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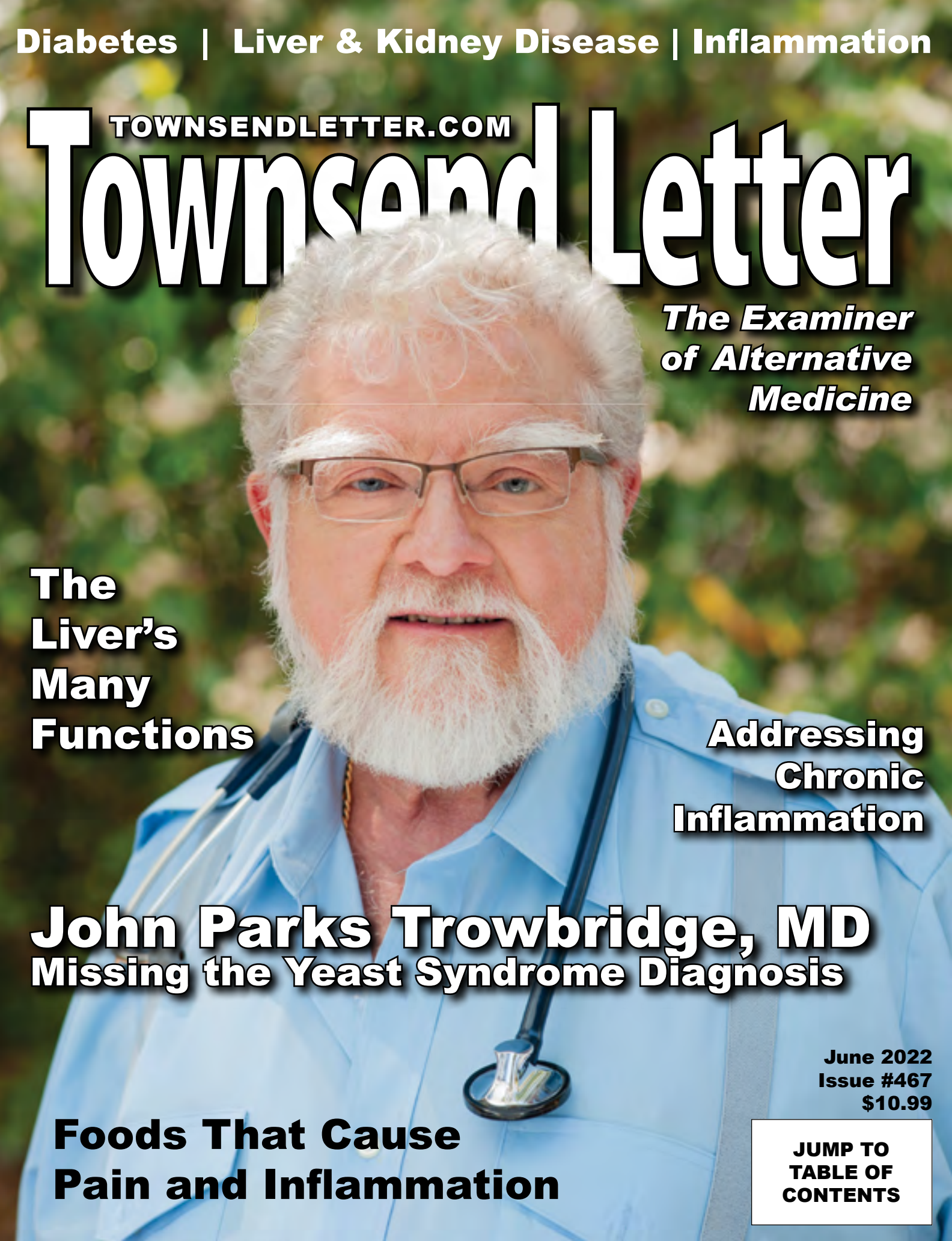

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Foods That Cause Pain and Inflammation

June 2022
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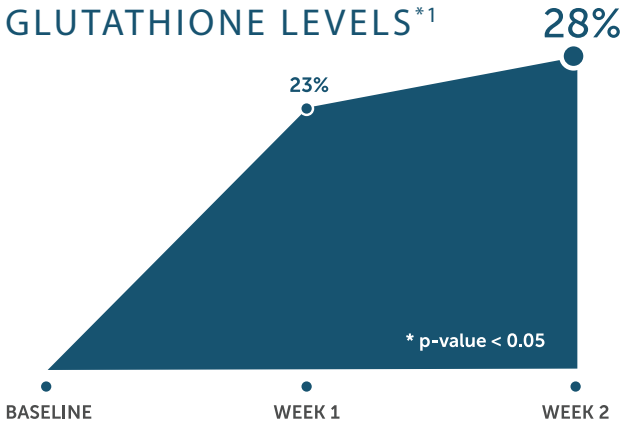

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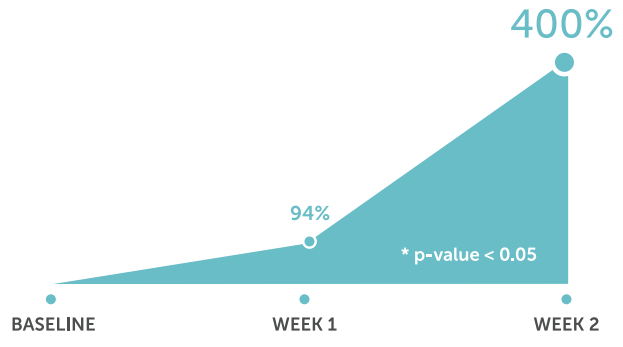

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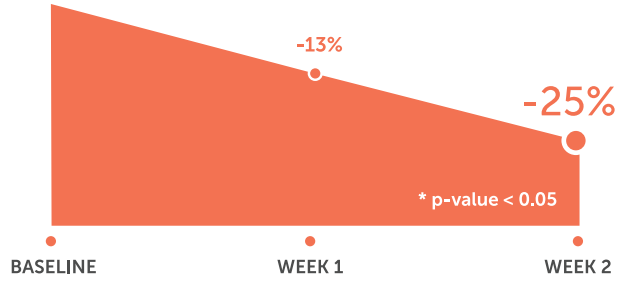

Learn more.

[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 Monstrosity and Overreach of the US Food and Drug Administration

While the pandemic has upended our lives for the past three years and life has begun to resume some manner of normalcy, we are all being held hostage by a madman intent on bombing his way to victory threatening Armageddon if we get in his way. As I write this, the UN Security Council is considering charging the perpetrator with war crimes. Of course, when said perp controls the "red" button that authorizes launching of ballistic missiles containing armed hydrogen bombs, one cannot send in a SWAT team to arrest him. In fact, one can expect that we will all needlessly suffer in the weeks, months, and (?) years ahead, until both sides come to some mutual armistice. There Is no answer to countering such barbarism except to stand at the crossroads like Bertolt Brecht's "Mother Courage" supplying food and arms to those who fight. Both sides lost but Mother Courage made out handsomely selling provisions to all the combatants. Unfortunately, millions of Ukrainians are now dispersed or in hiding; the country of Ukraine is a wreck (can you imagine the

continued on page 4 ➤

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Letter from the Publisher

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insanity that would ensue if New York or Moscow were similarly destroyed?) Yet the terrorism continues unchecked; said perp denies all wrong-doing claiming no responsibility for people killed and property destroyed.

It is ridiculous to consider regulatory activities of the Food and Drug Administration as anything nearly as monstrous as what is occurring in eastern Europe. Of course, the FDA's purpose is to oversee the food and drug industries. The compounding of bio-identical hormones, the manufacturing of injectable vitamins and minerals, as well as production of food supplements all fall within the purview of FDA oversight. However, the intent of the FDA now is not simply to regulate but to inhibit, interfere, and prohibit such compounding, manufacturing and production. We are not talking about adulterated products flooding the marketplace and being administered in doctors' offices. No, this is a direct effort to shut down compounding pharmacies, set impossible hurdles for the manufacturing of injectables, and create a list of nutraceutical supplements that are to be prohibited.

In the midst of the US efforts to support the Ukraine, the White House found time to ask Congress to provide additional budgeting to support the FDA's plan to create a complete listing of all nutritional supplements. The White House was not alone, of course; Senator Dick Durbin (D) of Illinois was spearheading such efforts. Fortunately, the secret effort to add such funding to the overall budget was defeated by Congress. Nevertheless, it is apparent that efforts by the FDA to take an adversarial stance against natural and integrative medicine are not just being contemplated but are now planned for execution. In 1994 after years of badgering by Rep. Claude Pepper and Henry Waxman, Congress passed DSHEA which stopped the FDA harassment of the supplement industry. In the past few years the FDA has been slowly muscling up their regulatory activities, seeking to halt various nutraceuticals from being manufactured. The most recent blatant effort has been to outlaw the manufacture of N-acetyl-cysteine (NAC). Recent submissions have been made to the FDA to provide evidence that NAC was manufactured as a supplement prior to the passage of DSHEA. A decision by the FDA regarding NAC is forthcoming.

Last month the FDA set forth new regulatory requirements for the compounding of injectable vitamins and minerals. One of the explicit requirements was to set a "best use date," effectively an expiration date, that is 60-90 days following manufacturing. Given the need to test all injectables for contaminants, chemical and microbiologic, this would effectively mean an injectable would have a shelf life of 30 days or less. One can only imagine the outrageous expense compounding pharmacies will incur making such injectables. One doesn't need much imagination to understand that the intent of the FDA is to shut down the compounding of injectable vitamins and minerals.

We have had numerous discussions here and elsewhere about the FDA's intention to essentially ban the compounding of bio-identical hormones. Some have said that we have complained about this so much that our word should not be trusted – like the boy who cried wolf too often. Unfortunately, the FDA is not forthcoming. When they make a decision, then and only then do they announce their stiff regulatory codes and at that point there is no turning back. There is strong background information suggesting that the FDA will decide about compounding hormones in the very near future. Understand that there is no credible reason that bio-identical hormones should not be compounded. Yet, the FDA has made it clear that a skewed report disputing compounding hormone effectiveness and safety correctly impugns the validity of compounded hormones.

While we await normalcy in our day-to-day lives during a never-ending pandemic, while we await an end to a war that terrorizes Ukraine and holds the world hostage, those of us who practice naturopathic and integrative medicine now must wait with bated breath on the actions of a renegade FDA. Of course, we do hold power to reign in the FDA. It's time to call and write our Congress people and express our displeasure with their overzealous regulations.

Cover Article: Candidiasis and the Yeast Syndrome by John Trowbridge, MD

It is very gratifying to have Dr. John Trowbridge write about yeast and the yeast syndrome in this issue. Trowbridge together with Morton Walker, DPM, authored a best-selling 1980s book, *The Yeast Syndrome.* The book popularized what William Crook, MD, had written about a few years earlier in his book, *The Yeast Connection*. Trowbridge and Crook learned about candidiasis after reading a journal article by Orian Truss, MD, who had written several years earlier on the benefit Nystatin had on the treatment of severely depressed patients.[1] Truss's work was summarized in his 1982 book, *The Missing Diagnosis* (republished as *The Missing Diagnosis II* in 2009). Trowbridge comments in his article that Truss's first observation of the importance of Candida yeast was while in training in 1953 when he encountered a coal miner who had developed organ failure following a seemingly minor finger cut. Although the patient had been treated with antibiotics and corticosteroid as were available in the 1950s, his condition deteriorated and sputum cultures demonstrated *C. albicans.* While the attendings thought that this growth was an irrelevant opportunistic organism, Truss thought otherwise and initiated Lugol's iodine, an antifungal treatment. It was the iodine that led to the patient's recovery.

In the 1980s diagnosis and treatment of the yeast syndrome became an important tool for orthomolecular psychiatry and integrative medicine. Psychiatry was very limited in its pharmaceutical care, employing benzodiazepines for anxiety, tricyclic anti-depressants for depression, and phenothiazines for psychosis, the latter frequently leading to tardive dyskinesia. Families and patients seeking alternatives to such drugs were enthused with Truss's work and appreciated the writings of Dr. Crook and Trowbridge. Those integrative and naturopathic physicians who employed anti-Candida drugs together with a yeast-controlling diet accomplished substantial improvements in patients' mental health. Regrettably, conventional psychiatry ignored the yeast connection to psychiatric disorders. Of course, this disdain for the yeast syndrome's role in mental health was similar to psychiatry's negative stance on the use of nutraceuticals like vitamin B12 and niacin. It was so divisive that psychiatrists would, in knee-jerk manner, always require patients to stop all supplements and anti-Candida treatments. I recall spending a number of years in the 1980s working at Seattle's Well Mind Association clinic counseling patients and

continued on page 6 ➤

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Letter from the Publisher

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family members about yeast control diets as well as prescribing anti-Candida supplementation and drug treatment. It felt very much like a guerrilla or hippie medical clinic offering diagnostics and treatments that were outside the mainstream and without authorization.

Of course, just like Truss's aforementioned coal miner, the yeast syndrome applies to physical concerns just as much as mental health ones. In fact, the diagnosis of irritable bowel syndrome should strongly suggest a yeast connection until proven otherwise. As Trowbridge discusses in next month's Part Two of his yeast syndrome article, a yeast control diet eliminates gluten as well as many other foods. We think of gluten elimination in relationship to celiac disease and gluten sensitivity, but its consumption also plays a key role in controlling yeast overgrowth. We may surmise that when we eliminate gluten that we are treating gluten enteropathy when its major impact might be the control of *C. albicans's* fermentation activities. The problem with yeast, just as with other intestinal organisms, is whether its metabolism is producing metabolites suitable or detrimental for human nutrition and metabolism. Clearly formaldehyde, a *C. albicans'* metabolite would lie in the latter category.

As part of a comprehensive stool analysis done by many laboratories much more is studied than simply the presence of parasites. Examination of the microbiome reveals a diversity of bacteria, fungus, and parasites. *C. albicans* is generally included with a quantification of how much yeast is present. Of course, the presence of a high level of yeast organisms would certainly lead to a Candida diagnosis but what about a low or negative finding for yeast? Trowbridge would argue that one cannot exclude a yeast diagnosis based simply on a paucity of yeast organisms on stool analysis. He makes his yeast diagnosis by understanding a patient's symptom complaints established through a Yeast Syndrome questionnaire, a form including 42 questions. (You can request a questionnaire from him by emailing info@healthCHOICESnow.com.) A high score demands consideration of a yeast syndrome diagnosis and treatment.

One of the irritating aspects of fashion vogue is that clothing styles one year are out of fashion the next. Strikingly old styles often come back in fashion years later. The yeast syndrome seems to have gone out of fashion over the past three decades. We have had hypoglycemia, chronic fatigue, Epstein Barr Virus, chemical sensitivity, fibromyalgia, Lyme disease, EMF/WiFi sensitivity, and now, of course, long-Covid. Viruses are no joke; SARS-CoV-2 has made its mark, and HIV-AIDS remains a cruel killer. With all that, the yeast syndrome seems to be so out-of-date. The skeptics never bought into it and belittle the diagnosis online. Nevertheless, *C. albicans* has not gone away and persists in being a troublemaker for lots of folks. An entirely different Candida species, *C. auris*, has plagued hospital surgical units causing severe fungal disease.

Yes, Candida is an organism that is opportunistic, but isn't every bacteria, fungus, and virus opportunistic? The tick that springs onto your leg while you walk through the forest or grass by the beach is certainly taking the opportunity to enjoy drinking your blood just as much as a mosquito does. All organisms take advantage of weakened prey; the Candida yeast established within our mucosal cavities is no exception. When our internal "terrain" is depleted, when our immune system has been weakened, when we are stressed, when we do not have adequate nutrient co-factors, the cohabiting yeast digest food yielding metabolic chemicals absorbed through the digestive tract then circulated throughout our body, including to our brain. *C. albicans* is part of our microbiome and one that we are obligated to treat seriously. It should not be an afterthought. We need to appreciate that for many folks it can be the source of their troubles that is not being addressed.

Breaking News: FDA Guidance Approves NAC Use as Food Supplement

As of April 20, the FDA announced an unpublished (not finalized) decision that the supplement NAC which was to be restricted to drug use only was restored to food supplement use. The FDA did note in its memorandum that NAC has been used as a supplement for more than 30 years.

https://www.federalregister.gov/public-inspection/2022-08560/guidance-policy-regarding-n-acetyl-l-cysteine?utm_medium=email&utm_source=govdelivery

Jonathan Collin, MD

1. Truss, O. Tissue injury induced by Candida albicans: Mental and neurologic manifestations. *J. Orthomolecular Psych.* 1978; 7 (1): 17-37.

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Shorts

briefed by Jule Klotter
jule@townsendletter.com

Vitamin D Resistance and Autoimmunity

Is vitamin D resistance a cause of autoimmune diseases? A group of German researchers, led by Dirk Lemke, argue that it is and that high-dose vitamin D3 therapy is an effective treatment. They have used a high-dose vitamin D protocol, developed by Prof. Dr. Cicero Coimbra in Sao Paolo, Brazil and available in Germany since 2016, to successfully treat multiple sclerosis patients. "Underlying the Coimbra protocol is the hypothesis of a non-hereditary, but acquired form of vitamin D resistance…," which the researchers discuss in their 2021 article for *Frontiers in Immunology.* The concept of vitamin D resistance first arose in 1937 when Fuller Albright, MD, and colleagues wrote that, in rare cases, some children required very high doses to resolve rickets. Later, it was shown that this resistance was often caused by hereditary vitamin D receptor (VDR) defects, which also produced hypocalcemia, secondary hyperparathyroidism, and alopecia (in about half of the patients). Unlike hereditary resistance that is identified in childhood, acquired vitamin D resistance "could develop during aging based on an interaction between genetic susceptibility polymorphisms of the vitamin D system and an accumulation of environmental factors…," say Lemke, et al.

The authors discuss factors that can contribute to acquired vitamin D resistance. The first is inhibited VDR expression. The vitamin D receptor binds to calcitriol, the most active form of vitamin D; this molecular complex then enters the cell nucleus where it activates or inhibits gene expression. VDR is found in nearly all cells, including most immune cells. Among its many effects, the VDR-calcitriol complex is known to inhibit B and T helper lymphocyte proliferation, thereby regulating antibody production and inflammatory cytokines – which are factors in autoimmune disease. Lemke and colleagues say, "…work of Booth et al who studied polymorphisms within the context of VDR binding to genes in human monocytes and dendritic cells, suggests that certain polymorphisms predispose to autoimmune diseases by perturbing VDR binding at autoimmune disease risk gene variants. In other words, SNPs of the VDR may predispose to acquired vitamin D resistance…."

So, what environmental factors could heighten the risk of autoimmune disease in genetically susceptible people? Elevated glucocorticoids (cortisol, cortisone) for long periods due to chronic stress or long-term cortisone treatment is one factor. When the body experiences stress and produces glucocorticoids, it shifts energy to the motor system (for fight or flight) and away from immune function. Pathogens are another factor. Lipopolysaccharides (sepsis-inducing bacterial toxins) inhibit VDR expression in THP-1 human monocytes. Live *Borrelia burgdorferi* caused a 60-fold downregulation of the VDR. Epstein-Barr virus also inhibits VDR mRNA and protein expression. Both chronic stress and infections have been correlated to autoimmune activity. In addition, environmental toxins, such as aluminum, can inhibit enzymes that convert the storage form of vitamin D into the active form that binds to VDR.

Lemke and colleagues use the parathyroid hormone (PTH) as a biomarker for acquired vitamin D resistance: "If 25(OH) D3 levels are high, PTH should be low and vice versa." This inverse relationship tends to be "disturbed" in people with autoimmune disease. They suggest that the optimal 25(OH) D3 level of >40 ng/ml should accompany "a PTH value in the middle of the lower third of its laboratory-specific reference range" – since laboratory measures for PTH vary. The authors say, "…high PTH values are indicative for vitamin D resistance, assuming that dietary calcium and phosphate intake are adequate and a differential diagnosis of hyperparathyroidism has been ruled out."

Vitamin D3 therapy under the Coimbra protocol for autoimmune disease treatment uses very high doses: 1000 IU/kg body weight for people with multiple sclerosis; 300-500 IU/kg body weight for people with rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, psoriasis, Crohn's disease, and ulcerative colitis; 300 IU/kg body weight for systemic scleroderma, ankylosing spondylitis, and Hashimoto's thyroiditis; and 150 IU/kg body weight for other autoimmune conditions. "Doses are successively adapted (almost always

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lowered) during follow-up according to a standardized procedure, which considers parathyroid hormone and calcium concentrations as well as the clinical condition of the patient," Lemke and colleagues explain. Patients need to avoid milk products and drink at least 2.5 liters of fluid each day. The German authors have treated 41 patients with multiple sclerosis, who have reported significant improvement in their symptoms.

This protocol needs to be monitored by certified Coimbra practitioners to ensure that neither hypercalcemia nor kidney damage occur.

Lemke D, et al. Vitamin D Resistance as a possible Cause of Autoimmune Diseases: A Hypothesis Confirmed by a Therapeutic High-Dose Vitamin D Protocol. *Frontiers in Immunology.* April 2021;12:655739.

The Wim Hof Method for Decreasing Inflammation

At age 17, early one icy winter morning, Wim Hof jumped into a body of cold water at a local park in The Netherlands. He stayed in the water for just a minute or two, but the "connection within" that he experienced "felt great." In his book *The Wim Hof Method – Activate Your Full Human Potential* (Sounds True, 2020), he writes:

> The body's default mode is survival. It does what it needs to do to keep its vital organs functioning, and that's precisely what it does when it is confronted by an environmental stressor like the cold. The cold is a teacher. It's merciless. You don't picnic when you go into the cold. You don't think about your mortgage or your kid's braces or your divorce; you just survive. You reactivate the deepest part of your brain.

In repeating the process, Hof became aware of his body's habit of gasping – taking in a deep breath. Following his body's lead, he took 25 deep breaths: "…it made my body tingle like crazy, like electricity….It was an amazing feeling, and over time, a routine gradually took shape. It was organic and progressive, and this physical experience of the cold and following my gut led me to a true personal discovery of my own consciousness, my own mind-body connection."

Cold water exposure (immersion or in a shower), deep breathing (30 deep breaths followed by breath retention), and a positive, committed mindset are the core of the Wim Hof method. Over the years, Hof has astounded the public and researchers alike as he broke world records for cold exposure. But more importantly, the physiological effects of his method, which include voluntary activation of the sympathetic nervous system, have expanded our understanding of the mind-body connection and offered new ways to address inflammation, pain, depression, and perhaps even aging.

Hof's abilities are not unique to him. In 2013, Matthijs Kox and colleagues conducted a small randomized controlled trial. Healthy male volunteers (age 19-27) were taught the Hof method during a four-day intensive training involving cold exposure, breathing techniques, and third eye meditation. After practicing on their own for another five to nine days, they underwent experimental endotoxemia (IV administration of 2 ng/kg *Escherichia coli* endotoxin) to incite inflammation and immune response (n=12). An untrained group (n=12) acted as the control. Despite less than two weeks of practice, the intervention group "exhibited profound increases in the release of epinephrine, which in turn led to increased production of anti-inflammatory mediators and subsequent dampening of the proinflammatory cytokine response elicited by intravenous administration of bacterial endotoxin." In response to the endotoxin, the trained group had fewer flu-like symptoms, higher anti-inflammatory IL-10 levels, and lower pro-inflammatory TNF-α, IL-6, and IL-8 levels than the control group.

A 2015 follow-up study found that a more optimistic outlook correlated to higher plasma epinephrine levels (Rho=0.76, p<.01) and IL-10 levels (Rho=0.60, p<.05), and having a greater expectation of the training's benefit correlated to fewer flu-like systems (Rho=-0.71, p<.01): "The findings suggest a possible role of especially optimism as a predictor of the autonomic and immune response to inflammatory stress after a brief training program. If replicated, these findings may be used for predicting training responses and potentiate their effects by means of optimism-inducing interventions…."

Five years later, the Dutch researchers published a study on the participants' plasma metabolome. They identified 224 metabolites in plasma that had been obtained from both the control group and the training group at six timepoints; 98 metabolites "were significantly altered following [endotoxin] administration." At baseline, the trained subjects had higher lactate and pyruvate levels than the control group. These higher levels corresponded to higher IL-10 levels that occurred after endotoxin exposure. "In vitro validation experiments revealed that co-incubation with lactate and pyruvate enhances IL-10 production and attenuates the release of pro-inflammatory IL-1βand IL-6 by LPS-stimulated leukocytes."

The Hof method reduces inflammation in young, healthy males but what about people with inflammatory disease? A 2019 randomized proof-of-concept trial enrolled 24 patients (18-55 years old) with "moderately active" axial spondyloarthritis (ASDAS >2.1 and hs-CRP ≥5 mg/L). This condition is characterized by chronic rheumatic inflammation of the spine and involves altered innate immune responses. It mainly affects young adults with few comorbidities. Only 60-70% of these patients respond to current treatment, and 30% of respondents show only a partial response.

The participants in this study were divided into early intervention that started training at baseline and continued until week 8 or a late intervention group. The late intervention group received no training for eight weeks (acting as a control) before receiving training. Study visits were done at baseline, week 4 and week 8; and a final follow-up occurred sixteen weeks after the intervention period. The Hof training was an add-on, not a replacement for medication therapy that was stable for at least 6 weeks before screening and throughout the study. In addition to the Hof method, participants took part in strength and yoga balance exercises.

Safety assessment was the primary objective of this study. The authors reported no serious adverse events during the intervention period. The common cold, the most frequent

adverse event, occurred in four participants during the intervention and two during the control period.

After eight weeks of training, the participants showed a significant decrease in erythrocyte sedimentation rate (ESR; p=0.04), indicating less inflammatory activity, and a decline in ASDAS-CRP (p=0.044), indicating a decline in disease activity. This study simply aimed to assess the method's safety in people with this condition; the authors would like to see more research with larger sample size to evaluate it clinical efficacy.

The Wim Hof Method explains the basics of the method and contains exercises to regulate pain and to decrease heart rate during times of stress; information is also available at https://www.wimhofmethod.com/. People who follow the method report improved physical and mental health. For Hof, this method is not just a way to strengthen the body and improve health, it is a way to "harness the consciousness and to direct it back toward the light and rediscover the soul." Wim Hof does not recommend his program for people with epilepsy, high blood pressure, coronary heart disease, or those with a history of serious health issues like heart failure or stroke. Also, migraine sufferers need to be cautious about taking ice baths. He urges participants, "Listen to your body and never force the practices."

Buijze GA, et al. An add-on training program involving breathing exercises, cold exposure, and meditation attenuates inflammation and disease activity in axial spondyloarthritis – A proof of concept trial. *PLOS ONE.* December 2, 2019.

Kox M, et al. Voluntary activation of the sympathetic nervous system and attenuation of the innate immune response in humans. *PNAS.* May 20, 2014.

Van Middendorp H, et al. The role of outcome expectancies for a training program consisting of meditation, breathing exercises, and cold exposure on the response to endotoxin administration: a proof-of-principle study. *Clin Rheumatol.* 2016;35:1081-1085.

Zwaag J, et al. Involvement of Lactate and Pyruvate in the Anti-Inflammatory Effects Exerted by Voluntary Activation of the Sympathetic Nervous System. *Metabolites.* 2020;10:148.

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No Deaths from Vitamins – Safety Confirmed by America's Largest Database

by Andrew W. Saul, Editor

Orthomolecular Medicine News Service

The 38th annual report from the American Association of Poison Control Centers shows **zero deaths from vitamins**. Supporting data is in Table 22B, p 1476-1478, at the very end of the report published in *Clinical Toxicology*.[1] It is interesting that it is so quietly placed way back there where nary a news reporter is likely to see it. The AAPCC reports zero deaths from multiple vitamins. And there were no deaths whatsoever from vitamin A, niacin, pyridoxine (B-6) or any other B-vitamin. There were no deaths from vitamin C, vitamin D, vitamin E, **or from any vitamin at all**.

On page 1477 there is an allegation of a single death attributed to an unspecified, unknown "Miscellaneous Vitamin." The obvious uncertainly of such a listing diminishes any claim of validity.

There were no fatalities from amino acids, creatine, blue-green algae, glucosamine, or chondroitin. There were no deaths from any homeopathic remedy, Asian medicine, Hispanic medicine, or Ayurvedic medicine. None.

Zero deaths from vitamins. Want to bet this will never be on the evening news? Well, have you seen it there? And why not? After all, over half of the US population takes daily nutritional supplements. A Harris Poll showed that for American adults, the number is 86%.[2] But let's just use the low number. Should each of those people take only one single tablet daily, that still makes close to 170,000,000 individual doses per day, for a total of well over 60 billion doses annually. Since many persons take far more than just one single vitamin tablet, actual consumption is considerably higher, and the safety of vitamin supplements is all the more remarkable.

Throughout the entire year, coast to coast across the entire USA, there was not one single death from a vitamin. If vitamin supplements are allegedly so "dangerous," as the FDA, the news media, and even some physicians still claim, then ***where are the bodies***?

References

1. Gummin DD, et al. 2020 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 38th Annual Report. *Clinical Toxicology* 2021, 59:12. https://doi.org/10.1080/15563650.2021.1989785 or https://www.tandfonline.com/doi/abs/10.1080/15563650.2021.1989785
2. https://osteopathic.org/2019/01/16/poll-finds-86-of-americans-take-vitamins-or-supplements-yet-only-21-have-a-confirmed-nutritional-deficiency/

Andrew W. Saul is Editor-in-Chief of the Orthomolecular Medicine News Service, now in its 18th year of free publication. He is also a member of the Japanese College of Intravenous Therapy; the Orthomolecular Medicine Hall of Fame; and is author or coauthor of twelve books. He has no financial connection whatsoever to the supplement or health products industry.

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** Percent Daily Values are based on a 2,000 calorie diet.
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In this Issue

June 2022 | #467

The June issue may arrive late, due to a backlog at our printer; the printer was recently hacked.

Letter from the Publisher | Jonathan Collin, MD | 2
TL's *publisher calls for action as FDA strives to increase its regulatory activities against compounding pharmacies and nutraceutical supplements. He also highlights the importance of* Candida *yeast as a contributor to poor physical and mental health.*

Shorts | Jule Klotter | 7
This month's column looks at the possibility that acquired vitamin D resistance underlies autoimmunity and at research that shows the Wim Hof Method decreases inflammation.

News | No Deaths from Vitamins – Safety Confirmed by America's Largest Database | Andrew W. Saul | 9
Once again, the American Association of Poison Control Centers' annual report shows no deaths from supplements.

Literature Review & Commentary | Alan R. Gaby, MD | 12
Sourdough bread, Mediterranean diet benefits, magnesium for nocturnal leg cramps, suspected adverse reactions to alpha-lipoic acid, and more are among this month's topics.

Integrating Functional and Naturopathic Medicine Concepts and Therapeutics into Medical Practice or Common Primary Care and Specialty Conditions: Key Concepts and Paradigm Shifts in Clinical Care from *Inflammation Mastery: Textbook of Clinical Nutrition and Functional Medicine* | Alex Vasquez, DO, ND, DC | 19
A simple mnemonic encourages practitioners to assess seven factors that can contribute to sustained inflammation in order to help patients suffering from autoimmunity and other inflammation-related conditions.

On the Cover **| Still Missing Diagnosis of The Yeast Syndrome? – Part 1**
John Parks Trowbridge, MD, FACAM | 26
John Parks Trowbridge, MD, co-wrote The Yeast Syndrome *thirty-six years ago; yet, yeast overgrowth and the many physical and mental symptoms it causes are still often ignored. In Part 1, Dr. Trowbridge gives the history of the yeast syndrome, its contribution to chronic illness, and the foundation treatment that he uses.*

Managing Yeast Overgrowth | Joseph J. Burrascano Jr., MD | 34
Oral hygiene measures and nutraceuticals can help control yeast overgrowth.

Bile Acids as Regulators of Inflammation | 36
Steven Sandberg-Lewis, ND, DHANP
Bile salts appear to have systemic inflammation-modulating effects and may eventually be used clinically to reduce inflammation, apoptosis, and necrosis in the liver, intestine, central nervous system, myocardium, and retina.

The Character of the Liver | Chris Chlebowski, ND, DC | 39
The liver does far more than detoxify the blood; it also has a role in hormone balance and the distribution of nutrients.

Reversing Chronic Kidney Disease with Niacin and Sodium Bicarbonate
Stephen McConnell and W. Todd Penberthy | 42
A combination of niacin and sodium bicarbonate reduces phosphorus levels and decreases protein levels in the urine, thereby reversing kidney damage in some patients.

Klotho: The Super-Antioxidant You've Never Heard of | 46
Jenna Henderson, ND
An antioxidant made by the kidneys has multiple anti-aging properties and may be helpful in many types of kidney disease.

Lifestyle, Inflammation, and Food Pain | Hal S. Blatman, MD | 50
Common foods that trigger inflammation are a too-often overlooked cause of pain.

LDN: A Game Changer for Many Patients | 55
Pamela W. Smith, MD, MPH, MS
Naltrexone, traditionally used to treat drug overdose, has anti-inflammatory, immune-modulating, and pain-relieving effects at low doses, making it a useful treatment for many illnesses.

Letters to the Editor | 61
Allergy Management | Diego Saporta, MD
Too often, skin prick tests and RAST-like blood tests are negative in people with clearly allergic symptoms. Intradermal dilutional testing is the most accurate way to identify allergic disease.

Response to Orthomolecular COVID Protocol | Ronald Steriti, ND, PhD
The author adds a few more treatment options to the Gonzalez Covid-19 orthomolecular protocol.

News | FDA's Threat to cBHT Puts Millions of Patients at Risk | 63

List of Advertisers in this Issue | 64

Guest Editorial | 'Ministry of Truth' vs Nutritional Medicine | 65
Damien Downing, MBBS, MRSB
Despite published studies that demonstrate the benefits of vitamins C and D during the Covid pandemic, UK's National Health Service continues to ignore nutritional medicine.

Book Review | *Extra Life: A Short History of Living Longer* | 67
Steven Johnson | review by Jacob Schor, ND, FABNO
A new book examines the consequences of the increase in human lifespan.

Calendar | 68

The Lobay Viewpoint | Douglas Lobay, BSc, ND | 69
Peanuts and Poppycock: The Science Behind Magnesium Bioavailability
The author takes a deep dive into the magnesium compounds used in supplements and the differences in their absorption and bioavailability.

Healing with Homeopathy | Judyth Reichenberg-Ullman, ND, MSW | 73
Homeopathy for Restless Legs Syndrome with Anxiety
Improved sleep, reduced anxiety, and much needed weight gain are among changes that occurred in a patient who resolved restless leg syndrome with a common remedy.

Curmudgeon's Corner | Jacob Schor, ND, FABNO | 75
Arming the Immune System
The necessity and benefits of a fever are the subject of a new, well-referenced book.

Women's Health Update | Tori Hudson, ND | 77
Desquamative Inflammatory Vaginitis
Identification and treatment of desquamative inflammatory vaginitis are the topics for this month's column.

Editorial | Alan R. Gaby, MD | 80
Practice Guidelines for the Treatment of Hypothyroidism Need to Improve
Too many patients suffer with symptoms of hypothyroidism because mainstream medicine continues to adhere to levothyroxine (T4) treatment, despite published evidence that many do better with a combination T3 and T4 treatment.

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A Hallmark of Covid-19: Cytokine Storm/Oxidative Stress and Its Integrative Mechanisms | Richard Z. Cheng, MD, PhD
Covid-19 and many other infections can induce a cytokine storm (severe oxidative stress) that may be prevented with the use of integrative antioxidant therapies.

Top Vitamin D Papers in 2021 – Benefits Ignored at a Time They Are Most Needed | William B. Grant, PhD
Studies published last year show that vitamin D reduces Covid-19 incidence, severity, and death rates as well as reducing the risks of cardiovascular disease, cancer, and autism.

ON THE COVER: John Parks Trowbridge, MD – Missing the Yeast Syndrome Diagnosis (pg. 26); Foods That Cause Pain and Inflammation (pg. 50); Addressing Chronic Inflammation (pg. 19); The Liver's Many Functions (pg. 39)

Literature Review & Commentary

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

Decreasing FODMAPs Intake by Switching to Sourdough Bread

The fructans content of sourdough bread was found to be, on average, 72% lower than that of bread made with baker's yeast. This reduction in fructans content appeared to be due to the degradation of fructans by an enzyme produced by the lactic acid bacteria that are used to make sourdough bread. The fructans concentration in sourdough bread was below the cut-off level (< 0.3 g of oligosaccharides per serving of grains or cereal) that is used to allow the food to be consumed as part of a low-FODMAPs diet.

Comment: "FODMAPs" is an acronym for Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols. Many people with irritable bowel syndrome (IBS) do not tolerate foods that contain large amounts of these compounds, and low-FODMAPs diets have been used successfully to treat IBS. Fructans are fermentable oligosaccharides that consist of polymers of fructose molecules. The two main categories of fructans in foods are fructooligosaccharides and inulin. Wheat contains a relatively high concentration of fructans, and wheat intake is restricted on a low-FODMAPs diet.

