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Dr. Anne Marie Fine, NMD
Skin Absorption and Personal Care Products

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Antonio MAD, *et al. Journal of Infectious Diseases* 1999;180:1950–6.

Clinical Study #2 (2007)

In another study involving 126 healthy pregnant women, *L. crispatus* and *L. gasseri* were the most dominant species found, followed by *L. jensenii* and *L. rhamnosus*.*

Kiss H, *et al. BJOG: An International Journal of Obstetrics & Gynaecology* 2007;114: 1402-1407.

Clinical Study #3 (2014)

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Kaufmann U, *et al. Eur J Obstet Gynecol Reprod Biol.* 2014 Jan;172:102-5.

Clinical Study #4 (2016)

In immunosuppressed pregnant women with herpes infection, oral supplementation with the four Astarte strains significantly reduced undesirable microbes in the intestines and vagina, and simultaneously increased vaginal *Lactobacilli* 3-fold compared to placebo.* This was accompanied by reduced incidence of placental insufficiency, pre-eclampsia and fetal distress in the probiotic supplemented women.

Anoshina TM, *et al. Perinatologiya I Pediatriya* 2016;4(68):22-25.

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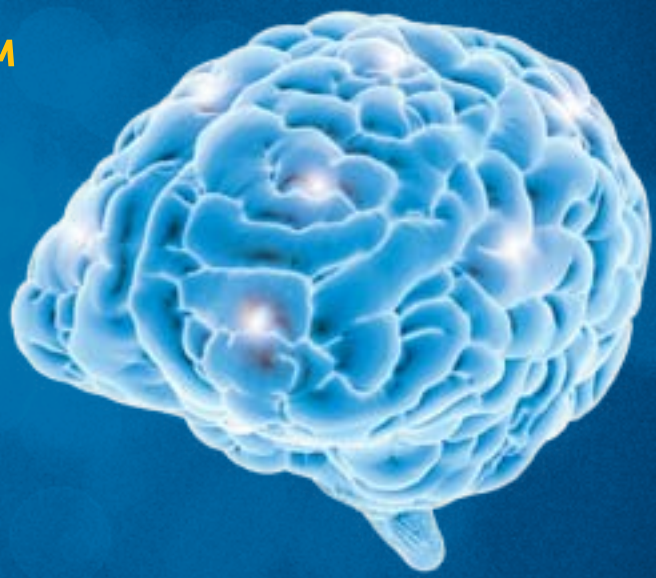

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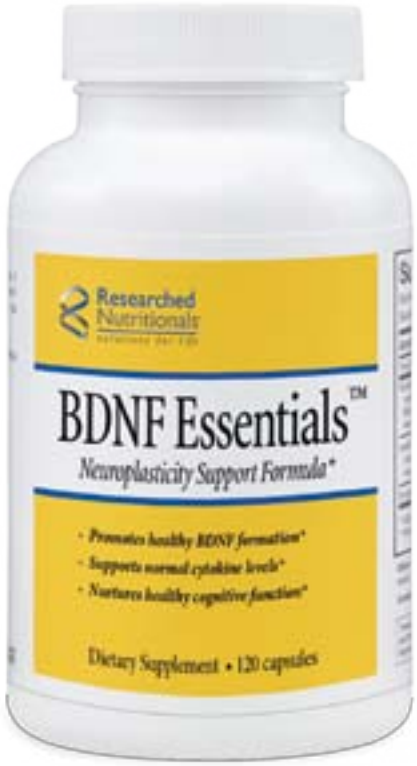

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From the Publisher

Sussanna Czeranko, ND's *Hydrotherapy in Naturopathic Medicine*

The other day I treated myself to a day at the spa; well, not quite, it was what I could improvise at home. First, I sustained a 20-minute session on the vibration plate, a device that shakes you from side-to-side at variable speeds. My machine claims that you burn calories although I doubt that it runs up anywhere near the number that the stationary bicycle or elliptical machine will. However, much to the dismay of naysayers, everyone who gives it a fair trial notices relaxation of their musculature better than a hand-held massager but not quite as good as time with the masseuse. Next, I submitted myself to 30 minutes inside the infrared sauna unit. I set the temperature to 139 degrees F and it took a good 10 to 15 minutes before the sweat begins to drip. By the time I was done I was definitely ready to cool off. So I prepared a cool bath – I'm not quite ready for the cold bath – to which I add some lavender and peppermint essential oil, hydrogen peroxide, and Epsom salts. I did follow that up with a cool shower and ended it with a short cold shower, then after donning a thick bath robe, lay down and napped for a brief time. From my perspective it did feel as energizing and relaxing as a day at the spa, and I look forward to treating myself to the same routinely. Make no mistake about it, however, if I have the opportunity to do a mud bath and massage at the spa in the future, I will jump on it.

In the summer of 2016 I was invited to speak at the Saskatchewan Association of Naturopathic Physicians meeting (which will be meeting again this June) at the pristine mineral lake of Manitou

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Letter from the Publisher

➤ *continued from page 4*

Beach. Sussanna Czeranko, ND, and her husband, David Schleich, hosted my wife, Deborah, and myself at their home close by the lake's shore. Sussanna invited us and their other guests down for a dip at the lake each morning at 7 a.m. Manitou Lake is fed from underground springs maintaining its high mineral composition. Even though it was August, the water temperature was cold but became quite tolerable and embracing as one swam about. The immersion went on for 15-30 minutes and then we emerged feeling invigorated, a sensation that lasted much of the day. When Sussanna and David retire from the National University of Natural Medicine this June, they plan to move from Portland to Manitou Lake where Sussanna will open her clinic and spa in the spatial home in which we sojourned. Dr. Czeranko will be employing a full range of hydrotherapy services including much of what she writes about in the book she edited, *Hydrotherapy in Naturopathic Medicine*.

