coal-fired power plants, burning of municipal and medical waste, and from factories that use mercury.

Inorganic mercury. Mercury salts are found in some cosmetic products, laxatives, teething powders, diuretics, and antiseptics. It is formed from the metabolism of elemental mercury vapor or methylmercury. Just like elemental mercury, it is emitted from coal-fired power plants, burning of municipal and medical waste, and from factories that use mercury.

Organic mercury is the most toxic and the most common form of mercury exposure. There are several forms of organic mercury. Methylmercury found in fish and poultry that has been fed fishmeal. Ethylmercury is currently found in the flu vaccine and some antiseptics. In the past, numerous vaccines contained ethylmercury, but it has been removed from all except the flu vaccine, which makes methylmercury from fish the most common source of exposure of organic mercury. Methylmercury is a result of industrial contaminants in the air. It deposits in rivers, lakes, and oceans. In short, methylmercury is formed by living organisms (fish) that convert inorganic or elemental mercury emitted from industry and power plants.

Mercury Testing

Mercury exposure in humans in regulated by several agencies depending on the possible source of exposure. The Environmental Protection Agency (EPA) has set a limit of 2 parts of mercury per billion parts of drinking water (2 ppb). The Food and Drug Administration (FDA) has set a maximum permissible level of 1 part of methylmercury in a million parts of seafood (1 ppm). The Occupational Safety and Health Administration (OSHA) has set limits of 0.1 milligram of organic mercury per cubic meter of workplace air (0.1 mg/m^3) and 0.05 mg/m^3 of metallic mercury vapor for eight-hour shifts and 40-hour work weeks.[4] Both blood and urine tests are used to detect elevated levels of mercury in the body. For possible methylmercury exposure, blood testing is best. For possible elemental mercury exposure, a urine test is best for detection; and for inorganic mercury, both blood and urine can be utilized.

According to the Agency for Toxic Substances and Disease Registry, blood mercury levels are usually less than 5 micrograms of mercury per liter of whole blood. Since the elemental mercury that is absorbed into the body is excreted almost exclusively in the urine, urine samples provide the best indicator of exposure to this form of mercury. Urine samples may be either collected over a 24-hour period or may be taken once in the morning. Urine mercury concentrations over 10 micrograms per liter would indicate that a person has been exposed to higher mercury levels than the average population.

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Mercury Chelating Agents

Common chelating agents to remove mercury from the body include 2,3-dimercaptosuccinic acid (DMSA), and 2.3-dimercapto-1-propanesulfonic acid (DMPS). DMSA increases excretion of methylmercury and inorganic mercury and when administered orally, its absorption rate is about 20%, which differs from DMPS, whose absorption rate is about 40% when taken orally. DMPS is often administered intravenously; it promotes the excretion of methylmercury and inorganic mercury in the urine.[5] N-acetylcysteine, NAC, is also a useful chelator of metals. It increases glutathione S-transferase activity, repleting glutathione, scavenges free radicals, and has antioxidant and anti-inflammatory properties. Several animal studies and a few human studies show its effectiveness for metal chelation, including mercury.[6]

Mercury and Cardiovascular Health

Mercury is prevalent in the environment, and human exposure is common. In its vapor form, elemental mercury is commonly absorbed through the respiratory tract, where it is poorly absorbed in the gastrointestinal tract. It is highly diffusible through cell membranes, the blood-brain, and placental barriers to reach target organs and cells where it can cause damage. Once in the blood stream, elemental mercury is oxidized in cells and tissues into inorganic mercury. The main excretory pathways include urine and feces, with a half-life of about two months.[5]

Inorganic mercury, which is produced and released into the air by industry, is biomethylated to methylmercury in living organisms such as fish. It bioaccumulates in the food chain from small to larger predatory fish (i.e., swordfish, shark, king mackerel, tilefish). People with a diet high in seafood are likely to be exposed to high levels of mercury that can harm the brain, lungs, kidneys, the nervous and immune systems, and the heart and cardiovascular system.[5]

For decades studies have linked mercury to cardiovascular conditions such as high blood pressure, stroke, and variable heart rate. Various mechanisms of action have been proposed, including depleting the body of essential antioxidants and minerals, inducing oxidative stress, and creating mitochondrial damage.[7] Mercury is also linked to cardiovascular disease by creating vascular inflammation, thrombosis, vascular smooth muscle dysfunction, endothelial dysfunction, and dyslipidemia.[7] The clinical effects include hypertension, coronary heart disease, myocardial infarction, cardiac arrhythmias, reduced heart rate variability, increased carotid intima-media thickness and carotid artery obstruction, stroke, and generalized atherosclerosis.[7]

Research is mixed on linking methylmercury exposure from fish intake to high blood pressure. The inconsistencies are attributed to various methods of testing for mercury. Some studies measure mercury in the hair. Others use blood or urine, and one even measured mercury levels in toenails. One study looking at blood mercury levels in adults (mean age 34 years old) found an association between high blood mercury levels and elevated systolic blood pressure.[8] Based on dietary questionnaires the source of mercury exposure in this study population was from fish intake. It is important to note that not all fish contain mercury and given the extraordinary beneficial health effects form eating fish, the best approach is to educate people on types of fish high and low in mercury.