Most leavened breads use baker's yeast to make the dough rise. In contrast, the production of sourdough bread involves fermentation by "wild yeast" and lactic acid bacteria that are naturally present in flour. The results of the present study indicate that sourdough bread has a low concentration of fructans, and may therefore be an acceptable alternative to bread made with baker's yeast for patients with IBS who are on a low-FODMAPs diet.

Intolerance to fructans is not the only mechanism by which wheat consumption triggers gastrointestinal symptoms. In some

continued on page 14 ➤

Exciting Study Results for Post Covid Symptoms

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Firefly Light Therapy™ Shows Positive Results for Post Covid Lung Symptoms

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.

5 days after his second treatment all symptoms subsided and improvement was verified with Spirometer Scores. After 3 more 5-minute Firefly sessions, the patient reported he can now exercise for 60 minutes before needing rest.

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

TYPE OF SCORE	BEFORE	AFTER	AMOUNT OF INCREASE
(PEF) Peak Expiratory Flow	77 L/min	138 L/min	**79.2%**
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Gaby's Literature Review

➤ *continued from page 12*

cases, the symptoms appear to result from an allergic reaction to one or more of the proteins present in wheat. In those cases, people would likely develop symptoms from sourdough bread.

Menezes LA, et al. Reducing FODMAPs and improving bread quality using type II sourdough with selected starter cultures. *Int J Food Sci Nutr*. 2021;72::912-922.

Magnesium for Nocturnal Leg Cramps

One hundred eighty-four Ukranian individuals (mean age, 57 years) with nocturnal leg cramps were randomly assigned to receive, in double-blind fashion, 226 mg of magnesium (as magnesium oxide monohydrate) once a day at bedtime or placebo for 60 days. The mean number of nocturnal leg cramps per week decreased by 63% ($p < 0.001$) in the magnesium group, from 5.4 at baseline to 2.0 at the end of the study. This improvement was significantly greater ($p = 0.01$) than the 41% decrease in the placebo group. Compared with placebo, magnesium treatment also resulted in a greater decrease in the duration of nocturnal leg cramps ($p < 0.007$) and greater improvement in sleep quality ($p < 0.001$).

Comment: Nocturnal leg cramps are a common problem, particularly among elderly people. In most cases, a cause cannot be identified. The results of the present study indicate that magnesium is an effective treatment for nocturnal leg cramps. Magnesium has an antispasmodic effect, which may explain its mechanism of action. The dosage of magnesium used in this study (elemental magnesium versus magnesium oxide monohydrate) was clarified in a personal communication with one of the researchers.

Barna O, et al. A randomized, double-blind, placebo-controlled, multicenter study assessing the efficacy of magnesium oxide monohydrate in the treatment of nocturnal leg cramps. *Nutr J*. 2021;20:90.

Adverse Reactions to Alpha-Lipoic Acid

Suspected adverse reactions to alpha-lipoic acid (ALA)-containing products were identified from the Italian Phytovigilance System. From March 2002 to February 2020, 116 reports concerning 212 adverse reactions were identified. Skin conditions (44.9%) and gastrointestinal disorders (10.8%) were the most frequent reactions. Causality was considered definite in 15 cases, probable in 35, possible in two, unlikely in five, and unclassifiable in 37. Ten people developed insulin autoimmune syndrome, a potentially serious condition. The likelihood that this condition was caused by ALA was considered definite in one case, probable in eight, and possible in one. Insulin autoimmune syndrome is characterized by transient hypoglycemia, the presence of anti-insulin antibodies in serum, and very high serum concentrations of insulin during hypoglycemic attacks. It has been suggested that ALA might bind to insulin and thereby increase its antigenicity.

Comment: ALA has generally been considered safe with few side effects reported at usual therapeutic doses. Allergic skin reactions and gastrointestinal symptoms have previously been reported but I have not seen previous reports of insulin autoimmune syndrome. While side effects of ALA are uncommon, practitioners should consider adverse reactions to ALA in the differential diagnosis of the conditions described in this report.

Gatti M, et al. Assessment of adverse reactions to alpha-lipoic acid containing dietary supplements through spontaneous reporting systems. *Clin Nutr*. 2021;40:1176-1185.

Can Increasing Fiber Intake Help You Lose Weight?

Two hundred forty-two overweight or obese men and women (aged 30-70 years; body mass index, 27-35 kg/m^2) were randomly assigned to consume high-fiber rye products or refined wheat products for 12 weeks. All participants were prescribed a low-calorie diet and were advised to minimize intake of sugar and fast food, increase intake of vegetables, and decrease portion size. After 12 weeks, mean body weight fell to a greater extent in the group consuming rye than in the group consuming refined wheat (2.86 kg vs. by 1.79 kg; $p < 0.004$). Mean loss of body fat was also greater in the rye group than in the refined-wheat group ($p = 0.03$). Daily energy intake decreased from baseline to week 12 by 172 kcal in the rye group and by 92 kcal in the refined-wheat group.

Comment: Among whole grains, rye is the richest source of dietary fiber. Consuming a high-fiber diet may help prevent or reverse obesity by several different mechanisms. First, high-fiber foods tend to have low caloric density. Second, such foods require additional chewing, which slows the rate at which a person eats. Third, fiber holds water and thereby promotes a feeling of fullness and satiety. In this study, compared with a diet containing low-fiber refined wheat, a diet containing high-fiber rye products decreased total energy intake and enhanced weight loss in overweight and obese individuals who were trying to lose weight.

Iversen KN, et al. A hypocaloric diet rich in high fiber rye foods causes greater reduction in body weight and body fat than a diet rich in refined wheat: A parallel randomized controlled trial in adults with overweight and obesity (the RyeWeight study). *Clin Nutr ESPEN*. 2021;45:155-169.

Can Eating Olive Oil Prolong Your Life?

The association between consumption of olive oil and total and cause-specific mortality was examined in prospective cohort studies of 60,582 US women participating in the Nurses' Health Study (1990-2018) and 31,801 men participating in the Health Professionals Follow-up Study (1990-2018) who were free of cardiovascular disease and cancer at baseline. Diet was assessed by a food-frequency questionnaire every four years. During 28 years of follow-up, 36,856 deaths occurred. After adjustment for potential confounding variables including age; ethnicity; marital status; cigarette and alcohol use; physical activity; family history of diabetes, cancer, and myocardial infarction; history of hypertension and hypercholesterolemia; use of multivitamins; body mass index; total energy intake; and intake of red meat, fruits, vegetables, nuts, whole grains, and soda, the pooled hazard ratio (HR) for all-cause mortality among participants who had the highest consumption of olive oil (more than 0.5 tablespoon per day or more than 7 g per day), as compared with those who never or rarely consumed olive oil, was 0.81 (95% confidence interval [CI], 0.78-0.84). Higher olive oil intake was associated with a 19% lower risk of cardiovascular disease mortality (HR = 0.81; 95% CI, 0.75-0.87), a 17% lower risk of cancer mortality (HR = 0.83; 95% CI, 0.78-0.89), a 29% lower risk of neurodegenerative disease mortality (HR = 0.71; 95% CI, 0.64-0.78), and an 18% lower risk of respiratory disease mortality (HR = 0.82; 95% CI, 0.72-0.93). In substitution analyses, replacing 10 g per day of margarine, butter, mayonnaise, and dairy fat with the equivalent amount of olive oil was associated with an 8%-34% lower risk of total and cause-specific mortality.

Comment: In this prospective cohort study, olive oil consumption was associated with a lower risk of all-cause mortality, as well as a lower risk of death due to cardiovascular

continued on page 16 ➤

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Gaby's Literature Review

➤ *continued from page 14*

disease, cancer, neurodegenerative disease, and respiratory disease. While observational studies cannot prove causation, the possible protective role of olive oil is biologically plausible. As compared with oils such as corn oil, soybean oil, and safflower oil, olive oil has a higher concentration of monounsaturated fatty acids and a lower concentration of polyunsaturated fatty acids. Olive oil is therefore less likely to form potentially toxic lipid peroxides during cooking. Lipid peroxides may play a role in the pathogenesis of most, if not all, of the diseases mentioned above. In addition, unrefined (extra virgin) olive oil contains compounds that have anti-inflammatory activity. Unrefined olive oil might therefore help prevent the development or progression of diseases that have an inflammatory component.

Guasch-Ferre M, et al. Consumption of olive oil and risk of total and cause-specific mortality among U.S. adults. *J Am Coll Cardiol*. 2022;79:101-112.

Beneficial Effect of Mediterranean Diet and Mindfulness-Based Stress Reduction During Pregnancy

Pregnant women (n = 1,221) in Barcelona, Spain, who were between 19 and 23 weeks of gestation and considered at high risk of having a small-for-gestational-age (SGA) baby were randomly assigned to consume a Mediterranean diet, to participate in a mindfulness-based stress-reduction program, or to receive usual care (control group). Participants in the Mediterranean diet group received two hours per month of individual and group educational sessions and free extra-virgin olive oil and walnuts. Women in the stress reduction group underwent an eight-week program consisting of weekly 2.5-hour sessions and one full-day session. SGA (the primary outcome measure) was defined as birth weight below the 10th percentile. SGA occurred in 21.9% of infants in the control group, 14.0% of infants in the Mediterranean diet group ($p = 0.004$ vs. control group), and 15.6% of infants in the stress reduction group ($p = 0.02$ vs. control group). The secondary outcome measure was a composite of at least one of the following: preterm birth, preeclampsia, perinatal mortality, severe SGA, neonatal acidosis, low Apgar score, or presence of any major neonatal morbidity. The secondary outcome occurred in 26.2% of participants in the control group, 18.6% in the Mediterranean diet group ($p = 0.01$ vs. control group) and 19.5% in the stress reduction group ($p = 0.02$ vs. control group).

Comment: Being born SGA is a leading cause of perinatal morbidity and mortality. Maternal suboptimal nutrition and high stress levels have been associated with poor fetal growth and adverse pregnancy outcomes. In the present study of pregnant women at high risk of having an SGA baby, treatment with a Mediterranean diet or with mindfulness-based stress reduction, compared with usual care, significantly reduced the percentage of newborns with birth weight below the 10th percentile.

Crovetto F, et al. Effects of Mediterranean diet or mindfulness-based stress reduction on prevention of small-for-gestational age birth weights in newborns born to at-risk pregnant individuals: the IMPACT BCN randomized clinical trial. *JAMA*. 2021;326:2150-2160.

Consumption of Ultraprocessed Foods Is Increasing

Consumption of ultraprocessed foods among US children aged 2-19 years (mean, 10.9 years) was examined over 10 cycles of the National Health and Nutrition Examination Survey (NHANES) from 1999-2000 to 2017-2018. Ultraprocessed food was defined as food produced from a series of industrial processes. Ingredients characteristic of ultraprocessed foods include high-fructose corn syrup, hydrogenated oils, flavor enhancers, colors, and emulsifiers. Examples of ultraprocessed foods include sweet or savory packaged snacks, sugar-sweetened beverages, candy, industrial bread, industrial breakfast cereal, ready-to-heat-and-eat pasta dishes and pizza, and sausages and other reconstituted meat products. From 1999 to 2018, the estimated percentage of total energy consumed from ultraprocessed foods increased from 61.4% to 67.0% (p for trend < 0.001), whereas the percentage of total energy consumed from unprocessed or minimally processed foods decreased from 28.8% to 23.5% (p for trend < 0.001).

Comment: Studies have shown that consumption of ultraprocessed foods is associated with higher total caloric intake and may promote the development of obesity. Observational studies have found that higher intake of ultraprocessed foods is associated with increased risk of cardiovascular disease and cerebrovascular disease, even after adjusting for other dietary factors such as intake of saturated fat, sodium, sugar, and fiber. The trend toward increasing consumption of these types of foods is worrisome, in that it may portend an increasing burden of chronic disease in our society.

Wang L, et al. Trends in consumption of ultraprocessed foods among US youths aged 2-19 years, 1999-2018. *JAMA*. 2021;326:519-530.

Iron Supplementation for Postpartum Depression or More Iranian Research Fraud?

Seventy Iranian women (mean age, 32 years) with postpartum depression on day 7 after delivery and a median serum ferritin level of 24 mg/dl were randomly assigned to receive, in double-blind fashion, 50 mg per day of iron or placebo for six weeks. The median score on the Edinburgh Postnatal Depression Scale improved significantly by 25% ($p < 0.001$) in the iron group and improved nonsignificantly by 8% in the placebo group ($p < 0.05$ for the difference in the change between groups). These results indicate that iron supplementation improved postpartum depression in Iranian women, many of whom had low or borderline-low iron status.

Comment: When I first read this paper (published online in 2015), I was not fully aware of what appears to be an epidemic of fraudulent research coming from Iran. I even cited this research in the second edition of my textbook, *Nutritional Medicine*. I recently took a closer look at this paper and discovered a number of issues that cause me to doubt its credibility.

1. Impossible or implausible timing: The paper stated that at 1 week postpartum the mothers were randomly assigned to receive iron or placebo. However, in the Methods section of the paper, it was stated that at 1 week postpartum the mothers were contacted by phone and invited to participate in the study. Those who agreed to participate were asked to complete the Edinburgh Postnatal Depression Scale. Mothers who had a score of 11 or higher were interviewed by a psychiatrist to confirm the diagnosis of postpartum depression. The procedures described in the Methods section – being home to receive the phone call, filling out the questionnaire, returning the questionnaire, having the questionnaire analyzed, scheduling an appointment with the psychiatrist, and seeing the psychiatrist – all take time. It is therefore virtually impossible that the women could have been started on iron or placebo on the same day they were first contacted by phone and invited to participate.

continued on page 18 ➤

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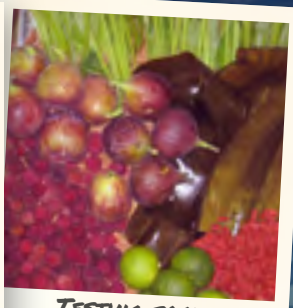

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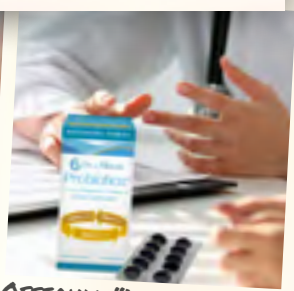

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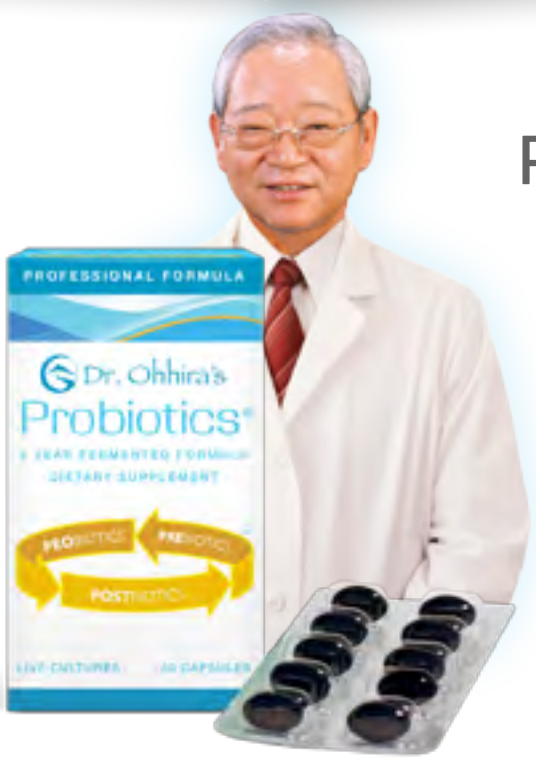

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Gaby's Literature Review

➤ *continued from page 16*

The paper also stated that the women were reevaluated at 7 weeks postpartum, which was after they had received iron or placebo for 6 weeks. However, this reevaluation could only have occurred at 7 weeks postpartum if the treatment was started at 1 week postpartum (which, as discussed above, was virtually impossible).

2. Discrepancy regarding timing: The Iranian Registry of Clinical Trials (IRCT) document that is connected to this study stated that hemoglobin and hematocrit will be measured during hospitalization, at the time of hospital discharge after delivery, and 1 month later. However, according to the paper, hemoglobin was measured seven days after delivery and six weeks later.
3. Discrepancies regarding inclusion criteria: The IRCT document stated that women had to be 15 to 49 years of age to participate. The paper stated that women had to be 20 to 40 years of age. The IRCT document stated that all postpartum mothers were eligible to participate. The paper stated that mothers were eligible if they had delivered a healthy term infant through an uncomplicated elective cesarean section and did not have any medical illness.
4. Discrepancies regarding exclusion criteria: The IRCT document stated that women were excluded if they had thalassemia or a hemoglobin level below 10.5. The paper listed additional exclusion criteria, such as a history of any psychiatric disorder before or during pregnancy, any medical illness upon enrollment, or a family history of psychiatric disorders.
5. Discrepancy regarding the treatment: The IRCT document stated that women received 30 mg of ferrous sulfate daily for 1 month. It was not stated whether this dose referred to 30 mg of elemental iron or to 30 mg of ferrous sulfate (which would be equivalent to 6.0 mg or 11.1 mg of elemental iron, depending on whether the ferrous sulfate was desiccated or hydrated). The paper stated that the women received 50 mg of elemental iron from ferrous sulfate daily for six weeks.
6. Discrepancy regarding the method of assessment: The IRCT document stated that depression would be assessed by both the Beck and Edinberg's questionnaires. In the paper, only the Edinburgh Postnatal Depression Scale was used.
7. Improper reporting of units: The paper used mg/dl as the unit for serum ferritin, with a cutoff level of less than 15 for iron deficiency. However, the typical unit for ferritin is µg/L or ng/ml. Using mg/dl as the unit of measurement, the cutoff level for iron deficiency should have been 0.15, not 15. The paper also used a hemoglobin level of less than 10.5 mg/dl as the cutoff level for anemia. However, hemoglobin is typically measured in g/dl. Using mg/dl as the unit of measurement, the cutoff level for anemia should have been 10,500 mg/dl, not 10.5 mg/dl.

Sheikh M, et al. The efficacy of early iron supplementation on postpartum depression, a randomized double-blind placebo-controlled trial. *Eur J Nutr*. 2017;56:901-908.

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Integrating Functional and Naturopathic Medicine Concepts and Therapeutics into Medical Practice or Common Primary Care and Specialty Conditions: Key Concepts and Paradigm Shifts in Clinical Care from *Inflammation Mastery: Textbook of Clinical Nutrition and Functional Medicine*

by Alex Vasquez, DO, ND, DC

Editor Note: This article is adapted from the edited transcript of Dr. Vasquez's May 2020 video presentation with the above title. The video presentation contains at least 136 slides or "pages" that include the scientific citations, additional commentary, and notes, as well as illustrations, diagrams, and excerpts from other publications, including his book *Inflammation Mastery.* The video is available for viewing and purchase at https://www.inflammationmastery.com/medical.

Learning new information that is consistent with a previously learned model or paradigm is easy: just "plug and play" new data into an old mainframe. However, learning *new information* within a *new model* requires that we first create some space for that new information. If people are rigidly adherent to the medical paradigm, then the mind is not open to a new way of seeing things. Being open to a change in paradigm does not indicate that a person thereafter ignores previous information, or to the extreme "stops using drugs to treat patients," but rather has more options and can use drugs within a framework of **cognitive flexibility**, *rather than* ***blind obedience*** *and* ***repetitive routine****.*

The clinical employment of nutrition, naturopathic principles, and functional medicine involves a paradigm shift – a completely different (relative to the drug-centered medical model) way of looking at disease and treatment, not simply the employment of different treatments that replace drugs within a medical model. Using nutrients to replace drugs is sometimes called "green medicine," such as when we substitute a pharmacologic HMG-CoA-reductase inhibitor (i.e., lovastatin or any of the other "statin" drugs) with a natural cholesterol-lowering supplement such as red yeast rice, niacin, or policosanol. Using nutrients to replace drugs is not equivalent – neither in terms of conceptualization, efficacy, clinical acumen, nor global impact – to either naturopathic medicine or functional medicine; however, it is a common and understandable entry point for doctors transitioning from one paradigm to the other.

To think of *what is causing a condition that a patient presents with* [patient-centered model] is very different from thinking *what drug do I need to use in order to treat or alleviate this condition* [drug-

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➤ *continued from page 19*

centered model]. "Treating the cause" as we do in naturopathic medicine is very different from asking oneself, "How do I manage this condition? And what drugs do I use to treat this condition?" So what I am going to show you is how we can shift that paradigm to focus more on **the cause** *that we can correct*, rather than thinking how can we simply medicate these numbers and medicate these symptoms so that the condition is therefore "successfully medically managed."

In functional medicine and naturopathic medicine, we use ***clinical nutrition interventions to change gene expression*** rather than think our patients have "irreversible genetic diseases" that we can never influence. Obviously, some diseases do originate genetically (from specific gene defects); however, unknown to most medical physicians is the fact that many of these conditions can be *at least* ameliorated by functional and nutritional interventions to reduce the disease impact, reduce drug dependence, improve functional capacities, and maintain higher quality of life.

Specific to naturopathic medicine is the concept of the **"hierarchy of therapeutics,"** which is an especially important concept. What we do in naturopathic medicine is start with the *least invasive* intervention possible – usually botanical medicines, nutritional intervention, diet, and lifestyle – before we think of going on to using drugs, or even surgery. I am sure, as we all know in so-called conventional or standardized drug-centered medicine, drugs are primary first-line "day one" therapy. A patient with a health problem can expect *to have their nutritional needs ignored* and *to have drugs prescribed on the first visit* when they see a so-called standardized or conventional medical practitioner.

Nutrition is conceptually different from drug-based medicine. Whereas drugs work on *individual pathways* mostly by inhibiting enzymes and blocking receptors, nutritional interventions work on *multiple systems* by improving enzymatic function and *normalizing metabolism and immune function*.

Inflammation

By now, I think all healthcare providers should know that inflammation is a major component to all major so-called chronic health problems. I prefer to refer to these as *sustained* inflammatory conditions, not *chronic* inflammatory conditions. If we say that these conditions are *chronic*, then we pretty much stop thinking and we accept the "fact" that the patient is going to have this condition or these conditions for long periods of time. Hence the title *chronic*, which becomes a self-fulfilling prophecy. If we change the language slightly in our description of these conditions, and instead of calling these *chronic* inflammatory conditions, we refer to these conditions as disorders of *sustained* inflammation then we change our mental perception of the condition and **instead of accepting these as chronic, we begin to look for what are the causes of the sustained inflammatory response** and what can we do to address and eradicate those causes that are sustaining the inflammatory response.

In functional medicine and naturopathic medicine, we use clinical nutrition interventions to change gene expression.

The four main types of *sustained* or so-called "chronic" inflammation are 1) metabolic inflammation, 2) allergic inflammation, 3) autoimmune inflammation, and 4) neuroinflammation or brain inflammation. I want you to start categorizing inflammatory conditions into metabolic, allergic, autoimmune, and neuroinflammation or brain inflammation.

Metabolic Inflammation: We commonly see patients who have what I call metabolic inflammation. This is cardiovascular disease, hypertension, diabetes mellitus type-2, and metabolic syndrome. Standard medical treatment for these patients is to simply lower the abnormal numbers that represent the metabolic disease process; a patient comes into the office with hypertension, and we lower their blood pressure with drugs; another patient comes into the office with elevated glucose when they have diabetes, and we lower their glucose with drugs. In both cases, when we operate from the drug-centered medical paradigm, we are addressing the abnormal numbers without really addressing the underlying metabolic-inflammatory causes of the imbalances that result in those abnormal numbers. So that is obviously treating a manifestation of the problem, not the problem itself.

Allergic Inflammation: Category number two is allergic inflammation, asthma, allergic rhinitis and conjunctivitis, eczema and atopic dermatitis, which has a strong dysbiotic component in it as well. Typically, these patients are having an allergic reaction to bacteria on their skin; sometimes the trigger is a food allergic response. Eczema patients also show a higher body burden of mercury, which is a toxic heavy metal known to trigger inflammatory reactions in the skin and to promote worsening of allergic reactions.

Autoimmune Inflammation: Another inflammatory type or inflammatory subtype is autoimmune inflammation. The prototypes include rheumatoid arthritis and psoriasis also, of course, other conditions such as inflammatory bowel disease and multiple sclerosis. The standard medical treatment is just to provide those patients with a buffet of anti-inflammatory drugs but not to address the underlying cause of the inflammation. We simply treat the inflammatory response, not the inflammatory trigger, and that is an important distinction.

Brain Inflammation: And category number four, as I have already mentioned, is neuroinflammation or brain inflammation. This includes depression, brain injury, autism, schizophrenia and bipolar disorder, neurodegenerative conditions such as Alzheimer's and Parkinson's, hyperphagia, obesity and insulin resistance, multiple sclerosis, PANDAS, brainstem encephalitis, migraine, and fibromyalgia.

Functional Inflammology Protocol

After many years of teaching functional medicine to postgraduate audiences internationally, plus teaching my graduate students how to organize a large amount of information efficiently so they could quickly transition from familiarity to understanding to memorization to implementation, I developed this functional inflammology protocol, and the accompanying acronym to accelerate mastery of these concepts for practical

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use and clinical implementation. Again, the four types of inflammation that I am going to deal with most specifically are metabolic inflammation, allergic inflammation, autoimmune inflammation and neuroinflammation. Also in this presentation, I will make a little mention of infectious inflammation whether that comes from dysbiosis or from viral infections.

With this functional inflammology protocol, we are addressing the upstream contributors to *chronic* sustained inflammation and the underlying immune activation. Rather than dealing with the long-term "management" of inflammatory consequences, what we try to do in naturopathic medicine and functional medicine is address the upstream contributors to that systemic inflammation and immune activation so that the inflammatory response is dampened, overall health is improved, and our patients can ultimately and hopefully be *liberated from their diseases* rather than having to carry those diseases throughout their lifetime.

The benefit of this functional inflammology protocol is that it organizes the major causes of inflammation into a mnemonic that helps doctors clinically apply this information in an organized manner.

Let me share this example from my own clinical practice, my own clinical experience of a patient with severe aggressive drug-resistant rheumatoid arthritis. This patient had already been seen by several medical specialists; she had also gone to the local naturopathic medicine clinic – this was in the Pacific Northwest region of the United States, where we have two naturopathic universities with their respective teaching clinics. She had already been given all of the drugs for rheumatoid arthritis; none of them had worked for her, and she continued with severe aggressive drug-resistant rheumatoid arthritis and debilitating inflammatory pain.

In rheumatoid arthritis, one of the laboratory markers that we use for diagnosis is called CCP – blood levels of a protein called cyclic citrullinated peptide. In her case, her CCP level was actually so high that the lab could not measure how high it was – it was greater than 250. The actual level could have been 400, 600 or 700. But it was very "positive"; that means *very bad* in this case at more than 250. The normal level of CCP should be less than 50 or 60; so, obviously a value greater than 250 is extremely abnormal. That was her level of disease activity in March of 2012, when I was first developing and restructuring this clinical protocol.

About nine months later, we had reduced her levels from greater than 250 down to 195. I was pretty happy because we could see that we were making progress in normalizing this important clinical marker, and she was clinically asymptomatic, able to work in her garden at her farm without pain and without any anti-inflammatory drugs.

Within two more months in April of 2013, her antibody levels had almost normalized at 54. So in summary: within one year, we were able to transition her from having severe aggressive drug-resistant rheumatoid arthritis with pretty severe pain every day to being relatively asymptomatic, not taking any anti-inflammatory or anti-rheumatic drugs, and with nearly normal laboratory results. This was not simply "successful management" of her rheumatoid arthritis but rather ***successful reversal*** of her rheumatoid arthritis.

With rheumatoid arthritis, CCP antibodies are part of the disease process. So when we can achieve clinical benefit along with reduction of these antibodies, we know we are on the right track, and that we are not simply managing the disease or treating the disease, but we are actually reversing the disease. And that is what we were able to show with these results.

So now let us dive into this clinical protocol that we can use to treat these disorders of *sustained* inflammation. Inflammation is always in response to one or more triggers; prolonged inflammation is due to prolonged exposure to one or more inflammation-generating causes (inflammogens).

Inflammatory responses should be acute and short term and responsive to a specific trigger or small number of triggers. Chronic inflammation is not physiologically normal, even though we have been taught to accept it as normal because we see so many conditions characterized and labeled as chronic inflammatory conditions. But we need to see that that is *not normal*. Chronic inflammation is *not normal*. **Inflammation exists as a response to resolve problems**, not to sustain and perpetuate those problems or engage in a long-term relationship with those problems. We as clinicians need to try to identify what is triggering this ***sustained inflammatory response***.

What are the common causative themes among obesity, hypertension, diabetes, metabolic syndrome, allergy, asthma, autoimmunity, and neuro-inflammation? In this section, I will help you identify the major inflammatory triggers and to differentiate those which we can correct from those which we cannot. You will see that we can nearly always correct or at least ameliorate the inflammatory triggers, and that this also applies to so-called "genetic diseases." Clearly, a few diseases have legitimate genetic causes; in some rare cases, specific gene defects result in the production of abnormal proteins that fail to function properly, and the result can be an impaired process that affects the brain, muscles, or other organs and systems such as the immune system. Much more commonly, undefined "bad genes" are blamed for lifestyle-generated and food-promoted illnesses.

Food and Diet: We need to look at dietary excess, especially carbohydrate excess, sometimes food allergies, nutritional deficiencies and imbalances and other conditions that have a positive response to skillful nutritional intervention. I call those conditions, **diet-responsive disorders** or **nutrition-responsive disorders**. If a condition is dietarily responsive or nutritionally responsive, that does more than merely provide us therapeutic advantage and success – it also provides us some information about the underlying cause and the pathophysiology of that condition.

Microbes: We know that many long-term inflammatory responses are also induced by microbial exposures whether those are subclinical infections or dysbiotic relationships.

Immune recalibration with nutritional supplementation: We can also help our patients to kind of recalibrate their immune system through anti-inflammatory interventions to increase the production and effectiveness of their T-regulatory cells (Tregs) and to dampen the responses induced by pro-inflammatory Th1, Th2 and Th17

cells. My phrase for that is nutritional immunomodulation.

Metabolic imbalances, mitochondrial dysfunction: We need to appreciate the role of mitochondrial dysfunction in sustained inflammatory responses.

Stress, sleep deprivation, lack of exercise: Stress, sleep deprivation, psychology, sociology, social inequality, failure to construct a healthy lifestyle, failure to get enough exercise – many of the individual items that fall into category number five can be called style of living, sleep hygiene, stress management, and sociological considerations. So in my listing of these things, these start mostly with the letter S or at least the sound "S", as in psychology.

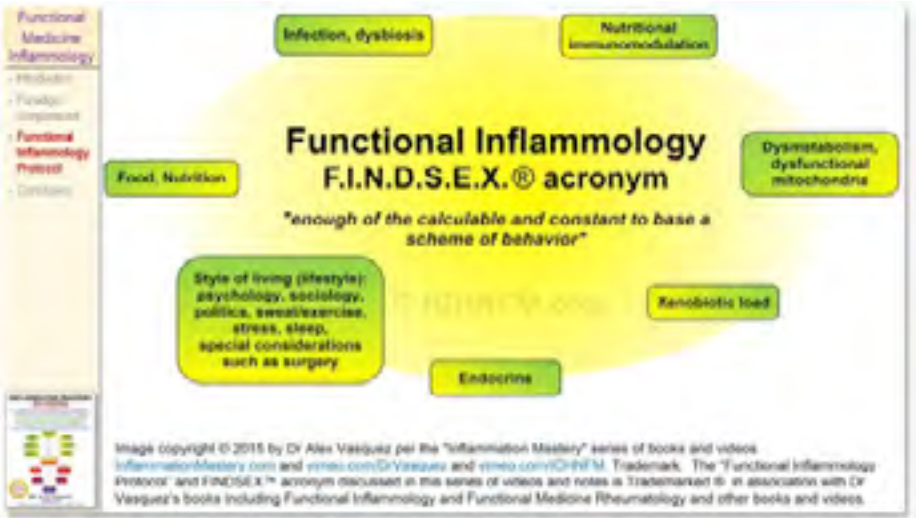
Hormone imbalances: We can also look at hormonal imbalances that promote inflammation or that result from inflammation.

Toxic exposures: Most foreign chemicals (for example: pesticides and plastic residues) are toxic to metabolic processes if the exposure or consumption of those chemicals is excessively high, excessively prolonged, or if it occurs in combinations wherein two or more chemicals have an additive or synergistic effect; the same is true of toxic metals such as lead, mercury, and aluminum. Foreign substances are also called "xenobiotics" and strictly this applies to chemicals, but more casually and practically we can also use this term to apply to toxic metals.

Any foreign substance – whether a metal or a chemical – that might result in harm to the organism is reasonably labeled a "toxin" or a xenobiotic. (Again, strictly speaking, "toxins" are produced by other organisms whereas "toxicants" are any substance such as a chemical or metal that has a toxic or harmful effect, either obvious or subtle.) Exposure to toxic chemicals and metals can promote inflammation and alter function of the immune system; this can be described as "xenobiotic immunotoxicity" because it is a toxic effect on the immune system caused by xenobiotics, whether those are metals or chemicals.

Non-modifiable mechanisms include the genes that we have inherited from our parents, while the modifiable mechanisms include diet, dysbiosis, nutritional immunomodulation, mitochondrial dysfunction, psychoneuroimmunology, hormonal imbalance, xenobiotic immunotoxicity. We need to memorize those, and we need to incorporate those into a clinical strategy that we can use with great facility so that we can then liberate our mental capacities to focus on other details. Memorizing the list of categories is the first step.

Note that the standard medical evaluation fails to consider these important modifiable components other than faint lip-service to "diet and lifestyle."



I want you to consider memorizing these seven items because this is going to be the focus of our clinical assessments and therapeutic interventions. You will notice that this list is actually pretty hard to memorize. For that reason, we are going to use a mnemonic (memory aid), by which we are going to simplify that complex list into something more manageable, and we are going to focus on memorizing these seven items: **F**ood, **I**nfection, **N**utrition, **D**ysfunctional metabolism, **S**tress and style of living, **E**ndocrine imbalances, **X**enobiotics and **T**oxins (FIND SEX or FIND SET). I have now taken a complex list and made it simpler.

The benefit to using the functional inflammology protocol as a clinical tool is that it provides the clinician a memorable and structured organization of the major concepts that we need to address clinically in order to help our patients to be liberated from these so-called chronic inflammatory diseases. Instead of repeating the medical rhetoric of "combination of genetic predisposition and environmental factors," we start asking answerable questions: What factors are sustaining this disease process? Is it dietary indiscretion, is it carbohydrate excess? Is it insufficient exercise? Is it microbial colonization or small intestine bacterial overgrowth? Is it mitochondrial impairment, due to a viral infection or due to xenobiotic exposure? We have to start asking different questions if we are going to get different results. We can always fall back on prescribing drugs to meet the "medical standard of care." If all we want to do is manage high blood pressure by lowering the numbers with drugs, we can do that. If all we want to do is lower blood sugar by giving our patients so-called antidiabetic drugs, we can do that too. But if we want to liberate them from their diseases, and if we want to improve our true clinical success and the management of those conditions, then we need to ask different questions, search for other causes, and find other solutions to help these patients restore homeostasis and metabolic health.

The pathologic triggers for these inflammatory conditions typically come from one or more, or all seven of these areas of focus. By addressing these seven areas of focus with individualized treatment, we can then gain better success in treating our patients.

Food. The foundational diet is a plant-based protein-adequate diet of fruits, vegetables, nuts, seeds, and berries with high-quality protein. I call this the Paleo-Mediterranean Diet. In addition to the diet, we add a high-potency broad-spectrum multivitamin-multimineral. We want to make sure that our patients are getting enough vitamin D, typically that is 4,000 to 10,000 international units (IU), then we add combination fatty acids and then probiotics and phytochemical

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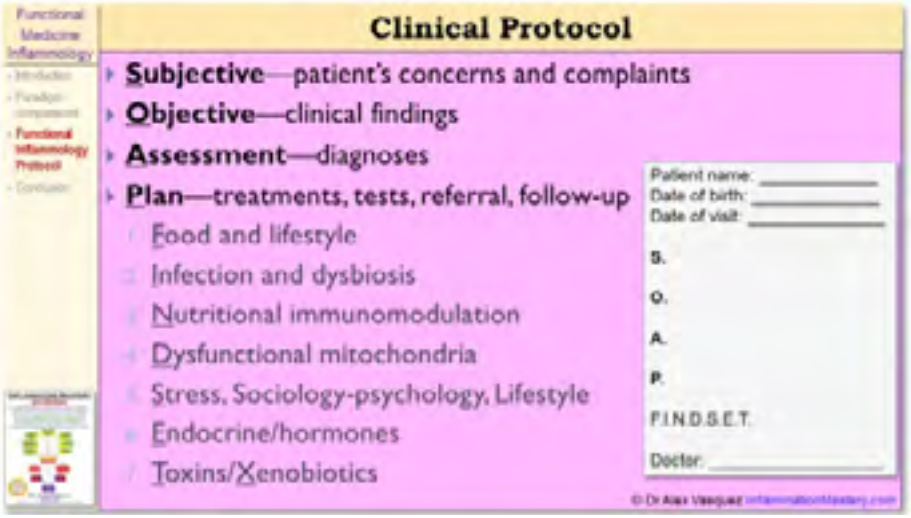
prebiotics. This is the five-part dietary plan that I recommend and that I have used personally and clinically for more than 20 years. I first published on the Paleo-Mediterranean Diet in 2005 and again in 2011, and it is also included within my textbooks. You can download a free copy of these articles, which I recently compiled together: https://ichnfm.academia.edu/AlexVasquez/Books.