The book is one in a series of twelve books edited by Czeranko in the Hevert Collection. The books include *Origins of Naturopathic Medicine, Philosophy of Naturopathic Medicine, Dietetics of Naturopathic Medicine, Principles of Naturopathic Medicine, Practice of Naturopathic Medicine, Vaccination and Naturopathic Medicine, Physical Culture in Naturopathic Medicine, Herbs in Naturopathic Medicine, Mental Culture in Naturopathic Medicine, Clinical Pearls of Naturopathic Medicine, Vol. I, and Clinical Pearls of Naturopathic Medicine, Vol. 2.* The articles published in each of the books come from the journals and books of the NUNM Rare Book Collection on Natural Medicine in Portland, Oregon, the largest and most complete collection of its kind in the US and Canada. Czeranko informed me that she has seen another large repository of older naturopathic literature in Austin at the University of Texas, but access to it is restricted!

Sussanna Czeranko, and Jonathan Collin

With twelve books to choose to review (one is still at press) why should I choose one on hydrotherapy? Perhaps, because of all naturopathic treatments and modalities, it is the one that is least prescribed and utilized. We begin the day with a shower or bath so what is so special about a soak in water? It's a good question and the writings of Benedict Lust, a New York naturopath practicing in the early 1900s, attempts to answer it in numerous articles in his journal, *The Naturopath and the Herald of Health.* Lust based much of his writing on the experiences

continued on page 8 ➤

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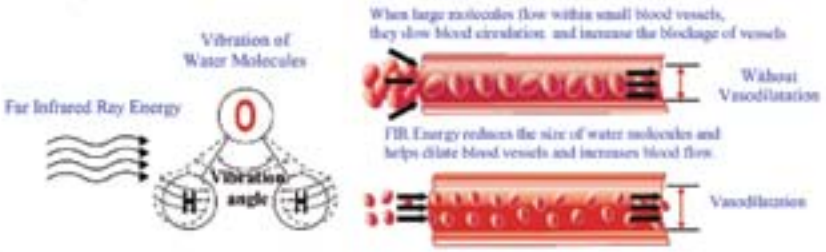

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Letter from the Publisher

➤ *continued from page 6*

of a German priest, Father Sebastian Kneipp, who established a major center for the water cure in a small German town in the late 1800s. Kneipp, in turn, based much of his thinking after reading about the water cure in a book by Johann Hann, *On the Power and Effect of Cold Water,* written a century earlier in 1737. Kneipp was to miss observing much of the experiences of an Austrian peasant, Vincent Priessnitz, who is considered by many to be the Father of Hydrotherapy. A farmer in the town of Graefenberg, Austria, in the early 1800s, Priessnitz observed the healing powers of cold water with its attendant heating reaction. Without any formal education, Priessnitz began administering cold water treatments to one and all with astounding benefit in restoring health – so dramatic that local doctors tore apart his home searching for the hidden cure. The hoteliers in Graefenberg later housed all the sick and invalid individuals who sought Priessnitz's water cure. Much of the therapies employed by Father Kneipp in his large center in Worshofen, Bavaria, were originally developed by Priessnitz including the wet sheet wrap, full bath, sitz bath, foot bath, and "douches" (showers). Father Kneipp's water treatment ultimately led to thousands of Europeans undergoing the water cure despite the hostility of the medical profession. Much of Benedict Lust's writing focused on Kneipp's techniques administered in his spas in New York City; Butler, New Jersey; and Tangerine, Florida.

So, what is the answer to why hydrotherapy should offer so much to be a water cure, or a cure at all? The answer appears to be that cold water or cool water initially causing cutaneous and localized vasoconstriction leads shortly and immediately to vasodilation. It is the compensatory vasodilation or heat reaction that is sought and initiates the healing response. In patients with acute febrile illnesses, the brief cold-water immersion lowers the temperature. Those with chronic inflammation modify their inflammation with exposure to cold water whether under sheets, in a bath, or under a shower.

Of course, the water cure was developed in a time before antibiotics, corticosteroids, NSAIDs, and related pharmaceuticals. Diets were often based on meat and potatoes or, in the poor, just the potatoes. The herbalist was visited infrequently. Doctors were very limited in resources; blood-letting was still practiced, tonics were peddled, and surgery was quite primitive. Water abundant everywhere, available cheaply, with no side effects was a perfect panacea. By the time Lust published his journal of naturopathy, spas across Europe and the US offered hydrotherapy to very accepting patients. Only when medicine sought to shut down naturopathic clinics and natural medicine treatments in the 1920s did hydrotherapy lose favor.

Despite its inclusion in current naturopathic medicine education, hydrotherapy remains underutilized and ignored. Czeranko's *Hydrotherapy* book amply explores its ins-and-outs in detail; her introduction details its history and major proponents in detail. Why should we take up a technique that largely has

been abandoned for a century? For one, it works; for two, it is non-toxic; and for three, it is a simple, but effective alternative to drugs and surgery. The ND and the integrative health practitioner would be well served with a read of Czeranko's book.