According to the Agency on Toxic Substances and Disease registry, increases in heart rate and blood pressure have been reported following inhalation of elemental (metallic) mercury in humans. Short-term higher doses of mercury vapor and long-term lower doses of mercury vapors can increase blood pressure. The sources of exposure cited were inhaling mercury vapor from old paint that used to contain mercury and from amalgam fillings.[4]

Case Example

In September of 2020, a 45-year-old male patient presents with chief complaint of a new onset of fatigue and lightheadedness. He has been under my care for over 10 years for general health concerns and was last seen by me one year prior for muscle tension headaches that resolved with massage and chiropractic care. In the past his blood pressure has always been normal (below 120/80). PMHX is unremarkable and family history is also unremarkable. In 2019 he had left knee ACL repair and no other previous surgeries or hospitalizations. Labs last done by his MD prior to knee surgery, and everything was 'normal' per patient.

He states the fatigue and lightheadedness began three weeks prior. It comes and goes and is not constant. It started gradually and has not increased in intensity. He is not experiencing vertigo, he describes feeling 'off balance' and 'lightheaded'. It doesn't happen when he sleeps, and he sleeps well eight hours a night and wakes refreshed. His fatigue comes on in the late afternoon. The lightheadedness is not positional. He states he has no headaches, no allergies, no recent cold, or flu or Covid. He has not had any trauma, injury, or other illness. He has been very stressed with work the last four months and has felt what he describes as an occasional heart flutter a few times in the past four months. He has been working from home for six months sitting at a desk working on a computer. He takes no medications but does takes a fish oil, multivitamin, B-complex, and magnesium 350 mg powdered supplement. He exercises almost daily but has been tired and felt too lightheaded to work-out for the past three weeks.

Review of systems on history:

- Head – no headaches
- Hair – no hair loss
- Eyes – no blurred or double vision or changes in vision
- Ears – no tinnitus, no congestion or pain, no hearing changes
- Nose, mouth, throat – within normal limits (wnl)
- Energy – low
- Sleep – good
- Heart – no palpitations, no flutter

- Lung – no cough, no shortness of breath
- GU – wnl, no sxs BPH

Diet and lifestyle intake: Drinks 70 ounces of water a day, one cup of coffee, 4-5 drinks a week, no smoking, no cannabis. Minimal refined sugar eats mostly organic foods, lots of fruits and vegetables. Eats fish weekly, tuna once a week, sushi once a week; pescatarian diet.

Physical screening exam: Unremarkable. Gait and balance normal. HEENT, Heart, Lung, skin, abdomen, all wnl.

Vitals: height 5'9; weight 170; temperature 98.1; Pulse 81; Pulse Oxygen 98%.

Blood pressure in-office, taken several times, averaged 150/95 with both arms while sitting and repeated after resting quietly in the office for 10 minutes. This is new; he has never had high blood pressure in the past.

Initial plan. Fasting labs and resting EKG. Monitor blood pressure at home and go to urgent care or ER if symptoms or blood pressure worsens.

Lab results two weeks later:

- Resting EKG at cardiac test location – normal
- Fasting CBC, CMP, TSH, DHEA, AM-cortisol, B12, folate, Lipids, iron, ferritin, ESR, CRP-cardiac were all normal.
- Fasting glucose high at 102 but HgA1C 5.3%
- Vitamin D low – 18
- Mercury 11 – elevated per the CDC NHANES reference range.