Infection. My definition of dysbiosis is that it is a noninfectious, non-acute microbial colonization or exposure that adversely affects the human host. Important concepts include the following: **subclinical infections are common in patients with *chronic* or *sustained* inflammatory diseases, especially all types of autoimmunity**. We need to remember that the microbe alone is not the problem; we need to look at the patient's total inflammatory load (TIL) and address that, as well as promoting immune ***defense*** and immune ***tolerance*** in order to reduce the consequences of that microbial colonization. Clinical assessments include laboratory tests such as blood and stool testing; obviously what is most important is the clinical response to treatment.

Our therapeutic categories include antimicrobials, whether those are drugs or botanicals, immunorestoration, and functional immunomodulation or nutritional immunomodulation to enhance tolerance to inflammatory stimuli. **Often what we find when working with autoimmune and inflammatory patients is that they are having a pathogenic inflammatory response to a nonpathogenic microbe.** We see evidence for that in every single autoimmune disease.

Remember, we are not looking for classic infection here: we are looking to determine which underlying disruptions may be exacerbating inflammation and the patient's symptomatology. We have to look beyond the basic infection-associated characteristics of the microbe to see the patient's individualized response to that microbe. Patients can have individualized responses to particular microbes. Dysbiosis in one patient may present with dermatitis, while what appears to be the same microbial imbalance in another patient can present as peripheral neuropathy or inflammatory arthritis.

Dysbiosis occurs in various locations throughout the human body, including the gastrointestinal tract, orodental cavity (mouth and throat), sinorespiratory tract, and parenchymal tissues. We see evidence of microbial dysbiosis, for example, in internal organs including the brain. Dysbiosis can also occur in the genitourinary tract – such as we see with reactive arthritis following sexually transmitted infections – and the skin, such as we see in patients who have eczema.

Some of the mechanisms through which microbes can create systemic or tissue specific inflammation or autoimmunity include molecular mimicry, bystander activation, Th17 cell induction and suppression of T-regulatory cells, also immune complex formation and deposition.

When we talk about treating gastrointestinal dysbiosis, we commonly use either drug antibiotics or botanical antibiotics. One of the botanical antibiotics that we can reach to with good reliability is oregano oil in a time-released emulsified tablet. The emulsified form of the oregano increases dispersion of the oil and the time release tablet helps to increase delivery of that oregano oil throughout the gastrointestinal tract. When oregano oil is used in the treatment of gastrointestinal parasites, the common dose is 600 milligrams per day in divided doses for six weeks.[1] Another botanical that we commonly use is berberine; this is well-studied, and a typical dose of berberine these days would be 500 milligrams, two to three times per day for three months.

Nutritional immunomodulation – per my use of the term – is specifically the induction of T-regulatory cells via a defined evidence-based multi-component nutritional protocol. My nutritional immunomodulation protocol reduces inflammation by enhancing endogenous physiologic control mechanisms, contrasted against the use of antiinflammatory drugs that ***block*** enzymes, ***block*** receptors, ***block*** cytokines, or ***globally suppress immune function***.

Nutritional deficiencies, especially but not exclusively of vitamins A and D, promote a pro-inflammatory gene expression pattern, resulting in pro-inflammatory cellular behavior and an inflammatory clinical phenotype.

Therefore per this evidence, by providing nutrients, including but not limited to vitamin A and vitamin D, we can increase the production and function of these regulatory T cells to provide an endogenous anti-inflammatory effect through endogenous immune-modulating mechanisms.

Dysfunctional mitochondria. Let us go on now to component number four of my functional inflammology protocol, which is dysfunctional mitochondria and also – more broadly – metabolic dysfunction. Nutritional deficiencies, carbohydrate and fructose excess, also exposure to microbes and dysbiosis, xenobiotics such as herbicides and pesticides and also oxidative stress – all of these contribute to mitochondrial dysfunction, which then increases the production of free radicals. This increased production of free radicals leads to antioxidant vitamin

depletion, which then leads to nutritional deficiencies, which then promote mitochondrial dysfunction and obviously a vicious cycle here.

The major concept here is that while everyone knows that mitochondria make ATP, the cellular currency of energy, people also need to know that **damage and dysfunction to mitochondria can occur as a result of deficient diets and chemical pesticide exposures resulting in changes in mitochondrial function with consequences in gene expression, immunity, and the amplification of inflammation**.

The clinical presentations associated most strongly with mitochondrial dysfunction are diabetes, insulin resistance, hypertension, migraine, fibromyalgia, also Alzheimer's and Parkinson's diseases. So the interventions we can use when we are addressing mitochondrial dysfunction include dietary intervention, especially a low-carbohydrate nutrient-dense diet, nutritional supplementation, and as needed, detoxification and depuration to detoxify and remove those poisonous chemicals that are damaging mitochondrial structure and function.

Stress. We want to help our patients reduce their stress, manage it better, and obviously avoid the causes or sources of their stress. Other considerations in this category include **sociopsychology** (including politics) quantity and quality of **sleep**, **sweat** as a metaphor for exercise, **spinal** health, including osteopathic and chiropractic manipulation or adjustments, **specialized supplementation** – including selenium for its antiviral effects, melatonin for immune and mitochondrial stimulation, and B6 to lower glutamate and raise GABA levels within the brain. **Surgery** might be necessary in some cases, and sometimes people will simply need to **stamp their passport and take a vacation**. So you can see that this fifth category of the protocol helps us open our minds to additional considerations ranging from surgery to additional supplementation, to spinal manipulation, to exercise and improving people's sleep hygiene and their psychosocial situation.

Endocrine/Hormone Imbalances. When we are assessing and managing and treating these patients with *persistent* or *chronic* or *sustained* inflammatory disorders, we need to look at their hormones and either directly intervene to optimize the levels or indirectly intervene to address the underlying cause of their hormone imbalance so then they can attain better inflammatory balance overall. In other words, one of the ways that we reduce inflammation is to optimize hormone levels, and one of the ways that we optimize hormone levels is to determine the cause of those hormone imbalances. As I have said more recently, we have to treat not simply the cause of the disease, but we have to treat the *causes of the causes* of the disease.

Toxins/Xenobiotics. Now finally, let us talk about toxins and xenobiotics. The basic summary is very simple. We are all poisoned with chemicals, especially pesticides, and we need to manage that poisoning responsibly through a ***detoxification lifestyle***, not simply isolated events every other year or every year. Detoxification support needs to be a component of the daily lifestyle.

Supporting detoxification and reducing exposure may include using a water filter, getting sufficient exercise to sweat and to therefore remove those toxins from the body, eating organic foods, taking nutrients to support detoxification, and also, of course, engaging politically because we would not live in a poisoned environment had the politicians not allowed this to occur, and the reason they allow it to occur is because they are paid by big corporations. From a clinical perspective, xenobiotics includes chemical toxins and also includes heavy metals such as mercury, lead, aluminum; all of these, including pesticides and other persistent organic pollutants (POPs), contribute to persistent inflammation.

Conclusion

As I said before, and as I have said for many years to my graduate students, *organized and declarative knowledge is the most valuable type of knowledge for intellectual pursuits and practical application*. So again, what are the four main types of inflammatory conditions that we see in outpatient clinical care? Metabolic inflammation, allergic inflammation, autoimmune inflammation, and neuroinflammation. What are the seven main components that create chronic or sustained systemic inflammation? So, I taught you to use my acronym, which is FIND SEX, or alternatively, FIND SET. F stands for *F*ood, then *I*nfections, *N*utritional immunomodulation, and *D*ysmetabolism or *D*ysfunctional mitochondria. That is the FIND. The SEX is **S**tress, **S**ocial inequality, **S**weat as a metaphor for exercise, **S**leep deprivation, **S**pecialized **S**upplementation, **S**pinal manipulation, and sometimes **S**urgery. The E stands for **E**ndocrine imbalances. We look for three hormones that are typically elevated, and three that are typically depressed, and we also make a complete assessment of thyroid function. And finally, the X or the T stands for **X**enobiotics or **T**oxins.

You can apply this protocol to all conditions of *metabolic* inflammation, *allergic* inflammation, *autoimmune* inflammation, and *neuroinflammation* or brain inflammation.

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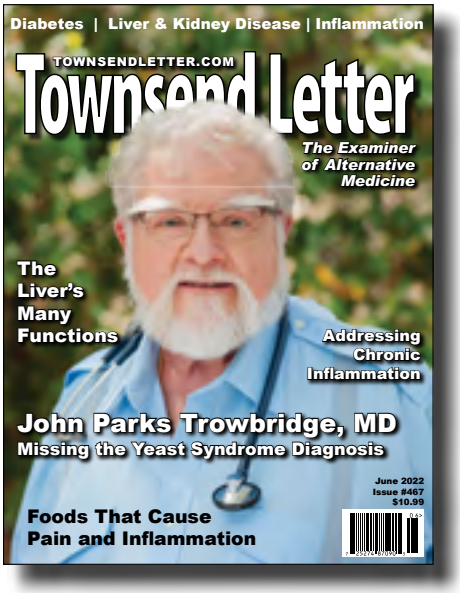
Alex Kennerly Vasquez, DO, ND, DC (USA), Fellow of the American College of Nutrition (FACN), Overseas Fellow of the Royal Society of Medicine: An award-winning clinician-scholar and founding program director of the world's first fully-accredited university-based graduate program in human nutrition and functional medicine, Dr Alex Vasquez is recognized internationally for his high intellectual and academic standards and for his expertise spanning and interconnecting many topics in medicine and nutrition. While in the final year of medical school, Dr Vasquez completed a pre-doctoral research fellowship in complementary and alternative medicine research hosted by the US National Institutes of Health (NIH). Dr Vasquez is the author of many textbooks, including *Integrative Orthopedics* (2004, 2007 2012), *Functional Medicine Rheumatology* (Third Edition, 2014), *Musculoskeletal Pain: Expanded Clinical Strategies* (commissioned and published by Institute for Functional Medicine, 2008), and *Brain Inflammation in Migraine and Fibromyalgia* (2016).



On the Cover

Still Missing Diagnosis of The Yeast Syndrome? – Part 1

by John Parks Trowbridge, MD, FACAM

"There are known knowns. There are things we know we know. We also know there are known unknowns. That is to say, we know there are some things we do not know. But there are also unknown unknowns, the ones we don't know we don't know."

Secretary of Defense Donald Rumsfeld

I Haven't a Clue

I didn't know about yeast, so I didn't think of it.

I had heard about yeast, but I forgot to consider it.

I knew about yeast, but I didn't think it could be causing these problems.

I didn't know any tests could show yeast problems, so I didn't order them.

I had heard that yeast maybe could cause illness problems, but I didn't accept that explanation.

I know that women had yeast problems – but I couldn't see that recurrent infections for them or for men could be related.

I know that treating a persistent rash is easy, but I never thought that yeast overgrowth could explain why it keeps coming back.

I've been treating infections all my life – just learning how to use newer antibiotics is probably what my patients need.

I've heard that antibiotics upset gut bacteria, but I can't see how that could lead to any recurrent health issues, so I'll just keep treating persisting problems the best ways I know … or refer to specialists as needed.

When the Yeast Syndrome Is *Not* Treated As Needed

Let's get one thing perfectly clear: "yeast" is ***NOT*** the problem.

Yes, a startlingly wide panoply of discomforts and illnesses relate to toxins produced by yeasts – but yeast is ***NOT*** the problem.

So … what is the real answer?

Our patients, quite simply, are sick. Their immune systems are failing, their physiology is twisting all wrong, their nutritional status is compromised, their food selections are abysmal, stresses in their lives are overwhelming – and our "doctoring" *often* worsens their conditions and addresses none of these root causes.

Root causes? Yes. The Yeast Syndrome is nothing more than the result of *our* inadequacies, our failures to advise our patients on how to correct their underlying challenges.

In other words, they *are* sick … and *stay* sick … and get worse over time for one simple reason – it's ***our*** fault!

"I don't do anything wrong!"

Actually, you probably don't do anything right.

But you hold yourself out as a "health professional" – allopathic physician, osteopathic physician, naturopathic physician, chiropractic physician, physician assistant, nurse practitioner, nutritionist, health coach. That means that patients innocently believe that you know what you're talking about, that you know how to assess their problems, that you know how to propose and manage treatments to help them regain and maintain better health.

But you don't. Because you simply don't know what to do. Because you lack the training, the experience, and the perspectives to "see" what's really happening with regard to yeast.

Remember – it's not the yeast. It's the deficiencies in the patient.

For those of you who treasure medical history – this misunderstanding is the classical and predictable result of relying on the discredited views of Pasteur rather than recognizing the more realistic ones of Béchamp and Bernard. Pasteur – a chemist – insisted that his "germ theory" easily explained that a microbe was responsible for every disease. In contradistinction, Béchamp, a physician and pharmacist, and Bernard, a medical physiologist, both endorsed the body's natural healing mechanisms, maintaining that microorganisms only become pathogenic after environmental factors cause the host's cellular "terrain" to deteriorate.

History records that Pasteur recanted his conclusions on his death bed, admitting that Bernard was correct, the "terrain" was the best explanation for development of disease. Did Nature consider that his opinion actually mattered? Not at all. Galileo spent the last nine years of his life in house arrest, having been adjudged by the Roman Catholic Church of promoting heresy,

namely the proposal by the Polish astronomer Copernicus, that the earth orbited around the sun. Did Nature consider that the judgment of the church mattered? The only thing that ever matters is the Law of Nature because that's how the real world works.

So, the question must be asked – can you do *anything* right?

I don't mean to sound antagonistic. But honestly I'm not here to win friends. I'm here to influence people. Practitioners. So that dozens of millions of patients can – finally – be treated, correctly and well, with their health being restored and preserved for years to come.

Are you now *ready* to learn how to do "what's right"?

The real question, of course, is whether you're ready to admit the prospect that preconceived ideas limit your ability to see what is causing illness in many of your patients…to abandon those that fail to deliver the best results…and then to learn more fundamental principles of disease and health that will enable you to treat your patients well. Finally. For real.

Let's Start from the Beginning

Descriptions of what sounds like "thrush" (oral yeast colonization) hearken back to the time of Hippocrates *circa* 460–370 BCE. Vulvovaginal candidiasis was first described in 1849 by Wilkinson; and in 1875, Haussmann demonstrated the causative organism in both vulvovaginal and oral candidiasis is the same. For dozens of years, these persistent, often recurrent, infections were considered and treated in isolation, unrelated to other clinical circumstances. In almost all instances, *Candida albicans* is the invading organism.

Medical advances come from keen observations and a willingness to learn their explanations. With regard to The Yeast Syndrome, the story is profound in its simplicity. During his training, Alabama internist C. Orian Truss, MD, in 1953 evaluated a coal miner with a cut finger whose organ functions were rapidly deteriorating despite antibiotics and steroids. "When were you last well?" was his question: "Before I cut my finger." *C. albicans* growing in sputum cultures had been dismissed by his physicians as opportunistic – but Truss chose to treat him with Lugol's iodine solution. The antifungal effect was startling … and the patient fully recovered.

Dr. Truss was called to the psychiatry service to treat a young woman with yeast infections of the vagina and intestine, seemingly associated with allergic asthma and hives. Reviewing her chart, he realized the coincident onset of mental confusion and suicidal depression. But then came the surprise…the rapid disappearance of mental and virtually all *other* symptoms when he aggressively treated her yeast infections. His reluctant conclusion: the apparent capacity of this fungus to cause serious systematic illness.

Not yet fully obligated to his observations, Truss was confronted with more patients suggesting that yeast could be a significant pathogen. After completing studies in female endocrine pharmacology, he found that many women seemed to suffer from a constellation of symptoms that baffled their doctors – leading, as expected, to their diagnosis as hysterical or hypochondriacal. A pattern emerged: many had a long history of repeated vaginal yeast infections. Could the variety and persistence of their symptoms represent an undiagnosed sub-clinical infection with *C. albicans*? Truss prescribed nystatin (isolated in 1955 from bacteria found in a barnyard in ***N***ew ***Y***ork ***stat***e) rather than the usual gentian violet used for comfort with yeast overgrowth. Many patients experienced dramatic recovery.

In 1978, Truss authored a landmark article entitled "Tissue injury induced by Candida albicans: Mental and neurologic manifestations."[1] Several other papers followed, detailing his experiences. Coining the term "The Missing Diagnosis," Truss later summarized his unique observations in a self-published book of that title in 1983. He expanded the scientific explanations for these unique perspectives in his sequel, *The Missing Diagnosis II*, self-published in 2009.

Remember – it's not the yeast. It's the deficiencies in the patient.

Truss' revolutionary concepts came at a time when rampant antibiotic use, refined carbohydrate consumption, and medical infatuation with steroids unwittingly turned many patients into "yeast factories." A wide variety of symptoms unexpectedly improved, irritable bowel discomforts, as did skin conditions, allergies, mood problems, including anxiety and depression, as well as inordinate food cravings associated with obesity and pre-diabetes. The brilliance of Truss' insight is that *Candida* was more than just a superficial infection of the skin or mucus membranes. Rather, its presence triggered a storm of allergic, metabolic, and immunological reactions that affected many organ systems – including the brain. Dr. Truss recognized the diagnostic confusions, since the manifestations vary greatly from patient to patient, depending in part upon the location and extent of tissue colonization, but principally upon the patient's immunologic and allergic response to yeast antigens and to possible toxins released by the fungus.

Pediatric allergist William "Billy" G. Crook, MD, pushed these ideas into the public awareness by his easily understandable trade paperback, *The Yeast Connection*, published privately in 1984 and then by Random House since 1986. He was justifiably excited to share with me sheafs of typewritten pages as he was assembling his book. As I learned from him and others how to "treat yeast," I knew I had to share more academically supported information, and Bantam Books published *The Yeast Syndrome* in 1986.

Let's Get Real

Medical advances are routinely resisted by mainstream practitioners who fail to understand the bases upon which better diagnosis and treatments are evolving. The Yeast Syndrome has been no different – except, perhaps, that such opposition now has a 40-year history…thanks to astonishing ignorance and arrogance.

The formal position of the purported clinical experts, published in 1986, remains virtually unchanged to this day. Their pejorative statements, utterly lacking any serious clinical trials, simply dismiss that The Yeast Syndrome could, in any believable way, explain a great number of conditions with which adults (and children) are suffering, which have been *ineffectively* treated by such "expert allergists" for years:

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Yeast Syndrome

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> Candidiasis Hypersensitivity Syndrome – *Approved by the Executive Committee of the American Academy of Allergy, Asthma and Immunology:* The alleged basis for the syndrome is described by Crook as follows: Antibiotics, especially broad spectrum antibiotics, kill friendly germs while they're killing enemies. And when friendly germs are knocked out, yeast germs (Candida Albicans) multiply. Diets rich in carbohydrates and yeasts, birth control pills, cortisone and other drugs also stimulate yeast growth. Large numbers of yeasts weaken your immune system.
>
> Your immune system is also affected adversely by nutritional deficiencies, sugar consumption, and by exposure to environmental molds and chemicals (such as formaldehyde, petrochemicals, perfume, and tobacco). When your immune system is compromised and your resistance is lessened, you may feel bad all over and develop respiratory, digestive, and other symptoms. And you're apt to develop adverse reactions to additional foods, inhalants, and chemicals. As a part of these reactions, mucous membranes throughout your body swell, and you develop infections caused by bacteria and viruses that a strong immune system would ordinarily conquer.
>
> When you develop an infection, you're apt to be given broad spectrum antibiotics. Such antibiotics, while at times essential, promote the growth of Candida albicans which depress your immune system. And your health problems continue until the vicious cycle is interrupted by a comprehensive treatment program designed to decrease the growth of Candida albicans and increase your resistance (Crook WG: The yeast connection: a medical breakthrough, ed 2. Jackson, Tenn., 1984, Professional Books, pages 15,16).[2]

Perhaps *someone* could have realized that "the science" was clearly confirming the original observations of Truss. Well…*that would have been nice*.

Steven Novella, MD, an academic clinical neurologist at the Yale University School of Medicine, offered these outright false and fallacious conclusions on his website https://sciencebasedmedicine.org, making the following claims in a post, dated September 25, 2013:

> Science-Based Medicine is dedicated to evaluating medical treatments and products of interest to the public in a scientific light, and promoting the highest standards and traditions of science in health care. Online information about alternative medicine is overwhelmingly credulous and uncritical, and even mainstream media and some medical schools have bought into the hype and failed to ask the hard questions.[3]

The site asserts independent and reliable scientific authority: "SBM is entirely owned and operated by the New England Skeptical Society, a non-profit organization dedicated to promoting science and critical thinking."

In this light, you should critically review his following unsupported assertions:

> Compromised immunity can lead to overgrowth of the fungus *Candida albicans*, but this doesn't happen in people with intact immune systems, and it doesn't lead to the vague, unrelated symptoms described as "systematic candidiasis" by alternative medicine proponents….
>
> One popular fake illness is chronic candidiasis. *Candida albicans* is a fungus that colonizes about 90% of the population (meaning it is present in the body but not causing an infection or any problems). It can, however, become an infection, usually at times of stress or immunocompromise. The most common manifestations are thrush (a superficial *Candida* infection in the mouth) and vaginitis, also commonly referred to as a yeast infection….
>
> Over 25 years later *Candida* hypersensitivity remains an unproven claim, but popular among "alternative" practitioners. The claims have also spread, unhindered by logic and evidence….
>
> *Candida* hypersensitivity is an implausible syndrome, simply another "one cause of all disease" alternative claim. Such claims are useful only for generating demand for fanciful and worthless treatments.[3]

At least the American Academy of Allergy and Immunology kindly and correctly listed an incomplete number of prominent symptoms that have, in my clinical experience, been dramatically improved by treatment for The Yeast Syndrome:

> The symptoms are described as wide ranging, involving multiple systems, and include fatigue, lethargy, depression, inability to concentrate, hyperactivity, headaches, skin problems, including urticaria, gastrointestinal symptoms such as constipation, abdominal pain, diarrhea, gas and bloating, respiratory tract symptoms, and symptoms involving urinary tract and reproductive organs.[2]

Sadly, their chronicle of such *discomforts* blatantly ignores the number of actual chronic *diseases* that can (and often do) appear as fungal interruptions persist and later impair normal physiologic functions. They missed the boat – the horse is already out of the barn – their false presumptions condemn them to subjecting their innocent and trusting patients to a lifetime of suffering, disability, and even death.

Digging their professional grave even deeper – and condemning *their* patients to *never* regaining and maintaining better health by proper treatment – they offered the following, again unsupported assertions:

> The Practice Standards Committee finds multiple problems with the candidiasis hypersensitivity syndrome.
>
> 1. The concept is speculative and unproven.
>
> 2. Elements of the proposed treatment program are potentially dangerous.
>
> On the basis of the evidence so far reviewed and until appropriate published evidence to the contrary is brought to its attention, the Practice Standards Committee recommends that the concept of the candidiasis hypersensitivity syndrome…is unproven.[2]

Poorly designed and conducted "clinical studies" unfailingly reach the desired conclusion with which they began, namely that The Yeast Syndrome is fallacious and ungrounded in any science: "Given the dearth of controlled data on various aspects of this syndrome – including its pathogenesis, diagnostic criteria, and response to therapy – controversy and skepticism persist."[4]

Because Grandma Lives 1500 Miles Away

Did you ever wonder…why are there pediatricians? After all, kids are mostly healthy, and while growing up, they have

remarkable resiliency and recover quickly. It all has to do with your cousin Beatrice.

Cousin Beatrice? Yep. In the old days, if you got "sick," your Grandma would reassure your parents, "When your cousin Beatrice got that, we just did such-and-so, and she got better just fine."

Sadly, we have lost most of the old-time cures and remedies. Settlers and pioneers, both on farms and in the towns, were literally "off the grid." They had to rely on herbs and other traditional treatments that exploited your body's natural ability to heal and repair. Lacking these and other effective ways to help our families, we have learned to turn to pediatricians. And a zillion other specialists as well.

The Yeast Syndrome is the archetypal example of how our modern medical approach has succumbed to the Law of Unintended Consequences. Our almost blind reliance in adopting the claims of "scientific advances" has led us down the path where convenient choices have produced complications both unintended and unforeseen, apart from the desired advantages.

Environmental conditions have set the stage for the overgrowth of yeast, almost unhampered by natural defenses that have protected human beings for millennia.

Remember: yeast is *not* the problem…our compromised immune system allows us to be inundated by toxins that progressively damage our physiology, nutritional status, and endocrine functions…and we succumb in ways never before seen.

As evidence supporting Bernard and Béchamp, consider the key factors of how we become "sick" with yeast overgrowth:

- **A** = **a**ntibiotics, widely used, often abused – and microbiome replenishment ignored leads to reduction of bacteria antagonistic to yeast growth
- **B** = **b**irth control pills – hormonal disruption favoring yeast growth
- **C** = **c**ortisone – in all its flavors – widely used, even over the counter for topical – favoring yeast growth
- **D** = deplorable **d**iet – more on this later, but sugars and starches favor yeast growth and nutritional deficiencies impair immune defenses and other systems
- **E** = **e**nvironmental toxins – we're engulfed in more of them every year
- **F** = **f**ull of stress lifestyles – surging of stress hormones alerts yeast to an organism facing challenges, ideal for yeast exploitation
- **G** = **g**enetic predispositions – some people more readily surrender to attack
- **H** = **h**ealth **h**abits adverse to recovery and repair: reduced sleep, on-the-go hurry hurry, and so much more

Human beings can withstand many challenges when healthier and "all systems GO"; but when circumstances alter the situation, always-present yeast (especially *C. albicans*) are aroused to grow more readily. Each "event" encourages yeast to flourish more, and finally body systems are unable to meet the threat as debilitating yeast metabolites and toxins ("*Canditoxins*") flood your cells and organs. Welcome to…*The Yeast Syndrome*.

The Allergy and Immunology Monkeys Are Mocking You

Hear No Evil, See No Evil, Speak No Evil. This widely recognized Japanese proverb refers to those who deal with problems by refusing to recognize them, ignoring the goodness of the truth literally in front of them and the results that are available to those who live in the truth.

As a classical illustration how today's "cancel culture" is incredibly effective to bear down on professionals and public alike, to suppress consideration of diagnosis and treatments by having their minions relentlessly parrot the same old stories, the following fake data is promoted by the Rare Disease Database of NORD, the National Organization for Rare Disorders:

> Since Candida Albicans is supposed to be present in healthy people, treatment is very rarely needed. The American Academy of Allergy and Immunology has stated that the concept of yeast allergy or Candidiasis hypersensitivity is speculative and unproven. Health foods and vitamins are not effective treatments.[5]

"Tell a lie loud enough and long enough and people will believe it," said Adolph Hitler, in his dark declaration, *Mein Kampf*, and he went on to offer: "It is a quite special secret pleasure how the people around us fail to realize what is really happening to them." American humorist Mark Twain observed: **"**How easy it is to make people believe a lie, and [how] hard it is to undo that work again!**"**

You Can't Fix "Perfect"!

Patients and practitioners alike fail to understand one profound operation of biology: your body *never* makes a mistake. Whatever it is doing, that is absolutely correct, *given the circumstances*. Our efforts to slap the system around with drugs is but a futile band-aid, flailing against the functions hard-wired into our systems for survival. Simply put, if you want the body to *do* something different, then you must change the *circumstances*…in response to which, appropriate changes will appear in body systems. *Never* a mistake, *always* the perfect response to the situation presented.

Given this understanding, your body is forever trying to tell us what is "going on." Sadly, we're so busy trying to "fix it" that we aren't listening. Certainly this applies to "taking a complete history." But this also highlights a fundamental problem obvious not only with conventional medicine but also, on inspection, with "functional" medicine and any "casual" understandings of The Yeast Syndrome. Intensive efforts to test for and determine chemical functional aberrations can get caught up in the briar patch and easily miss "the big picture." Prescribing medications or supplements aimed at "correcting" each identified issue is the *sine qua non* of "A-to-B" medical practice: you have "A," we do "B"; you have "C," we do "D." The limits to this approach are *endless* because failure to know and correct the underlying cause will mean adding more items as ever more issues can be identified – focusing on the *trees* instead of the *forest!*

One illustration of how practitioners "get in trouble" (that is, fail to get their patients better) is "3-D chess." If you've played chess, you know that pieces move differently; some go in straight lines on the squares, some go diagonally, and so on. With 3-D chess, pieces can move up or down on 3 levels (each stacked above the other) rather than being confined to just one flat surface. Well, think of your metabolism as having eight boards, each stacked on top of the other. Some pieces can "start here" but end up "over there"! How does this relate to The Yeast Syndrome? A patient might focus on a particular problem – say, a square up on the seventh board and 3 over from each edge – because he has future plans and needs "that" fixed. But the body is busy

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working in other squares, first on this level then on that and then on another and so on. Remember: your body has a very clear priority: it *must* survive for the next 10 minutes or nothing else matters. While the patient's priority is important, it might be way down the list, with many survival items ahead of it. The delay experienced by the patient is frustrating, "I'm doing all these things and I'm *still* not better with (fill in the blank)." However, the body is attending to priorities in order of critical need, laying the foundation for finally getting all of the biochemical processes more in line. Patience and persistence is the order of the day in order to resolve all the issues related to yeast overgrowth. Remember: no mistakes, just *exactly* what is needed given the current circumstances.

The real treatment for The Yeast Syndrome must rely on changes in our lifestyle, literally *changing the situation* in order to alter your body's responses toward normal. There is no short-cut to better health. **It is a biological imperative: *"We must follow 'the Science'"***

I need your help designing an airplane – got any good ideas? We're entitled to our ideas on this – our opinions – our beliefs. But…the physics of aviation is…*science*. That means, established facts. We can cling to our ideas, our opinions, our beliefs – but we're not entitled to our own facts. They is what they is, period.

The Wright Brothers showed, in 1903, a whole new realm of science for our investigation and exploitation. Over a hundred years of experiments have revealed physics facts that have allowed us to design and enjoy incredible aviation advances today.

Pasteur, Bernard, and Béchamp in the later 1800s blessed us with new understandings of microbes, first observed by the Dutch microscopist Antonie van Leeuwenhoek who accurately described microorganisms (bacteria and protozoa) that he called 'animalcules' (little animals) in 1676. Alabama internist Orian Truss, MD, from 1978 through the 1984 publication of his book, *The Missing Diagnosis*, gave us deeper insights into the physiologic interruptions possible when yeast toxins are elaborated from pathologic growth in our gut, our lungs, our sinuses. *The Yeast Connection* (Tennessee pediatrician William Crook, MD) first published in 1984, explained in simple language how many people get sick (and can get well) when *Candida albicans* "overgrows" unrecognized. *The Yeast Syndrome*, published 36 years ago by Bantam Books, supported these theses with dozens of citations to the scientific literature. Incidentally, we edited the manuscript twice before submission…then Bantam removed one-third of our definitive document, claiming they could not sell a trade paperback of that length. Patients and practitioners forever lost access to those ideas and treatments.

Despite the many disparaging pronouncements from professional organizations and governmental agencies, the *facts* established by science are not "consensus" but *reality*. And therein lies the fundamental fallacy to how most practitioners attempt to "treat yeast": they have heard or read someone's impressions "about yeast" and "about yeast treatment." But sadly they have minimal understanding of the definitive pathophysiology and the corrections that are essential to restore and maintain better health. We could have similar debates regarding the many beneficial effects of vitamin C, well documented since the 1960s by Stanford University chemistry professor Linus Pauling, PhD, and *many* others – but again, we are obligated to recognize and tightly adhere to the constraints established only by…*the facts.*

We can agree to disagree – but you'll be wrong if you dispute settled facts. In the final analysis – which is the health of our patients – ***we must follow the science!***

More recent studies have shown that, despite a psychological bias against "invasion" through the gut and against systemic distribution of the ubiquitous enteric fungus, *C. albicans* may require less opportunism than had previously been considered. High enteric levels (yeast overgrowth!) have demonstrated the ability to spill-over in significant numbers into the host's peripheral circulation. Further, it can shed its characteristic cell wall and vary its cell-surface immunogens, allowing it to camouflage its identity from host immune defenses, permitting proliferation into the systemic circulation as non-transients.[6]

The genome of *C. albicans* is very flexible and can withstand a wide assortment of variations in a continuously changing environment, challenging our usual concepts of fungal infection. While it exists as a harmless commensal in a healthy individual (vagina, oral, and gastrointestinal mucosa), infections can be established when the local microbiota is disturbed, normal tissue barriers are weakened, or an individual becomes immunocompromised. *C. albicans* displays unusual genome dynamics and can transition between different cell types. These adaptive mechanisms to the immune defenses of its human host are very subtle and extensive, and by these it evades nearly all efforts directed against it at every level. Interestingly, these elegant adaptive responses display a well-adapted parasitism, occurring only in the especially virulent species but not in the less pathogenic other *Candida* species.

My Secrets

Since first learning of the disastrous effects of yeast overgrowth in 1983, I have gleaned a few fundamental understandings that have been uniformly effective in helping to restore and maintain better health for people suffering from varied discomforts and disorders. Even where The Yeast Syndrome is not the definitive problem, in many chronic conditions its imprints are often there. Failure to address yeast overgrowth as well will generally limit the results available when treating other pathologies.

MEVY Diet

First and foremost: once you go out your front door, you are in dangerous territory.

Our "food system" has been corrupted in ways never foreseen a hundred years ago. We used to have farms and gardens. Now we have agri-business. We used to have only organic, wholesome crops. But then…experiments started in 1943 to improve yields of American hemp – *Cannabis sativa* – vital for the war effort. This research blossomed in the late 1940s into sudden and widespread application of fertilizers as ammonium nitrate (no longer needed for explosive weapons), phosphorus, and potassium were used to enhance various harvests. Cardboard-tasting tomatoes are plump and moist but lacking in virtually all the rewards of home-grown fruits.

When populations rely on the "foods of commerce," consisting largely of white flour products, sugar, polished rice, jams, canned goods and vegetable fats, the result is loss of their immunity to dental caries and loss of freedom from degenerative processes,

as shown by Weston A. Price, DDS in his 1939 book, *Nutrition and Physical Degeneration, A Comparison of Primitive and Modern Diets and Their Effects.* Price was director of research for the American Dental Association and collected extensive research materials, available from Price-Pottenger Foundation: https://price-pottenger.org/.

As of 2001, the Cooperative Extension of the University of California noted that over 1,000 food items came in cans – often with processing chemicals, preservatives, excessive sodium and sugar, and heating/packaging intended to preserve edibility for years. Not necessarily healthy nutritive value but satisfaction for the belly. Only 13 percent of our food dollar is now spent in grocery stores. We consume 31 percent more packaged food than fresh food.

When Americans want to skip the effort of meal preparation, they eat in restaurants. Or, more often, they head for over 200,000 quick-serve or casual serve restaurants…spending, in 2019, some 51 percent of their total food dollar – about 10 percent of their disposable income! In 1955, when Ray Kroc opened the first McDonald's in Des Plains, Illinois, traditional restaurants claimed only 25 percent. Now about 20 percent of all American meals are…*eaten in the car!*

The US Department of Agriculture determined in 2015 that American households spent just 6.4 percent of their income on food. Nearly 23 percent of that current total is purchasing *processed* foods and sweets. Back in 1900, families spent about 40 percent of their income on food. By 1950, the percentage was just under 30. What should become outrageously clear is that our food production, processing, preparation, and selection are "sweeter and saltier and more efficient and convenient" as we become fatter and sicker.

So, my very first step in helping patients recover with The Yeast Syndrome is to have them modify their eating to the **MEVY** diet: ***M***eats, ***E***ggs, ***V***egetables, and ***Y***ogurt.

In many respects, my program is similar to the low-carbohydrate diet first espoused by my friend, New York cardiologist Robert C. Atkins, MD (*Dr. Atkins' Diet Revolution*, New York:Bantam Books, 1981). The MEVY diet is extensively presented in Chapters 13, 14, and 15 of *The Yeast Syndrome* ("*TYS*"), coauthored with Morton Walker, DPM. Many patients have survived on surprisingly limited food choices, never having eaten a rainbow selection of vegetables. Others claim a dislike for milk products – but daily yogurt intake *often* overcomes that aversion. Homemade yogurt is easy and can be more appealing, and "makers" are inexpensive and easy to use. I encourage patients to create appetizing snacks by adding any of over 200 rich flavors (www.bickfordflavors.com); placing cups in the freezer provides a real treat. Alternatively, stirring in spices of choice can create delightful "dips" for carrots, celery, cauliflower, broccoli, other fresh vegetables. Those with professed "milk intolerance" often can mix into the yogurt Lactrase or Lactaid (lactase enzymes) and do quite well.