Jenna Henderson, ND, on Assessing Kidney Disease

Long-term readers will recall that Dr. Henderson has contributed four articles to our publication on diagnosing and treatment of kidney disease (please see our index on the website). Her practice has focused on naturopathic support for the patient with chronic nephrology, a specialty that is largely ignored by most of us because of the sheer difficulty in preserving, much less restoring nephron functioning. I am particularly pleased that the article she has written for this issue provides a "nuts-and-bolts" approach to measuring kidney pathology as well as offers an excellent overview of herbals and nutraceuticals that show in rodent experimentation incremental support of kidney filtration. I would keep a copy of this article in your review file – it will come in useful.

A few pearls that she offers: The eGFR and the creatinine provide important clues to kidney pathology but need to be weighed against interfering circumstances such as age, hydration, dietary protein consumption, and blood pressure status. Patients with chronic glomerulosclerosis may be living a charmed, asymptomatic life and then abruptly develop renal failure. Once the kidney is scarred restoration of filtration activity is very limited (perhaps one day stem cells may change this). Health food store supplements labelled as kidney formulations are usually directed at ameliorating cystitis or kidney stones but offer very little for maintaining nephron functioning.

Debby Hamilton, MD, MPH, on the Role of T helper Cells in Autoimmunity

This issue of the *Townsend Letter* focuses on inflammation and its role in acute and chronic disease. We all have a general idea of what inflammation represents especially in acute injuries and infections, but how does inflammation manifest on a more chronic basis? Moreover, when we consider autoimmune conditions such as rheumatoid arthritis, multiple sclerosis, Hashimoto's thyroiditis, and autistic spectrum disorder, how would we characterize the role of inflammation and immune dysfunctioning in causing and perpetuating the disorders? We often talk about various cytokines promoting inflammation while others calm it. Separating out two primary T helper cells, Th1 and Th2, provided a useful model to differentiate T-cell functioning.

Th1 cells were thought to primarily fight off intracellular viral infection, while Th2 cells were believed to attack extracellular bacterial or parasite invasion. The thinking was that if the Th1 and Th2 cells became imbalanced there would be immune dysfunction, with excess Th1 cells leading to autoimmunity and too many Th2 cells causing allergy and asthma. But this model failed because patients with autoimmunity, supposedly with a high Th1/Th2 ratio, were unable to fight off acute and chronic viral infections effectively. And not a few of these patients suffered with allergies thought to be related to excess Th2 cells.

As Dr. Hamilton discusses in part one of her two-part article a new T helper cell was discovered in 2003, the Th17 cell. Now the balance is drawn between three Th helper cells and maintaining that balance is ever so much more complicated than just balancing two helper cells. The evidence points to those patients whose cellular function is overwrought with Th17 cells will suffer autoimmunity. And those patients not only have too many Th17 cells but also a low Th1/Th2 ratio susceptible to viral infection and allergy. While these helper cells are running amuck, it is unlikely that the all too important T regulator (T-reg) cells, the fourth of the T helper cells, are sufficient to dampen the intensive immune response driven by an overproduction of pro-inflammatory cytokines.

Hamilton's article will give you an entirely new perspective on the immune system and inflammation.

Cover Story: Dr. Anne Marie Fine on the Skin as a Route of Entry for Toxins

When it becomes clear that a patient is loaded with toxins my first recommendation is to ask him/her to initiate sauna treatment. Steam can be used but dry heat, infrared sauna, is perfect to induce sweating. Sweating is remarkable in unloading toxic chemicals and metals. A combination of exercise followed by sauna enhances the detoxification process dramatically. Chemical analysis of subcutaneous fat before and after a series of sauna treatments demonstrates a significant reduction of pesticides, solvents, plasticizers, and toxic metals. The skin serves as an excellent excretory organ but only under the stimulus of a vital circulation and heat to sweat out the toxins.

What we ignore is the opposite process. It should be no surprise, physiologically, that if the skin can excrete chemicals it can absorb chemicals as well. As functional medicine physicians we employ this principle routinely with our prescriptions of bio-identical hormone creams. Hormone testing following daily application of hormones demonstrates a marked increase in hormone levels. However, if hormones are capable of being absorbed by the skin, so are the carrier excipients in the hormone cream. Moreover, our routine use of cosmetic products containing a wide variety of chemicals to enhance cleansing and tonifying our hair and skin, can also be absorbed by the skin and enter our circulation. What is the outcome of years of use of cosmetic products on our system? How much of a toxic chemical burden are we subjected to by skin absorption?

Anne Marie Fine, NMD, examines the major chemicals that we absorb daily through routine cosmetic use. The most concerning ingredients are parabens, phthalates, and triclosan. Toxic metals are also indiscriminately employed: lead is found in lipstick and aluminum in most anti-perspirants. Not surprisingly the cosmetic industry utilizes carcinogenic chemicals that go largely unnoticed because chemicals like quaternium-15 and polysorbate appear to be innocuous.

Reproductive problems, early menopause, breast and prostate cancer, and metabolic syndrome may be initiated and exacerbated by chemicals derived from cosmetics. Shouldn't we consider dermal toxicant absorption as part of our medical workup? Should we require chemical-free cosmetics as part of our medical prescription?

Jonathan Collin, MD

◆

Ninth Circuit Affirms Jury Verdict in Favor of Homeopathic Remedy for Flu-Like Symptoms

On November 8, 2018, the Ninth Circuit affirmed a jury verdict in a consumer class action deceptive advertising case in favor of Defendants Boiron Inc. and Boiron USA, Inc. (together, "Boiron"), the sellers of a homeopathic treatment for flu-like symptoms called Oscillococcinum ("Oscillo"). Although the Ninth Circuit's memorandum decision is marked "Not for Publication" and therefore is non-precedential under Ninth Circuit rules, the decision is still worth noting, as jury verdicts in class action false advertising cases are rare.