Treatment – DMSA oral was recommended in addition to the following supplements. He did not want to do chelation and wanted to try to lower the mercury levels and blood pressure without any pharmaceuticals. The initial plan consisted of the following:

1. Vitamin D3, 5,000 iu a day
2. Stop tuna and all fish for three months, then reintroduce fish that are low in mercury
3. NAC, 600 mg a day for three months
4. Cofactor support supplement, two capsules twice a day for three months
5. Hepa cleanse supplement, two a day for three months
6. Track blood pressure at home and keep a log and message each week with averages
7. Stress management – meditation, deep breathing, app for phone

After one month his blood pressure at home averaged 140/90. His fatigue was better and lightheadedness better. He states he felt 50% better after one month. He continued the treatment plan; and after two months his blood pressure at home averaged 130/90 and he felt 90% better. His fatigue and lightheadedness were resolved, but he still felt stressed. He then lowered sodium in his diet to 1500 mg a day. At the three-month follow up in-office, his blood pressure was 120/85. He stated that at home his average readings were lower and averaged 115/76.

He stated his symptoms of fatigue and lightheadedness had completely resolved. The repeat lab test at the three-month mark showed his fasting glucose at 95, Vitamin D increased to 49 and the blood mercury dropped to 5. He felt great and less stressed overall. It was recommended he establish care with a cardiologist for additional cardiac workup. A month later he had a normal stress test and 24-hour halter monitor, and it was determined he did not need an echocardiogram. To date, his blood pressure has remained normal; he has not had any fatigue, blood pressure or cardiac concerns.

This case is interesting for several reasons. Although the research linking mercury from fish intake to hypertension is mixed, in this case there appears to be a link. Avoiding fish and using three supplements to support metabolism of mercury helped lower the blood level. Also, this patient worked on managing stress, which can be a risk factor for high blood pressure as well as sodium in the diet. Patients never present as clear cut as research and often a multipronged approach and environmental medicine perspective achieves optimal health.

Summary

According to the Centers for Disease Control, about 659,000 people in the United States die from heart disease each year. It is the leading cause of death for men, women, and people of most racial and ethnic groups. Environmental factors are an often-overlooked risk factor for hypertension, atherosclerosis, and coronary artery disease. Toxic metals such as mercury, arsenic, lead, and cadmium are all linked to cardiovascular disease. It is important that health care providers include testing and treatment for toxicant in both the prevention and treatment of heart disease.

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The Lobay Viewpoint

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Spring of Hope

"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair…" or so goes the beginning of Charles Dickens book, *The Tale of Two Cities*. There is no shortage of words to describe the current state of displeasure and vexation most people feel as the winter of 2022 lumbers on and winds down. "Winter of despair" is a popular aphorism meaning anguish, dissatisfaction, and hopelessness with the current times or situation, especially with respect to politics. Winter of despair and spring of hope aptly describes the situation we are currently living in.

As if you need a reminder, just turn on the news. The SARS coronavirus pandemic has caused a worldwide shutdown and led to several million deaths and an innumerable amount of pain and suffering. Lockdowns, restrictions, and cancellations are commonplace. Masks, isolation, and lineups are the new norm. Fear, hysteria, and anger are frequent. Anxiety, depression, and fatigue are prevalent. The economic situation is poor and shaky. News of recessions and depressions abound. Grocery and dollar stores are rife with supply chain issues. The cost of everything is rising exponentially. The price of gas keeps on going up. Inflation is out of control. Most governments have responded discordantly and haphazardly. Conspiracy theories are rife. Many people are unhappy with government policy and their leaders. Most governments have printed too much money and artificially boosted the economy. The effects of this unbridled monetary policy are unknown and potentially catastrophic. The price of housing is unaffordable and astronomical. Need I go on. The present situation untenable. The future is uncertain.

I am somewhat disappointed with the powers that be. Governments and people in power basically didn't know what they were doing as the Covid pandemic began and took shape. They reacted in knee jerk fashion to the situations as they developed. First there were masks then no masks and then masks again. Social distancing didn't matter and then it mattered. Isolation wasn't important and then it was important. And then vaccinations were developed. At first they were the godsend that would end the pandemic. Medical experts touted the vaccine as the game changer. Just believe in the science they said. New technology, fast turnaround time and poof all our problems would be gone. I believed what the medical experts said. I did my due process as a good citizen for the benefit to society and the herd. I made an appointment, stood in line and got my jab. I got a second booster 10 weeks later. Everything was good. I was vaccinated. I had immunity. I could go on with life with an assurance I did the right thing.

I have been blessed to practice naturopathic medicine in the beautiful Okanagan valley of southwestern British Columbia. I have had a busy family practice. I have been practicing for thirty years. Now I am older somewhat experienced and reasonably seasoned. I have seen a lot of things and believe I have some worthwhile knowledge and experience to share. I am also humble enough to known that I haven't seen it all, I don't know everything and realize I can't help everybody. I have seen a plethora of patients with a multitude of problems. I counsel people in what I believe is a right diet and lifestyle choices that contribute to good health. I try to eat relatively healthy, exercise and get a reasonably good sleep without medication. I personally take some vitamins and nutritional supplements. I preach temperance and moderation. I frequently advise that too much of anything is no good and the same thing applies to nutritional supplements.