Food choices, of course, ideally should be as "organic" and "fresh" as readily available and affordable. The emphasis is on wholesome nutrition and supporting a healthier gut microbiome. Those who fear elevating their cholesterol by eating meats and eggs should take comfort from the 70 years of research summarized by Fred A. Kummerow PhD, in his engaging book written at age 100: *Cholesterol is Not the Culprit: A Guide to Preventing Heart Disease* (Summerfield, Florida:Spacedoc Media, 2014). Those concerned about increasing risks associated with insulin resistance known as cardiometabolic syndrome – first described in 1988 as "Syndrome X" by my friend, Stanford endocrinology professor Gerald Reaven, MD – can find reassurance in his book, *Syndrome X: The Silent Killer: The New Heart Disease Risk* (New York:Simon & Schuster, 2001). Indeed, for many of my patients, their "pre-diabetes" condition improves dramatically when implementing the MEVY program; and Type 2 diabetics often see reduced symptoms and substantially better control, often with lowered medications.

Nutritional Supplements

While healthier eating is essential, recovery from the ravages of The Yeast Syndrome requires addition of general and *specific* nutritional factors, such as vitamins, minerals, essential fatty acids, and the like. As we reviewed, the problem is not "the yeast" but rather "the terrain," the body in which these symptoms are being manifested. In virtually all patients, interruptions to normal physiologic functions have resulted from metabolites and toxic substances produced by overgrowing yeasts. Like dominos, interferences and deficiencies can tumble haphazardly, such that fundamental cellular and endocrine functions are damaged, destroyed, or defeated quickly. Part of the confusion surrounding The Yeast Syndrome is that some patients suffer sudden and dramatic symptoms while others seem to amble along, only gradually developing discomforts over years or even decades. Biochemical individuality is obvious, and each patient must be assessed and treated appropriately.

Some key tenets have stood the test of time. Yeast overgrowth has usually been associated with magnesium deficiency, relative deficit of pyridoxine (Vitamin B6, cofactor for many magnesium-dependent reactions), and frank scarcity of EPA (eicosapentaenoic acid), an omega-3 fatty acid commonly found in cold-water fatty fish. These and other nutritional challenges are reviewed in Chapter 12 of *TYS*. As you can readily suspect, deficiencies in these and other essential components can result in a broad spectrum of biochemical interferences. In other words, patients can complain of widely diverse symptoms, discomforts, and even diseases while they are suffering with similar degrading functions in virtually all cells and systems. Afflictions will arise first in their "weakest link," which will differ for everyone, and then progress unwaveringly to the next feeble systems, and so on. When "enough dominos have fallen," patient distresses will lead them to seek relief. Sadly, conventional medical approaches will uniformly overlook metabolic interferences resulting from toxic products from yeast. To better identify these issues, I have successfully used Micronutrient Testing from SpectraCell Laboratories (www.spectracell.com), Red Blood Cell Elements Analysis from Doctor's Data (www.doctorsdata.com), and Zone Labs Cellular Inflammation Test Kit (eicosapentaenoic acid and arachidonic acid, www.zonediet.com), among others.

You might have heard of the "Die-Off Reaction," also known as the Jarisch-Herxheimer Reaction (JHR). This was first described in the late 1880s by Adolph Jarisch, an Austrian dermatologist treating syphilis with mercurials and then, in the early 1900s, was recognized also by Karl Herxheimer, a German dermatologist. JHR is an acute, self-limiting, transient clinical phenomenon induced when antibiotics are used to treat infections of bacterial, fungal,

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and protozoal origin. The mechanism is thought to result from the breakdown of the targeted microbe, suddenly releasing proteins, toxins, and cytokines that provoke inflammation. Symptoms can include body aches, headache, fever, chills, rashes, nausea and vomiting, flushing, fatigue, malaise, perhaps worsening of skin lesions, although more severe reactions are possible, usually starting within hours of starting antibiotic treatment. The severity of JHR appears related to the organism burden in the body.

When I first began treating The Yeast Syndrome in 1983, fully one-third of my patients *refused* to return for their second or third office visit. I was perplexed because clinically their problems obviously could be resolved by reducing their yeast overgrowth and correcting the pestering biochemical interferences. Their common complaint: "I only *thought* I felt bad until I came to see you!" Treating their yeast had triggered a robust JHR that I did not anticipate.

This dreadful situation was preventing patients from restoring their health, enjoying life once again free from many discomforts and distresses. What soon became apparent to me was a different understanding of JHR. Yes, its severity can be related to excessive yeast burden in the body, where a massive amount of proteins, toxins, and cytokines can be released. But additionally – even a minimal body burden of yeast can be provocative of JHR if the treatment administered is notably and quickly effective.

Truss and Crook taught the use of nystatin, the first polyene antibiotic, in treating The Yeast Syndrome. The drug is a "channel-forming ionophore," having both fungistatic and fungicidal activity, binding preferentially to the dominant yeast membrane sterol, ergosterol. The result is formation of transmembrane channels that lead to rapid leakage of potassium and intracellular contents and death of the fungus. In clinical practice, I describe to patients that nystatin literally "explodes" the yeast cells, flooding the area with yeast toxins. In contrast, ketoconazole (Nizoral) and similar "azoles" inhibit the cytochrome P450 14a-demethylase enzyme, hindering biosynthesis of triglycerides and phospholipids, specifically production of lanosterol, a necessary precursor for ergosterol synthesis. I describe to patients that ketoconazole "punches holes" in the yeast membrane, with gradual deflation of the cells and a more controllable "trickle-release" of noxious proteins and cytokines. In the 1980s, scientists had identified at least 20 yeast toxins that directly interfered with human biochemistry. Today, that number is dramatically higher – a toxicity that is appreciated and addressed *only* by practitioners who acknowledge the profound interruptions associated with The Yeast Syndrome.

This realization led to my developing of a program to "ease into" treating The Yeast Syndrome, minimizing the expression of JHR symptoms. After a patient has adopted the MEVY diet for a week or more – where reduced intake of sugars and starches is less stimulating for yeast growth in the gut – I introduce a supplement of caprylic acid (derived from coconut oil) or undecylenic acid (undecenoic acid, from castor bean oil), gradually increasing the dosage and frequency. Either of these gently "squeezes" on the yeast, reducing the enzymatic activity that allows them to become pathogenic. At the same time, I prescribe Zymex-II, a proteolytic enzyme formulation (Standard Process) that appears as well to have salutary effects for the gut microbiome. My suspicion is that the proteolytic component is "digesting" released toxins and cytokines before they provoke JHR symptoms, and I have used other proteolytics when needed.

And *Finally* – Antifungal Medications

Within two or three weeks, I add ketoconazole (Nizoral) or fluconazole (Diflucan) as a once daily dosage for about 6 weeks. This approach is slowly reducing the yeast body burden while minimizing release of toxins and cytokines that can provoke JHR symptoms. After another two or three weeks, most patients are ready for the gradual addition of nystatin, a safe yeast-control medication they will need for many months.

Shouldn't I have more to say about the medications? Not really. My intention is to have the patient arrive, within weeks, on a stable MEVY diet, on needed nutritional supplements, and on nystatin (or Amphotericin-B, a similar polyene). This program, with enhancements noted below, will continue for many months. How long? For as long as we need to repair and restore the disrupted cellular and endocrine functions while we "hold the yeast in check." Many months. Sometimes years. Suppressing yeast growth/overgrowth is needed in order to give your body the opportunity to recover…and *that* is how long we need to treat.

My frustration with many practitioners is that they institute a "yeast treatment program" for just a matter of weeks. Then they advise their patient that "something else must be going on," since their initial symptoms haven't shown enough improvement. Often abandoning most of the principles upon which I have based my treatment of The Yeast Syndrome for almost 40 years, they embark upon an exploration involving various expensive tests and curious treatments, often with frustrating (sometimes worsening) results as years go by. In failing to understand the pathophysiology of TYS but holding themselves out as capable of treating it, such practitioners have failed their primary duty to their patient. (Truss offered an excellent review on his evolving approach, including injections of yeast antigens – one that I rarely have used: Truss CO. Restoration of Immunologic Competence to Candida Albicans. *Orthomolecular Psychiatry*. 9(4):287-301, 1980.)

If yeast toxins and the resulting interferences in biochemical and endocrine functions are the root of the patient's problems, failure to appropriately treat these impairments sets the stage for continuing symptoms, year after year. Often patients will say they "feel better" when doing other alluring treatments – but they're never quite well. Percolating yeast toxins continue to antagonize their physiology because their practitioner *abandoned* the only program that could control the yeast overgrowth and allow for restoration of better health. If yeast producing toxins is their problem, then treatment *must* be aimed at reducing yeast overgrowth and the continuing damage to their biological environment. Close counts only in horseshoes, hand grenades, and shotguns. Treatment for TYS is specific – and can be very effective to restore normalized cellular terrain.

Hamlet's Struggle Was Real!

We immediately think of "To be, or not to be: that is the question." But perhaps he was squaring off against many who failed to see the correctness of his position: "Though this be madness, yet there is method in't." Just like treatment for TYS!

But let us pause to consider: "To meat, or not to meat: that is the question." As more people investigate the challenges presented by the defective Standard American Diet ("SAD"),

the pressures of fast-food ("quick-serve") restaurants, and the increasing use of unpronounceable additives (some literally toxic), preservatives, flavorings, canola oil, and such, a variety of approaches have been proposed. Many of these are espoused for those suffering with chronic diseases, cancer, and other aging conditions. And many focus on reducing dietary intake of meat products. The potential consequences of gradual malnutrition can be deleterious and far-reaching.

"Farm meats" are *vastly* different *now* than "free range meats" of many decades past – now we are exposed unwittingly to hormones, antibiotics, and fattening feeds used to bring the greatest poundage (profit) to market. Indeed, everyone gets low level deleterious exposure to those antibiotics *and* to many bacteria that have been able to develop resistance to them! We used to have farms and ranches, now we have agri-business. When affordable and possible, intake of free range "organic" meats clearly can have benefits for longer and healthier life unless a personal choice intervenes.

But…the definition of "meats" can have many interpretations: beef, buffalo, elk, deer, lamb, pork, rabbit…chicken, turkey, duck, pheasant, dove, emu(?)...fishes – freshwater, saltwater, deep water, lobster, crab, crawfish, shark, squid, eel, turtles, and so on. And each of these categories can have products marketed as free range, farmed, fresh-caught, organic, and so on. Some dietary plans also exclude eggs as meat products, also milk, yogurt, and cheeses. So – the MEVY diet has to be adapted to one where these particular preferences can be accommodated – and adjustments likely will be needed over time.

There are many variations of the vegetarian diet, making for an entertaining challenge: an ovo-lacto vegetarian diet includes both eggs and dairy products (easiest to assist!), an ovo-vegetarian diet includes eggs but not dairy products, and a lacto-vegetarian diet includes dairy products but not eggs. As the strictest of vegetarian diets, a vegan diet excludes all animal products, including eggs and dairy (yes, most difficult to manage!).

Each of these diets that intend limitation of meat-related proteins poses certain risks for nutritional deficiencies: amino acids, minerals, vitamins, even fatty acids. Beyond your professional effort to treat TYS while adjusting for MEVY limitations, you *must* address basic nutritional maintenance. Lingering deficiencies can create or enhance disease conditions, worsen overall health, and shorten lifespan…and these dietary issues might also represent underlying digestive dysfunctions that *must* be corrected for your treatments to be successful.

Protein-energy malnutrition/undernutrition is a very real prospect, especially for people who have been limiting intake for years. Symptoms can include or mimic those of TYS as well: muscle loss (even contradictory sarcopenic obesity), weakness, fat loss, edema, fatigue, depression, loss of appetite, immune impairment, osteopenia, aggravation of inflammation (inflammaging), alterations in microbiome, and the body simply "not working" as it usually would. Each of these factors can amplify any of the others and they all join in cumulatively, confirming my assertion that "aging is not a natural calendar process but rather a disease happening one day at a time."

One major cause of protein and mineral deficiencies is simply not getting enough essential nutrients from food or supplements. Many vegetarian programs rely heavily on beans, peas, lentils, nuts, seeds, and soy products. An overdependence on soy can lead to hormonal imbalances. Various grains and rice often are prominent choices. Reliance on these products – along with fruits – to the exclusion of vegetables can lead to excessive starches and sugars, encouraging the growth of gut yeast. Careful counseling is required, including advising patients that a much longer and more regulated treatment program is needed to resolve TYS.

Adding spices and herbs to meals and snacks can help boost flavor and eating interest. Choosing acceptable high protein drinks can help nutritional replenishment, including shakes, smoothies, and milk (especially unpasteurized/unhomogenized, when that is the patient's choice), as well as high protein bars. When acceptable, choose seafood options that are higher in beneficial fatty acids (omega-3s) and lower in methylmercury, such as salmon, anchovies, and trout. Remind patients that many (most?) packaged foods (including meal replacement bars) rely on canola (rapeseed) oil rather than more healthy oils.

Are these special challenges? Of course! These patients will require your devoted and continuing attention – and often they will stretch your understanding and your continuing search for more knowledge. Helping these folks will dramatically enhance your care of all patients in the future. You will succeed more often with those who give greatest credence to Hamlet: "You cannot, sir, take from me any thing that I will more willingly part withal: except my life, except my life, except my life."

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John Parks Trowbridge, MD, recognized for a career of innovative integrative solutions, has been named a Marquis Who's Who Top Doctor in Advanced Medicine and a recipient of the Alfred Nelson Marquis Lifetime Achievement Award. An Eagle Scout and then a National Merit Scholar educated at Stanford, Case Western Reserve, Mount Zion Hospital (now a UC San Francisco campus), the Texas Medical Center, and the Florida Institute of Technology, his exceptional experiences in medicine, surgery, and nutritional technologies encouraged him to ask provocative questions. His persistent curiosity in resolving perplexing issues has enabled him to find effective answers. Serving for years as a senior aviation medical examiner for the FAA, a "company doc" for heavy industry, and medical director for a mold remediation company provided invaluable expertise in toxicology and environmental science. A Fellow of the American College of Advancement in Medicine, he is recipient of the Distinguished Lifetime Achievement Award of the International College for Integrative Medicine. He has served as president, officer, or director of several integrative medical, dental, and lay organizations, has lectured around the world, has produced dozens of hours of CDs and DVDs, and has authored many articles and several books, all sharing his unique perspectives. He and his devoted staff at Life Celebrating Health near Houston, Texas, continue to welcome those who insist on enjoying a healthier future: 1-800-FIX-PAIN, www.healthCHOICESnow.com.

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Managing Yeast Overgrowth

by Joseph J. Burrascano Jr., MD

Introduction

A long time ago, after failing to control yeast overgrowths in my patients, I realized that the problem begins not in the GI tract, but in the mouth, with these organisms overgrowing on the oral mucous membranes and tongue ("thrush"). Then with every swallow, organisms would spread to the intestinal tract. Therefore to successfully control this problem, I instructed my patients to begin by cleaning out oral yeasts, then to immediately replenish the beneficial flora in the mouth. Finally, specific general anti-yeast support is added to maximize their chance for success. Here are the specifics.

Oral Hygiene

Brush the teeth, gums, inner cheeks, tongue and palate for 30 seconds while holding an antiseptic mouthwash in the mouth (see below). Then, rinse one or two times by brushing while holding plain water in the mouth. Follow by brushing with a gentle toothpaste to be sure all debris is removed. Don't forget regular flossing!!

Antiseptic Mouthwash. Because most antiseptic mouthwashes contain harsh chemicals, colorings and flavorings including sweeteners, I recommend a more unusual but logical antiseptic that you make yourself: a very weak Modified Dakin's solution. Make this by mixing one teaspoon of household liquid bleach (yes, bleach like Clorox®!) into four ounces of water. Note that using a rather strong antiseptic is usually a one-time treatment and is not meant to be done daily. However, it may have to be repeated from time to time if necessary.

Because the germ count, both harmful and beneficial, will be artificially reduced after such a cleaning and because yeasts are opportunists, the yeast infection can come back if this is all that you do. Therefore, after using an antiseptic, it is necessary to immediately replenish the beneficial flora in the mouth so the yeast will be crowded out and a more normal oral flora can result. The product I recommend is OraMax by Researched Nutritionals, the first and best product crafted to optimize oral hygiene in this way. Use it by dissolving one tablet in the mouth twice a day, preferably right after routine oral hygiene and definitely after using the antiseptic mouthwash.

GI Tract

An overgrowth of yeast here will ferment dietary sugars and starches, forming acids, gas, alcohols and a variety of organic chemicals. In addition, intestinal yeasts can form biofilms that can trap other pathogens, including viruses. To control intestinal yeast, first the oral cavity must be managed as described above so yeast does not reenter the system with every swallow. Then use agents designed to support intestinal defense and clean out unwanted pathogens. Finally, just as with the oral cavity, replenish the GI tract with beneficial organisms.

Intestinal Support. General antimicrobial support with Microbionate® is where I begin. I often add Elim-A-Cand™, which is more specific for problematic yeasts.

Probiotics. I have found it essential to use a product that contains a variety of beneficial organisms, including spore-based ones. No longer is a single agent like *Lactobacillus acidophilus* thought to be sufficient. The one I prefer is Multi-Biome™ by Researched Nutritionals. Use daily.

Prebiotics. Although not meant to be specific for GI yeast, one of my favorite supplements for my chronic TBD patients is ATP Fuel®. Turns out, not only does this offer support for cellular membranes and therefore mitochondrial health, it also contains significant amounts of prebiotics. Prebiotics are a form of dietary fiber that support the growth of beneficial bacteria in the gut. A win-win!

Diet. Since yeast germs feed on sugars and starches, the diet must be low in simple carbohydrates. Adding a variety of high-fiber foods is also important to supply additional prebiotics.

I hope that you are able to benefit from my recommendations. Best wishes for the best in health! ◆

Joseph Burrascano, Jr., MD, an early innovator in the field of tick-borne diseases, began his clinical research in the mid-1980s in cooperation with several other key pioneers. A founding board member of ILADS, he also served as a director of the ILADS Educational Foundation. In addition, he is well known for his educational presentations and for his monographs on diagnostic and treatment guidelines for Lyme and related tick-borne illnesses – a classic series that has been freely circulated around the world since 1989. He is an active writer and ghost writer and has authored or edited articles (both lay and peer-reviewed), book chapters, whole textbooks, web page content, public relations releases, book reviews, and more. In addition, he serves on the editorial review board for several medical journals.

A graduate of the NYU School of Medicine with a specialty in internal medicine, Dr. Burrascano left clinical practice in 2006 to enter the biotech space. He currently works full time as a project analyst and manager for a private biotech company, helping to bring advanced technologies and treatments out of the lab and into general use. In addition, he is a clinical advisor for a specialty diagnostic lab, and his lifelong interest in nutrition has resulted in his ongoing consultative work with various nutritional supplement suppliers.

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Bile Acids as Regulators of Inflammation

by Steven Sandberg-Lewis, ND, DHANP

The sterolbiome is a term that exemplifies the interaction of the intestinal flora and bile as a steroid-based endocrine system. In addition, there are continuous interactions among these essential systems in the gastrointestinal skin, oral, respiratory and reproductive tracts.

"The gut microbial community through their capacity to produce bile acid metabolites distinct from the liver can be thought of as an **endocrine organ** with potential to alter host physiology, perhaps to their own favor''[1]

The sterolbiome alters the function of human cells and tissues for its own advantage, while also having major effects that benefit the host. The focus of this article will be on the sterolbiome's regulation of host inflammation. Hepatocytes synthesize and secrete the water-soluble primary bile acids – cholic acid and chenodeoxycholic acid. These are conjugated with glycine, taurine, sulfate or glucuronide. The intestinal microbiome metabolizes these into the fat-soluble secondary bile acids – deoxycholic and lithocholic acid. In addition, the bacteria may also deconjugate them.

Bile belongs in the small intestine and typically only 5% enters the colon. Bile salts are present in tiny amounts (or not at all) in the other parts of the digestive tract. Bile flows through the entire 18-20 feet of small intestine and is then reabsorbed in the terminal ileum. The bile returns via enterohepatic recirculation for reprocessing and recycling back to the gall bladder and the process starts over. Diseases in the terminal ileum (eg. Crohn's disease) or resection of the terminal ileum often lead to bile malabsorption. If too much bile enters the colon, it acts as an irritant and can be a cause of severe diarrhea (bile acid diarrhea). Some irritable bowel syndrome patients are ultrasensitive to even normal amounts of bile in the colon and develop diarrhea. Sometimes bile flows up to the stomach (this is called bile reflux) and causes irritation of the stomach lining (bile gastritis).

Primary bile acids participate in micelle formation with lecithin and cholesterol to expedite absorption of fats and fat soluble vitamins. The secondary bile acid metabolites influence nuclear receptors (such as the farnesoid X receptor) and cell surface receptors (G-protein coupled receptors) exerting major effects on inflammation. Primary and secondary bile acids both activate other nuclear receptors such as the pregnane-x-receptor (PXR),[2] the constitutive androstane receptor (CAR),[3] and the vitamin D receptor (VDR).

Farnesoid X Receptor (FXR)

FXR influences glucose and lipid metabolism, tumor suppression, drug metabolism, cell differentiation and inflammation. FXR is found in the GI/liver axis, cardiac,[4] endocrine/metabolic,[5] renal,[6] pulmonary,[7] breast,[8] vascular,[9] and nervous systems.[10] Research suggests that FXR activation is tissue protective in acute inflammation and appears to reduce intestinal inflammation in digestive diseases. In colitis, FXR activation decreases local IL-1β and increases systemic IL-10 expression.[11] FXR activation upregulates physiological hydrogen sulfide production, important for the maintenance of gastrointestinal mucosa in the presence of NSAIDs.[12] In chronic inflammatory states, FXR activation reduces colitis and inhibits pro-inflammatory cytokines in humans.[13] Single-nucleotide polymorphisms in the FXR gene are significantly associated with altered barrier function and upregulation of inflammation of Crohn's and ulcerative colitis.[14] When ligands activate FXR nuclear receptors, metabolic changes within cells are rapidly sensed leading to transcriptional responses. Responding to elevations in intracellular bile acid concentration, FXR induces protective gene expression. This induces bile salt export pumps, avoiding bile acid toxicity in the liver and intestine.[15] This signaling also prevents bacterial overgrowth in the ileum.[16] Impaired bile flow may down-regulate FXR signaling, leading to enterocyte damage, increased bacterial translocation and systemic infections.

Fecal microbiota transplantation is associated with increased FXR activity.[17] Similar results are seen with supplementation with the anti-inflammatory bile acid ursodeoxycholic acid (UCDA) in murine *C. diff* models. UDCA administration leads to increased expression of the FXR pathway in both cecal and colonic tissue, likely through its salutary microbiome effects.[18]

FXR knockout mice were found to have lower expression of the tight junction proteins ZO-1 and claudin-1. Chenodeoxycholic acid, the primary bile acid that is considered the strongest endogenous FXR ligand, has been found to prevent decreases in ZO-1, occludin, and claudin-1 in response to lipopolysaccharide.[19]

G Protein Coupled Receptors (GPCRs)

G protein coupled receptors are a superfamily of cell surface receptors. They are found on immune cells and enteric nerves as well as epithelial cells in the intestine and biliary tracts. They support functional intestinal permeability, anti-inflammatory activity in dendritic cells, monocytes, macrophages, and natural killer cells and also mediate motility via enteric nerves.[20] Bile acids and short chain fatty acids activate GPCRs, which are found in the gallbladder, spleen, some intestinal and white blood cells, bile duct, and fat cells. When stimulated, GPCR increases

levels of incretins, glucagon, and insulin.[21]

Microbial-derived short chain fatty acids and bile acids influence the immune system as ligands for GPRCs. Intestinal bacteria produce hormones (e.g. serotonin, dopamine and somatostatin), as well as responding to and regulating host hormones. Examples include inhibiting genes that transcribe prolactin or converting glucocorticoids to androgens). There are regulatory effects from these receptors on intestinal permeability and possibly autoimmune pathology. Gut microbial dysbiosis may be an etiological factor in autoimmune disease by this mechanism. Treating dysbiosis with dietary interventions such as botanicals, prebiotics and probiotics may prevent or treat autoimmunity.[22] A meta-analysis found that compared to patients in remission, patients with active ulcerative colitis had decreased abundance of *Clostridium coccoides* and *leptum*, *Faecalibacterium prausnitzii* and *Bifidobacterium* spp. Patients with active Crohn's disease had fewer *C. leptum*, *F. prausnitzii*, and *Bifidobacterium*, but no decrease in *C. coccoides*.[23] In a second meta-analysis, the abundance of *F. prausnitzii* was reduced in both active CD patients and active UC patients when compared with the patients with CD or UC in remission, respectively.[24]

Bile Salts as Therapy for Inflammatory Conditions

In a mouse model of *Clostridium difficile* enterocolitis, ursodeoxycholic acid (UDCA) improved NF-KB signaling and reduced inflammation in the colon. It was given early in the course of the disease, acting through FXR and TGR5, the major G-protein-coupled membrane receptor.[25] In the *World Journal of Hepatology*, researchers studied bile therapies and non-alcoholic steatohepatitis: "Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid with immunomodulatory, anti-inflammatory, antiapoptotic, antioxidant and anti-fibrotic properties. UDCA can improve insulin resistance and modulate lipid metabolism through its interaction with nuclear receptors such as, TGR5, (and the) farnesoid X receptor…."[26] UDCA is perhaps best known for preventing eosinophilic degranulation and reducing eosinophil counts in primary biliary cholangitis. It is standard therapy for preventing progression to cirrhosis in this autoimmune disorder. It has also been found to reduce eosinophilic inflammation beyond the GI tract. In a ovalbumin-induced model of asthma in mice, UDCA was found to modulate dendritic cell/T cell interactions, reducing eosinophilic inflammation in vivo.[27]

Brazilian researchers found that UDCA had a local protective effect of murine ileitis induced by indomethacin. They found that this unique bile salt protected against intestinal barrier dysfunction and oxidative stress and suggest it as a possible treatment for Crohn's disease.[28] UDCA has also been studied for symptom amelioration in bile gastritis. A small prospective placebo-controlled study in men and women found 1000 mg of oral ursodeoxycholic acid daily resulted in a highly significant decrease in the intensity and frequency of the epigastric pain. In addition, nausea and vomiting were all but abolished. During bile acid therapy the proportion of the anti-inflammatory bile salt rose from 2% to 50% of total bile acids.[29] ➤

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Over the last twenty years, research – most of which is murine based – reveals that bile can significantly reduce neurodegeneration, accumulation of amyloid material and markedly prevent memory loss in Alzheimer's disease. Both UDCA and its taurine conjugated form – tauroursodeoxycholic acid (TUDCA) – are inhibitors of apoptosis. This cellular protection is achieved by reducing the mitochondrial pathway of cell death, reducing ER stress, inhibiting the production of oxygen-radicals and stabilizing protein unfolding.[30] Protection of essential nerve tissue has been shown in amyotrophic lateral sclerosis, Parkinson's, Huntington's, stroke and retinitis pigmentosa.[31] The stroke research did not employ oral bile salt treatment, but rather injection into the carotid one hour post ischemic event. The fascinating results included significantly increased bile acid levels in the brain, improved neurologic functioning, and a 50% reduction in the area of the stroke.[32] Rats given IV UDCA prior to ligation-induced myocardial infarction had significantly smaller areas of infarction and caspase 3 activity.[33]

In human studies of overweight men and women, oral supplementation of bile salts increased insulin sensitivity by 30% with no increase seen in the placebo group. There were also improvements in blood sugar, insulin, and transaminases in the bile-treated group, but not in controls.[34] A small prospective, double-blind, randomized, placebo-controlled crossover study of UDCA in male CHF patients used 500 mg UDCA twice daily for four weeks and placebo for an additional four weeks. The treatment was well tolerated and increased peripheral circulation and lowered GGT and AST compared to placebo.[35]

Bile starts in the liver but appears to have systemic inflammation modulating effects!

In summary, preliminary research shows that bile may be important in reduction of inflammation, apoptosis and necrosis in the liver, intestine, CNS, myocardium and retina. It appears to be important in maintaining insulin sensitivity. Bile starts in the liver but appears to have systemic inflammation modulating effects!

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The Character of the Liver

by Chris Chlebowski, ND, DC

In the minds of many, the liver's sole purpose is the body's primary detoxifier; but the more complex truth is that it has an array of responsibilities that are incredibly diverse, interwoven, and complex. This complexity arises from the fact that this organ must constantly integrate countless forms of biological information, including endocrinological, hematological, dietary, immunological, and toxicological. Consequently, when I think of the liver, I picture it in all its archetypical manifestations – the General of the Blood, the Queen of Hormones, and the King of Detoxification.

Due to the diversity of information the liver receives, this can lead to it becoming a seat of either great illness or health – depending on how well it is taken care of. When great care is taken and it is operating efficiently, the blood and skin are clear, hormones are balanced, energy abounds, and toxins are moved through with ease. When the liver is unwell, people feel tired, full, fat, in pain, and can have a multitude of symptoms in every system in the body.

The purpose of this writing is to help you better appreciate the varied roles of the liver. This recognition should aid your ability to see subtle dysfunction in this organ long before it becomes pathological. I have also provided some less common treatment ideas that may be used in order to keep this precious organ well.

The General of the Blood

Ancient tradition holders in Chinese medicine were the first to name the liver the "Commanding General of the Body." It earned this anthropomorphized moniker due to its foremost duty – moving blood and chi about the body. The liver is unique in that it receives a dual supply of deoxygenated and oxygenated blood from both the portal vein and the hepatic artery respectively – filtering this blood from the digestive tract at nearly a gallon of blood every two and half minutes.[1]

Armies need fuel and the liver is a major storage site for our primary energy source – glucose (in the form of glycogen.) Around 6% of the organ's weight is glycogen stores. The vitamins A, B12, and D are also stored in large quantities in the liver as well as ferritin, the body's substantial iron repository. "Transport protein" synthesis also occurs largely in the liver, without which, hormones would not arrive safely and intact at their required destinations. And like the general who can conscript new members into his troops when the others have been killed off, the liver is the only organ capable of complete regeneration in the body – if as little as 25% is intact it can grow back into a completely new organ.[2]

Protecting our livers assures excellent metabolism, healthy hormones, and proper processing of toxicants.

The Queen of Hormones

Kingdoms need generals, but they also require a queen. In the liver's role as the female sovereign, she brings balance to the body regarding sex, thyroid, and adrenal hormones. For example, the total amount of circulating hormones, say estrogen from the ovaries, is determined by both the ovaries and the liver, but the liver has the final say; if she deems it necessary to remove, inactivate, or transform estrogens she can excrete them into the bile. And if the corresponding glands (thyroid, adrenal, ovary, testes) are under-functioning, the liver can help maintain a normal level of hormones by decreasing excretion. Thus, the healthy functioning liver may, for some time, maintain the normal balance of hormones when the endocrine organ is disturbed.[3]

The queen is also the transformer. She brings hormones into action for use. The thyroid hormone thyroxine (T4) is transformed in the liver into its four times more biologically active form triiodothyronine (T3) – much "hypothyroidism" is due to the poor liver function. Vitamin D3 is also remodeled into its biologically active form 25-OH in the hepatocytes.

The King of Detoxification

In its most widely recognized and celebrated duty, the liver acts as one of the body's primary organs of detoxification. The King protects us from toxic chemical assaults via his ability to convert fat-soluble compounds into water-soluble metabolites that can be more easily excreted in the urine or stool. It does this through a complex series of enzymes that oxidize, reduce and hydrolyze (Phase 1) or conjugate (phase II) the toxins. These toxins can include plastics, mycotoxins, metals, and a host of the other chemicals – and they are everywhere. In 2009, the Environmental Working Group commissioned several laboratories to check the stored umbilical cord blood of ten random infants born in US hospitals during the summer of 2004. What they discovered was astounding. Each of the infant's blood contained more than 200 chemicals, including substances like mercury, organochlorine pesticides, and polyaromatic hydrocarbons.[4] This landmark study showed that these exposures start before we ever leave the womb; the number and diversity of chemicals our newborns are exposed to is astronomical.

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Every single patient we check in our clinic has some combination of molds, metals, pesticides, and plastics in their body and there is hardly a patient whose liver could not use some additional assistance. Simple natural medicine therapeutics can reverse fatty liver, cure jaundice, purge congested gallbladders, lower transaminases, and remove harmful toxicants from the liver. But first we need to be able to recognize liver dysfunction in order to decide on the correct course of action.

You See What You Look For

To recognize liver dysfunction, we can return to the lost art of the in-depth history and physical examination. These highly accessible and inexpensive tools can point to brewing dysfunction when we don't have access to a comprehensive metabolic panel, ultrasound, MRI, or CAT scan to illuminate elevated transaminases, NASH, NAFLD, fibrosis or cirrhosis.

Systems like Chinese medicine, iridology, reflexology, Western herbalism, chiropractic, and homeopathy all have a long history of assessing physical signs associated with the liver to uncover pathology. These are the subtle signs (or not so subtle in advanced disease) in the physical examination and history that can point towards liver and gallbladder dysfunction. If we listen for the faint sounds perhaps, we can head off disease before it becomes a raging symphony.

Below is a simple reparatory, which can help to assess the need for further investigation or treatment of liver dysfunction.

Findings in the Physical Examination and History Suggesting Liver Dysfunction

- Hair: Early graying of the hair whether it is the whole head or just a streak. This is a sign of compromise of detoxification pathways and points to liver dysfunction particularly when it occurs before the age of thirty.
- Forehead: A high forehead indicating a cerebral nature – one who spends many hours locked in their mind as opposed to the heart or body.
- Head: Acne or eruptions on the temples, above the eyes, or along the eyebrows. Headaches, pain, or pressure in the region of the temples or forehead.
- Ears: Red and swollen ear lobes.
- Nose: Frequent runny nose. Allergies.
- Eyes: Yellowed or darkened sclera. Floaters in the field of vision. Loss of vision, in general, points to a taxed and overburdened liver. Between 7 and 8 o'clock in the right iris is the region associated with the liver; look for dark dots or discoloration in this region.
- Mouth: A bitter taste in the mouth. Acne along the jaw line.
- Teeth: Gum loss, pain or cavities at teeth (#6, 11, 22, 27).
- Tongue: A dark tongue, blue spots or discoloration particularly on the right side of the tongue. Dark, engorged and branched sublingual veins are highly indicative of liver dysfunction.
- Skin: Excessive sweating or the absence of sweat – both can point to liver congestion. Jaundice or any yellowing of the skin. Spider veins on the chest. Hot flashes of menopause. Acanthosis nigricans can indicate fatty liver.
- Abdomen: Cherry angiomas (indicating estrogen dominance) point to the need for liver assistance. Lipomas. Caput Medusa. Inability to lose abdominal adiposity.
- Gastrointestinal Tract: Nausea. Easy intoxication. Light or clay-colored stools.
- Back: Pain/weakness in the rhomboids. Pain at inferior angle of the right scapulae. Subluxation of ribs or vertebra in the region of T5.
- Upper Extremities: Weakness or pain in the pectoralis major muscle. Bluish lunula of the fingernails. Pain or weakness in the tendons or joints.
- Lower Extremities: Pain in the big toe. Nail fungus, particularly of the big toe.
- Seasonality: Complaints that reoccur every spring.
- General Constitution: High energy. Inappropriate regulation of temperature or warm blooded. Easy perspiration.
- Mental State: Easy to anger. Quick to judgement. Impatient. Always in a hurry. Easily annoyed by little things. A mind predominated by the intellect.
- Food cravings: Rich foods. Alcohol. Sweets. Coffee and stimulants.
- Sleep: Difficulty falling asleep due to busyness of the mind. Waking between 11-1 am (Gallbladder). Waking between 1-3am (Liver). Perspiration at night.

Before we begin any treatment in our clinic for chronic infections, balancing sex or adrenal hormones, or general gastrointestinal health we always assess and treat the liver. If we skip this step patients will often fail treatment and must start back at more basic steps before reaching a new desirable level of health. Detoxification is fundamental in all CMSDD (chronic multisystem degenerative diseases), and you can't talk detoxification without discussing the liver.

Our armamentarium is vast with tools for the treatment of the liver, including countless herbs, remedies, supplements and physical procedures and is well beyond the scope of this article. That being said, I would like to discuss a common botanical that is frequently overlooked for liver health as well as a simple procedure that can dramatically improve the health of this critical organ.

Liver Lovers

Most people and practitioners know about the most common herbs used for the liver (dandelion, milk thistle, bupleurum, berberis, reishi, etc.). These appear in countless herbal combinations or supplements and form the foundation of botanicals used to treat hepatic dysfunction.

But what about one of the less common plants that grow easily and prolifically in the wild? A plant that can be recognized, cultivated, and utilized for improving the health of one of our most important organs. Let's discuss the often-overlooked Red Root.

Red Root (*Ceanothus americanus*)

On sunny rocky hillsides in North America, you will find this low-lying bush thriving in poor, well drained soils. Hummingbirds and butterflies are attracted to its groupings of five petalled white flowers. This natural attraction has helped to make it a staple and subtle addition to many gardens.