According to the appellate briefs, Oscillo's active ingredient is a compound (extracted from the heart and liver of the Muscovy duck for those foodies in our readership) that is subjected to a homeopathic dilution process. The diluted compound is then sprayed onto specially-manufactured granules. Plaintiff argued that, due to the homeopathic dilution process, Oscillo was essentially "water sprayed on sugar," which could not provide the relief from flu-like symptoms that Boiron advertised. Plaintiff claimed that Boiron had therefore violated two California deceptive advertising statutes, the Unfair Competition Law ("UCL") and Consumers Legal Remedies Act ("CLRA").

At the conclusion of a one-week trial in the Central District of California, the jury found in Boiron's favor that its representations that Oscillo relieves flu-like symptoms were not false. On appeal, the Ninth Circuit affirmed, finding that the jury verdict did not constitute plain error because Boiron presented sufficient evidence from which the jury could have concluded that Oscillo actually works against flu-like symptoms. This was a "battle of the experts" for the jury, the court wrote, that could not be relitigated on appeal. And the jury appeared to have believed Boiron's expert, clinical studies, and anecdotal evidence more than it believed the plaintiff's expert, according to the court.

The Ninth Circuit further noted that in explicitly finding that Boiron's claim that Oscillo treated flu-like symptoms was not false, the jury must have implicitly rejected Plaintiff's argument that Oscillo was merely a sugar pill or water sprayed on sugar. Nor did Plaintiff offer a theory of how Boiron's representations could be false if the product did indeed treat flu symptoms.

The case is *Christopher Lewert v. Boiron Inc., et al.*, No. 17-56607 in the Ninth Circuit.

◆

Vanilla – The Next Curcumin?

by Jacob Schor, ND, FABNO

When Vanessa Linares came to Denver last November, she changed everything I knew about the history of vanilla. Linares presented a paper at the annual meeting of the American Schools of Oriental Research, and in doing so she sparked my appreciation for an underutilized medical food.

Linares, an archaeologist working on her PhD at Tel Aviv University in Israel, has been investigating a tomb discovered in 2016 in the ancient city of Megiddo, a place better known by its biblical name, Armageddon. Carbon dating tells us that the tomb was first sealed up an estimated 3600 years ago, when Megiddo "…was a major metropolis of the Canaanites, the ancient inhabitants of present-day Israel and Lebanon."[1]

The tomb contained the remains of three bodies, "… an adult female, an adult male and an 8-to-12-year-old boy. Elaborate types of bronze, gold and silver jewelry were found on and around the three skeletons. Exact replicas of several pieces of jewelry appeared on each individual."[2] Three ancient earthen jugs were found along with the body remains. Linares conducted a careful chemical analysis of the jugs and found that they had once contained olive oil (no surprise) and the chemical 4-hydroxybenzaldehyde, what we commonly know as vanilla (a total shock).[3]

Until Linares reported her findings, the earliest reported archaeological traces of vanilla had been found in Mexico, which were dated to about a thousand years ago. Linares' discovery meant that vanilla has been used, and in this case seemingly treasured, for far longer and in an entirely different part of the world. The other striking consideration about her discovery is just how far that vanilla must have traveled to reach Megiddo; vanilla is not grown anywhere nearby (understatement). There are about 110 species of vanilla orchids found in the world, yet the traces of vanilla in the

➤

Vanilla

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Megiddo jugs narrowed the match to only three possible orchid species, either *V. polylepsis Summerh* (from central east Africa), *V. albidia Blume* (from India), or *V. abundiflora J.J. Sm.* (from southeast Asia).[3] Consider how far and how slowly the Megiddo vanilla must have been carried from any of these possible origins to reach Armageddon 3600 years back; this suggests both how highly developed global trade routes were, even back then, and just how great a value was placed on vanilla.

Vanilla Jugs at Megiddo

Mexico nevertheless still played a rich role in vanilla history. Recall the story that when Cortés and his army arrived in the Aztec capital Tenochtitlán in 1519, the Aztec emperor Montezuma was drinking a vanilla and chocolate beverage, a beverage that was reserved for members of the 'military.' A specific bee lives in Mexico that pollinates vanilla orchids. As a result, for centuries, Mexico had a natural monopoly on vanilla bean production. While vanilla orchids grow elsewhere, without the bees, the chance of pollination and seed pod production was low. In 1841 a 12-year-old slave boy, Edmund Albius, living on the French island of Reunion in the Indian Ocean, figured out by chance how to hand pollinate vanilla flowers. His discovery allowed for global cultivation of vanilla.[4]

Reading of the Linares's research prompted me to read other research on vanilla, some of which has proven to be fascinating. In order to explain why it is so exciting, we must detour for a moment and consider the recent history of another medicinal spice, turmeric and its concentrate curcumin. In the mid-1990s there was great excitement about the potential medicinal uses of curcumin based on *ex vivo* animal research. Animal studies suggested that curcumin was a potent antioxidant, anticancer agent, and was protective against Alzheimer's and other neurodegenerative diseases.[5-7]