Along with certain nutritional supplements, I also prescribe drugs when I think they are appropriate for certain conditions. Antibiotics can be lifesaving and nothing short of miraculous. When I have exhausted certain natural interventions, I might prescribe certain medicines that I think will be appropriate and help specific patients. I believe in vaccinations. I believe that in the past, vaccinations have been nothing short of a medical miracle to end such diseases as smallpox, polio, measles, diphtheria and other horrible diseases.

I try to stay abreast with advances in medicine, reading the literature and taking online courses. I think that being in alternative natural medicine genre attracts a hugely eclectic group of people and patients. I try to sift through the mountain of information that presents itself with a reasonable amount of openness and healthy skepticism. During the pandemic I have been inundated with all sorts of alternative and conspiracy theories. I try to fact check things as time and resources permit. While some of theories are genuine and scientifically sound, others are somewhat non-nonsensical and downright gibberish.

Communication, debate, and exchange of ideas, observations and information are at the forefront of medical advances. Censorship, muzzling, and restrictions are not acceptable responses to presenting new ideas. The scientific hypothesis begins with if and then what. Challenging a hypothesis with reasonable alternative ideas is acceptable and welcomed. Reality and truth will rise to the surface. I am often reminded of the oft used analogy that reality and truth are very seldom on the extreme of two diametrically opposite goalposts. More often than not, they are usually somewhere in between. In the not too distant future, we will look back and evaluate whether our responses to the pandemic and economic crises were correct or not. Our pains will be nothing more than a footnote in historical context. Reality and truth will be revealed.

It is a truism that nobody knows what the future holds. Reality is every changing. I can guarantee you one thing – that life, will go on. With you or without you. I have learned a few things in the course of my clinical practice. Even in the darkest times of despair and melancholy, there is always hope. Hope is an expectation that you can have that despite the current situation things can get better. Hope may be in this life or it may be in something after and beyond. I have seen some people in extremely poor condition and with grave medical diagnoses; and yet some of them have and show unwavering hope. Those who have some hope seem to do the best when confronted with poor and dire medical diagnoses. It is ultimately how you respond to a situation that matters most.

Mindfulness is the concept that we should focus on the present moment. That is all we got. The past is gone and behind us. It may have been good, and it may have been bad. We can't change the past. The decisions that we made, good or bad, right or wrong, poor or wise are behind us now. We may have to live with the consequences, but life does go on. The future is uncertain.

Angst about the future presents itself as anxiety for many people. Dwelling on the potentiality of bad outcomes in the future doesn't help much. While it may be an evolutionary adaption to worry about future outcomes, we have to let go and focus on the present and do what we can to affect what is going on now. We should focus and live in the present as much as possible.

When I was in college in Seattle, a friend of mine gave me a little book to read. It was called *Man's Search for Meaning*, written by a psychiatrist named Viktor Frank. It was about this man's experiences in a Nazi concentration camp in World War II. It basically was his response and interpretation to having virtually everything taken away from him, members of his family killed, and his dignity as a human being trampled. I think the basic outcome of the book explains what true freedom is and that accepting personal responsibility is tantamount to discovering a fundamental meaning in life. It exemplifies the true value of love and hope. It shows how the role of the individual's beliefs and response to a horrible, harrowing experience is determined by their outlook. With love and hope all things are possible.

I found in clinical practice that those with the best possibility of surviving a dire and tragic diagnosis are those with a strong spiritual belief. Whatever you believe is your belief. It is deeply personal and hard to objectively prove. A belief in higher power, whether it is God or some other deity or perhaps not, is important to survival. My mother used to often quote and read Matthew 6 chapter of the Bible, which basically says to put your prayers and burdens to God. Put your faith in God above. All your anxieties, troubles, and vexations will pass. Sharing your pain and sufferings helps to ease your troubles. The Dalai Lama often is quoted as saying that no matter what religion you believe or follow there isn't anyone who doesn't appreciate a little kindness and compassion. Try to be a good person and try to do some good things.

So now even in the face of these terrible times, there is always hope that things will change. I can guarantee you that nothing stays the same and these times will not last. Everything changes. Everything comes and goes. It might get better or it may also get worse. But that will change too. Optimism provides a better outlook to the future. Everybody is going through something. Showing a little kindness and compassion can go a long way. Have some courage to stand up and do what you think is right. I always tell patients to make their own decisions based on the facts known and presented. Follow what you believe, but also have the humbleness to know that nobody knows everything and accept the fact that you may be wrong.