Ceanothus' introduction into Western herbalism was via the surgeons of the Civil War as an indispensable antihemorrhagic on the battlefield. Subsequently, the eclectic physicians began to utilize the plant in their formulas because of the coagulation properties of its leaves.[5,6] Not only do the leaves stop bleeding but apparently, they lower blood pressure – in a 1940s study the leaves were shown to be antihypertensive in a cohort of rats.[7]

Over time the use of leaves faded from Western herbalism, and it was the root that gained notoriety – primarily due

to the writings of English homeopath Dr. James Compton Burnett. Burnett taught the world that red root was one of our most important lymphagogues, spleen remedies, and indispensable in cancer.

Red Root performs well in cancers of the liver, pancreas, spleen, and Hodgkin's lymphoma. It should be thought of in cases where there is fullness, swelling, enlargement or pain in any of these organs secondary to cancer, running neck and neck with remedies like Chelidonium, Lycopodium, and *Carduus marianus*.

What has largely gone unrecognized is Ceanothus' direct and powerful effect on the liver. And this really should come as no surprise if we remember that the liver is the largest lymph-producing organ in the body.[8] With our lymphatic systems and livers toxic like never before, it is time Ceanothus (re)gains it recognition for its liver-healing abilities.

I give this plant in so many cases but the ones that stand out are where the patient has a markedly enlarged spleen or liver due to Epstein Barr virus, a Bartonella infection, or painful cysts and swollen breasts during the menstrual cycle, which all subside when ceanothus is given.

A tea or a tincture of the root is the traditional preparation. The medicinal part of the plant that effects the lymph and liver is the root bark. Bring a good shovel and a strong back when you go to dig up the roots in the fall or spring – the soil Ceanothus prefers is rocky and hard to break up. Wash and strip the roots of their dark red bark. Make medicine quickly as the properties tend to fade rapidly. Teas and tinctures work well, and I have seen as little as 10 drops once a day of the tincture make a dramatic difference in swollen lymph nodes and painful livers in both children and adults.

Plants that heal our bodies and the earth at the same time are of the greatest interest to me and red root is one of these. It is a plant that fixes nitrogen.[9] And it sprouts up after fires to regenerate the soil, providing food for animals and then dying back to allow growth of more hardy long-lasting plants. Ceanothus' use in future regenerative agriculture just makes sense.

Physical Means to Move the Liver Chi

In any detoxification plan I always like to add something physical to help move the blood and lymph. Patients get tired (as do their pocketbooks) of taking too many supplements. Providing a few physical treatments they can do at home helps balances out expenditures and means by which we heal our organs.

We have many techniques that accomplish this task like rebounding, deep tissue massage, dry skin brushing but there is one simple one that I use in case after case that does some very deep work in healing the hepatic system.

Castor Oil Packs. This is an old tried and true method for encouraging discharge and detoxification of both the hepatocytes and the lymphatic system of the liver. And no, you don't have to drink the castor oil. To encourage the detoxification and cleansing of the liver, perform the following technique two to five times per week. This practice is best done in the evening before bed as it will often led to relaxation and better sleep.

The Simple Castor Oil Pack

1. Buy a bottle of organic castor oil.
2. Lie on the couch or in bed on your back in a relaxed position.
3. Apply a half dollar sized amount of castor oil over your liver. Your liver is in the upper right-hand quadrant of the abdomen, below the diaphragm and mostly above your ribs.
4. Place an old towel over the area where you applied the castor oil.
5. Place a hot water bottle or heating pad over the towel for twenty to thirty minutes. Be careful not to burn yourself with the heating element or fall asleep with the heating pad still turned on.
6. When you are finished most of the castor oil should be absorbed leaving very little clean up.

Countless patients in my practice have noted the following effects after using castor oils packs on a regular basis:

- Diminished intensity or frequency of hot flashes
- Improved liver enzymes
- Better blood sugar control
- More restful sleep
- Healthier bowel movements
- Clearer skin
- Diminished Herxheimer reactions
- Fewer headaches and neck pain
- Less gallbladder/liver pain
- Improved tolerance for fatty foods
- Less anger and irritability
- Less perspiration

For such a simple procedure, it is worth trying if you have signs of liver congestion.

A Kingdom of Good Health

As in any country, region, or kingdom for true prosperity to reign all aspects of the society must be attended to. The kingdom of our body is no different. Recognizing dysfunction before it progresses to pathology and protecting our livers assures excellent metabolism, healthy hormones, and proper processing of toxicants. And in a world where toxicity is rising with no end in sight it makes sense to take the best care possible of our organs that do so much for us. Viva La Liver!

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Dr. Chris Chlebowski is naturopath, chiropractor, clinical herbalist, and homeopath with a medical practice, Ashland Natural Medicine, in southern Oregon. At the clinic, Dr. Chlebowski and his staff use cutting-edge technology blended with traditional therapies, with particular specialty in the treatment of chronic Lyme disease, mold illness, cancer, neurological disorders, and – most commonly – "mystery" diseases that other doctors have been unable to diagnose. Dr. Chlebowski lectures regularly on holism and the root causes of illness and his articles have appeared in *Naturopathic Doctor News and Review* and *Simillimum*. He holds doctorates from Western States Chiropractic College and the National College of Natural Medicine. His upcoming book published by Chelsea Green, *The Virus and The Host: How to Protect Yourself from Infectious Disease by Reducing Toxicity, Improving Immunity, and Minimizing Chronic Illness* will be on bookstore shelves September 2022. When he isn't working up a difficult case or spending time with his wife and their two children, you can find Dr. Chlebowski climbing up the rocks or skiing down the mountains of southern Oregon and northern California.

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Reversing Chronic Kidney Disease with Niacin and Sodium Bicarbonate

by Stephen McConnell and W. Todd Penberthy

Orthomolecular Medicine News Service

This story began with initial discovery, motivated by necessity. It would lead a few years later to reproducible documented reversal of chronic kidney disease (CKD) stages 1 or 2. Success was achieved using 3 to 5 cents/day of 100-500 mg niacin TID [three times a day] along with 1.0-1.8 grams of sodium bicarbonate (baking soda, 600 mg at lunch and 1.2 g before bed) with or without <2g/day elemental calcium, as calcium carbonate.

Excellent results from the use of niacin to treat CKD have now been documented for more than 25 case-studies. This approach is well supported by continuous basic and clinical research, including dozens of clinical trials that provide substantial evidence for the use of niacin and sodium bicarbonate. These approaches directly address the needs of the typical CKD patient. Unfortunately, this approach is rarely implemented in the clinical setting.

CKD commonly progresses with age as it is observed in 68% of Americans ≥60 years of age.[1] Patients with CKD usually experience progressive loss of kidney function moving towards an increasing risk of end-stage renal disease (ESRD). CKD is the 9th leading cause of death in the US.[2] Fortunately, there are several simple approaches including the addition of modest doses of niacin (immediate release- or IR-Niacin) that can reverse CKD in many patients as described here.

Approximately 786,000 people per year, in the US progress to ESRD (stage 5 CKD), which is generally considered an irreversible condition. Most of these become completely dependent on regular trips to dialysis. Estimation of the stages of CKD is based on (GFR) glomerular filtration rates starting with ≤60mL/1.7m2 for three months as definitive of initial CKD diagnosis. Unfortunately, a creatinine derived GFR (crGFR) is only as reliable as the serum creatinine measure. Use of this creatinine-based test has a "blind-area" in the earlier stages and frequently leads to an under-estimation of the true risk.

Stages of CKD

1. Mild kidney damage, eGFR 90 or higher
2. Mild loss of kidney function, eGFR 60-89
3. Moderate loss of kidney function
   a. eGFR 45-59
   b. eGFR 30-44
4. Severe loss of kidney function, eGFR 15-29
5. Kidney failure or close to failure, eGFR less than 15

Niacin for CKD

Supplementation with daily low-dose niacin reliably reverses a large amount of the functional loss. This simple treatment is effective and critically important. Mortality rates with CKD are striking, as the five-year survival rate for patients doing long-term dialysis is 35% compared to 25% in those with diabetes [T2DM] in the USA.[3]

Routinely, the first treatment approaches utilized for CKD patients, in the later stages, generally targets control of dysglycemia and reduction of hyperphosphatemia according to KDIGO guidelines.[4] Fortunately, there is an ever-increasing abundance of data revealing that simple niacin treatment is a profoundly effective treatment for reducing hyperphosphatemia – and that is just the beginning. In basic research the evidence in favor of niacin for CKD has continuously accumulated. Clinical research proves that the niacin stimulated pathways involving increased NAD synthesis, PCSK9 inhibition, sodium transporter effects, PPAR gamma activation, and more, are exceptionally well-suited to addressing CKD, multimorbidity, and ultimately all-cause mortality.[5-41]

The clinical and financial impact of CKD when it progresses to end-stage renal disease (dialysis-dependence; ESRD) is profound. Clinically, CKD progression quickly leads to lifelong dialysis with co-morbid life-threatening cardiovascular disease. Financially, the out-of-pocket cost of CKD is greater than cancer and stroke with ESRD dialysis costing 30.9 billion per year in 2013 or approximately 7.1% of total Medicare costs.[42] Medicare spends approximately $250,000/y for every CKD patient, ***prior to*** the transition to ESRD and dialysis. Annual costs per dialysis patient can range from $720k to $2.2m per year.[43] These problems and their associated costs can be reduced by using 5 cents per day of niacin.

Originally, I (SM) was formally trained to operate a heart-lung machine, maintain full life-support and anesthesia, in the operating

room monitoring patients undergoing open-heart surgery. Much later, I transitioned to working as a field scientist, MSL (Medical Science Liaison) in the advanced laboratory diagnostics industry. My primary clinical focus since that time has mainly been lipidology. Because of my initial education/training, addressing cardiovascular disease, I now focus on prevention: lipidology. This training gave me an appreciation for nicotinic acid (niacin, vitamin B3).

I have now personally observed more than 25 documented cases of individuals having their CKD progression not only halted but reversed with the addition of 3 to 5 cents worth of niacin, per day (with 1.8-2.4 g/day sodium-bicarbonate with/without 250-500 mg/day calcium-carbonate).

A Family Story

While I (SM) was learning lipidology in the period between 2002-2007, my father suddenly went to the ER late one Sunday night and my mother called me hysterically, "I took your father to the ER and now they are scheduling him for placement of stents." I was concerned, as any son would be, but also as a scientist because I felt I may have 'failed him,' somehow: If only what I had already learned, I had only learned it, sooner.

My father was 81 at the time and he had been jumping rope for 30-minutes, twice daily. His body had a deceptively healthy look, and his triglycerides were low, but when we put it all together, he was "Pattern-B" – insulin resistant. He had always been a 'stodgy,' stubborn, stoic World War II veteran. He was very introverted and typically had a limited range of emotions: rage, laughter, and silence. Later, I would find out he had Asperger's.

When I received the advanced laboratory data, it showed that he had low HDL2 and high ApoB. This is far more specific and confers much greater risk vs. an elevated LDL-C. Most importantly, this revealed he was insulin resistant (a.k.a. pre-diabetic). At the time, I really didn't fully understand this. Even today, most clinicians really do not, due to continued reliance on using only tests for FBG and HbA1c. Ultimately, my father survived, and we continued to institute aggressive medical management: A hard lesson learned.

My father and my mother traveled everywhere together. They commuted, seasonally to Florida each winter, to escape the cold weather in Northwest Pennsylvania. On New Year's Day, about six months after his MI and stent-placement procedure, I received a call from my mother, "Your father is in the hospital! They're going to have to do open heart surgery!"

They needed to do an aortic-annuloplasty (aortic heart valve repair), in addition to a quintuple CABG (5 bypass grafts). I thought to myself, "this is getting worse and worse." Having had previous personal experience working with thoracic surgeons during open-heart operations, I didn't want the procedure to begin until my brother and I were able to be present. Fortunately, the young thoracic surgeon and the techniques planned were excellent.

Later, in the spring, they returned home to Erie, Pennsylvania, for the follow-up visit. Dr. Dave (the physician who asked me to set-up my 1st lipid clinic) said, "Hey I got some bad news for you. Your dad has renal insufficiency." I said, "Oh my God, he's in renal failure, what stage is he?" He did not know. That was a flag. Most clinicians don't know what stage their CKD patients are because the lab doesn't do calculations and the creatinine measure is not reliable or accurate. The creatinine measure has very little accuracy until after the CKD has 'hit' stage 3B, and beyond.[44,45] So, a lot of these patients along the CKD disease continuum, through each progressive stage, appearing to have less risk vs. the 'true' risk that is present. It's better to test a urine sample and see how much protein is recovered and run a Cystatin-C and a crGFR to calculate a more accurate value. At that time, I only knew he was in failure; but when I did the crGFR calculation, I could see that he was well into the latter portion, of CKD-stage 4.

Recently, I had been putting together a new treatment algorithm with substantial literature support, data, on CKD. I was lucky to have been mentored by Dr. William F. Finn.[46] Even if a patient has not already been scheduled for dialysis, he explained, and especially if they are currently on dialysis, you must ***get the serum phosphorus down***. Excessive phosphorous is toxic to the kidneys as well as virtually every organ system and the entire body.[47,48] Phosphorus is a primary initiator of vascular calcification, among several other pathologies. If the kidneys start to lose a certain fraction of their normal function, the body can no longer efficiently clear phosphorous. When phosphorous serum levels reach abnormal levels, then you begin to saturate the tissues. Then phosphorous binds to calcium and it's the phosphorous, not the calcium that starts the pathology leading to calcium phosphate stones.

Clinical research proves that niacin is exceptionally well-suited to treatment and prevention of kidney disease.

Niacin Helps to Get the Phosphorous Down

Even after you bring serum phosphate down you still have it in the tissues. The only biomarker available in a clinical setting, Fibroblast Growth Factor-23 (FGF-23), reflects the pathology behind long-term exposure to elevated phosphorus. FGF-23 can be decreased, simply by administering niacin.[14] However, the sodium phosphorous transporter works through a feedback mechanism to make more receptors to compensate.

So, calcium carbonate (from an antacid tablet) is commonly used first to bind the readily available intestinal phosphorous. This is among the cheapest and most effective phosphorus chelator approaches. Calcium carbonate should not be used above 2g/day elemental calcium, which is 40% of most of the formulations: ➤

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Total 5g/day as calcium-carbonate. This should be administered at mealtime. The idea is to 'treat the meal', as there is generally very little phosphorous available to bind, outside of mealtime. When the kidney is in 'failure', after meals, excess phosphorous remains uncleared and leads to deposition in the tissues: valve leaflets; at the endothelial barrier; arterial subendothelial space (Mönckeberg's medial calcification: arteriosclerosis).[49] When sodium bicarbonate (baking soda) is administered, based on the landmark study,[50,51] the transition from stages-3 & 4 to Stage-5/ESRD/Dialysis, can be reduced by ~80%, with just 1.8 grams sodium bicarbonate, alone. Mealtime dosing BID, (1X 600 mg at lunch and 2X 600 mg at dinner each day, i.e 1.8 g total per day), optimizes the therapy.

In that study, the fraction of people that went to dialysis by the end of two years was roughly 35% on placebo, but the fraction that went to dialysis with the modest dose of sodium bicarbonate, was reduced roughly >80%.[50] However, the concerns about sodium intake are frequently expressed. The literature is quite clear on this. The chloride salt of sodium is the issue, not the bicarbonate salt of sodium. This is a key point. We just need to do a better job of identifying them early on. Do not assume the patient is stage 1 or 2 if the creatinine indicated that. We need better, more reliable biomarkers (EXAMP: Cystatin-C) and should insist the insurance companies reimburse for it.

This approach worked amazingly well for my father because he reversed his CKD, by more than two stages! I calculated it incrementally based on where he was at each stage. He was nearing end-stage renal disease (stage 5) and he reverted back to stage 2, which was a virtual miracle at that time! I had never heard or seen of anything similar.

Niacin interested me when I came across a company that was working on a new chelator for phosphorus. I had already seen some literature on an extended-release niacin (ER-niacin) study showing a phosphorus-lowering effect and IR-Niacin having an antiproteinuric effect. Niacin was so effective that it moved the GFR up enough to reverse the baseline status by a full stage, even at very low doses. This seemed to be the plausible explanation for this net result.

Niacin (as well as no-flush niacinamide/nicotinamide) inhibits the sodium phosphate transporter. There are at least twenty peer-reviewed publications demonstrating this.[5-41,52-59] What was discovered was, if you want to control phosphorus, niacin is one the most effective methods and its efficacy is not affected by timing relative to meals. As little as 100 mg of niacin will effectively reduce the serum phosphorus.

Some studies refer to this niacin-mediated effect as the "phosphorous fix." The additional CKD benefits of niacin include the antiproteinuric, as well. If you compare a blood test vs. urine test, then the urine is probably a much more reliable indicator because when the basement membrane is damaged, filtration is impaired such that the basement membrane between the podocyte processes no longer conserves plasma proteins and the amount lost, 'leaked' is present in the urine. The appearance of albumin (protein) in the urine is a 'flag' that loss of serum protein due to impaired renal function. Often, this is one of the earliest markers. Blood biomarkers have some variables that could result in misclassification of CKD stages. Protein leaking from the kidneys, is a direct correlate to the podocyte/basement-membrane damage. This is the gold-standard measure of endothelial function. I always like to use at least one blood marker (ideally CystatinC) in addition to the urine test, to facilitate extrapolating, "pinpointing" the true stage at baseline and where they are at follow-up.

I believe niacin is probably one of the best treatment options for a variety of chronic conditions/pathologies. CKD is a complex disease state. At its 'core', it is a vascular disease, but ***if*** you "hit all the right buttons" it is clearly possible to 'drive' CKD backwards.

With stage-5-CKD, a.k.a. end-stage renal disease (ESRD), the scarcity of donor organs is a primary challenge. The reality is usually that dialysis will be required for the rest of the patient's life. That is a powerful motivator to the patient to consider niacin.

Ultimately my father's CKD, reversed from stage 4 to stage 2. When the sum of all the data, connecting-the-dots with all the biomarkers, he was close to end stage renal disease as he was scheduled to have a first encounter with a nephrologist. So, he was likely headed to dialysis, sooner vs. later.

The Current State of CKD Treatment and the Importance of Addressing Multimorbidity

In regard to prevention, many physicians choose not to believe there is any way to prevent or reverse CKD. Unfortunately, most patients end up on dialysis, or at the very least their CKD continues to get worse.

Too often, a less than adequate job of correctly identifying pre-diabetes is implemented, early on in the CKD disease state. It is vitally important to have a method of measuring the glucose post-prandial (PPG) level at 1h and 2h post-glucose challenge (OGTT). Currently, this is the gold standard test for assessing pre-diabetes. There are blood biomarkers that have a VERY high level of precision determining the 1-hr PPG: 1,5-AG and AHB (*Alpha-HydroxyButyrate*).

Measures of fasting insulin, fasting glucose, and HbA1c can miss an unacceptably large number of pre-diabetics. The OGTT test, will reliably capture a pre-diabetes diagnosis. HOMA-IR (HOMA-IR; homeostasis model assessment as an index of insulin resistance) is an effective method to calculate and evaluate insulin resistance using conventional reference lab biomarkers: insulin levels, fasting glucose levels, and A1C.[60,61] If you have

these three, you can then calculate the HOMA-IR. This enables accurate documentation and validates spending the modest expense to do the proper tests.

As much as 70% of adults over the age of 30 do not have normal postprandial glucose (PPG). It's that bad! They say it's only 30% or 40%, but that's likely based on poor statistics. In fact, during every year in the last several decades, the percentage of individuals over the age of 30 with obesity has risen. The antiquated Frederickson classification was based on cholesterol/triglyceride parameters, but we are presently in the 'particle age' of clinical lipidemia assessment. Like the Frederickson classification for lipid disorder sub-types (which was largely based on cholesterol measurements), current methods to assess the presence and severity of insulin-resistance (a.k.a. pre-diabetes) are essentially obsolete.

Another aspect to consider is multiple comorbidities. Modern medicine currently generally takes the approach of treating one condition at a time, but there are nearly always multiple disease symptoms present that are tightly associated and anything that can ultimately address this is going to result in the most effective therapies, ideally prior to the fulminant disease.

The Academy of Medical Sciences declared in 2018 that multimorbidity is the number one top priority in healthcare research.[62] Estimates for a cure of cancer reveal that this would only increase lifespan by a mere three years on average because the associated co-morbidities were not addressed.[63] Niacin, however, addresses so many common denominators for disparate diseases that the impact of niacin treatment for CKD/ESRD is likely to benefit many more indications, especially the number one killer, cardiovascular disease.

At the end of the day, it is the effect on all-cause mortality that matters the most for any treatment. After the termination of the Coronary Drug Project-CDP trial, it was determined that all-cause mortality was reduced by 11%, nine years after stopping niacin treatment (avg. dose 2.4 g/day).[64] This may be a feat unparalleled in proven clinical medicine. By contrast, statin all-cause mortality data has yielded mixed results.

Conclusion

In over 25 documented individual cases of CKD stages 2 through 4, after initiation of a combination-therapy of supplements based on GFR, including 500 mg TID IR-niacin, over a three-month period, it was possible to improve their disease by at least one stage.

In basic and clinical research the evidence in favor of niacin for CKD is strong. Clinical research proves that the niacin is exceptionally well-suited to treatment and prevention of CKD, multimorbidity, and ultimately all-cause mortality.

Sampathkumar explained the current CKD treatment with niacin situation best:

> Pharmaceutical industry driven large-scale studies are unlikely to be undertaken given the low-cost of niacin. David is up against the formidable Goliath of players promoting costly non-calcium containing phosphorus binders. It is time that international bodies like Kidney Disease, Improving Global Outcomes (KDIGO) take a call on usefulness of niacin as a low-cost, effective, and low pill burden agent for phosphorus reduction in CKD with multiple pleotropic benefits.[29]

Recommended Doses to Address Chronic Kidney Disease

- Low-dose immediate release-niacin, 100 mg - 500 mg, 1 to 3x/day. No-flush niacin or niacinamide will have equal efficacy on lowering phosphorus levels, but negligible cardio-vascular benefits compared with standard niacin.
- Sodium Bicarbonate (baking soda) 1.8 g/d (1/3 at lunch and 2/3 at dinner).
- Calcium carbonate antacid pills (400-1000 mg elemental calcium or 2-4 gms antacid tablets) with food to bind phosphorous in food.
- Low-Dose-Thyroid Supplementation (25-50 µg T4/Levothyroxine or ½ grain of Desiccated Thyroid).
- Methyl Folate (0.8 g to 2 mg L-MethylFolate).

Recommended Additional Monitoring

A full panel of metabolic parameters [baseline and 90-day f/u] can also determine 'collateral' benefit[s], especially related to cardiovascular health:

- Apo-B decreases
- Apo-A1 increases (INTERHEART Study)
- Lp(a) mass decreases
- Lp-PLA2 decreases
- MPO/myeloperoxidase| decreases
- AST/ALT/GGT hepatic parameters improved
- Symptomology/Signs-Symptoms: TIA; Chronic Angina; Claudication; Dyspnea upon Exertion.

The views of the authors, who are not physicians, are presented here for educational purposes. All readers are reminded to be sure to work with their own health care provider(s) before commencing this or any nutrition-based approach.

Orthomolecular Medicine News Service free subscription link http://orthomolecular.org/subscribe.html and also the OMNS archive link http://orthomolecular.org/resources/omns/index.shtml are included.

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References are available online at www.townsendletter.com.

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Klotho: The Super-Antioxidant You've Never Heard of

by Jenna Henderson, ND

Klotho is a renal protein antioxidant found in mammals that was first identified in 1997. When there was a defect in expression of the gene for Klotho, lab animals aged quickly and died prematurely. Overexpression of the Klotho gene resulted in lab animals living unexpectedly long lives. Destruction of the Klotho gene in mice resulted in accelerated aging and premature death.[1] In addition to the shortened lifespan, it was also observed that Klotho-deficient mice fail to grow and had changes in multiple organs of the body, ectopic calcification, arteriosclerosis, osteoporosis, and atrophy of the skin. Although Klotho is most highly expressed in the kidneys and brain, it affects multiple organs in the body. Klotho deficiency is associated with multiple diseases of aging, and therapies to increase Klotho levels provide a new strategy for addressing the problems of an aging population.[2]

This protein of longevity was named for one of the three Fates in Greek mythology. The first Fate, Klotho, spun the web of life for each person, while the second Fate decided on the length of life and the third Fate cut the web of life. The Klotho protein is most noted for its effect on lifespan and kidney health but has far reaching consequences, including cardiovascular health, bone health, and blood sugar regulation, as well as cognition.[2]

The description of Klotho in many ways sounds like jing in Traditional Chinese Medicine (TCM). In TCM, the kidneys store the jing, an inherited vitality involved in growth, aging, and reproduction. Most of the jing is inherited before conception; this is part of ancestral chi. But jing can also be nourished and strengthened during our lives. One of the botanicals in TCM that supports the jing is *Polygonum multiflorum* (Fo-ti or He Sho Wu). The anti-aging properties of this herb are part of TCM legend. When an old gray-haired man was down on his luck, he got lost in the forest and ate Fo-ti to survive. After the ordeal his hair turned black and he went on to father 10 children. We have now identified Fo-ti as one of the herbs that supports Klotho production.[3]

Klotho exists in two forms – membrane Klotho and secreted Klotho. Membrane Klotho works in conjunction with FGF-23 to regulate the calcium/phosphorus balance. Secreted Klotho is a soluble protein that regulates ion channels and transporters. It also inhibits oxidative stress and the insulin-like growth factor pathway.[1] Three types of Klotho have been identified – alpha, beta and gamma forms. Most research focuses on the alpha form, which is generically referred to as Klotho.[4]

Klotho-deficient mice are indistinguishable from their wild type and heterozygous littermates for the first three weeks of life. After three weeks they stop growing and gaining body weight until they die at eight to nine weeks of age. Although they display diseases of aging found in humans, the precise cause of death is unclear. Klotho-deficient mice also display hypogonadism in both sexes. This appears to be due to disruption of the pituitary or hypothalamus signaling. Function was restored with gonadotropin treatment. It was noted that ovaries transplanted from Klotho-deficient mice to wild type mice worked normally.[2]

Extensive ectopic calcification of various soft tissues is observed in Klotho-deficient mice. These changes resemble the vascular calcification associated with chronic kidney disease rather than typical atherosclerosis. Calcification was found in the gastric mucosa, trachea, renal tubules, renal arteries, and the aorta. It occurred in the media without intimal thickening or accumulation of foam cells. With chronic kidney disease, this problem is attributed to the handling of calcium/phosphate metabolism.[2]

Unsurprisingly Klotho-deficient mice have osteopenia with reduced bone formation and resorption similar to the osteomalacia found in kidney patients. This is most similar to senile osteoporosis in the elderly and is distinct from bone issues caused by a lack of estrogen. While estrogen-related bone loss causes increased bone resorption and an increased number of osteoclasts, Klotho deficiency causes a reduction in both bone formation and resorption.[2]

Skin atrophy characteristic of Klotho deficiency most closely resembles age-related changes. There is a reduced number of hair follicles and a reduced thickness of the dermal and epidermal layers. A lack of subcutaneous fat is also observed.[2]

Insomnia becomes increasingly problematic in the aging population. A study of sedentary middle-aged adults found a significant correlation between sleep quality and duration and Klotho levels.[5] As insomnia is a major problem among kidney patients, further research

may find an association with sleep and Klotho levels in that population as well. Another study showed a relationship between sleep apnea and low Klotho levels.[6]

Thyroid disorders increase with age. One study in an animal model showed that T3 treatment increased Klotho homologous genes.[7]

In TCM the kidneys relate to the ears, and hearing loss is often a part of the aging process. The Klotho gene is expressed in the inner ear, and Klotho-deficient mice have a significantly higher threshold for an auditory response than wild type mice. The exact role of Klotho on the ear is still being researched, but preliminary information suggests Klotho is involved in electrolyte homeostasis of endolymph in the cochlear duct.[2]

The loss of libido and sexual function, which comes with aging, may relate to loss of Klotho. Interestingly libido and sexual function are associated with the kidneys in TCM. In one study, higher Klotho plasma levels were strongly associated with sexual desire and function in sedentary middle-aged adults. This trend was seen in both males and females.[8]

Cognitive decline in aging affects over 50% of the population, and lower levels of Klotho may play an important role. Klotho in the brain is localized in the choroid plexus and hippocampal neurons.[9] Animals overexpressing Klotho perform better than controls on multiple tests of learning and memory.[10]

Klotho is necessary for oligodendrocyte maturation and myelin integrity. Klotho protects hippocampal neurons from amyloid and glutamate toxicity through its antioxidant properties.[9] As Alzheimer's disease is the most prevalent form of dementia, upregulating Klotho may help target this condition. Increased Klotho levels were shown to significantly reduce amyloid plaque, neuronal and synaptic loss, and cognitive deficits in a murine model.[11]

Not only is low Klotho associated with cognitive decline, a study of nursing home residents found that low Klotho was associated with increased psychological frailty and dependence. Also, more falls occurred in a six-month period in the group with the lowest Klotho levels.[12]

Lowering Klotho levels in the aging population may also play a role in sarcopenia. Under normal circumstances, fibroblast growth factor-19 (FGF-19) increases the size of human myotubuals in vitro. In a murine model, Klotho-deficient mice were unresponsive to the muscle building effects of FGF-19.[13] More evidence of low Klotho affecting the muscles was found in a study of 804 adults, which correlated plasma Klotho levels with grip strength.[14]

Understanding Klotho can give practitioners a deeper insight into how many therapeutics address aging and ailments of the kidney.

Serum Klotho levels are inversely correlated to metabolic syndrome. Lower Klotho levels were also associated with increased abdominal obesity and high triglycerides in adults.[15] A study in a murine model showed that administration of Klotho improved body composition and energy expenditure and reduced lipid content of both the liver and adipose tissue.[16]

Klotho has many other functions in addition to its antioxidant properties, which include acting as a co-factor for fibroblast growth factor 23 (FGF-23). FGF-23 is a bone-derived growth factor that increases urinary excretion of phosphorus.[17] Klotho serves as a non-enzymatic molecular scaffold for FGF-23 signaling.[18] It also suppresses production of calcitriol and active vitamin D metabolites, which also helps lower serum phosphorus, as calcitriol increases phosphorus absorption from the GI tract. It has also been suggested that FGF-23 directly suppresses parathyroid hormone secretion, which also helps control serum phosphorus levels.[19] Issues of phosphorus control are well-known to kidney patients, but excessive phosphorus may be more of an issue with aging than previously understood.[20]

In chronic kidney disease, FGF-23 increases dramatically while Klotho levels decline.[21] Increasing FGF-23 can serve as a biomarker for chronic kidney disease, and high levels of FGF-23 are associated with increased mortality in kidney patients.[22] Dialysis patients at end-stage renal disease typically have very high levels of FGF-23.[23] Tests for serum FGF-23 can be found through many laboratories, although it is not commonly tested for by nephrologists. Tests for Klotho levels are not, however, easily available.

FGF-23 secretion by osteocytes increases in response to dietary phosphorus intake and increases in 1,25-dihydroxy vitamin D (1,25D) levels.[24] Kidney patients are usually not told to limit phosphorus intake until they are in an advanced stage of kidney disease and phosphorus levels on blood tests are rising. However, it may be beneficial to limit unnecessary sources of phosphorus intake even in early-stage kidney disease to help suppress rising FGF-23 levels. It may also be useful to have enough vitamin D to avoid deficiency, but not overload with vitamin D supplementation.

Keeping FGF-23 low and Klotho high may be useful for a many types of kidney disease.

Diabetic nephropathy: Over-expression of Klotho increased the antioxidant response of Nuclear factor-erythroid 2 – related factor 2 (Nrf2) as well as downstream targets of SOD2 and NQO1 in podocytes. Klotho overexpression inhibited high-glucose-induced oxidative stress and apoptosis in podocytes. Increased Klotho also improved kidney filtration and reduced sclerosis of the kidney.[25]

Although low Klotho levels are typically associated with aging, children with type I diabetes were found to have low levels of Klotho.[26]

Hypertension: Low levels of Klotho may play a role in essential hypertension. Klotho suppresses the renin-angiotensin system. Low Klotho and high FGF-23 levels were found to be especially detrimental.[27] A lack of Klotho was also associated with increased sensitivity to salt loading.[28] Increased ➤

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hypertension due to sensitivity to salt is more prevalent with age. Klotho supplementation improved blood pressure by reducing high salt-induced reduced renal blood flow.[29]

Polycystic Kidney Disease: PKD like other kidney diseases, shows the same trend of increased FGF-23 levels. Unlike other kidney diseases, autosomal dominant PKD shows an increase in Klotho levels. FGF-23 and soluble α-Klotho levels were both found to be negatively correlated with estimated glomerular filtration rate. This is a significant aberration from the general trend with kidney health. It is unclear if this is due to increased Klotho production or reduced Klotho clearance. (It is interesting to note that unlike most kidney disease, erythropoietin levels can be high with PKD, due to increased production in the cysts.)[30]

Lupus: Serum levels of Klotho were not found to be different from those in the general population.[31] However, the compound microRNA-199a, which is believed to be part of the pathogenesis of lupus, was found to suppress the renal protective effect of Klotho.[32]

IgA Nephropathy: In a murine model of IgA nephropathy, treatment with Klotho inhibited inflammatory compounds and proteinuria. Klotho also reduced blood pressure and attenuated mesangial expansion characteristic of IgA damage.[33]

Focal Segmental Glomerulosclerosis (FSGS): This autoimmune inflammatory condition of the kidney has an especially poor prognosis, causing parenchymal kidney tissue to be permanently scarred. In a murine model of FSGS, there was an expected increase in FGF-23, PTH, and serum phosphorus. Treatment with a phosphorus binder helped ameliorate these markers but also caused an increase in Klotho. The renoprotective effect helped slow disease progression, most notably on tubular epithelial cell injury.[34]

Renal Cell Carcinoma: Klotho is expressed in the kidney tubular cells, where clear cell renal carcinoma (ccRCC) originates. Klotho inhibits cell proliferation, tumor growth, and migration with ccRCC. Higher levels of Klotho are a favorable prognostic indicator.[35]

Dialysis: As kidneys are the main source of Klotho, those with end stage renal disease have reduced Klotho levels. Low Klotho in maintenance hemodialysis patients is associated with uremic cardiomyopathy.[36]

It is interesting to note that Klotho attenuated the effect of the uremic toxin indoxyl sulfate (IS). As an oxidant, IS causes endothelial damage and inhibits production of nitric oxide. Klotho was demonstrated to work as an antioxidant against IS-induced endothelial dysfunction and improved the IS-induced reducing of nitric oxide.[37]

Kidney Transplant: Higher expression of Klotho in donor kidneys is associated with better transplant outcomes. Higher Klotho levels from the donor kidney gave the recipient a better eGFR after transplantation. This trend was seen to observed to continue one year after transplantation.[38]

Another study found high FGF-23 and low Klotho was a significant predictor of peripheral arterial stiffness in renal transplant patients.[39]

Cardiorenal Syndrome: Long-term the greatest cause of mortality in kidney patients is secondary heart disease. Cardiorenal syndrome is a complex disorder where acute or chronic kidney disease induces cardiovascular disease and vice versa. Although Klotho is not expressed in cardiac tissue, the anti-aging properties of Klotho have an indirect cardioprotective effect.[40]

Raising Klotho levels is a new frontier in research. There are companies seeking to develop an easily injectable Klotho treatment.[41] Another company is looking to develop therapy with Klotho and mesenchymal stem cells together.[42] Fortunately, there is evidence that diet and herbal supplementation can raise Klotho levels. Some supplements can help support function when Klotho levels are low. Many of these herbs are already known for kidney support and/or anti-aging properties.

Diet

Dehydration strongly downregulates Klotho, giving kidney patients another reason for adequate hydration.[43]

Alcohol also has a negative impact on Klotho levels. Further information may bring more clarity to the effect of diet on Klotho levels.[44]

One study found that an anti-inflammatory diet correlated to higher Klotho levels in young adults.[45] Another study found that a higher inflammatory index of the diet corresponded to better Klotho levels in middle-aged adults.[46]

Fish oil, although it had other benefits, did not improve Klotho levels.[47] However, EPA helped prevent arterial calcification in Klotho-deficient mice.[48]

Interestingly, the probiotic drink Dahi, made with buffalo milk and several strains of acidophilus and bifido bacteria improved many markers of aging, including Klotho.[49]

Dr. Jenna Henderson's practice, Holistic Kidney, is dedicated to the unique needs of renal patients. A kidney patient herself since 1993, she has experienced all stages of kidney disease firsthand. She is a graduate of the University of Bridgeport. Dr. Henderson has had several articles on kidney health published in *Natural Medicine Journal*, *NDNR* and the *Townsend Letter*. She has lectured extensively across the US to naturopathic doctors, kidney patients, and kidney professionals.

Dr. Henderson seeks to bridge the gap between mainstream nephrology and natural medicine. In her practice she helps patients sort through often conflicting information to understand what is appropriate for their individual needs and stage of kidney function. She is often able to help patients delay the need for dialysis. For those already in kidney failure, she helps patients find optimal wellness with dialysis or a transplant.