However human clinical trials generated disappointing results. When researchers from UCLA developed technology to measure blood levels of curcumin, they reported that there was next to no curcumin in the blood of study participants. Strategies were developed to increase curcumin absorption and bioavailability.[8] We can now choose between several curcumin products that claim greatly enhanced absorption, based on liposomal micro-encapsulation technologies. These new products have demonstrated substantially better clinical benefits in human trials than the original curcumin products. Yet still relatively small amounts of curcumin are found in the blood.[9] The reason is that curcumin is rapidly degraded in the body through hydrolysis. Attention has turned away from attempting to increase absorption to instead focus on curcumin degradation. Taking curcumin seems to be helpful but clearly the curcumin doesn't last in the body long enough to deserve much credit for the benefits seen. It has been suggested that degradation products are responsible for curcumin's beneficial actions.[10]

In 2012 Shen and Ji posed a question, asking how can curcumin do what it does? The low bioavailability was the obvious problem, but they took their query a step further examining the enzymes curcumin appears to inhibit and pointed out that the recognized binding pockets on these enzymes do not accommodate curcumin.[11]

In a series of papers these two researchers analyzed the degradation products of curcumin and suggested that the credit for benefits should be attributed to one or more of these other chemicals.[11,12]

Curcumin in the body is broken down to two main products, vanillin and ferulic acid.[13] Vanillin is the primary flavor chemical found both in natural vanilla extracts and in synthesized 'artificial vanilla flavoring.' Thus research attention has suddenly turned toward vanillin and how it acts in comparison to curcumin.

An elegant study by Clara Iannuzzi and colleagues from Naples, Italy, was published in November 2017. Curcumin interferes with amyloid aggregation making it an attractive potential drug to use for treating Alzheimer's disease. In a surprising twist, Iannuzzi also tested vanillin comparing its action with curcumin's. The authors suggested that vanillin may "… be responsible for mediating its [curcumin's] beneficial effects."[14] In their research, both curcumin and vanillin acted similarly protecting against advanced glycation end products (AGEs); and they wrote that their "novel findings not only suggest that the main health benefits observed for curcumin can be ascribed to its degradation product vanillin, but also open new avenues for developing therapeutic applications of curcumin degradation products."

In other words, we might see the same or better health effects from vanillin as we do from curcumin. A search of the medical literature yields a short but tantalizing list of *in vitro* studies that have reported similar actions of vanillin to what we previously have seen from curcumin.

A paper, published in August 2018, used lipopolysaccharides (LPS) to trigger inflammation in microglia cells, the resident macrophages of the central nervous system. Microglia cells regulate the nerve inflammation that is currently blamed for diseases such as Alzheimer's and Parkinson's. Vanillin significantly decreased the production of nitric oxide and inflammatory cytokines including interleukin-1β, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). "Vanillin

also reduced the protein levels of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), as well as the mRNA expression levels of IL-1β, TNF-α, and IL-6. Moreover, vanillin inhibited the phosphorylation of mitogen-activated protein kinases (MAPKs) and nuclear factor (NF)-κB."[15]

Another paper published in 2018 described the mechanism of how vanillin has an anticancer effect on hepatic carcinoma and neuroblastoma cells. This puts vanillin in the category of potential anti-cancer agents that possess minimal side effects.[16] Earlier studies suggest that vanillin and dimers of vanillin sharply decrease the metastatic potential of cancer cells.[17] Another study reported that vanillin enhanced TRAIL-induced apoptosis in cancer cells by inhibiting NF-KappaB activation, an action that is often reported to be how curcumin triggers cancer cell death.[18] It's through apoptosis, cell suicide, that vanillin stops growth of colon cancer cell lines.[19]

As already mentioned, vanillin prevents formation of AGEs.[20] It was reported in 1977 that vanilla could potentially fight sickle cell anemia, at least in *in vitro* experiments.[21,22]

We should note that ferulic acid, the other primary degradation product of curcumin, also possesses a wide variety of desirable biological activities such as antioxidant, anti-inflammatory, antimicrobial, antiallergic, hepatoprotective, anticarcinogenic, antithrombotic, increased sperm viability, antiviral and vasodilatory actions, metal chelation, modulation of enzyme activity, activation of transcriptional factors, gene expression and signal transduction.[23]

At this point there is little research on using vanilla in animals and even less on using it medicinally in humans. In several trials, vanilla was given to pre-term babies to assess its calming effects. "Breast milk odor can decrease the variability of premature infants' heart rate and blood oxygen saturation during and after venipuncture."[24] (It should be mentioned though before anyone gets too excited, that the odor of breast milk itself has a greater calming effect than vanilla does.[25])

What is fascinating about all this information is that at this time no one yet appears to be using vanillin or vanilla therapeutically at least not as a substitute for curcumin. Certainly, a range of protein powders contain vanilla flavoring, more to cover up the taste of other ingredients than for medicinal effect. Given vanilla's long history as a food additive, there is no reason for concern about toxicity or side effects. It is possible to be allergic to vanilla extract, albeit a rare problem. On the other hand, contact dermatitis from sap of the orchid is common among vanilla plantation workers, and care must be taken when grafting plants.

One significant problem with vanilla use that became evident from the sickle cell research has not been mentioned. Though vanillin prevented sickle cells from doing their sickle thing in the laboratory, it did not work in humans. The human stomach breaks down vanilla prior to absorption; "orally administered vanillin is rapidly decomposed in the upper digestive tract."[26]

Thus, sadly, eating large quantities of Breyer's vanilla ice-cream will not have therapeutic benefit.

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Vanilla

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There is a vanillin prodrug called MX-1520 that has been developed as a way to bypass digestion and get vanillin into the body. Early research testing of this drug on mice suggests it may do the job.[26]

More recently, a liposomal form of vanilla has been reported to increase absorption.[27] One must wonder whether curcumin and vanillin might be combined together into one liposomal product? This brings to mind the websites that offer instructions for home-made, do it yourself (DIY), liposomal vitamin C. A similar routine might be used to make homemade liposomal vanillin. Synthetic vanillin is ridiculously cheap, about $10 US/pound.