I am often reminded of the quote by Charles Darwin, "it is not the fastest, smartest or strongest that succeed in life, it is those who are the most adaptable." Those who adapt the best to the changing times of life are those who will survive. The simple things are important. Be kind and friendly, show some compassion, live in the moment, be hopeful, believe in a higher power and share your burdens. Even in this winter of despair, it is encouraging to know that snow will melt and the dark days of winter will disappear. The beauty and renewal of spring will bloom and the warm, sunny days of summer will be upon us. Have a nice day.

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Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Laughter and Heart Disease: A Question of Association vs. Causation

As naturopathic doctors we rely heavily on epidemiological research to help us steer patients toward health-promoting lifestyle choices. Epidemiology is the study of the distribution and determinants of diseases and other health-related states in specified populations. The word epidemiology comes from three Greek words: "epi", which means on or upon, "demos," meaning people, (as in democracy) and "logos," meaning the study of. Epidemiology is the study of what befalls the people.

In contrast to other scientific disciplines, epidemiology is hampered by the difficulty of setting up experiments to test theories. Ethical considerations prevent scientists from setting up straight forward clinical trials to give people a disease. Epidemiological research is generally limited to careful observation. Without controlled experiments we are left with multiple possible explanations for observed associations. Associations may be due to chance, bias, confounding, reverse causality, and every once in a while, true cause and effect. Proving the later, is anything but simple. Here's an interesting example.

There is a significant association between how frequently a person laughs and their risk of heart disease and mortality. This data was published April 2020 in the *Journal of Epidemiology* by Sakurada et al. These authors gathered data on a large Japanese cohort that participated in annual health checkups starting in 2009. At the start, the participants completed a questionnaire that included a question asking how often they laughed out loud (LOL). Over a six-year period adequate data was collected on 17,152 (10,149 females) of these participants. Mean age at recruitment was just less than 63 years old. The participants were divided into three LOL categories: ≥1/week; ≥1/month but <1/ week; or <1/month. Data on cardiovascular events and death was compared with LOL frequency using both Kaplan-Meier and Cox proportional hazards modeling.

During the study 257 (1.5%) of the subjects died and 138 (0.8%) had cardiovascular disease (CVD) incidents. Kaplan-Meier analysis showed all-cause mortality to be significantly higher in subjects with a low LOL frequency (log-rank test, P = 0.003). A similar curve was observed for cardiovascular disease incidence (log-rank test, P < 0.001).

Cox-proportional analysis showed similar independent associations between LOL frequency and both all-cause death and cardiovascular disease. In an unadjusted model, all-cause mortality was significantly higher among individuals who laughed <1/month (HR 2.38; 95% CI, 1.42–3.74) than in those who laughed ≥1/ week. After adjusting for age, gender, hypertension, diabetes, smoking status, and alcohol drinking status, risk of all-cause mortality remained significantly higher in subjects who laughed <1/ month than in subjects who laughed ≥1/week (HR 1.95; 95% CI, 1.16–3.09). Risk of cardiovascular disease incidence was significantly higher in subjects who laughed ≥1/month but <1/ week than in subjects who laughed ≥1/week (HR 2.06; 95% CI, 1.38–3.00) in the unadjusted model. After adjusting for the above-mentioned potential confounders, cardiovascular disease incidence was significantly higher in subjects who laughed ≥1/ month and <1/week than in subjects who laughed ≥1/week (HR 1.62; 95% CI, 1.07–2.40).[1]

These are not subtle differences. Frequent LOL was associated with half the risk of disease, or the opposite, infrequent LOL with double the risk. For the sake of comparison, a 10% reduction in cholesterol reduces heart disease incidence by only about 30%.[2]

This is not the first study to report this inverse association between CVD and laughter frequency. Hayashi et al reported in 2016 that among 20,394 individuals, higher frequency of laughter was associated with significantly lower risk cardiovascular disease and stroke incidence among older Japanese adults.[3]

We would love this association between LOL and CVD to be one of causation, a simple cause and effect where laughter protects against CVD; invest more effort in making our patients laugh.

Epidemiologists have a mantra that they probably chant when alone in their offices: "Association does not prove causation." The world is filled with coincidences, and it is no easy task to discern coincidence from cause and effect.