Supplements

Cordyceps reduces damage of angiotensin II by increasing Klotho and reducing cellular apoptosis.[50]

Curcumin attenuates Cyclosporine-induced renal fibrosis by inhibiting hypermethylation of the Klotho promoter.[51]

Fo-ti (Polygonaturm multiflorum): Reported to prolong lifespan in animal models, this herb increased neuronal levels of Klotho.[3]

GABA (gamma-aminobuutyric acid): In vitro GABA stimulated production and secretion of Klotho by human islet cells. Klotho protected and stimulated beta cells of the pancreas.[52]

Gotu Kola (Centella asiatica): In a cell culture, this herb stopped declining Klotho levels. It also improved telomere length.[53]

Green tea (Camilla sinensis): ECGC's ability to induce keratinocyte differentiation was shown to be due to upregulation of Klotho.[54]

Hesperidin: In a murine model, hesperidin significantly increased Klotho in the serum, kidney and liver.[55]

Hibiscus: Under conditions of diet-induced obesity, hibiscus increased the number of FGFR1 and beta-klotho receptors in adipose tissue.[56]

Korean Red Ginseng increased Klotho expression in a murine model of induced kidney injury.[57]

L-theanine improved memory in Klotho-depleted mice.[58]

Magnesium: High magnesium levels prevented vascular calcification of Klotho knock-out mice.[59] Magnesium deficiency increases FGF-23.[60]

Melatonin: When kidney damage was induced by cisplatin, melatonin ameliorated the damage through both its antioxidant properties and upregulating Klotho.[61]

N-acetyl cysteine (NAC) preserved Klotho expression under conditions of induced nephropathy in a murine model.[62]

Resveratrol increased Klotho expression in the kidney and the brain in a murine model of d-galactose-induced aging.[63]

Salvia miltiorrhiza: An injection of Tanshinone IIA, an extract from *Salvia miltiorrhiza*, was given to dialysis patients. Compared to controls, the patients that received the injection, had higher Klotho levels and fewer cardiovascular events.[64]

Zinc: Klotho-deficient mice with a subtotal nephrectomy and cholecalciferol-overload showed phosphate-induced calcification of vascular tissue. This is similar to the conditions of renal failure. Zinc supplementation reversed this vascular calcification.[65]

As more research into Klotho emerges, there hopefully will be more options for kidney patients and the elderly. Increased levels of this protein may help many conditions with a poor prognosis. Understanding Klotho can give practitioners a deeper insight into how many therapeutics address aging and ailments of the kidney. ◆

References are available online at www.townsendletter.com.

Lifestyle, Inflammation, and Food Pain

by Hal S. Blatman, MD

Integrative practitioners have long recognized a strong relationship between lifestyle and health. And just about everyone has heard of the relationship between cigarette smoking and lung disease. But what about pain? We hear things like: "you are what you eat" and "stay away from the white stuff," but where does it really matter, how much does it matter, and why does it happen?

Two major roadblocks to a deeper understanding of food pain include plausible deniability and unbelievability. Plausible deniability occurs when a generally accepted cause of the issue helps you avoid the real answer. When you awaken with a stiff neck, plausible deniability is the general acceptance that:

- You slept wrong
- The window was open
- Used the wrong pillow
- Etc.

Unbelievability is that unless you have Ehrler's Danlos, you can't really sleep that wrong, and the issue did not come from the window or the pillow. The stiff neck came from some combination of wheat, cow dairy, sugar…and most likely a pizza. That the feeling of a pinched nerve was really set off by food is very hard for most people to believe.

When it comes to pain there are many who realize that lifestyle plays a part, but the significance of food is generally underappreciated. Integrative practitioners have long realized that better nutrition in general will provide for better healing. On the other hand, few really understand and communicate to their patients how their food choices complicate healing from chronic pain. And of those who do, there are even fewer who not only understand how absolute the issues are, but they are further willing and able to communicate the details with their patients without fear of risking the relationship.

It is one thing to suggest that avoiding white processed foods may help a person feel better. It is another to advise a chronic low back pain patient that a teaspoon of a mashed potato can make them miserable for four days. Partial credit can be helpful, but absolute adherence can reduce chronic pain in most patients by more than 40% within six weeks.

And then there is *rain pain*. This is the term we use for the increased pain that comes with barometric change. Indeed, rain pain means you have eaten something inflammatory to your biology sometime *in the past six weeks.* Get this right and a chronic pain patient will be surprised by the rain when looking out the window instead of learning about it the day before.

People often refer to a painful area as inflamed. Instead of reporting a painful elbow and forearm the language might be that "my elbow and forearm are inflamed." We are taught by advertising that taking OTC inflammation-reducing medications will help make us feel better and reduce the pain of activity and injury. Russ Jaffe of Perque Integrative Health stresses that our biology is designed to have inflammation for repair and defense. If we have inflammatory pain, then we have a repair deficit, and our body has switched to a defensive mode and made us hurt. A repair deficit occurs when injury to the body is too great for the available healing resources. If on the other hand we have the resources to make the repair, our body will often heal the injury under our radar, and we won't even know we got hurt. The soreness we expect to feel on to three days after a hard workout usually represents a repair deficit and food-based inflammation resultant from the workout-related injuries. If on the other hand our body-wide inflammation is low and resources are high, the soreness will be much less if at all – as the injuries repair under one's radar.

Most people think little about *why* do we eat? Hunger is about when, and taste is about what. The primary reasons why we eat include:

- Providing fuel to burn for energy,
- Providing raw materials for building new and spare parts.

As a person is trying to heal, low octane fuel will provide for less energy and quicker fatigue. One of the lowest octane fuels is empty calorie sugar. Low quality raw materials will create parts that don't hold up. A low-quality material might be partially hydrogenated fat for making cell membranes.

In other articles I have described a new paradigm for understanding and treating pain. Anatomy studies have suggested that most pain is reported from free nerve endings sensing shear forces and pressure within the cords of fascia that go through almost all tissue and hold us together. Anything that changes these shear and pressure forces will have an effect on perception, kinesthesia, and pain.

Lifestyle and food choices bring two major effects into the systems that affect pain. On one hand they can impact the shear and pressure forces within the fascia. This does not necessarily cause

new injury within the tissue, but it can make areas of injury that are under the radar come up front and center to awareness. Another effect is to change how effective are the mu receptor effects from opiates. Some commonly ingested items have more affinity to pain-relieving receptors than do the opiates.

How food brings old injuries to new awareness is about the dynamic interaction of fascia with our immune system. The same immune system that sets off pain from repetitive strain injury also reacts to substances identified as inflammatory food. And the pain reaction to inflammatory food is body wide…everywhere…and people say they feel like they have been hit by a truck.

The foods we have found to be universally inflammatory to our species include the following:

- Wheat
- Sugar
- Potato (white, red, blue, purple)
- Fruit juice and some fruits
- Fake fat (hydrogenated)
- Artificial sweeteners
- Dairy from cow

Some real-life repeatable examples of how much pain can come from food have astounded me over many years. One does not have to test positive for celiac or even have gut symptoms and a tiny bit of gluten in soy sauce can bring crippling lower back pain for two weeks and another two weeks for it to go away. A teaspoon of mashed potato can bring on lower back pain for four days. A bite of banana or watermelon can bring on pain for two days. If my rheumatoid arthritis patient has a teaspoon of sugar, they will hurt for four weeks. Aspartame from soda can cause FMS pain for six to eight weeks. And then there is dairy from cow, arguably among the most inflammatory substances in a common diet. Your upper shoulders are tight because of a lifetime of injuries to fascia from carrying book bags and holding up the world. The reason the fascia strings and cords in the upper traps are glued together and tender to squeeze is likely an immune/fascia reaction to dairy from cow. A little bit of butter and the shoulders, upper back, and neck will tighten for three to four weeks.

Potatoes have been considered healthier food. Unfortunately, there are glycoalkaloids in potato that increase intestinal permeability, and frying concentrates them and makes them even more dangerous.[1-3]

Aspartame elevates serum methanol and increases oxidative stress.[4,5] Neither is good for a person in pain.

Pain does not fall down from the sky. If you wake up in pain in the morning that you did not have when you went to ➤

Do Not Eat List

Do Not: Bread Flour: Wheat, Barley, and Rye
Common in breads, pastas, baked goods, and fillers in many canned and processed foods.

Alternatives: Gluten-free flours that have little to no added starches typically made from almonds, coconut, or rice and quinoa.

Do Not: Sugar
Fructose, sucrose, starch, potato starch, tapioca starch, tapioca four, cornstarch, corn syrup, and cane juice. NO ARTIFICIAL SWEETENERS like aspartame, Nutrasweet, Equal and Splenda.

Alternatives: Stevia

Do Not: Drinks
Fruit juice, carbonated beverages like Pepsi, Sprite, and Mt. Dew, Gatorade, Powerade, and your regular vitamin water.

Alternative: Water with lemon/lime, club soda, or Vitamin Water Zero

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Do Not: Fruits
Banana, watermelon, dried fruits (raisins, craisins, etc.), canned fruits and fruitcups. Dried fruits, bananas, and watermelon can increase pain due to higher starch/carbohydrates content. Fruit cups are stored in syrup and raise blood glucose and inflammation.

Alternatives: Berries, apples, peaches, pomegranates, pears, etc.

Do Not: Fats
Vegetable oils, margarine, Crisco, deep-fried foods, any partially or fully hydrogenated oils. Peanut oil may also want to be avoided as it increases plaques in the arteries. Peanut oil, however, may not directly increase inflammatory pain.

Alternatives: Coconut oil, avocado oil, grapeseed oil, and olive oil

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Do Not: White Potato
Red skin potato, anything with a white center except that Japanese sweet potato. Potatoes are full of starch and have inflammatory properties.

Alternatives: Sweet potatoes and Japanese sweet potatoes, cauliflower for masked potato alternative.

Do Not: Dairy
Cow's milk and cheese are known to increase cardiovascular disease and vessel inflammation in addition to chronic inflammatory pain.

Alternatives: Almond milk, coconut milk, and/or hemp milk. Goat's milk and cheese may be better tolerated.

Do Not: Alcohol
Many alcohols are high in sugar and many contain wheat. Titos is gluten-free; Grey Goose is not.

Alternatives: Organic wine, Titos or Svedka vodka, gin, gluten-free beers and ciders.

This list is NOT a one size fits all: please take into account any foods or allergens you may not tolerate in addition to the foods or ingredients on the list.

For meal ideas look for gluten-free, paleo, and gluten-free vegan recipes on websites.

Food Pain

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bed…and you do not remember falling and hurting yourself during the night, then the increased pain most likely came from last night's food. It wasn't the pillow or the window…it was cheese and bread in the pizza. And the stiff neck is not a pinched nerve, and the pain from food goes away in three weeks. If you bend over at 10:30 am and "throw your back out," it was likely also last night's food. If you go to bed in pain, you did not have in the morning, the cause was most likely something in breakfast or lunch.

I'm in total agreement: the absoluteness and repeatability are unbelievable. And if you take out dairy and do not see improvement, you likely need to take out the rest. AND then YOU might have some dietary issue peculiar to you that is not on this more universal list. Food elimination strategy and lab testing might be helpful next steps.

Another interesting issue is the affinity of mu (opiate) receptors to sugar. Sugar has been shown to augment the nociceptive properties of morphine in the rat.[6] Amazingly consistent, even in the most drug-tolerant patients, is that their medication works a lot better if they do not eat anything that looks or acts like sugar in their body for at least two weeks.

Trigger point injections, acupuncture, and hands on body work will often reduce pain because these techniques can release some of the pain-causing kinks in the myofascia (muscle/fascia as one). If the muscles tighten right back up, glue right back together, and pain returns in on to two days after treatment…it is almost always the food.

There are many lifestyle issues that contribute to an increased perception of pain. These include oxidative stress and other things that decrease a body's resilience. We might be quick to point out how bad is smoking, but very few practitioners emphasize the relationship of pain and food. I have a trigeminal neuralgia patient who admits being 80% improved from self-care of her fascia and an absolute avoidance of food that is inflammatory to her body.

I believe that there is no one diet that is best for everybody. I do, however, see a "do not eat" list that applies to our entire species. Your body's job is to make you feel good 24 hours/day. If it is not doing that, it is sending you to your room for doing something it does not want you to do. When your patients report exacerbation of their pain, carefully question their food choices in the 12-24 hours before the noticed onset. Then observe the duration of the increased pain. It is rare that careful examination of ingredients fails to reveal a food cause to an exacerbation of pain.

Hal S Blatman, MD, is founder and medical director of the Blatman Health and Wellness Center, based in Cincinnati, Ohio, and also in NYC and Seattle where he is affiliate faculty at Bastyr University. When we look through the lens of integrative/functional/holistic medicine many feel that this new world is much different than the medicine we were taught. Understanding the relationship between food and pain opens up an understanding of injury and healing from pain that sets a new standard for care. Dr. Blatman leads a team that specializes in restoring our biology from the many dimensions of injury, utilizing 30 years of experience in medicine.

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LDN: A Game Changer for Many Patients

by Pamela W. Smith, MD, MPH, MS

I have been blessed to be a physician for 44 years. It is rare in my career that there is a drug that comes out that is a game changer for many patients. Compounded low-dose naltrexone (LDN) is one of those medications.

Naltrexone has traditionally been used for drug overdose. Naltrexone is a reversible competitive antagonist at μ-opioid and κ-opioid receptors, which when used at standard doses of 50 to 150 mg was initially intended for use in opioid and alcohol use disorders.

In recent years, there have been novel and significant findings on the off-label usage of naltrexone in much lower dosage forms for many purposes. The following are some examples.[1]

- Immune modulator in autoimmune diseases
- Anti-inflammatory
- Chronic pain control
- Weight loss
- Reduction of cytokine storm

Some of the proposed mechanisms of action include blockade of the opioid growth factor receptor (OGFR) axis, which normally stimulates B and T cell proliferation and stimulation of beta-endorphin and enkephalin release, which has anti-inflammatory effects on T and B cells.[2] In addition, a study examined how LDN also helped to normalize immune system function.[3] Moreover, low-dose naltrexone has shown promise to reduce symptoms related to chronic pain conditions such as fibromyalgia, inflammatory bowel conditions, and multiple sclerosis. The mechanism of action appears to be modulation of neuro-inflammation, specifically, the modulation of the glial cells and the release of inflammatory chemicals in the central nervous system.[4] Consequently, LDN has also been shown to be very effective for pain control.[5]

Low-dose naltrexone has many references in the medical literature concerning its use in different diseases. This exposé will explore the use of LDN in a multitude of medical disorders.

Low-dose naltrexone refers to daily dosages of naltrexone that are approximately one-tenth of the typical opioid addiction treatment dosage.

Autoimmune Diseases That Are Not Dermatological Disorders

Consider using LDN for every patient with an autoimmune disease. For example, LDN has been reported to reduce not only self-reported pain in Crohn's but also lower objective markers of inflammation and disease severity. The response rate of LDN in Crohn's disease was over 80 % of the participants exhibiting significant improvement in several studies.[6-8] In another study, low-dose naltrexone induced clinical improvement in 74.5%, and remission in 25.5% of patients with inflammatory bowel disease. In addition, LDN directly improved epithelial barrier function by improving wound healing and reducing mucosal endoplasmic reticulum stress levels in yet another trial. The authors concluded that low-dose naltrexone treatment was effective and safe and could be considered for the treatment of refractory IBD patients.[9]

Low-dose naltrexone has also shown some promise in improving disease severity in multiple sclerosis (MS). LDN significantly improved mental health quality of life indices.[10] Moreover, a 17-week randomized, double-blind, placebo-controlled, parallel-group, crossover-design clinical trial was conducted at two universities. A total of 96 adult patients ages 15 to 65 years with relapsing-remitting or secondary progressive clinically definite MS with disease duration longer than six months enrolled into a study. The study clearly illustrates that LDN is a relatively safe therapeutic option.[11] Likewise, a trial involving MS patients revealed that the use of LDN resulted in inhibited cell proliferation.[12]

Rheumatoid arthritis is an additional autoimmune disease that LDN works effectively for. In a trial, in persistent LDN users, there was a 13% relative reduction in daily doses of all medicines and a 23% reduction of analgesics. Specifically, persistent LDN users had significantly reduced daily use of NSAID and opioids, and a lower proportion of users of DMARDs, TNF-alpha antagonists, and opioids. The results support the hypothesis that persistent use of LDN reduced the need for medication used in the treatment of rheumatic and seropositive arthritis.[13]

The discovery of the widely expressed transient receptor potential melastatin 3 (TRPM3) as a nociceptor channel substantially targeted by certain opioid receptors, and its implication

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in calcium (Ca^{2+})-dependent natural killer (NK) cell immune functions has raised the possibility that TRPM3 may be pharmacologically targeted to treat characteristic symptoms of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). The authors of a study reported that ME/CFS patients taking LDN have restored TRPM3-like ionic currents in NK cells. These data support the hypothesis that LDN may have potential as a treatment for ME/CFS by characterizing the underlying regulatory mechanisms of LDN treatment involving TRPM3 and opioid receptors in NK cells.[14]

Dermatological Disorders: Both Autoimmune and Non-Autoimmune Related

Dermatology is encountering increasing rates of autoimmune diseases manifesting in primary skin conditions that are difficult to treat without a risk of immunosuppression.

Hailey-Hailey disease, also called benign familial pemphigus, is a late-onset blistering disorder that affects the flexures. There are typically painful erosions and cracks in affected areas. Lesions generally begin between 20 and 40 years of age. Maceration and superinfections are frequent. The lesions are typically distributed symmetrically within intertriginous regions such as the retroauricular folds, lateral aspects of the neck, axillae, umbilicus, inguinal, and perianal regions. The disease is characterized by a chronic relapsing course with spontaneous remissions and multiple recurrences. Severe disease can be very frustrating and have a major psychological and social impact. Low-dose naltrexone has been shown to be an effective therapy.[15]

Lichen planopilaris is an inflammatory, primary cicatricial alopecia with several different patterns of hair loss. It is considered a follicular variant of lichen planus. Findings suggest that low-dose naltrexone is safe and effective in the treatment of Hailey-Hailey disease and lichen planopilaris. Furthermore, LDN successfully treated the pruritus associated with this and other dermatological disorders.[16,17]

Likewise, LDN has been shown to improve dermatologic conditions such as systemic sclerosis.[18]

In addition, a study revealed that the PI3K/AKT/mTOR pathway was significantly inhibited by 1% Naltrexone HCl in XemaTop™, suggesting protein synthesis was affected. The production of IL-6 was inhibited by 70% in drug-treated tissues. The results suggest that this compounded drug is efficacious in down-regulating molecular markers associated with the pathogenesis of psoriasis and provides a basis for a clinical evaluation of 1% Naltrexone HCl in XemaTop™ in psoriasis patients.[19] Moreover, a patient with a history of psoriasis was treated with 4.5 mg of LDN during a flare-up. She showed significant improvement in her flare-up and psoriasis remission after only three months of 4.5 mg of LDN nightly.[20] In another case report, a 60-year-old white female was successfully treated with LDN for her moderate plaque psoriasis over a six-month period.[21]

Guttate psoriasis is a less common form of psoriasis. It manifests with numerous small, teardrop shaped, scaly plaques on the trunk and extremities. The etiology includes both environmental and genetic factors. It commonly arises three to four weeks following a beta hemolytic streptococcal infection. It is more common in children and adolescents than adults.[22] LDN has been shown to be beneficial in a case report: 80% improvement was seen in two months.[23]

Atopic dermatitis is a pruritic, hereditary skin disorder and is the most common form of eczema. The life-time prevalence is 10% to 20% with many cases starting as a baby. Twenty percent to 40% of people continue to have atopic dermatitis as adults.[24] A double-blind, placebo-controlled study studied 38 patients with eczema complaining of pruritus. The study found that LDN was more effective than placebo in the treatment of pruritus in patients with eczema.[25]

As you have seen, LDN likewise works wonderfully topically for itching. The objective of another trial was to correlate the clinical efficacy of topically applied naltrexone in different pruritic skin disorders to a change of epidermal μ-opiate receptor (MOR) expression. The findings supported by the biopsy showed regulation of MOR expression in the epidermis after treatment with topical naltrexone.[26]

Cancer

Low-dose naltrexone has been shown to be a promising complementary medication for patients with a broad range of medical disorders as already discussed. Although not a proven cure, evidence from clinical trials supports LDN as being a valuable adjunct for disorders in which the immune system plays a centralized role. One of these diseases processes is cancer. Clinical trials have proposed a unique mechanism(s) allowing LDN to affect tumors, including non-small cell lung cancer, at the cellular level by augmenting the immune system.[27,28]

Moreover, it has been reported that at lower doses naltrexone is able to reduce tumor growth by interfering with cell signaling. Scientists evaluated the gene expression profile of a cancer cell line after treatment with low-dose naltrexone and assessed the effect that adapting treatment schedules with LDN may have on enhancing efficacy. LDN had a selective impact on genes involved with cell cycle regulation and immune modulation. Similarly, the pro-apoptotic genes BAD and BIK1 were increased only after LDN use. Continuous treatment with LDN had little effect on growth in different cell lines; however, altering the treatment schedule to include a phase of culture in the absence of drug following an initial round of LDN treatment, resulted in enhanced cell killing. Furthermore, cells pre-treated with LDN were more sensitive to the cytotoxic effects of a number of common chemotherapy agents. This data supports further the idea that LDN possesses anticancer activity, which can be improved by modifying the treatment schedule.[29]

Irritable Bowel Syndrome (IBS)

Forty-two IBS patients participated in an open-label study. Global assessment

improved in 76% of the patients that used LDN. There were no significant adverse reactions.[30]

Pain Control

Low-dose naltrexone has been used off-label for treatment of pain and inflammation in multiple sclerosis, Crohn's disease, fibromyalgia, and other diseases.[31] At the low dosage level, naltrexone exhibits paradoxical properties, including analgesia and anti-inflammatory actions, which have not been reported at larger dosages.[32-35]

The mechanisms by which LDN might relieve pain are not all known. Among the several postulated explanations are that by blocking opioid receptors, LDN provokes a compensatory elevation of endogenous opioids.[36,37] In addition, LDN attenuates inflammatory responses by blocking receptors on immune cells.[38] It also reduces pro-inflammatory cytokines and superoxides.[39-41] These effects appear to be unique at low dosage, compared to FDA-approved dosage for alcohol and opioid dependence.[42] When used in doses of 1 to 5 mg, LDN acts as a glial modulator with a neuroprotective effect via inhibition of microglial activation. It also binds to toll-like receptor 4 and acts as an antagonist, therefore inhibiting the downstream cellular signaling pathways that ultimately lead to pro-inflammatory cytokines, therefore reducing inflammatory response. In addition, LDN has been found to be neuroprotective by modulating mitochondrial apoptosis.[43]

Low-dose naltrexone has been used in many disease processes for pain control.

- One study showed that LDN was an effective therapy for diabetic neuropathy.[44]
- Another study suggests that the novel TLR4 antagonists naloxone and naltrexone can each fully reverse established neuropathic pain upon multi-day administration.[45]
- LDN has been shown to be an effective treatment for fibromyalgia.[46] LDN reduced fibromyalgia pain significantly greater than placebo in six out of the 10 women. While the pilot study was encouraging, it had limitations such as a single-blind design. To help validate the findings, a second study in 30 women with fibromyalgia was conducted. In that double-blind, crossover, counterbalanced study, 57% of the participants were observed to exhibit a significant (1/3) reduction of pain during LDN. At the end of the LDN treatment, half of the participants reported feeling "much improved" or "very much improved" from LDN.[47] Moreover, in a 10-week, single-blind, crossover pilot trial the authors tested the immune effects of eight weeks of oral administration of low-dose naltrexone (LDN). They found that LDN was associated with reduced plasma concentrations of interleukin (IL)-1β, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p40, IL-12p70, IL-15, IL-17A, IL-27, interferon (IFN)-α, transforming growth factor (TGF)-α, TGF-β, tumor necrosis factor (TNF)-α, and granulocyte-colony stimulating factor (G-CSF). They also found a 15% reduction of fibromyalgia-associated pain and an 18% reduction in overall symptoms.[48]
- In a case report, the patient was a 35-year-old male who had experienced nonspecific left-side chronic low back pain for two years and many therapies had been tried. LDN successfully improved his refractory chronic low back pain.[49]
- Complex regional pain syndrome (CRPS) is a neuropathic pain syndrome, which involves glial activation and central sensitization in the central nervous system. The authors describe positive outcomes of two CRPS patients, after they were treated with low-dose naltrexone in combination with other CRPS therapies. Prominent CRPS symptoms remitted in these two patients, including dystonic spasms and fixed dystonia (respectively), following treatment with low-dose naltrexone. These patients had previously failed conventional therapies.[50]

Psychiatric Disorders

Given the proposed dopaminergic mechanism of LDN, researchers examined its efficacy as augmentation for depressive breakthrough on pro-dopaminergic antidepressant regimens. LDN was shown to be beneficial for breakthrough symptoms of major depressive disorders that are already on antidepressants.[51]

Moreover, since LDN can upregulate endogenous opioid activity, it may also have a role in promoting stress resilience, exercise, social bonding, and emotional well-being, as well as amelioration of psychiatric problems such as autism and depression. It is proposed that LDN can be used effectively as a buffer for a large variety of bodily and mental ailments through its ability to beneficially modulate both the immune system and the brain neurochemistry that regulate positive affect.[52]

LDN

Low-dose naltrexone refers to daily dosages of naltrexone that are approximately one-tenth of the typical opioid addiction treatment dosage. In most published research, the daily dosage is 4.5 mg with the dose ramped up to this level over a three-week time frame – although the dosage can vary a few milligrams below or above that common value.[53-55] Consequently, there are now many dosage forms used for low-dose naltrexone, including ultralow-dose naltrexone. The closely related concept of ultralow-dose naltrexone involves the use of microgram, nanogram, and picogram dosages of naltrexone co-administered with opioid analgesics.[56]

There are a few possible short-term side effects that may occur with the use of LDN: insomnia, vivid dreams, fatigue, loss of appetite, nausea, hair thinning, mood swings, and mild disorientation. They are usually dose dependent. Consequently, lowering the dose usually resolves the short-term symptoms. Potential long-term side effects include the following: possible liver and kidney toxicity, possible tolerance to the beneficial effects (rebound effect), and other unknown sequelae. Low-dose naltrexone is contraindicated in individuals with acute hepatitis, liver failure, and recent or current opioid use

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or alcohol abuse. Although, as previously mentioned, ultra-low-dose naltrexone is now being used judiciously if the patient is on a mild narcotic in limited cases.

Clinical Applications

LDN has been used by practitioners world-wide for many disorders.[57]

Cardiac Disorders
- Autoimmune cardiomyopathy
- Autoimmune myocarditis
- Autoimmune thrombocytopenic purpura
- Congenital heart block
- Coxsackie myocarditis
- Dressler's syndrome (post-myocardial infarction syndrome)
- Giant cell myocarditis
- Kawasaki disease
- Polyarteritis nodosa
- Postpericardiotomy syndrome
- Subacute bacterial endocarditis (SBE)
- Vasculitis

Chronic Pain
- Complex regional pain syndrome/RSD
- Diabetic neuropathy
- Migraines
- Peripheral neuropathy
- Temporomandibular joint disorder

Dermatological Disorders
- Alopecia areata
- Alopecia universalis
- Amyopathic dermatomyositis
- Anti-synthetase syndrome
- Atopic allergy
- Atopic dermatitis
- Autoimmune progesterone dermatitis
- Autoimmune urticaria
- Bechet's syndrome
- Cicatricial pemphigoid
- Cutaneous leukocytoclastic angiitis
- Darier disease
- Dego's disease (thrombotic vasculopathy)
- Dercum's disease
- Dermatitis herpetiformis
- Dermatomyositis
- Diffuse cutaneous systemic sclerosis
- Discoid lupus erythematosus
- Erythrodermic psoriasis
- Essential mixed cryoglobulinemia
- Familial cold autoinflammatory syndrome (FCAS)
- Frontal fibrosing alopecia (FFA)
- Hailey-Hailey disease
- Herpes gestationis/pemphigoid gestationis (PG)
- Hidradenitis suppurativa (HS) (acne inversa)
- Lichen planus
- Lichen sclerosus
- Morphea Mucha-Habermann disease, PLEVA (pityriasis lichenoides et varioliformisacuta)
- Myositis
- Neonatal lupus
- Parry Romberg syndrome
- Pemphigus vulgaris
- POEMS syndrome
- Progesterone dermatitis
- Psoriasis
- Pyoderma gangrenosum
- Benign mucosal pemphigoid
- Blau syndrome
- Bullous pemphigoid
- Eczema
- Epidermolysis bullosa acquisita
- Erythema nodosum
- Linear IgA disease (LAD)
- Majeed syndrome
- Schnitzler syndrome
- Subacute cutaneous lupus erythematosus (SCLE)
- Sweet's syndrome
- Vitiligo
- Vogt-Koyanagi-Harada Disease
- Linear IgA disease (LAD)
- Majeed syndrome
- Kawasaki disease
- Schulman disease

Ear, Nose, Sinus, and Throat
- Autoimmune inner ear disease (AIED)
- Churg-Strauss syndrome
- Cogan syndrome
- Meniere's disease
- Susac's syndrome

Endocrine Disorders
- Addison's disease
- Autoimmune polyendocrine syndrome
- Cushing's syndrome
- Diabetes mellitus type 1
- Diabetes mellitus type 2
- Eosinophilic esophagitis (EoE)
- Glycogen storage disorder (GSD VII)
- Graves' disease
- Hashimoto's thyroiditis
- Hypoglycemia
- Hypopituitary or secondary adrenal insufficiency
- Hypothalamic dysfunction
- Hypothyroidism
- Juvenile diabetes (Type 1 diabetes)
- Ord's thyroiditis
- Pituitary dysfunction
- POEMS syndrome
- Polyglandular syndromes type I, II, III
- Schmidt syndrome
- Thyroid eye disease (TED)
- Thyroiditis

Gastrointestinal Disorders
- Autoimmune hepatitis
- Autoimmune enteropathy
- Autoimmune pancreatitis
- Celiac disease
- Churg-Strauss syndrome
- Crohn's disease
- Eosinophilic gastroenteritis
- Gastritis
- Gastrointestinal pemphigoid
- Gastroparesis
- Gluten sensitivity
- Gut dysbiosis
- Inflammatory bowel disease (IBD)
- Irritable bowel syndrome (IBS)
- Lupoid hepatitis
- Nonalcoholic steatohepatitis (NASH)
- Mesenteric Panniculitis
- POEMS syndrome
- Polyarteritis nodosa
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Pyoderma gangrenosum
- Small intestinal bacterial overgrowth (SIBO)
- Schnitzler syndrome
- Ulcerative colitis

Hematological Disorders
- Agammaglobulinemia
- Antiphospholipid syndrome
- Autoimmune aplastic anemia
- Autoimmune hemolytic anemia
- Autoimmune lymphoproliferative syndrome
- Castleman's disease (CD) – lymph node hyperplasia
- Cold agglutinin disease
- Evans syndrome
- Hemolytic anemia
- Henoch-Schonlein purpura (HSP)
- Immune thrombocytopenic purpura (ITP)
- Kawasaki disease
- Majeed syndrome
- Microscopic polyangiitis
- Monoclonal gammopathy of undetermined significance (MGUS)
- Myelodysplastic syndromes
- Neutropenia
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Pernicious anemia (PA)
- POEMS syndrome
- Pure red cell aplasia (PRCA)
- Raynaud's phenomenon
- Thrombocytopenic purpura (TTP)

Hepatic Disorders
- Hepatitis C
- Primary biliary cholangitis

Immunological Disorders
- Amyloidosis
- Autoimmune angioedema

- Common variable immunodeficiency
- Epstein-Barr virus
- IgG4-related sclerosing disease
- Juvenile myositis (JM)
- Mast cell activation syndrome (MCAS)
- Pernicious anemia (PA)
- Vitiligo
- Chagas disease
- Complement component 2 deficiency (increases the risk of infection)
- Coxsackie myocarditis
- Herpes
- Herpes Zoster (shingles)
- HIV/AIDS
- Hypogammaglobulinemia (leads to infections)
- Lyme Disease
- PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)
- Sydenham chorea

Cancers

- Adenoid cystic carcinoma
- Bladder cancer
- Breast cancer
- Carcinoid colon & rectal cancer
- Cholangiocarcinoma
- Colon cancer
- Esophageal carcinoma
- Glioblastoma
- Glioma
- Leukemia
- Liver cancer
- Lung cancer (non-small cell)
- Lymphocytic leukemia (chronic)
- Lymphoma (Hodgkin's and non-Hodgkin's)
- Malignant melanoma
- Mesothelioma
- Multiple myeloma
- Neuroblastoma
- Ovarian cancer
- Pancreatic cancer
- Parotid carcinoma
- Prostate cancer
- Renal cell carcinoma
- Throat cancer
- Uterine cancer
- Hepatoblastoma

Neurological Diseases

- Achalasia
- Acute disseminated encephalomyelitis
- Acute hemorrhagic leukoencephalitis
- Adhesive arachnoiditis
- Alzheimer's
- Anti-mag IgM peripheral neuropathy
- Autoimmune dysautonomia
- Autoimmune encephalomyelitis
- Autoimmune peripheral neuropathy
- Axonal & neuronal neuropathy (AMAN)
- Baló disease/Baló concentric sclerosis
- Bickerstaff's encephalitis
- Brain fog
- Charcot-Marie-Tooth syndrome
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Crackly brain middle ear myoclonus (MEM)
- Cranial arteritis
- Devic's disease (neuromyelitis optica)
- Electromagnetic hypersensitivity
- Guillain-Barré syndrome
- Hashimoto's encephalitis
- Idiopathic inflammatory demyelinating diseases
- Inflammatory demyelinating polyneuropathy
- Lambert-Eaton myasthenic syndrome
- Leaky brain
- Migraines
- Miller-Fisher syndrome
- Movement disorders
- Multifocal Motor Neuropathy (MMN) or MMNCB
- Multiple sclerosis (MS)
- Myalgic encephalomyelitis
- Myasthenia gravis
- Myelin Oligodendrocyte Glycoprotein Antibody Disorder (MOG-AD)
- Myositis
- Narcolepsy
- Neuromyelitis optica
- Opsoclonus myoclonus syndrome
- Optic neuritis
- PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)
- Paraneoplastic cerebellar degeneration (PCD)
- Parkinson's disease
- Parry Romberg syndrome
- Parsonage-Turner syndrome
- Peripheral neuropathy
- Perivenous encephalomyelitis
- Progressive inflammatory neuropathy
- Rasmussen's encephalitis
- Restless legs syndrome (RLS)
- Stiff person syndrome (SPS)
- Susac's syndrome
- Sydenham chorea
- Tired brain syndrome
- Tolosa-Hunt syndrome
- Transverse myelitis
- Traumatic brain injury (TBI)
- Vogt-Koyanagi-Harada Disease
- Amyotrophic lateral sclerosis (ALS)
- Duchesne muscular dystrophy
- Dystonia
- Neuromyotonia
- POEMS syndrome
- Postural orthostatic tachycardia syndrome (POTS)
- Traumatic brain injury (TBI)
- Vogt-Koyanagi-Harada Disease

Ocular Disorders

- Autoimmune retinopathy
- Autoimmune uveitis
- Blau syndrome

LDN

- Cogan's syndrome
- Devic's disease (neuromyelitis optica)
- Ligneous conjunctivitis
- Miller-Fisher syndrome
- Mooren's ulcer
- Neuromyelitis optica
- Ocular cicatricial pemphigoid
- Optic neuritis
- Opsoclonus myoclonus syndrome
- Pars planitis (peripheral uveitis)
- Scleritis
- Susac's syndrome
- Sympathetic ophthalmia (SO)
- Thyroid eye disease (TED)
- Tolosa-Hunt syndrome (THS)
- Uveitis
- Vogt-Koyanagi-Harada disease

Pediatric Disorders

- Addison's disease
- Autism
- Celiac disease
- Congenital heart block
- Crohn's disease
- Juvenile arthritis
- Juvenile dermatomyositis
- Juvenile diabetes (Type 1 diabetes)
- Juvenile idiopathic rheumatoid arthritis
- Juvenile myositis (JM)
- Lupus
- Multiple sclerosis (MS)
- Neonatal Lupus
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
- Scleroderma
- Type 1 diabetes
- Ulcerative colitis (UC)

Psychological Disorders

- Alcohol use disorder
- Anxiety
- Depersonalization/derealization disorder
- Depression
- Dissociative Disorder
- Dissociative identity disorder
- General anxiety disorder (GAD)
- Hypervigilance
- Obsessive compulsive disorder (OCD)
- Opioid withdrawal
- Panic disorder
- Phobias
- Post-traumatic stress disorder (PTSD)
- Postpartum depression
- Premenstrual dysphoric disorder (PMDD)
- Social Phobia
- Stress
- Substance abuse disorders
- Trichotillomania

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Pulmonary Diseases
- Anti-synthetase syndrome
- Asthma Churg-Strauss syndrome
- Emphysema
- Fibrosing alveolitis
- Granulomatosis with Polyangiitis (formerly Wegener's granulomatosis)
- Goodpasture's syndrome
- Idiopathic pulmonary fibrosis
- POEMS syndrome
- Sarcoidosis

Renal and Neurological Diseases
- Anti-GBM/anti-TBM nephritis
- Autoimmune orchitis
- Autoimmune renal neuropathy
- Berger's disease – IgA nephropathy
- Glomerulonephritis
- Goodpasture's syndrome
- IgA nephropathy
- Interstitial cystitis (IC)
- Microscopic polyangiitis (MPA)
- POEMS syndrome
- Sperm & testicular autoimmunity

Rheumatological and Autoimmune Disorders
- Adult Still's disease
- Ankylosing spondylitis
- Anti-synthetase syndrome
- Arthritis
- Chronic fatigue syndrome (CFS)
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Complement component 2 deficiency – increased risk of lupus
- CREST syndrome
- Ehlers-Danlos Syndrome (EDS)
- Fibrodysplasia ossificans progressive
- Fibromyalgia
- Inclusion body myositis (IBM)
- Juvenile arthritis
- Juvenile idiopathic arthritis
- Juvenile rheumatoid arthritis – Still's disease
- Lupus erythematosus
- Majeed syndrome
- Mixed connective tissue disease (MCTD)
- Morphea myositis
- Myalgic encephalopathy (ME)
- Palindromic rheumatism (PR)
- Polymyalgia rheumatica
- Polymyositis
- Psoriatic arthritis
- Reactive arthritis
- Reiter's syndrome
- Relapsing polychondritis
- Rheumatic fever
- Rheumatoid arthritis
- Sarcoidosis
- Schnitzler syndrome
- Scleroderma
- Seropositive arthritis
- Sjogren's syndrome
- Spondylitis
- Spondyloarthropathy
- Enthesitis-related arthritis
- Eosinophilic fasciitis
- Retroperitoneal fibrosis
- Undifferentiated connective tissue disease (UCTD)
- Undifferentiated spondyloarthropathy

Sleep Disorders
- Insomnia

Vasculitis
- Blau syndrome
- Churg-Strauss syndrome (CSS) or eosinophilic granulomatosis (EGPA)
- Essential mixed cryoglobulinemia
- Giant cell arteritis (temporal arteritis)
- Kawasaki disease
- Leukocytoclastic vasculitis
- Polyarteritis nodosa
- Takayasu's arteritis
- Temporal arteritis/giant cell arteritis

Women's Health
- Autoimmune oophoritis
- Endometriosis
- Healthy pregnancy – new concepts
- Herpes gestationis/pemphigoid gestationis (PG)
- Infertility
- PMS (premenstrual syndrome)
- Polycystic ovary syndrome (PCOS)
- Pregnancy (under the direction of obstetrician or family medicine physician)
- Premenstrual syndrome (PMS)
- Progesterone dermatitis
- Recurrent vaginitis
- Reduced ovarian reserve (low AMH)
- Vaginitis
- Vulvodynia
- Painful periods (dysmenorrhea)

Veterinary Medicine
- Feline AIDS
- Feline leukemia

COVID-19

There are many etiologies of inflammation. One of them is infection.[58] Coronavirus disease 2019 (COVID-19) and the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a particular risk to people living with preexisting conditions that impair immune response or amplify a pro-inflammatory response. Early identification of possible hyperinflammation in these patients, and all individuals, is fundamental in having effective therapies for patients with COVID-19 and post COVID-19 syndrome.[59]

A very important article points out that the critical point where progressive COVID-19 ensues, appears to center on loss of the immune regulation between protective and altered responses due to exacerbation of the inflammatory components.[60]

In our practice, we use LDN to treat patients with all stages of COVID, from asymptomatic COVID to severe cases of COVID, to COVID-Long Haul Syndrome and have had excellent results.