It might also be possible to make a transdermal vanillin product. One has to assume that someone will figure out a way to efficiently get vanillin into the body sometime soon. Then it will only be a matter of time to see if vanilla lives up to its promise. In the meantime, it won't hurt to add a bit of vanilla to your morning smoothie.

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An exploration of why and how things happen.

GENERATIVITY

PETER D'ADAMO, ND

Editor note: In the January 2019 issue of *Townsend Letter*, Dr. D'Adamo introduced readers to Datapunk Circuits (https://www.datapunk.net/circuits), an open-source, genomic database that allows the application of current knowledge about genetic polymorphisms in individualized patient care. Datapunk Circuits is part of The Center of Excellence in Generative Medicine at the University of Bridgeport College of Naturopathic Medicine in Connecticut. In this new column, Dr. D'Adamo will present the concepts and tools of generative medicine.

What Is This?

While medicine has no shortage of *regenerative* therapies and *degenerative* diseases, little examination of the actual *generative* processes driving their genesis and propagation has been systematically undertaken. A technical barrier exists, to a certain degree, as the analysis of most generative processes is heavily reliant on computational assistance. However, there is a plus side to this limitation. These same processes are, by this very nature, also computational accessible; and with the right tools, it is possible to query heretofore unimaginable quantities of patient data in ways that play to our greatest strength as a species: our unrivaled skill at pattern recognition.

Generativity is partially reflected in several traditional disciplines, including systems biology, bioinformatics, Big Data, and artificial intelligence. However, it is my opinion that with a bit of creative coding and a healthy dose of *Vis Medicatrix Naturae* vitalism, these standard tools of data analysis can provide the backbone to a metasystem of unique practical value to the clinician that I've termed Generative Medicine (GM).

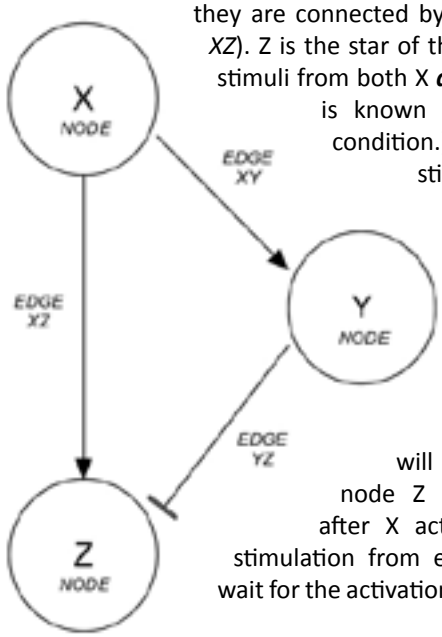
Welcome to a new column that I hope will provide a guided tour through some of the most exciting and relevant concepts and tools in GM. Don't worry, you're not going to need to learn how to write code or solve differential equations. That's what the technology is for. We'll concentrate solely on needs, possibilities, and solutions.

Each column will be written in three parts. The first part will be an elaboration on various key concepts in GM. The second, a discussion of how these concepts can be utilized to produce a computationally active device or tool. The third will be a tour of the tool itself.

Pathways vs. Networks

There are no such things as pathways. There are only networks. Although we've all spent many an hour learning various pathways, it turns out that they are not all that reflective of the actual mechanics of the complex systems they attempt to typify. A possible byline for most pathway representations could be 'don't just do something, stand there.' Networks, on the other hand, have an embedded relational structure. You can ride them, flip them, and even ask them which of their members is the prettiest or most popular, given its current status (also known as its *state space*.) For all its magical properties, networks are actually very simple constructs, typically produced by *things* and the various *relationships* between things, usually specified as a series of binary (one-to-one) relationships.

Things in networks are usually called *nodes* (or sometimes by their older name, *vertex*) and relationships are called *edges.* Edges connect nodes in some meaningful manner, much like verbs connect nouns in simple sentences. Graphs can be directed (the edges have a direction) or undirected (they don't). Since life does not function well with uncertainty, networks in living systems are always directed. Let's take a look at a simple three node network:



Our network has three nodes (X, Y and Z), and they are connected by three edges (*XY, YZ, XZ*). Z is the star of the show and requires stimuli from both X ***and*** Y to activate (this is known in logic as an AND condition.) Edges *XY* and *XZ* are stimulatory, while edge *YZ* is inhibitory. Now let's add the tincture of time to this little web. We can see that edge *XZ* is a direct connection and will thus probably cause node Z to fire very quickly after X activates, whereas the stimulation from edge *YZ*, which must wait for the activation of node Y from node

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Next issue examines Lyme Disease

Generativity

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X (by edge *XY*) to occur, will lag somewhat behind. So initially node Z activates, but sometime afterwards Y also triggers and its edge *YZ* fires which then suppresses node Z. As each node cycles between charging-up and releasing states, the circuit causes node Z to pulse on-off-on repeatedly.

Our little network is actually a well-recognized systems biology *motif* and is somewhat inelegantly titled an *incoherent feed-forward loop* (IFFL). The loop is 'incoherent' because two dissimilar impulses, stimulatory (*XZ*) and inhibitory (*YZ*) arrive at the trigger node (Z). An example of a pulsating gene regulatory circuit triggered by an IFFL is TP53, a tumor suppressor gene and so-called 'guardian of the genome.'