Epidemiologists reference all sorts of statistically significant associations that are merely coincidental. A common example is the correlation between swimming pool drownings and the number of movies that Nicholas Cage appears in each year.[4] The more movies, the more drownings. Association does not prove causation. Nor does the fact that the number of suicides by hanging, strangulation, and suffocation in the US per year is closely correlated with the total money spent on science, space, and technology. Per capita cheese consumption is correlated with the number of people who die by becoming entangled in their bed sheets. As I type this article, I'm living in Maine where divorce rates are correlated with per capita margarine consumption. There are enough of these implausible associations that there is a book listing them. Common sense allows us to reject most of them as absurd.[5] Yet, I admit, to be on the safe side, we're not eating any margarine.

Half a century ago, when epidemiologists were trying to establish whether cigarette smoking caused lung cancer, Bradford Hill came up with a list of criteria to help assess whether an observed association was causal. These are now called the Bradford Hill Criteria and include the strength of the association, the consistency in which the association is found, the specificity between exposure and outcome, the temporal sequence (obviously exposure must precede outcome), biological gradient (intensity of exposure should correlate with severity or risk), biological plausibility, coherence with current knowledge, experimental findings (removal of exposure alters disease frequency or severity), and analogy (the relationship is analogous to other cause-effect relationships). These criteria are used as a checklist to evaluate associations, but they don't always yield the definitive conclusions we want to read.[6]

This laughter relationship with heart disease may not be as straightforward as we assume. Sakaruda et al report that those who LOL the least frequently are more likely to be male, drinkers, diabetics, with low physical activity, and live without a spouse. Other studies have reported similar associations.[7] These are all factors that increase risk of CVD and may reduce the tendency to LOL.

So perhaps this association isn't true causality but instead reverse causality. Any one of these lifestyle factors might be cause for, or a sign of, depression; and depressed people may have lower frequency of LOL and stop laughing.[8] But what causes what is unclear. Those suffering from CVD might simply find fewer things to laugh about.[9] Low frequency of laughing may be an indicator of other risk factors for cardiovascular disease; similar to how not using a seatbelt is predictive of other risky driving habits.[10]

Proving an association does not prove causation, and it is conceivable that those with comorbid disease and impending cardiovascular events might via some still unknown mechanism lose their sense of humor. Infrequent laughter might be a sign of disease rather than an etiology for disease.

We want to believe that laughter acts as an antidote to stress and so lowers CVD risk; there is something attractive about this ➤

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idea. Norman Cousins' book title, *Laughter Is the Best Medicine*, has sunk deep into our collective consciousness. It is easy to accept the idea that laughter could be used as prophylaxis even if we do not have a controlled intervention trial to hold up as proof.

Certainly, this current study is a step in the right direction; it is a large, long-term, prospective cohort that looks at laughter frequency years prior to disease onset. It also takes into account the other major known risk factors for CVD and analyzes them for effect to show that laughter frequency was an independent predictor. Predictor certainly, but cause? It's probably more complicated.

Li et al suggested in October 2020 that the relationship between cardiac morbidity and depression is genetic in nature, a bi-directional expression of genetic phenotypes. Knowing that depression and CVD are associated with each other, Li's team determined that the genetic predisposition to depression was causally linked to CVD, myocardial infarction (MI), stroke and atrial fibrillation (AF) by analyzing data from the genome wide association studies (GWAS) and tested for correlation between two depression phenotypes and CVD. They reported that depression phenotypes are genetically correlated with MI and AF. While the connection was there, the effect does not seem huge. Doubling the risk of depression genetically increased risk of cardiac arterial disease (CAD) by about 10% (OR = 1.099; 95% CI 1.031–1.170; p = 0.004) and MI by 15% (OR = 1.146; 95% CI 1.070–1.228; p = 1.05 × 10−4). In other words, those prone to depression are genetically slightly more prone to have heart disease.[11] Infrequent laughing might simply be a signal that alerts us to the presence of this genetic phenotype, a sign that risk for both depression and cardiac disease may coexist in a patient. It might not be a cause or a solution. On the other hand, this information might also argue that increasing frequency of laughter could be a way to change phenotypical expression.

Angelman Syndrome, a rare neurologic condition characterized by paroxysmal laughter and ataxic movements, is now understood to be genetic in origin.[12] Our tendency or susceptibility toward laughter is clearly controlled to some degree by genetics.

At the same time, we know that laughter can alter genetic expression. Takashi Hayashi and Kazuo Murakami reported in 2009 that laughter improved blood sugar levels in diabetic patients through changing genetic expression. Their research identified specific genes that changed in response to laughter and also, "… revealed that laughter decreased the levels of prorenin in blood; prorenin is involved in the onset of diabetic complications."[13,14] In particular, "… prorenin and the (pro)renin receptor play a pivotal role in the pathophysiology of diabetic nephropathy"[15] Could prorenin, which plays a role in regulating the angiotensin pathway, effect cardiac disease risk?