Conclusion

Low-dose naltrexone plays a major role in the treatment of many different diseases. In the world of medicine, it is truly a game changer. ◆

References are available online at www.townsendletter.com.

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

Letters to the Editor

Allergy Management

I applaud the effort by Drs. Hurst and McDaniel to emphasize, through their paper "Diagnosis of the Pathophysiology of Chronic Mucosal Diseases of Allergic Rhinitis, Asthma, and Otitis Media as Seen by an Otolaryngologist,"[1] recently published in this magazine, very important issues pertaining to allergy management.

They bring to our attention the importance of which test is the one used for the diagnosis of the allergic condition. They also remind us that the allergic condition affects the whole body. There are many conditions, usually not associated with allergy etiologies that can therefore benefit from allergy management (allergy immunotherapy). Recognizing this will add to the patient's wellbeing and avoid unnecessary surgeries – sometimes repeated surgeries. Incorporating these concepts to medical practice would not only add to patient's comfort and health but also would help to decrease the burden of the ever-expanding cost of medical care.

It obviously follows that in order to provide appropriate care to the allergy sufferer an accurate diagnosis needs to be established. And this perhaps is the most important issue. What if the usual test, the one that is the most commonly used, is not accurate enough to make the allergic condition evident?

Drs. Hurst and McDaniel recently published another paper[2] where it was shown that patients with clear allergic disease were considered to be non-allergic if they had a negative skin prick test (SPT) so, treatment was not provided for these patients. They also showed that patients who were diagnosed as being allergic using the SPT and then received immunotherapy had poor results, as the number of allergens that the prick test diagnosed was not enough to provide appropriate clinical relief. In both circumstances, Dr. Hurst retested those patients with a different type of skin test obtaining different results:

a) The cases that were negative by SPT now showed reactivities to many allergens.
b) The cases where the SPT yielded a positive result but with few allergens, had upon retest, many more positive results. When adjusting treatment to this new level of reactivity, immunotherapy results were satisfactory.

This "different type of skin test" was the intradermal dilutional test (IDT). We already had the opportunity to discuss about the advantages of the IDT in this magazine.[3] Our clinical impression also is that patients diagnosed with the IDT, will rarely be misdiagnosed as "non-allergic" and results of allergy immunotherapy will be much more relevant than when treating from a SPT because the IDT is able to diagnose the allergic condition much more accurately. This fact is not well known in the medical community, including the general allergy community. Only physicians that use this test are aware of this. When these practitioners encounter patients previously tested with a skin prick test, it is not a rare occurrence to observe that either these patients were told that they were not allergic (as the SPT was negative) or they were receiving immunotherapy; but treatment results were not good.

In my opinion, the reason why the IDT performs so much better than the SPT is related to the fact that the mast cells are found in the dermis.[4] The prick test applies the allergen on the surface of the skin. The allergen needs to permeate to the dermis in order to be able to trigger the mast cells. Injecting the allergen directly into the dermis places this allergen in the immediate vicinity of these cells. Therefore, if these mast cells are sensitized against such allergen, they will degranulate and become biologically active.

Drs. Hurst and McDaniel point out that on the updated practice parameters on allergy diagnostic testing published by AAAAI and ACAAI,[5] the IDT is considered to be equivalent to the SPT only at high dilutions (meaning the 4th to the 6th dilutions); IDT uses six dilutions, each successive dilution carrying progressively less allergen. The allergen to be tested by IDT is diluted with 1:5 dilutions. The 4th dilution contains allergen diluted 625 times. In the 6th dilution the allergen is diluted 15,625 times.

This clearly suggests that in patients that are very sensitive (in other words their dermis is filled with sensitized mast cells), their skin will react to a minimal amount of allergen (very diluted). In these cases, depositing the allergen in the skin surface may be enough to stimulate the mast cells, as the skin may be overflowing with mast cells. It could be assumed that even the area immediately below the basal lamina, (area immediately "deeper" to the epidermis) will be filled with mast cells.

So, extrapolating from the information provided in the practice parameters

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above mentioned,[5] in an allergic person that is not very sensitive, the SPT will not be reactive, therefore the diagnosis will not be done. In other words, unless the patient is very sensitive, the IDT will outperform the SPT.

I would like to address one more time the significance of this problem: labeling a negative-prick test patient as non-allergic will deprive this patient of the only possible treatment able to correct the immune dysfunction leading into the profuse allergic symptomatology. This treatment is allergy immunotherapy.[6]

A concept observed in clinical practice, that is somewhat counterintuitive, is that the sensitivity not necessarily correlates to the degree of clinical disease. The sensitivity of the patient depends on the number or sensitized ("primed") cells. This means that a patient who, for example, has an IDT with all allergens reacting at dilutions 4-6 (meaning that very diluted allergen is sufficient to trigger the response) may not have very significant clinical disease, whereas another patient who, for example, reacts only to very strong allergen concentration (for example in the 2nd dilution, meaning that the response is only triggered by a high concentration of the allergen) may have severe allergies, asthma, and eczema. This second patient, even though clearly symptomatic, for sure will not be diagnosed with the SPT.

The inability to correctly diagnose an allergic patient occurs also with the usual RAST-like blood tests, where only determination of IgE is done, disregarding other immunoglobulins that can be involved in the immunological reactions as described by Gell and Coombs.[7]

This leads to a common apparent contradiction mentioned by Drs. Hurst and McDaniel and easily observed by any clinician who orders those tests: some patients are clearly allergic (an easy example is the case of the patient who develops asthma when close to a cat, or who is triggered during the spring) but has a "RAST" test that is negative.

In agreement with these authors, it is also my opinion, that establishing a diagnosis of allergy using poor performance tests and not considering the clinical presentation is the basis for describing other syndromes like non-allergic rhinitis with eosinophilia syndrome, non-allergic rhinitis, local allergic rhinitis, or Idiopathic rhinitis (considered a subtype of nonallergic rhinitis). Just entering these terms in the internet will show multiple references, always in the same style. For example, nonallergic rhinitis with eosinophilia syndrome (NARES) is defined as symptoms consistent with allergic rhinitis with negative allergen skin testing, but with nasal cytology showing eosinophils.[8] In other words, a skin prick test was non-reactive, and despite the patient having the clinical presentation consistent with allergic disease, the patient is called "NARES."

Nonallergic rhinitis[9] is defined as the presence of nasal symptoms consistent with the allergic condition but "without evidence of systemic allergic inflammation," meaning with a negative allergy test.

Local allergic rhinitis (LAR)[10] is considered to be a localized nasal allergic response with negative skin prick tests or specific IgE tests, characterized by local production of specific IgE when there is an exposure to an allergen, with a positive nasal allergen provocation test to the allergen being considered.

The common link to all these different syndromes is that the patients have clear allergic symptomatology but the workup is negative. This negative workup can only be a SPT (where the allergen has poor capability to reach the mast cells) or a RAST-type blood test that found no IgE (but did not evaluate for other immunoglobulins), and obviously neither test evaluated for the possibility of other different immunological mechanisms.

To add to this conundrum, it is acknowledged that the prevalence of nonallergic rhinitis can be up to more than 50.0% of the cases and conditions like asthma and eczema can be present with or without IgE.[9,11] It is even acknowledged that IgE sensitization is not the main causal mechanism of these diseases.[11]

Allergens, like molds and dust mites (but also others), can involve complex reactions with no IgE. In these cases, an IgE RAST-type of test will be negative, but the IDT will show a reaction. A skin test should be thought of as a "biological assay" as a positive wheal can contain, besides IgE, immunocomplexes (Type III reaction of Gell and Coombs) and immunological cells that can make a wheal persistent for many days or even appear 24-48 hours after the test. These are called delayed reactions and involve cellular immunity (type IV reaction of Gell and Coombs). [12]

In Summary

As already stated, Drs, Hurst and McDaniel are making a commendable effort to bring to the attention of any practitioners managing allergic patients that the clinical presentation of allergies is not only sneezing and runny nose. Many conditions like middle ear inflammation (leading to fluid accumulation and predisposing to infections), inflammation of tonsils and adenoids (leading to hypertrophy and also predisposing to infections), and inflammatory conditions in other parts of the body like the lower respiratory tree or the skin, have an allergic component.

The mismatch between the clear clinical presentation and the negative skin tests can only be understood when realizing that the skin tests are not all the same, the most commonly used skin test is unfortunately the least able to perform, and when understanding that an immunological response to an allergen can involve one or more of the immunological mechanisms described by Gell and Coombs, therefore a negative IgE "RAST" will not exclude an allergic etiology.

Diego Saporta, MD

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Response to Orthomolecular COVID Protocol

Respectfully, I would offer several relevant additions to this wonderful article: "COVID-19 Orthomolecular Protocol for Prevention and Treatment" by Michael J Gonzalez, DSc, NMD, PhD, et al (https://www.townsendletter.com/article/463-4-treating-and-preventing-covid-with-orthomolecular-medicine/)

Metoprolol. Metoprolol is a beta-blocker that is safe. It reduced exacerbated lung inflammation and improved oxygenation in COVID.[1]

Bromhexine. Bromhexine is a mucolytic drug used in the treatment of respiratory disorders associated with viscid or excessive mucus. It was originally derived as an extract derivative called vasicinone from the Indian plant, *Adhatoda vasica*. Two studies showed effectiveness in COVID.[2,3]

Ashwagandha. A study found that *Withania somnifera* (Ashwagandha) was comparable to hydroxychloroquine in the prophylaxis against COVID-19 in high-risk health care workers.[4]

Neem. A study found a reduced risk of COVID-19 infection in participants receiving neem capsules as a prophylactic treatment for the prevention of COVID-19 infection.[5]

Nigella sativa. Nigella sativa oil supplementation was associated with faster recovery of symptoms than usual care alone for patients with mild COVID-19 infection.[6]

Avoid Remdesivir. Remdesivir is associated with adverse effects.[7-10]

Ronald Steriti, ND, PhD©

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NEWS | NEWS | NEWS

FDA's Threat to cBHT Puts Millions of Patients at Risk

When the National Academies of Science, Engineering and Medicine released its FDA-funded report on cBHT in July 2020—which included a recommendation for across-the-board restrictions on compounded hormones—FDA issued a public statement saying the agency would base its next steps on compounded hormones on the NASEM report. That statement widely was interpreted to mean FDA will act to restrict compounded hormone therapy. We're talking therapies that millions of patients rely on for their quality of life.

But a third-party analysis of the NASEM report shows it to be compromised by potential bias, conflicts of interest and bad science.

FDA touted the NASEM report, which recommended restrictions on compounded hormone therapy, as "independent" and "comprehensive," but in fact it was neither. That's one of the key findings in the white paper by Dr. Alyson Wooten, a director at the nonpartisan Berkeley Research Group (BRG). The paper is titled "The Panel Put Policy-Making Before Patient Need: An Independent Analysis of the FDA-Commissioned NASEM Report, 'The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use.'" The Pharmacy Compounding Foundation commissioned Dr. Wooten to conduct the third-party, independent review of the NASEM report.

"Given the strong potential bias influencing the Committee's recommendations and the omission from the final report of key data supporting the safety and efficacy of cBHT, we recommend that FDA not rely on or consider the NASEM Report," the white paper advises.

Wooten's paper demonstrates that the agency exerted inappropriate influence and bias in almost every phase of the commissioned report, even recommending study committee appointees who had no expertise in prescribing or compounding hormones.

"The BRG paper shows how FDA inappropriately meddled in the composition of the NASEM committee, fed the committee selective research for its consideration and even advised the committee on its final recommendations for restricting compounded hormones," said Pharmacy Compounding Foundation CEO Scott Brunner, CAE. "And all so FDA could have a report that reflected its existing negative view of compounded hormone therapy. The paper reveals an FDA much more interested in documenting its own biases than in actual objective science. And it was apparently willing to spend $1.3 million in taxpayer dollars to do it."

Dr. Wooten's review is a repudiation

FDA's Threat to cBHT

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of an FDA staff that manipulated the process and NASEM committee members who lacked expertise in the subject matter they were engaged to study.

The white paper documents how:

- Bias may have influenced the conclusions and recommendations of the committee.
- The committee and its review team included individuals who may have been biased against compounded hormones.
- The committee did not include any prescribers or pharmacists with substantive, patient-facing experience with compounded hormones.
- Jane Axelrad, a former FDA official and outspoken critic of compounded hormones, played multiple key roles in the development of the NASEM report.
- The committee's conclusions regarding the safety and efficacy of compounded hormones are flawed.
- The definition of "clinical utility" developed and relied upon by the committee does not reflect an accurate or complete representation of the term.
- The studies relied upon by the committee do not reflect an accurate or complete representation of compounded hormones.
- The standards for evaluating the safety and efficacy of FDA-approved drugs cannot be reasonably applied to highly individualized compounded medications.
- The committee relied on the discredited 2002 Women's Health Initiative study in developing its conclusions.
- The committee ignored the body of evidence demonstrating the safety and efficacy of compounded hormones.

"These numerous flaws render the NASEM report so thoroughly compromised as to be useless in any discussion of compounded hormone therapy," said Brunner.

Despite those flaws, FDA continues to tout the NASEM report. In a February 2022 letter to 22 members of Congress who had written to FDA to express concern about the NASEM report, FDA doubled down on its 2020 statement, telling legislators it would base its next steps on compounded hormones in part on that NASEM report.

A report published online in February 2022 by *The Journal of the North American Menopause Society* and slated for print publication by NAMS in Spring 2022 accomplishes what was expected of – but not accomplished by – the NASEM Committee: a systematic review and meta-analysis of the existing evidence related to the safety and efficacy of commonly prescribed cBHT preparations in perimenopausal and postmenopausal women. Compared to the NASEM committee's cherry-picking of only 13 research clinical trials covering only four hormones, that NAMS-published paper reviews a total of 29 RCTs reported in 40 articles containing 1,808 perimenopausal and postmenopausal women. Notably, it finds that despite variations in absorption from different types of compounded hormones, routes, and strengths, the changes of serum hormone levels were consistent with published data from FDA-approved products. While still limited in scope, this thorough meta-analysis suggests that the NASEM committee's recommendation for restrictions due to safety concerns is at best not rooted in scientific rigor.

"Any public policy related to compounded hormones must be rooted in scientific evidence, not in FDA's anti-compounding bias," said Brunner. "It must also take into account abundant patient outcomes data demonstrating that these compounded therapies work well for millions of Americans."

What Can You Do to Help?

Members of Congress need to know about this issue and the potential impact FDA restrictions may have on many, many of their constituents. Go to www.compounding.com to read and hear stories, cataloged by state, from patients whose lives have been enhanced, even saved, by compounded hormone therapy. Then join APC and provide financial support for our Campaign to Save Compounded Hormones.

Scott Brunner
Alliance for Pharmacy Compounding
(https://a4pc.org/)

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'Ministry of Truth' vs Nutritional Medicine

by Damien Downing, MBBS, MRSB

Orthomolecular Medicine News Service

Just outside the local primary school here in north London, somebody has sprayed these words on a phone or cable junction box, highly visible to the mums and tots:

COVID
1984

I often cycle past there and have always thought "Mmm, a bit extreme," but now I'm starting to wonder.

In George Orwell's novel *1984*, Winston Smith works at the Ministry of Truth, which administers Newspeak, deciding what the "truth" is, propagating it, and rewriting history when necessary. Newspeak is "characterized by a continually diminishing vocabulary; complete thoughts are reduced to simple terms of simplistic meaning," according to our old friends Wikipedia. The purpose is thought control; you know the saying "The French have a word for it"? If you don't have a word for it you struggle to think it. So words like "anti-vaxxer" polarize opinions and prevent any subtlety of thinking about viruses and vaccinations.

For two years, we at the OMNS have been stating one simple message: **Nutritional therapy works on COVID, as it does on all viruses.**

On January 26, 2020 the OMNS Editor in Chief, Andrew W. Saul, wrote a news release: "Vitamin C Protects Against Coronavirus."[1] It also made recommendations for vitamin D3, magnesium, zinc and selenium, which strengthen the immune system. We have continued to repeat and expand the message again and again. And have been suspended by Facebook again and again.

Others, including highly respected front-line physicians such as Paul Marik, have also figured out the importance of these nutrients.[2] In fact we have known about the anti-infective potential of vitamin C for over 50 years, since it was reported by Frederick Klenner.[3,4] He described traditional sources such as acerola cherries, which are very rich sources of C. That puts the knowledge back way before we named it "vitamin C."

And it makes nonsense of the narrative that there is only one solution to COVID: vaccinate, again and again.

Two years ago I failed to persuade mainstream colleagues of the utility of this. "It's not evidence-based," they said. Now two review papers have shown the evidence, and it's pretty solid.

The first, in the journal *Life*, is called "Vitamin C Intervention for Critical COVID-19: A Pragmatic Review of the Current Level of Evidence."[5,6] It shows clearly that "this simple vitamin saves lives when given in the right dose." In fact, vitamin C saves about 80% of the lives of critically ill COVID patients.

With a rollcall of experts saying vitamin C can save lives, what has been the response of the authorities, the powers-that-be?

The UK's National Health Service responded back in 2020 by promising a trial of intravenous vitamin C. Until that evidence becomes available, they have continued to say that there is no good evidence that vitamin C works. Scientists, including the authors of the above paper, sent them studies and they still said that. Finally, a freedom of information (FOI) request established that the NHS had received the papers and had ignored them, for at least a year.

But the promised international multi-center trial would fix this, right? The only problem is, apparently, that the NHS had already signed an exclusive contract with a single company to supply the vitamin C, and that company was and still is unable to provide any. So the trial still has not started. Even for a piece of fiction, you couldn't make it up! I could lend them some tomorrow.

The second review is by my colleague, independent researcher Rachel Nicoll: "COVID-19: Presenting the case for vitamin D: A cheap, effective measure overlooked by most governments."[7]

As always with Rachel's writings this is very information-rich. Here's just one sentence: "A meta-analysis of 23 studies containing 11,901 participants found that in patients with vitamin D deficiency, the risk of being infected with COVID was 3.3 times higher and the risk of developing severe COVID was around 5 times higher compared to those with more healthy vitamin D levels."

Our knowledge of vitamin D and its importance for immunity has progressed by leaps and bounds in this pandemic, but a lot of this too we have known for ages. I wrote a book about it back in 1988; there's a team in San Diego that has been studying sunlight and health for decades.[8]

Just as modern agriculture has been depriving us of many essential nutrients,[9] modern lifestyles have been depriving us of sunlight and therefore vitamin D. Lucky you if you live somewhere sunny like San Diego because here in London nearly everybody is vitamin D deficient. Not that things are perfect in San Diego; we all shun the sun these days, often due to scare tactics about skin cancer.

That's a story for another time, but here's a take-home thought about vitamin D levels. It has been shown that a population needs a vitamin D blood level above about 75 nmol/L (30 ng/ml) to stop deaths from COVID,[10] but precious few of us manage it. So, what should our blood level be? Where's the benchmark when nearly everybody is deficient? If you take our nearest evolutionary relatives, non-human

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primates, they have around twice that level, 125 to 200 nmol/L (50-80 ng/ml).[11,12] We're not just falling behind them, we're missing it by a mile. You need at least 10,000 IU per day long-term to achieve that.

Guess what comes next? When the "experts," at least in the UK, are asked about the safety and toxicity of vitamin D, they say we should not take more than 2000 IU per day. But this is based on the UK's Scientific Advisory Committee on Nutrition (SACN) 2016 report. SACN cited a 2006 paper by Vieth as showing toxic effects above this level. However, the Vieth paper actually states that toxicity may occur at 25(OH) D concentrations beyond 500 nmol/L (200 ng/ml), levels which could not be achieved unless an individual was taking extremely high doses for a prolonged period of time (such as 30,000 IU/day for three months).[13] This warning has been misunderstood and misquoted and has given rise to a lot of pointless restriction of vitamin D intake. So even though the error about vitamin D safety was pointed out 15 years ago, and repeatedly since then, it is still being perpetuated by supposed experts.

Two years down the line, then, we at the *Orthomolecular Medicine News Service* are still saying the same simple message that nutrition works. And the bureaucrats at the 'Ministry of Truth' are still deleting it.

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Living Longer

review by Jacob Schor, ND, FABNO

Extra Life: A Short History of Living Longer by Steven Johnson
Riverhead Books; Penquin Publishing Group
Hardcover and eBook; 2021; 320 pp.

This pandemic business has tried my patience at times, giving rise to moments of irritation. I often try to follow that old suggestion and count to ten before I open my mouth. This isn't always enough so instead tried counting by twos to fifty, then threes to ninety-nine. I'm now better with my 12-times tables than I was in elementary school. Still, I am not a polymath.

I always thought a polymath was someone who was really good with numbers, but I am wrong. The term is actually from the Greek (πολυμαθής) and translates to something like, "having learned much." A polymath is a person who has expertise in a wide range of different subjects and is able to draw upon this knowledge to solve problems. It's got nothing to do with math.

My curiosity as to what a polymath is was incited by a description of Steven Johnson, the author of several books I've enjoyed reading, which described him as a polymath. I have always assumed that people were either good with numbers or good with words; I couldn't see Johnson who I think writes rather well, being categorized into the number camp. I was obviously wrong. He knows a great deal about a lot of things and shuffles between ideas in a fascinating way.

I found my first Steven Johnson book, *The Invention of Air*, in the Little Free Library in front of our home back in 2019. That book, a biography of Joseph Priestly, was so interesting that I sent my copy to Davis Lamson, ND, a one-time college chemistry professor, who many of us know better as the long-time professor of naturopathic oncology at Bastyr University. Sharing that book started something of a book club in which n=2.

The second Johnson book I read was *The Ghost Map*, a history of the London cholera epidemic and the hunt for the cause. Johnson has a way of using these detailed histories as vehicles to describe and understand the growth and advancement of human knowledge and understanding. Historical stories, in their own right interesting, are used to illustrate how knowledge moves through human society. In this telling of the cholera story, the normal hero, Dr John Snow, is portrayed somewhat differently. Rather than the brilliant doctor who alone solved the puzzle of cholera transmission and then stopped the epidemic by removing a water pump handle, Snow is one of many characters who formed a network whose mutual efforts lead to a dramatic change in the understanding of disease transmission.

Which came first, the book or the movie? I was about halfway through Johnson's most recent book, *Extra Life: A Short History of Living Longer*, when I discovered that the book was written in conjunction with a PBS television production that aired in April 2021. [When one lives in a cabin in the woods, there are things that happen in the world that go unnoticed.] As a person devoted to the written word, I haven't tried to watch the TV program yet. I found the book fascinating. So much so that I almost purchased a case of copies to distribute among friends. The cost of postage dissuaded me from doing so. By the way, the PBS version is at https://www.pbs.org/show/extra-life-short-history-living-longer/.

This book is not about how we might live longer now, one of the many suggesting recipes of vitamins and supplements to achieve longer life. It is not a how-to manual for life extension. It is a history of the lengthening of the human life span over the last 150 years.

> A century ago, at the end of the Great Influenza, global life expectancy was in the mid 30s. In the US, it was 47. Today, just a hundred years later, global life expectancy is in the 70s. Childhood mortality worldwide has been reduced by a factor of 10. The doubling of human life expectancy should be understood as the single most important development of our era. If a newspaper came out only once a century, that extra lifespan would be the banner headline: world wars, moon landings, the Internet would all be below the fold. (Steven Johnson)

We often take this shift in lifespan for granted but step back for a moment and consider how dramatic this change was. Human lifespans did not change much from the Paleolithic Age until about 1750. For the past 12,000 or so years, about 30% of those humans born alive died in childhood. The average life span was 35 years. In the last century lifespans have more than doubled, childhood mortality percentages have dropped down into the single digits if not lower.

How did this happen? Spoiler alert: it wasn't modern medicine. Johnson is quick to point out the medical doctors offered little that would extend life until the most recent decades. Rather it was knowledge of disease transmission, improvements in water supply and sewage handling, the understanding of how to influence public health and the need to institute and regulate broad factors in society by government that have made the difference. We take some of these measures for granted at the risk of losing some of the gains in lifespan we now enjoy.

We often find ourselves talking about our goal as naturopathic physicians in a manner that echoes the ideas of James Fries, MD. Dr. Fries (who sadly died in December 2021) was "… obsessed with how to lead a good life, even

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though his interest was more about physical than moral well-being."[1] Fries, along with other scientists, called our increase in life expectancy, 'the failure of success.' He argued that our "increase in life span did not mean an accompanying increase in 'healthspan,' or the duration of one's life free from chronic conditions like hypertension, diabetes and heart disease." Fries, and certainly our profession, has often said our goal is to maximize that portion of our lives in which we are leading a good life and minimize that portion that we aren't. To use Fries words, our goal should be to compress morbidity.[2]

Our suddenly lengthened lifespans are having impacts that we have yet to fully understand. The resultant explosive growth in global population is certainly a direct result of lower childhood mortality and of more people living long enough to reproduce. The added burden on global resources FROM this expanding population certainly is part of the climate change thing. We may want to compress morbidity, but we haven't yet come to grips with the fundamental changes that result from the increase in our lifespans.

> We added 5 billion humans to the planet since 1920, not because people were having more babies, but because we figured out all these new ways to keep people from dying. Global threats like climate change are also a byproduct of these public health and medical revolutions. If life expectancy had stayed where it was, atmospheric carbon levels would be much lower than they are today, because there would be far fewer humans living carbon-heavy industrial lifestyles. (Steven Johnson)

I can't think of a more important topic for us all to be well versed in. A broad perspective on human health is vital for us to navigate our way forward. Too often in working with individual patients, we lose sight of the big picture, that forest for the trees metaphor. Thus, this is an important book for all of us to read and understand. Or, you can watch the made-for-TV version….

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CALENDAR

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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The Lobay Viewpoint

by Douglas Lobay, BSc, ND
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Peanuts and Poppycock: The Science Behind Magnesium Bioavailability

In many native American cultures, the sighting of a bear has great practical and spiritual significance. The bear is a symbol of strength and courage. It also could invoke wisdom and impart magical healing properties.

One recent fall day I went looking for a bear in Scenic Canyon in Mission Creek Park. The walk was lovely, but I didn't see a bear. Somewhat disappointed I greeted another smartly dressed elderly hiker and told him my dilemma. He wisely pointed out that you seldom find what you are looking for when you are expecting to find it. The point was well taken.

Over the years I have been inundated with shoddy advertising claims from company specific, so called proprietary natural products. Often the claims are supported by cherry-picked and scanty science. Take the mineral magnesium for instance. Here are some of the things I have recently heard. One patient claimed their liquid magnesium was ionically charged and 100% absorbed and therefore the very low dose wasn't important. Another patient stated that their magnesium was better because it had a different orbital spin. Furthermore, another patient suggested magnesium malate was better for fibromyalgia because it went directly to muscles. Yet another patient told me their homeopathic *Mag Phos* 30C supplement supplied all the magnesium they needed. Another patient said magnesium orotate goes straight to the brain and helps anxiety better that the other forms.

Undeniably, most practitioners will agree that magnesium is a vitally important nutrient in human health. It is involved in over 300 biochemical reactions in the human body, including energy production, muscle and heart contraction, protein synthesis, brain and nerve function. It is the second most abundant intra-cellular cation or positive ion and fourth most abundant mineral in the human body. Magnesium deficiency is one of the most common mineral deficiencies in the world. A staggering 48% of the American population are estimated to be getting less than RDA or recommended daily dietary allowance. Magnesium has been recommended for muscle cramps, headaches, high blood pressure, heart arrythmias, gastritis and acid reflux, constipation, kidney stones, fibromyalgia, and other conditions too numerous to list here.[1-3]

Magnesium is a bright white or silver alkali earth mineral that has an atomic number of 12 and an atomic mass of 24.3 grams. Magnesium has a plus two positive ionic charge. Magnesium is bound with other compounds to form a magnesium complex. On a basic level, magnesium complexes are described as inorganic or organic, based on what the element it is bound to. From my collegiate organic chemistry days, I further realized that an organic magnesium complex is bound to a compound that contains carbon and an inorganic complex usually does not contain carbon. The many forms of magnesium used as supplements in nutritional medicine include magnesium bound to ascorbate, aspartate, carbonate, chloride, citrate, glycinate or biglycinate, hydroxide, lactate, malate, orotate, oxide, phosphate, taurate, threonate, sulphate and succinate. Of course, other forms of magnesium complexes exist in nature and are also used as magnesium supplements.[1-4]

After doing some preliminary research on Google and PubMed, I became focused on magnesium absorption and bioavailability. I was expecting to find exact or near exact absorption rates for the different types of inorganic and organic magnesium complexes that exist. I was hoping to summarize my research in the form of a concise table that would list each magnesium complex and its absorption rate. I quickly discovered that things just weren't that simple and no tablature of this type could be reliably made. Like my earlier futile pursuit of a bear that was probably not there, I learned that I expected to find something that probably didn't exist. I also learned what the current body of scientific research said about magnesium absorption and bioavailability.

A review of the basic chemistry of elements, compounds and molecular structure provides the following information.