The *coherent feed-forward loop* (CFFL) where the same type of signal occurs at the trigger node, does something quite different. Cellular circuits are inherently noisy due to fluctuations in viscosity, temperature, and probably a thousand other factors. The CFFL smooths out signals by filtering out jibber-jabber at X and Y so that the Z has only two states: high (on) or low (off). Another example of life eschewing uncertainty. Change edge *YZ* from inhibitory to stimulatory, add some tincture of time, and see if you can visualize in your minds how this might occur.

Networks fall under the mathematical category of *graph theory.* Most of us probably think of 'graphs' as an X axis-Y axis two-dimensional scree plot, but those are actually 'Cartesian Coordinates.' Graph theory was (more or less) invented by the mathematician Leonhard Euler as a way of solving 'The Seven Bridges of Königsberg' problem. This city was set on both sides of a river and included two large islands that were connected to each other, or to the two mainland portions of the city, by seven bridges. The challenge was to devise a walk through the city that would cross each of those bridges once and only once. Euler was able to show that it could not be done, while incidentally laying the groundwork for what is now *topology*, the study of the interconnected pattern of network elements. If you'd like to learn more about network motifs, Uri Alon's *An Introduction to Systems Biology: Design Principles of Biological Circuits* (Chapman & Hall/CRC Mathematical and Computational Biology) is an enjoyable read.

The Indirect Approach

Let's move from our very simple network to one much more extensive and intricate, the web of protein-protein interactions (PPI). PPIs are the lifeblood of biochemical cascades and the molecular etiology of disease, as well as the source of many protein targets of therapeutic interest. There is no shortage of published PPI data, and we'll use the data available from STRING (https://string-db.org/). After judicious data scrubbing, our PPI data file is comprised of entries that are surprisingly simple. Below are just a few lines from the data file which actually lists over 32,000 individual PPIs.

Each line contains three pieces of data, separated by the 'tab' character: the 'from' protein node, the 'to' protein node and (for the disbelievers) the PubMed PMID documenting the link.

INPP4A	PIK3R1	10097090
TAF1A	CD3EAP	15226435
GHR	PIK3R1	9632636
MAPK8	PIK3R1	7642542
PTK2B	PIK3R1	10797305
SLC2A4	CTSD	16396496
CRKL	PIK3R1	9461587

With these two nodes provided, their edge is implied. All we'll need to do to build our network is loop through the file, chop up the three pieces of data into independent variables, and store them somewhere. Since we're working in the Perl web scripting language, we'll be using a well-documented Perl code library known (unsurprisingly) as 'Graph'. As we loop through and chop up the data, we'll store its variables in Graph, which will then structure the data into a web-like network.

Once in Graph, we can perform some serious magic on the data. For example, from here we can interrogate Graph to supply us with the successors or predecessors for any given protein. Think of this from a functional standpoint: if we can identify the predecessor proteins in a disease cascade, we can engineer solutions that vivify compromised proteins or block dysregulated ones, a gambit that military strategists refer to as 'the indirect approach.'

Graph can also help us identify other juicy targets of opportunity such as highly connected nodes, colloquially known as 'hubs,' that sit at crossroads in the network and whose modulation affords a greater opportunity of widespread effect. We can also identify 'disease neighborhoods' in the network (known as subgraphs) that characteristically form a repeating pattern of dysfunction, much like how during a blackout, some towns will lose electricity whilst others will be untouched, depending on their place in the electrical grid.

Psychic

Psychic is one of the prescriptive apps bundled with my Opus23 software that normally runs on patient genomic data. We'll be using an open-source version of Psychic created for this column that will run generically. To fire it up, point your browser to **https://www.datapunk.net/tlfd/psychic/**.

Psychic allows you to search for natural products known to control gene expression. However, unlike a simple search engine, Psychic is able to crawl up and down the molecular 'interactome' to determine the upstream and downstream genes that interact with the gene you've searched for. In addition, you can choose how natural products (agonists/ antagonists) are included in the upstream and downstream results. Figure 1 shows the basic screen.

Figure 1. The Psychic user interface

By default, Psychic shows the interactome profile for the gene/protein MTOR, since it has to show something. The main infographic is comprised of a bar graph divided into two halves. The left half displays the 'upstream' results, while the right half displays the 'downstream' results, based on MTOR's position in the interactome. The labels along the x-axis display the various natural products and their gene targets Psychic has found that meet the search criteria. The y-axis value of each bar in the graph is determined by the evidence basis and strength of the position in the network for the gene depicted.

You can set filters on each half of the graph to limit results to a specific type (agonism or antagonism) by selecting an option from the pull-down menu below. There are four options:

- **Inhibit/ Drain:** This will tell Psychic to return all upstream antagonists and downstream agonists.
- **Inhibit/ Bottleneck:** This will tell Psychic to return all upstream antagonists and downstream antagonists.
- **Stimulate/Drain:** This will tell Psychic to return all upstream agonists and downstream agonists.
- **Stimulate/ Bottleneck:** This will tell Psychic to return all upstream agonists and downstream antagonists.

To select a gene/protein to run in Psychic, simply begin typing in its gene symbol in the text input field; Psychic will auto-complete the entry with any genes for which it has data. If multiple options are displayed, simply select the gene you wish to analyze. When you're ready, press the 'Run Psychic' button to have Psychic run results. Click on any bar to trigger a popup screen that will provide information on that natural product (see example Figure 2). Clicking any gene in the popup radar plot will load that gene into Psychic.