Results from research by Claudia Haase and colleagues published in 2013 suggest that the short allele of 5-HTTLPR polymorphism in the serotonin transporter gene has a significant impact on emotional expression, increasing the likelihood a person will laugh out loud.[16] Short 5-HTTLPR alleles also appear to increase the amount of influence environmental factors have on emotional development and on behavior.[17] This gene is associated with post stroke depression[18,19] and depression associated with coronary artery disease.[20] These relationships between depression and heart disease also appear to be bi-directional.[21]

Several aspects reported by Sakaruda et al point out differences between American and Japanese culture. Japanese men don't seem to laugh very much. Almost 2/3 of the men in their cohort reported laughing out loud less than once a month. That itself seems depressing.

A February 2020 study by Ikeda et al correlated laughter frequency with blood pressure, also conducted in Japan, reported that men who laughed infrequently (1- 3 times per month) had significantly higher systolic and diastolic blood pressure than those who laughed more often. In women, blood pressure did not vary with laughter frequency. In this Ikeda group, only 13% of the (72/554) male participants fell into the infrequent laugher category.[22]

Another peculiar thing reported in the Sakurada results is that the association between laughter, CVD, and mortality was only significant in women. When data from men and women were combined, the associations were significant, but when data from men were separated out, the association disappeared. This stands in contrast to the Ikeda results related to blood pressure where laughter improved blood pressure in men but not women.

Practice Implications

We should certainly pay attention to how often our patients laugh. Such knowledge can be a clue to their risk for both cardiovascular disease and overall mortality. A simple question on the intake form, as Sakurada's group used, appears to be adequate, but perhaps, paying attention when sitting with the patient will work even better. Do they laugh or not? This information may tell us something about their risk for disease.

Although Sakurada et al write that their "…findings suggest that increasing the frequency of laughter might reduce the risk of cardiovascular disease and increase longevity," it may be premature to call this 'evidence based' medicine. We hope that this association proves to be causal but until a prospective intervention confirms making people laugh lowers their risk of becoming heart disease patients, uncertainty remains.

Should we be encouraging our patients with CVD to laugh more? I believe so. Much of what we do in naturopathic medicine is informed by epidemiological associations that lack experimental proof of causality. In situations like this LOL and CVD data, we have no reason to believe that an intervention suggested by falsely assuming the relationship is causal will lead to harm. It might help. The patient's depression and heart disease may be genetic to some degree, but laughter has the potential to alter genetic expression, so why not give it a try? As happens so often when trying to use epidemiology to guide our way, we are left with our naturopathic refrain: "It can't hurt but might help so, what do we have to lose?"

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a good attitude. In contrast, all of his drug-taking friends were either dead or in wheelchairs. This anecdote does not prove anything, but it illustrates the point I am trying to make.

What alternatives do we have to the various medicines that are being given old folks? For the treatment of depression, there are lifestyle alternatives such as aerobic exercise and participating in more community activities. Biochemical treatments might include L-tryptophan, DHEA, magnesium, iron supplementation if iron deficiency is demonstrated, and an empirical trial of vitamin B12 injections. In some cases, vitamin B12 injections relieve not only depression in the elderly, but also anxiety and insomnia, which are other conditions for which CNS-active medications are prescribed. St. John's wort may also be effective against depression, but because it interacts with so many medications, its use could be problematic.

Potentially effective treatments for anxiety and insomnia include discontinuing caffeine and taking L-tryptophan near bedtime. Magnesium is also effective for some people, particularly those on magnesium-depleting drugs such as thiazide or loop diuretics or proton pump inhibitors.

For pain resulting from peripheral neuropathy, intramuscular administration of vitamin B12 may be beneficial as a potential alternative to gabapentin.[4] Laboratory evaluation often does not predict whether a patient will have a positive response to vitamin B12 therapy,[4] so an empirical trial would be reasonable.

Antipsychotic drugs such as risperidone and aripiprazole are approved by the Food and Drug Administration for the treatment of schizophrenia and bipolar disorder. They are also frequently prescribed off-label as a sedative for elderly demented patients who exhibit aggressive or violent behavior. Research suggests that such behavior can sometimes be improved by training nursing home staff to help resolve specific issues that are bothering patients.