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Magnesium chloride has a molar mass of 95.2 grams, is 25.5% elemental magnesium, and therefore 200 milligrams of this compound would provide 53.0 milligrams of magnesium. Magnesium oxide has a molar mass of 40.3 grams, is 60.3% elemental magnesium, and therefore 200 milligrams of this compound would provide 120.6 milligrams of magnesium. Magnesium carbonate has a molar mass of 84.3 grams, is 28.9% elemental magnesium, and therefore 200 milligrams of this compound would provide 57.8 milligrams of magnesium. Magnesium citrate has a molar mass of 214.4 grams, is 11.3% elemental magnesium, and therefore 200 milligrams of this compound would provide 22.6 milligrams of magnesium. Magnesium glycinate has a molecular weight of 172.4 grams, is 14.1% elemental magnesium, and therefore 200 milligrams of this compound would provide 28.2 milligrams of magnesium. Magnesium malate has a molar mass of 156.4 grams, is 15.5% elemental magnesium, and therefore 200 milligrams of this compound would provide 31.0 milligrams of magnesium. Furthermore, all other types of magnesium compounds can be reviewed this way. The conclusion of this review suggests that while all types of magnesium compounds contain variable amounts of elemental magnesium by weight, inorganic forms tend to contain a higher amount compared to organic forms.[4]

The solubility, or ability to dissolve in water, of different magnesium compounds is highly variable and can be pH and temperature dependent. Magnesium hydroxide is relatively insoluble in water and dissolves at a ratio of 12 milligrams per liter of water. Magnesium carbonate is more soluble and dissolves at a ratio of 600 milligrams per liter of water. Magnesium aspartate is somewhat soluble and dissolves at a ratio of 40 grams per liter of water. Magnesium lactate is also somewhat soluble and dissolves at a ratio of 84 grams per liter of water. Magnesium citrate is also more soluble and dissolves at a ratio of 200 grams per liter of water. Magnesium sulphate is much more soluble and dissolves at a ratio of 300 grams per liter of water. Different magnesium compounds have different degrees of dissociation or ionization in water at a specific temperature. The higher the degree of dissociation the greater the ability of the compound to ionize into anionic negatively charged elements or molecules and cationic positively charged elements or molecules. When magnesium dissociates from its bound compound form, it becomes a cationic positively charged plus two element. Generally, the greater the solubility of a magnesium compound, the higher the concentration of ionic elemental magnesium generated. It is also mentioned that pH can affect the degree of ionization of most magnesium compounds. The conclusion of this review suggests that different magnesium compounds have vastly different degrees of solubility in water at a standard pressure and temperature. In general, the greater the solubility of the magnesium compound, the greater the ionic elemental magnesium that is generated and the greater the probability of absorption.[4]

Elemental ionic magnesium tends to be more significantly absorbed than whole non-ionic inorganic or organic compounds. When magnesium is dissolved in solution, it ionizes and interacts with polarized water molecules to form a hydration shell around each atom of magnesium. Magnesium forms a relatively large hydration shell with at least two layers of water molecules, unlike calcium which forms a relatively small hydration layer. The diameter of the magnesium hydration shell is at least 400 times larger than the shell of elemental magnesium itself, while the calcium hydration shell is only 25X the size. For absorption the hydration shell must be stripped away to allow passage through intra- or inter-cellular pathways. Unlike most minerals, magnesium is absorbed through the entire length of the gastrointestinal tract: 11% of magnesium is absorbed in the duodenum, 22% in the jejunum, 56% in the ileum, and 11% in the colon. A significant amount of magnesium is absorbed in the distal ileum.[1,2]

There are two mechanisms of absorption of magnesium in the human gastrointestinal tract: intra- or trans-cellular and inter- or para-cellular. The trans- or intra-cellular pathway is basically through the cell itself. The para- or inter-cellular pathway is between cells, generally through tight junctions. The trans-cellular pathway through cells uses two transfer proteins called TRPM6 and TRPM7 otherwise known as transient receptor potential melastin member 6 and 7. These are two energy dependent proteins that span the cell membrane and facilitate trans-cellular absorption of elemental magnesium. The transporter proteins strip away the magnesium shell to make active transport of magnesium easier. This pathway tends to predominate at lower intra-luminal intestinal magnesium concentrations and occurs mainly in the lower ileum and colon. This pathway also accounts for between 10% to 20% of total magnesium absorption levels. The para-cellular pathway is the more predominant pathway and accounts for 80% to 90% of absorbed magnesium levels. Magnesium is absorbed by passive diffusion through tight junctions by an electrochemical gradient. Claudin proteins are found in the tight junction space and also strip away the hydration shell of magnesium to facilitate passive diffusion of elemental magnesium. At higher intra-luminal magnesium levels, a concentration gradient is created, and the direct passive absorption pathway predominates.[1,2]

Absorption rates of magnesium compounds vary from as low as 10% of total ingested magnesium levels to as high as 70%. The average absorption rates of most supplements is somewhere between 30% to 50%. Organic forms of magnesium compounds such as magnesium citrate, malate or glycinate have relatively higher absorption rates compared to inorganic forms such as magnesium oxide or hydroxide. Some studies show absorption rates as low as 4% with certain types of magnesium oxide supplements. Other studies show absorption rates in excess of 70% with specific types of magnesium citrate supplements. In some studies all forms of

supplemental magnesium improved overall magnesium status and combinations of different types of magnesium products perform equally well. This may be partially explained by the relative higher amounts of elemental magnesium in organic compounds compared to the lower amounts of magnesium in inorganic compounds. It should also be noted that the higher amounts of magnesium in inorganic compounds such as magnesium oxide and hydroxide and their relatively poor dissolution in water make them better at creating a higher osmotic intra-luminal concentration in the small and large intestines. And this generally leads to these types of compounds being better laxatives than organic compounds, although higher doses of all magnesium compounds can contribute to this.[1-3,5]

A low magnesium status in the body can slightly increase magnesium absorption capacity. At relatively low concentrations the trans-cellular active transport pathway predominates. At higher concentrations the para-cellular passive process of diffusion predominates. A larger dose of magnesium creates a higher concentration gradient under the same conditions to increase passive absorption. However, most likely there is a plateaued distribution of dosing. That is to say there is an optimal dose that saturates the two mechanisms of absorption. The exact dose that saturates the intestinal absorption capacity is not known. Any dose higher than optimal does not result in any increased absorption and can contribute to unpleasant intestinal side effects. More frequent dosing throughout the day results in higher serum concentrations than a once per day dosing schedule.[1-3]

After absorption magnesium is distributed throughout the body. Fifty-five percent to 70% of magnesium in the serum is free ionic magnesium; 20% to 30% is protein bound, and 5% to 15% occurs as complexes. Magnesium is then distributed to tissues. Ninety-nine percent of magnesium is utilized and stored in intra-cellular tissues and only 1% is found in extracellular fluids and spaces. After potassium, magnesium is considered to be the second most common intra-cellular element in the human body. Total human stores of magnesium have been calculated to be about 24,000 milligrams ranging from 22 to 26 grams in the average adult. Fifty-three percent of total magnesium is stored in bone, 27% muscle, 19% soft tissue, 0.5% in red blood cells, and 0.3% in serum. Fecal excretion accounts for 80 to 280 milligrams per day, and other gastrointestinal secretion accounts for 10 to 20 milligrams. Urinary excretion accounts for between 100 to 2,300 milligrams per day and is highly variable due to tissue requirements, serum levels and absorption rates. The kidneys filter up to 2,400 milligrams of magnesium per day and can re-absorb up to 95% of the filtered element. Excess doses of magnesium are not stored by the body above and beyond what is needed. Any amount beyond what is needed physiologically is excreted primarily by the kidneys. Serum levels of magnesium range from 0.65 to 1.0 millimoles per liter are tightly regulated primarily through kidney excretion. Serum, red blood cell, and urinary excretion rates are not reliable indicators of true magnesium status in the body. An intravenous magnesium loading dose followed by a 24-hour urine collection is a more reliable, though impractical way of assessing true magnesium levels.[1-3]

The RDA or recommended dietary allowance or RDI or intake of magnesium has been calculated as follows: 1-3 year olds require 80 milligrams per day; 4-8 year olds require 130 milligrams per day; 9-13 year olds require 240 milligrams per day; 14-18 year olds require 360 milligrams for females and 410 milligrams for males; 19-30 year olds require 310 milligrams for females and 400 milligrams for males; 31 to 50 year olds require 320 milligrams for females and 420 milligrams for males; and 51 year olds and older require 320 milligrams for females and 420 milligrams for males.[1,2,4]

Food sources of magnesium include vegetables, whole grains, beans and legumes and nuts and seeds. Dark, green leafy vegetables that are rich in the pigment chlorophyll have a high magnesium content. Drinking water, especially hard or alkaline water, can contain up to 10% of the total dietary intake of magnesium. One-half cup of cooked spinach contains 80 milligrams of magnesium.. Nuts and seeds contain a fairly high amount of magnesium. One ounce of pumpkin seeds contain 156 milligrams of magnesium, one ounce of chia seeds contains 111 milligrams, and one ounce of almonds or cashews contains 80 milligrams of magnesium. One medium-sized avocado contains about 80 milligrams. One ounce of dark chocolate contains about 64 milligrams. One cup of beans contains about 100 milligrams. One medium-sized banana contains 36 milligrams. Dairy products are considered to be a poor source of magnesium.[4]

There are many different and complicated factors that can ultimately affect magnesium absorption. It is not just the type and dose of magnesium but also other confounding factors that contribute or hinder magnesium bioavailability. Increased age, dehydration, gastrointestinal disease such as celiac disease, Crohn's disease and inflammatory colitis, the use of acid-inhibiting drugs like proton pump inhibitors or other medicines that affect digestion can inhibit absorption. The consumption of larger quantities of both soluble and insoluble fibers when taking magnesium may hinder absorption. Also, the concomitant consumption of larger doses of minerals like iron, calcium, zinc, and copper can decrease magnesium absorption. Some studies show that more physiologic doses of minerals, such as calcium doses less than 1000 milligrams has negligible effects on magnesium absorption. Also, an increased BMI or body mass index above 30 is associated with decreased magnesium absorption. Factors that increase magnesium absorption include the consumption of magnesium with food, including carbohydrates, fats and proteins. Simple carbohydrates increase magnesium absorption. Small and medium sized fats and oils improve magnesium absorption. Proteins and amino acids improve magnesium absorption. Taking magnesium with food can slow intestinal transit time

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and increase availability for absorption. As intestinal pH increased from 7.4 to more than 8.4, magnesium absorption decreased from 85% to 50%. A lower intestinal pH can improve solubility and increase magnesium absorption. Drinking some water can help improve solubility of magnesium and can potentially improve absorption. Probiotics, especially Bifidobacterium can increase magnesium absorption slightly. Vitamin D and PTH (parathyroid hormone) can slightly increase magnesium absorption. Estrogen can slightly increase magnesium absorption. There is also variation of magnesium absorption through biological circadian rhythm variability up to 6%.[7-13]

In conclusion, undeniably magnesium is an important nutrient in human health. Magnesium deficiency is a common deficiency in North America. Magnesium supplementation can help prevent deficiency and treat certain illnesses. There are many different types of magnesium supplements in the marketplace. Exactly which magnesium supplement is best for specific health conditions is debatable. Many factors affect magnesium absorption in the human body. It is difficult to provide a specific absorption rate for each different magnesium supplement due to many other confounding factors that can affect bioavailability. The absorption rate can vary from 10 to 70% of total ingested amounts, but probably averages between 30 and 40%. Inorganic forms of magnesium complexes are less absorbed than organic carbon-containing complexes. More soluble and ionic forms tend to be absorbed better. The higher dose of insoluble inorganic forms and increased percentage of magnesium offsets its relatively weaker absorption rate. Inorganic forms such as magnesium oxide and hydroxide have lower absorption rates but contain more elemental magnesium per equivalent dose by weight. Organic forms such as magnesium citrate, glycinate, and malate have higher absorption rates but contain less magnesium per equivalent dose by weight. Taking magnesium with water or food can enhance magnesium absorption. Taking more doses throughout the day is probably better than taking one larger single dose.

The type of magnesium compound, the amount of elemental magnesium per dose, its solubility and other dietary factors such as with food or without can influence absorption rates. I recommend taking a dose that meets or slightly exceeds the RDA for a specific age group of elemental magnesium per day as a nutritional supplement from a variety of natural complexes to meet the RDA and treat magnesium-related comorbidities. Occasionally, supra-physiologic doses may be recommended for specific health conditions and it is recommended to talk to a natural health care practitioner for specific dosing instructions.

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Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, MSW
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Homeopathy for Restless Legs Syndrome with Anxiety

Restless legs syndrome (RLS) is, at best, annoying and, at worst, maddening. It is characterized by an irresistible urge to move the legs and can be extremely disruptive to one's much-needed sleep. It typically occurs in the evening or during the night while one is sitting or lying down. RLS can begin at any age, but typically worsens with age What generally affects patients the most is daytime weariness or drowsiness, plus the nagging, even irresistible urge to move the legs or feet. The sensation is variably described as creeping, crawling, aching, throbbing, itching, shock-like, or throbbing. The particular sensation that each patient experiences can be the key to differentiating the correct remedy, particularly if the patient needs a plant remedy. More common in women than men, it may cause a patient to seek medical help or (s)he may self-manage with medications or self-help techniques.

Though I often present cases of more unusual homeopathic remedies, that is not the case in this article. What I prescribed happens to be the first remedy even beginning homeopaths consider for RLS, yet that was not the case with this patient. Though the case is simple, it allows for a good differentiation of other close remedies.

First Visit

Paula, 60 years old, was from Philadelphia. She had been given *Kali carbonicum* (potassium carbonate in LM potencies from 1 to 15) by a local homeopath for ten years. She was pleased with the results over a seven-year period, which she described as "almost getting a cure": "Just as I'm starting to fall asleep, a leg or foot twitches or moves by itself. They call it 'periodic limb movement disorder.' I was taking Lunesta four nights a week, then melatonin and cannabinoids the other nights. And Ambien for eight years."

I noticed from the beginning that Paula was organized, repetitive, and wanted to make sure I was getting the picture that she was trying to convey. She had obviously read up on the condition, in addition to having suffered from it for years. She wanted to be involved in all of the decision making in her case – nothing left to chance. Patients with this type of personality: organized, structured, thorough, suggest a mineral remedy, as opposed to an animal or a plant. Their speech tends to be to the point, straightforward, systematic, fastidious, repetitive.

"I'm now going to a sleep specialist at Temple University. She has me on time-release Ambien. The drugs have caused pressure inside my ears. I've lived in the same house for nine years. Saw the same homeopath for over ten. A few years ago, I decided to manage the potency changes of the *Kali carbonicum* myself, but the pressure in my ears returned, so I went back to my homeopath. Then all of my symptoms came back. I freaked out. I got very depressed and anxious. I'd start to fall asleep, then have a limb movement and wake up. It happens really quickly – a a foot or leg or arm will jerk or twitch by itself. Enough that it wakes me up. There is no pain. Last winter I tried strong coffee in the AM. Then sometimes pot to relax.

"Growing up I probably had ADHD. I was hyper, had a short attention span, and I didn't do well in school. I was pretty controlling. Wanted to have things my way. But I had a lot of friends. As an adult I worked for the phone company in a service capacity. I couldn't stand folks yelling at me. After all, I was trying to help them. They would get upset and I would feel victimized. A close friend told me that I was too introverted. I am so organized. I write everything down and feel bad if I forget something. I'm quite cautious and protect myself against danger.

"When I first got the movement condition, I would get a head tremor. It was aggravated when I was thinking of one thing then quickly switched to another. I have a history of hepatitis B, so I avoid anything with acid or high fat. It is better now. I took Effexor for a number of years. Then I titrated it down and quit. SSRIs can cause permanent side effects. Once I took an antihistamine for sleep and had a panic attack. I stopped breathing. Years ago, I had a panic attack trying to make a train. That's when the limb movement disorder began. Since then, I have it every time I fall asleep."

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Paula was a rule-oriented woman. If she didn't agree with what someone else did, she wouldn't have much to do with them. She felt that the *Kali carbonicum* had helped, but she still had to meticulously juggle a number of other medications to avoid being up with limb movements. She spent much of the first appointment describing in detail her medication regimen. Other annoying complaints were tinnitus (ringing) of the left ear, arthritic neck pain, tendinitis of the wrists, and stiffness of the neck and back.

Analyzing the Case

This is not a difficult case, especially using the *Sensation Method* of Dr. Rajan Sankaran. The remedy I prescribed happens to be the most common remedy in the homeopathic literature for restless legs. Paula's first homeopath came close to the right remedy but not just the right one (simillimum). So, Paula had responded well over the years, but not great, as can be seen since changing the remedy, especially by her most recent follow-up.

According to this method, Paula was a classic case for a mineral remedy: structured, organized, anxious about circumstances and relationships, nervous, fastidious, systematic. The first horizontal column in the homeopathic periodic table is the "*Kali*" line, which has to do with security and task. Common themes are a need for protection against external threat or attack, safety, tasks, vulnerability, home. The remedies belonging to this column includes *Kali and Calcium* (lacking a foundation and capacity for self-protection). The second column, in which the individual begins to develop the capacity to protect oneself includes *Scandium, Titanium, Vanadium,* and *Chromium.* These individuals do have the capacity to protect themselves and maintain their position, but they begin to face challenges and opposition. Remedies include *Manganum, Ferrum, Cobaltum, Niccolum, Cuprum, and Zincum.* On the righthand side of the periodic table for this group are *Galliium, Germanium, Arsenicum, Selenium*, and *Bromium*, where they begin, and continue to lose, the capacity for self-protection. This often happens with age. It so happens that *Zincum metallicum* is the first remedy a homeopath learns for restless feet and legs.

Rajan has created a beautiful system of differentiation between these remedies. I recently treated a new patient from Eastern Europe who was being treated conventionally for bladder cancer, was a highly responsible, matter-of-fact farmer, and has benefitted significantly from *Gallium* (a remedy further to the right on the period table from *Zincum*.)

Zincum uncovered the foot and leg twitches, anxiety, ear pressure at night. I've seen Paula for a year and a half. I started with *Zincum* 200C once and *Zincum* LM6 daily. So, Paula's previous homeopath's prescription, *Kali carbonicum*, was quite close, but didn't hold. She had prescribed exclusively LM remedies, but I prefer, in most cases, to jump start the case a higher potency, one to four times, followed by a daily, liquid LM remedy. I gave Paula one dose of *Zincum metallicum* 200C followed by five drops daily of LM6. She did not know what I gave her.

Six Weeks Later

A week after starting the *Zincum*, the leg symptoms were improved. Ear pressure is better. "I am sleeping slightly better. I used to take 50 mg of zinc to release the ear pressure. I cut it to ¼ tablet (she hadn't mentioned previously that she was taking a zinc supplement). I'm a little more patient with people. A little more friendly, caring, empathetic." I changed the prescription to *Zincum* 200C plussed as needed instead of an LM potency.

Three-Month Follow-up

"Something significant happened. The night I took this dose of *Zincum* 200C, I fell sound asleep, no restless legs syndrome. I took it again the next morning. You nailed it with the remedy. I read about it. You picked up on some things I didn't tell you. Everything about the *Zinc* personality traits was me. The neuropathy in my foot came and went. I hadn't had it for about ten years. My legs were 95% better. But I think the dose is wearing off, diminished." I repeated one dose of the *Zincum* 200C as needed and continued with the LM6 daiiy.

Over the Following Months

Paula continued to improve. I had a brainstorm, or so I thought, to prescribe *Zincum arsenicosum* (the *Zincum* symptoms plus the anxiety, fears, and disturbed sleep of *Arsenicum album*). I tried it, but she made it very clear that she felt worse, so I went back to the *Zincum.* She didn't feel comfortable going up to a 1M potency, so I continued with the *Zincum* 200C.

Then, over the following five months, on the same remedy in the same potency, she improved greatly. Her sleep improved. She noticed that she felt really well and slept soundly, even if she didn't take her supplements. This was quite a leap. She gained fifteen pounds, which was much needed. She suddenly felt like "testing the waters" of a new relationship, for the first time in over a decade. The improvement was remarkable but had taken time.

A Year and a Half After Changing to *Zincum*

The proof that a remedy is correct is to follow the progress of a patient over time. "I'm doing really well. The pressure in my ears is nearly gone. I am not needing anything for it. The tinnitus is not as loud. I've gained twenty-five pounds in all. I'm feeling stronger. I'm more comfortable going to the gym now because I look so much better. I'm feeling stronger physically and mentally. Not as weak. The arthritis in my wrist is much better. I'm not as afraid of things. The neuropathy in my left foot is completely gone. I have taken only the *Zincum* LM6 for the past six months, no 200C. I am sleeping nearly eight hours a night. I am just about to start a relationship with someone I found online. We have a lot in common. I'm thinking of getting a boxer like one I had a long time ago. I think this is going to be a good year for me. "

This was a night-and-day change in Paula. Over time, she is literally a different woman. The change was much more gradual than I expected, and I am still surprised that the *Zincum arsenicum* didn't work. But she is at least 80% better overall and much happier. Not only did the RLS improve dramatically, so has her life!

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Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Arming the Immune System

The most revolutionary idea I learned as a student at the National College of Naturopathic Medicine back in the day was that fever is good. Fever is Nature's reaction to infection, and our best course of action is to 'let it ride,' an expression that I don't recall using until I read it in Gurdev Parmar's new book, *Arming the Immune System*. As naturopathic doctors we learned to encourage a fever. It was the most important topic Anna MacIntosh taught us in our first year of study.

As I recall it, Dr MacIntosh's class was about how to read and critique scientific papers. Nevertheless, she had us read the famous lizard paper, the one that describes how lizards, fish, and other cold-blooded animals move to the heated portion of their terrariums or aquariums when infected by bacteria in order to raise their body temperatures so as to mimic the endogenously triggered fevers in warm-blooded animals. Fever is a universal strategy that higher organisms employ to fight infection, a technique of immune stimulation that has been conserved in evolution since almost the beginning of life.

The term 'revolutionary' might not be appropriate to describe such a conservative strategy, yet our naturopathic approach to encouraging fever seemed revolutionary when it was introduced in comparison to the commonly held view that fever should be suppressed. Up until then, I was of the modern school of thought that viewed fever as potentially dangerous and best suppressed with antipyretic measures.

The benefits of fever are the focus of our colleague Gurdev Parmer's new book*, Arming the Immune System.* Really, fever is pretty much what the entire book is about. Dr. Parmer describes the fever research in greater detail than we touched on during naturopathic training, in part because much of what he has to tell us is new research.

For those of you who are unfamiliar with Gurdev's naturopathic practice, he specializes in naturopathic oncology and is best known for treating his patients with hyperthermia, localized and whole-body hyperthermia. In fact, he is chiefly responsible for introducing hyperthermia treatments to modern naturopathic oncology and has likely supervised more hyperthermic treatments than not just any other naturopathic doctor in North America but likely more than all of us put together. Yet this aspect of his experience is barely touched on in his book. I had hoped to read more information gained from his experience.

Instead of being a book written for his friends and colleagues eager to learn from him, it feels like the book is targeted for a general audience who Dr. Parmer wants to convince of the benefits of fever in fighting disease. His writing style has been dumbed down considerably from the precise diction we appreciated in the *Textbook of Naturopathic Oncology*, which Dr Parmer was the driving force behind, into a style of chummy familiarity that pushes the limits of informality. I confess that I may sometimes be guilty of similar lapses, such as referring to authors of scientific papers as 'guys', but usually one of my diligent editors will catch me doing so and correct my choice of words. Simplifying one's choices in words to be more understandable to those lacking an advanced medical education requires more than referring to individuals as 'guys' and a plurality of specific things as 'stuff.' As much as the book seems to be carefully written, it lacks the polishing touch of an editor and professional proofreader. Perhaps this is a matter of economy, but I found myself reading with a red pencil in hand so I might circle errors. But that's me and I hope others aren't so cursed with a similar habit. Really, I am not the one to talk about this, guilty as I often am of sloppy writing myself.

Fever and hyperthermia are not exactly the same thing. A fever is an endogenous response in the body to a perceived threat, usually an infection, in which the body's temperature set point is increased so that body temperature rises. Hyperthermia is when the body's internal temperature is increased by an external heat source, and normal compensatory measures are insufficient to prevent overheating. Hyperthermia is perhaps closer to heatstroke than a fever. A naturally triggered fever may have more benefit in fighting infection or cancer than artificially induced hyperthermia. Various techniques have

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been used over the centuries to trigger fever responses. Perhaps the best known are the cancer treatments of a century ago pioneered by William Coley, who used live pathogenic bacteria to trigger infections and fever, or he employed bacterial extracts that he called 'toxins' to fool the body into thinking an infection was present. In his book, Parmar provides one of the most complete histories of Coley's contributions to cancer treatment that I have yet had the pleasure of reading. He goes on to put these techniques into the context of modern immunotherapy treatments.

What I would have enjoyed reading would have been a similar history of the development and use of the hyperthermia treatments Parmar uses in his clinic, in particular, how Dr. Parmer became so interested in these techniques, and more about both his experience and the research he has conducted on such artificial fevers. I had assumed prior to reading that Parmer's book would turn into something of a sales-pitch for his clinic, but he refused to go there. Oddly enough I find myself disappointed that he didn't. I was hoping that I would have been able to hand cancer patients this book to read and when finished or even before they were finished, they would be sold on the potential benefit of hyperthermia therapy and be making plans to go see Gurdev or be trying some DIY technique to induce hyperthermia at home, using some combination of sauna, herbs, hot tubs, or infrared heating pads. If it was a sales pitch, it was way too soft a sell and lacked any tangible push to close the sale. Gurdev, for all his success in practice, turns out to be a humble guy and not quite the self-promoter.

The wholehearted support for 'letting fevers ride', that is not suppressing the body's natural inclination to run a fever, is welcome to a point. There are two concerns regarding fever that I would have preferred to see addressed early on. The first is the long-standing belief that high fevers in infants may trigger febrile seizures. The second are the fevers that may occur in neutropenic cancer patients whose immune defenses have been trashed by chemotherapy. Dr. Parmer does address concern over febrile seizures adequately but late into the book, at a point that a concerned parent may have already put the book down. If Gurdev touched on the concern of neutropenic fevers in cancer patients, I must have missed it. Do we want our cancer patients to catch some sort of infection and run a fever during the course of treatment? I am not sure. I have a long list of questions in this regard and would have liked to read more specific responses as to where Dr. Parmer's opinions point.

In the past I have found fault in the literary contributions of colleagues because they or their publishers have, in order to save on printing costs, omitted references. This is not a problem here; in fact, Gurdev has done a superb job, including citations for every study and key idea he mentions. If I were to complain about anything, and those who know me expect I pretty much always will find fault somewhere, it is that the book ends too soon. Summing up what's written, basically Gurdev tells us that 'fever is good, it arms the immune system to fight infection and cancer, and therefore we should not suppress fever.' But that's where his book ends. Gurdev does bring up a tantalizing suggestion that perhaps our modern efforts to suppress fever may contribute to our modern preponderance of immune disorders and ongoing elevated cancer incidence. That's where the book ends. Perhaps there is a second book on the way. I'm hoping so as there is certainly more to this story. ◆

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Women's Health Update

by Tori Hudson, ND
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Desquamative Inflammatory Vaginitis

The term inflammatory vaginitis (IV) distinguishes a mild to moderate pattern from the florid inflammatory pattern of desquamative inflammatory vaginitis (DIV). Many symptomatic women who have an obvious abnormal wet prep with an inflammatory response do not meet the criteria for DIV. These women typically have a copious discharge with a subtle odor and vulvovaginal irritation that is mildly annoying rather than distressing, as with DIV.

Desquamative inflammatory vaginitis is one of those uncommon forms of chronic purulent vaginal discharge that you won't see frequently in a women's health practice, but you need to know of its characteristics and you must consider it when the most common causes of abnormal discharge in pre- and postmenopausal women such as bacterial vaginosis, vulvovaginal candidiasis, and trichomonas vaginitis, have been excluded. DIV is considered a noninfectious cause of inflammatory vaginitis with the highest incidence in perimenopausal Caucasian women.[1] One of the challenges with DIV is that the symptoms and signs are nonspecific, but the main symptoms are purulent discharge, vestibule-vaginal irritation and dyspareunia. A vaginal wall exam appears inflammatory with increased erythema and petechiae. Vaginal pH is >4.5. Under the microscope, a wet mount of the vaginal secretions shows up as an increase in inflammatory cells and immature squamous cells, called parabasal cells. Microscopic viewing also reveals numerous leukocytes and few to no lactobacilli. The background has clumps of bacteria, and squamous cells are speckled with bacteria.

The etiology and pathogenesis remain unknown; but because it responds to anti-inflammatory agents, this suggests that it is immune mediated. A conventional approach includes either local vaginal clindamycin and/or vaginal corticosteroids. A conventional approach also admits that it is considered a chronic condition with common relapses and thus ongoing or intermittent treatment is needed.

While DIV is considered a noninfectious etiology, there can be secondary bacterial microbiota disruption. Some investigators and clinicians believe the condition is due to altered vaginal flora, namely *Escherichia coli* and refer to it as aerobic vaginitis with a low or near absence of lactic acid-producing lactobacilli.[2] Others propose that the underlying mechanisms include estrogen deficiency, a toxic reaction to *Staphylococcus aureus,* or some immune abnormality.[3, 4]

Key Clinical History Points

- More common in perimenopausal women but can occur premenopausal or postmenopausal
- Women with DIV present with pain and copious vaginal discharge.
- The pain can be described as dyspareunia, vaginal/introital pain, burning, or a combination.
- The discharge can be white, gray, green or yellowish.
- A diffuse exudative vaginal wall inflammation may be visible.
- Women with DIV have often had symptoms for more than one year and have been treated multiple times for other causes of vaginitis without relief.

What to Look for on Exam

- External genitalia – Normal vulvovaginal architecture. The vestibule may be thinned, sensitive, erythematous, and edematous. (This may be a a result of irritation from the discharge or, more likely, due to inflammation of the vestibule similar to what we see on the vaginal wall.)
- Vagina – a spotty ecchymotic rash or diffuse or focal erythema or linear erosions.
- Cervix – Erosive lesions, similar to those seen with trichomoniasis infection; Ectropion may be visible.

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Laboratory Tests/Diagnostic Evaluation

- Vaginal pH >4.5 (Remember: inflammatory vaginitis (not desquamative), atrophic vaginitis and trichomonas may also have this elevated pH although atrophic vaginitis tends to be >5.)
- Wet mount microscopy: increased number of parabasal and inflammatory cells, and the leukocyte to epithelial cell ratio is greater than 1:1
- Microscopically, on low power, there are numerous leukocytes but with no clustering or sheets. On high power, there is a mixture of leukocytes but mainly agranulocytes (particularly lymphocytes) and few to no lactobacilli. The background has clumps of bacteria, and squamous cells are speckled with bacteria.
- Laboratory tests for gonorrhea, chlamydia, bacterial vaginosis, candidiasis, and trichomoniasis are performed to exclude these causes and any women with vesicular lesions should be tested for herpes simplex virus. Peri and postmenopausal women with a pH>4.5 with reports of vaginal and/or vulvar dryness and/or itching, and dyspareunia, likely have atrophic vaginitis due to low estrogen. Severe atrophic vulvovaginitis can mimic DIV. A trial of low dose vaginal estrogen and a result in relief of symptoms clarifies the diagnosis as atrophic vaginitis, now called genitourinary syndrome of menopause (GSM).
- Erosive or dermatologic disorders include erosive lichen planus, pemphigus vulgaris, and cicatricial pemphigoid. It is important to know that DIV typically occurs in perimenopausal women, while erosive lichen planus and cicatricial pemphigoid typically occur in menopausal women. Biopsies are needed to confirm these diagnoses.

The diagnosis of DIV requires ALL of the following criteria:

- At least one of the following symptoms: vaginal discharge, dyspareunia, pruritus, burning, irritation
- Vaginal inflammation (spotted ecchymotic rash, erythema, focal or linear erosion)
- Vaginal pH >4.5 (some report >6)
- Wet mount microscopy showing increased numbers of parabasal and inflammatory cells (leukocyte to epithelial cell ratio greater than 1:1

Treatments

The two most common conventional treatments are intravaginal clindamycin or glucocorticoids. Options for initial therapy include either of the following:

- 2% clindamycin cream; 5 grams (dosed by vaginal applicator) intravaginally once daily for one to three weeks, with some reports of up to four to six weeks. Consider maintenance of once or twice a week for two to six months

OR

- 10% hydrocortisone cream 300 to 500 mg (dosed by vaginal applicator) intravaginally once daily for three weeks and up to six to eight weeks. Consider maintenance once or twice a week for two to six months. It may be used longer if one lowers the strength to 0.5% or uses less of the 10%. Ten percent hydrocortisone cream is not commercially available but can be compounded by a pharmacist. For mild disease, twice daily vaginal insertion of hydrocortisone cream 0.5% could be considered. Duration is individual, but the goal is resolution symptomatically, visually with exam, and microscopically.

Also use:

- Low dose vaginal estrogen if also atrophic vaginitis; (one example Rx: 0.01% estradiol vaginal cream; 2 gm once daily for 1-2 weeks followed by 1 gm 1-3 times weekly maintenance and ongoing into the distant future.)

A More Integrative Approach

I have found that using the vaginal antibiotic is important for this condition along with vaginal estrogen in those women who also have atrophic changes, which is typically the perimenopausal and even more so, menopausal women. While I do frequently incorporate the hydrocortisone cream to reduce inflammation, there are specialty creams compounded from a compounding pharmacy that you can inquire about; consider a compounded formulation of glutamine 10 mg/gm-cromolyn sodium 20 mg/gm-aloe 20 mg/gm from the compounding pharmacy. If inadequate as a replacement for hydrocortisone, it may be a good follow-up strategy to prevent relapse.

My clinical experience, understanding of the underlying vaginal flora imbalance, and knowing of the low rates of cure and high rates of relapse with conventional treatment only has caused me to improve vaginal ecology with vaginal-specific lactobacillus. These vaginal suppositories need to include *Lactobacillus rhamnosus, L. rheuteri, L. acidophilus, L. plantarum, L. salivarius*, and possibly *L. crispatus*. I would insert one capsule daily for two weeks then one to two times weekly for 12 weeks.

Measures of Success. Complete symptom relief, clinical exam normal, and a normal microscopic exam are necessary to achieve complete success. If all of these are achieved, the clindamycin and hydrocortisone can be stopped. Keep in mind that during the use of clindamycin, colonization of lactobacilli are reduced, especially during use of hydrocortisone cream. This is why I advocate for using the vaginal-specific lactobacilli during and following the main phase of treatment.

Recurrence and Relapse. For those women who do not relapse within three to six months, they are likely cured. Unfortunately, with the conventional treatment only, recurrence is common after discontinuation of therapy and about 30% relapse within six weeks after discontinuing treatment. Twenty-five percent of women remained disease-free at one year after a single course of treatment.

The maintenance plan and tapering plan are quite variable from patient to patient. If one tried clindamycin first and there was relapse, then the second attempt could be switched to the hydrocortisone, and vice versa. The practitioner can continue

to taper slowly as long as she remains symptom free and there is no increase in leukocytes and parabasal cells on microscopy. I typically see these patients every four to six weeks for the first six months and then less often but again stressing the importance of achieving good vaginal colonization with lactobacilli and a return to a normal pH of 3.5-4.5

Some women may require use of suppressive therapy for months or years before it is possible to discontinue therapy without relapse. For women who do not respond to either the clindamycin or the hydrocortisone, there are careful regimens using tacrolimus 0.03% or clobetasol 0.05%. If you are not familiar with these medicines, then I would seek the advice of a specialist.

Be aware that when such robust use of clindamycin or hydrocortisone are used, a vaginal candida infection may occur. This is one more reason to incorporate the lactobacillus suppositories, but boric acid suppositories or oral antifungals such as fluconazole may be necessary.

Women's Health Update

Treating women with DIV requires being well informed, patience, creative and flexible thinking, empathy and availability to the women struggling with this condition. They've likely been to several doctors with an inaccurate diagnosis and thus an unsatisfactory outcome. We can't make promises, but with a deeper understanding of the condition, treatment options, and the fundamental principle of restoring a normal vaginal ecosystem, more women will be helped more of the time.

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Editorial

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resolved included low energy, "brain fog," sleeping difficulties, depression, and anxiety. Patients also reported they felt more alert and stronger. Two patients discontinued DTE because of cardiac symptoms.[2]

The other recent study was a double-blind crossover trial. Seventy-five hypothyroid patients (aged 18-65 years) who were on a stable dose of T4 for at least six months were treated in random order with T4, DTE, and a combination of synthetic T3/T4, each for 22 weeks. Six weeks after the start of each treatment period, TSH levels were measured, and the dosage was adjusted to maintain the level between 0.27 and 4.20 µIU/ml. Among the 20 patients who were the most symptomatic at the start of the study, 50% preferred the T3/T4 combination, 35% preferred DTE, 10% preferred T4, and 5% had no preference. Thus, in the subgroup of patients who were not doing well on T4 monotherapy, 85% felt better with a product that contained both T3 and T4. Among those 20 patients, treatments containing T3/T4, as compared with T4 alone, were associated with better scores on the 36-point thyroid symptom questionnaire, the 12-point quality of life general health questionnaire, and the Beck Depression Inventory.[3]

In 2014, the American Thyroid Association's Task Force on Thyroid Hormone Replacement updated its guidelines regarding the treatment of hypothyroidism.[4] The Task Force concluded that "levothyroxine should remain the standard of care for treating hypothyroidism. We found no consistently strong evidence for the superiority of alternative preparations (e.g., levothyroxine-liothyronine combination therapy, or thyroid extract therapy, or others) over monotherapy with levothyroxine, in improving health outcomes."

It is well known that around 5-10% of hypothyroid patients continue to experience profound and sometimes disabling symptoms such as fatigue, depression, and impaired cognition, despite receiving T4 in dosages that normalize laboratory tests for thyroid function. In my experience, these patients often fare much better when switched to DTE. Many other patients whose symptoms while on T4 are not profound or disabling also feel better with DTE than with T4.

I believe that the current American Thyroid Association's practice guidelines lead to substandard care for a substantial minority of hypothyroid patients. DTE has been used for more than 100 years, and anyone who has clinical experience with it knows that in some cases it is clearly more effective than T4 monotherapy. It is time for the practice guidelines to be updated, to acknowledge the appropriateness of using DTE or T3/T4 combinations in selected cases.

Alan R. Gaby, MD

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Practice Guidelines for the Treatment of Hypothyroidism Need to Improve

For many decades, the prevailing opinion in mainstream medicine has been that levothyroxine (T4) is the only appropriate treatment for nearly all patients with hypothyroidism. During that time, some practitioners (including this writer) have held a dissenting opinion. Our view is that a substantial minority of hypothyroid patients respond better to preparations that contain both T4 and triiodothyronine (T3; also called liothyronine) than to products that contain only T4.

It is generally agreed that T3 is the biologically active thyroid hormone and that T4 is a precursor molecule that is converted in the body to T3. The argument used to support the mainstream opinion about thyroid therapy is that the body is capable of converting T4 to T3 at exactly the rate it needs to. Thus, even though the human thyroid gland secretes both T3 and T4, T4 alone is all that is needed for complete thyroid hormone-replacement therapy.

Those of us who hold the dissenting view do so for a simple but important reason. We have seen many patients whose hypothyroid symptoms failed to improve with T4 therapy alone. When these patients were switched to a product that contained both T3 and T4, their symptoms improved dramatically, sometimes in as little as 24 to 48 hours. The T3/T4 product I have used most often is desiccated thyroid extract (DTE), which is an extract from porcine thyroid glands. Other practitioners have seen good results using the combination of synthetic T3 and T4.

A double-blind trial published in 2013 supported the observation that some hypothyroid patients have a better response to DTE than to T4. In that study, 70 patients (aged 18-65 years) who had been on a stable dose of T4 for at least 6 months were randomly assigned to receive T4 or DTE for 16 weeks, and then the alternate treatment for an additional 16 weeks. After 6 weeks on each regimen, thyroid-stimulating hormone (TSH) levels were measured and the dosage was adjusted to maintain a level between 0.5 and 3.0 µIU/ml. Compared with T4, DTE treatment was associated with a trend toward improvement on the general health questionnaire ($p < 0.1$), the thyroid symptom questionnaire ($p = 0.12$), and the auditory memory index ($p = 0.08$). At the end of the study, 34 patients (48.6%) preferred DTE, 13 (18.6%) preferred T4, and 23 (32.9%) had no preference. There were no significant changes in heart rate or blood pressure during the study.[1]

Two recently published studies provided further support for the idea that combination therapy with T3/T4 is more effective for some people than T4 alone. In one of these studies, 31 hypothyroid patients whose symptoms had failed to improve during treatment with appropriate doses of T4 were switched to DTE. The mean age of the patients was 49.4 years (range, 26-77 years), and the mean length of time since the diagnosis of hypothyroidism was 12.6 years (range, 2-40 years). At the six-month follow-up visit, symptoms had improved in most of the patients, although two patients reported that their symptoms were worse. The magnitude of the improvement in the group as a whole was considered large. Symptoms that frequently improved or

continued on page 79 ➤

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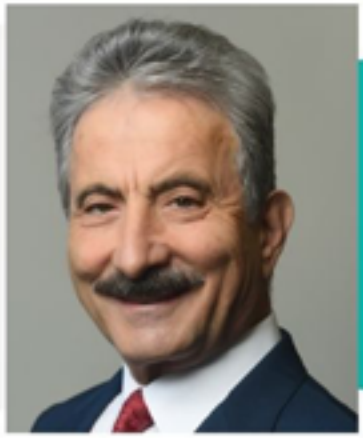

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