Dementia itself is difficult to treat effectively with natural medicine. However, there is evidence that some elderly demented individuals have a subnormal concentration of vitamin B12 in their cerebrospinal fluid despite having normal serum levels of the vitamin.[5] In those patients, intramuscular administration of vitamin B12 improved the dementia, whereas oral vitamin B12 was not beneficial. Oral administration of other B vitamins may also improve dementia in some cases.[6] Magnesium may also be useful, particularly in patients taking magnesium-depleting medications. I saw an 83-year-old woman who had been diagnosed with Alzheimer's disease, but who turned out to have furosemide-induced magnesium deficiency. Her mental status became essentially normal after she received a series of intravenous magnesium injections. Interestingly, her serum magnesium level was normal, which is not uncommon in patients with magnesium deficiency, since magnesium is primarily an intracellular ion.

If you have read this far, you probably have seen a pattern. Some elderly people may be able to substitute some of their CNS-active medications with treatments such as vitamin B12 injections, other B vitamins, magnesium, iron (if deficient), and L-tryptophan. It may also be worthwhile to encourage lifestyle changes and to work on conflict resolution. It should be noted that L-tryptophan can increase the adverse effects of selective serotonin-reuptake inhibitors and some other medications, so it should be used with caution.

The treatment of health problems in the elderly can be difficult and complicated, especially when dementia is involved. However, we can probably do a better job by seeking safer alternatives to prescription medications and remembering to include "adverse drug reactions" in our differential diagnoses.

Alan R. Gaby, MD

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Drugging Our Old Folks

Elderly people are particularly susceptible to the adverse effects of medications. A meta-analysis of observational studies found that, of 7,533 hospitalizations among people aged 65 years or older, 1,251 (16.6%) were judged to be due to adverse drug reactions.[1] Despite these risks, the practice of putting old people on multiple prescription medications is widespread. A 2015 study found that the median number of prescription medicines used by elderly individuals was four, and that 39% of old folks were taking five or more drugs.[2] According to one report, the average nursing home patient is taking seven medications.

Drugs that act on the central nervous system (CNS) can be particularly problematic. These medications can impair cognitive function and may increase the risk of fall-related injury and death. Drugs that are considered CNS-active include antidepressants, antipsychotics, antiepileptics/anticonvulsants (e.g., gabapentin [Neurontin]), benzodiazepines, benzodiazepine receptor agonists (e.g., zolpidem [Ambien]), and opioids. The risks associated with CNS-active drugs may be even greater in elderly people with dementia, since these individuals already have impaired cognitive function.

A cross-sectional study was conducted on 1,159,968 community-dwelling elderly adults with dementia (median age, 83 years) who were insured by Medicare from 2015 to 2017. The primary outcome measure was the prevalence of CNS-active polypharmacy, defined as exposure to three or more medications for longer than 30 days consecutively from the drug classes listed above. Approximately one of every seven subjects (13.9%) met the criterion for CNS-active polypharmacy. Of those with CNS-active polypharmacy, 57.8% were taking the drugs for longer than 180 days, and 29.4% were taking five or more medications. The most frequently used drugs were antidepressants (92% of polypharmacy days), antipsychotics (47.1% of polypharmacy days), benzodiazepines (40.7% of polypharmacy days), and gabapentin (33% of polypharmacy days).[3]

This epidemic of polypharmacy could become even worse in the future, now that the FDA has approved two new drugs (valbenazine [Ingrezza] and eutetrabenazine [Austedo]) for the treatment of tardive dyskinesia. Tardive dyskinesia is a movement disorder that occurs as a side effect of antipsychotic drugs and some antidepressants (drugs that are frequently prescribed for elderly demented patients). Ingrezza and Austedo are being heavily advertised to the general public, probably because the drug companies are charging around $7,000 per month for these drugs, and they figure that the money they can squeeze out of insurance companies will more than compensate for what they are spending on ads. These drugs can cause a wide range of side effects, including drowsiness, dizziness, gait disturbances, trouble with balance and coordination, and falls. Those side effects would be piled on top of all the other drug side effects that elderly patients are already experiencing.

There are often legitimate reasons for prescribing CNS-active medications for elderly individuals. However, the use of these drugs risks sending the patient on a downward spiral in which an additional drug is used to treat the side effects of a previously prescribed drug. Before you know it, the unfortunate patient is taking three, five, or even seven medications and faring poorly; possibly at least in part because of all the drugs they are taking. All too often, doctors fail to consider the possibility that discontinuing a medication and trying a safer alternative is preferable to adding another drug.

An 85-year-old patient that I treated for many years once remarked that he was the only person among his circle of friends who was not taking any medications. Instead he was doing well on diet, nutritional supplements, exercise, and

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