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Generativity

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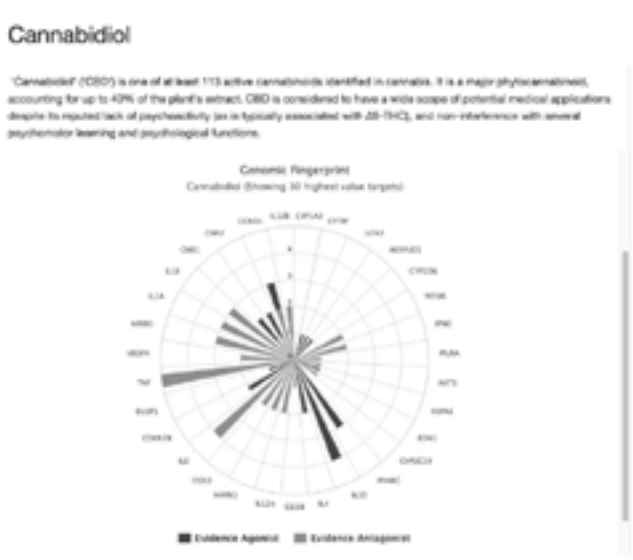

Figure 2. Agent info popup in Psychic

Well, there you have it, my first *TL* column. I hope it proved helpful. Feel free to email me (peter@dadamo.com) with comments, questions, and suggestions. Next time we'll investigate microbiome interaction networks and how the use of high-value targeted prebiotics, foods, and herbs might be used to demonstrate the old aphorism that *the enemy of my enemy may in fact be my friend.* ◆

Peter D'Adamo is a distinguished professor of clinical medicine at the University of Bridgeport School of Naturopathic Medicine. His *New York Times* bestselling books have sold over 8 million copies and have been translated into over 75 languages. He is the developer of the acclaimed *Opus23* genomic software suite and a variety of other generative apps that can be explored at www.datapunk.net and www.opus23.com. In his spare time, he brings old VW Beetles back to life at his garage on www.kdf20.com.

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Is This Actually Chronic Kidney Disease, and What Can Be Done About it?

by Jenna C. Henderson, ND

As a naturopathic doctor with a practice focusing on kidney health, I am often called upon by other holistic practitioners to collaborate with the renal issues of their patients' care. The first question most practitioners have is "does the patient actually have a kidney issue?" There can often be a fine line between a healthy kidney and a kidney we need to be concerned about. Once we've identified that there is a problem, how can we support a compromised kidney?

Most people use the eGFR number to gauge the percentage of renal function, but it is good to know how this number is arrived at and why it does not apply to all patients equally. The eGFR is a derived number that comes from plugging four values into a formula. Those four values are creatinine, age, gender, and race. Most labs will automatically calculate eGFR with the metabolic panel, but if it is not listed one can go to the National Kidney Foundation page for kidney professionals to calculate a patient's eGFR at https://www.kidney.org/professionals/KDOQI/gfr_calculator. This guide will also indicate if a referral to a nephrologist is warranted.

As age is part of the calculation of eGFR, the formula does not work well for the very young and the very old. Using this formula, a 70-year-old white male with an acceptable creatinine of 1.3, would have an eGFR of 55. While some loss of filtration is part of aging, this would not be a pathology. Traditional Chinese medicine would call it a loss of *jing*. Many elderly patients become needlessly panicked looking at their eGFR on a blood test, as it will always be low with the elderly. They might also become stressed when some labs use 1.0 at the high end of normal for creatinine, instead of 1.3. While they would benefit from a kidney-friendly diet and lifestyle, if the creatinine is under 1.3, it is within an acceptable range.

Even if the creatinine is elevated in the elderly, the first question I ask is how well hydrated were they at the time of the blood draw. As creatinine is measured per volume unit of blood, dehydration will cause the creatinine to be more concentrated in the urine.[1] Proper hydration may be an ongoing struggle with older patients. Sometimes with a retest after good hydration we can shave off several tenths of a point off the serum creatinine.

After inquiring about hydration, the next question I ask is how is the blood pressure running. Filtration within the kidney takes place across a pressure gradient, just as the more one squeezes a sponge the better it cleans. The kidney's natural tendency is that when the filtration is low, the blood pressure goes up. However, if the blood pressure is very low, whether due to over correction with medication, shock, or adrenal insufficiency, this can raise creatinine.[2] In practice, a patient with a creatinine of 8.0 would seem to be headed straight for dialysis. However, this patient's blood pressure was 90/60. Raising his blood pressure, the creatinine came down to 6.0. This is not a miracle by any means, but enough to delay dialysis several months.

Besides the elderly, very fit men may run a high creatinine. As creatinine is a breakdown product for muscle tissue, increased muscle mass will cause a higher baseline creatinine. Creatinine may be as high as 1.6 in a fit young man without indicating renal pathology. When in doubt, the blood test Cystatin C can be used as an alternative to creatinine. Cystatin C is not dependent on muscle mass like creatinine, and it can be used to calculate eGFR.[3]

Along with high creatinine, there are usually other indicators that may be off with progressed kidney disease. If one suspects kidney problems, there is usually a predictable pattern or some reason why the patient is not presenting typically. One should expect to see an elevation of BUN, as BUN and creatinine tend to track together. BUN comes from dietary protein, and it will be a direct indicator of how much protein the patient has recently ingested. As such it is more variable than creatinine. Dietary protein may go up and down, but muscle mass is relatively constant. A high BUN without any other indicator of kidney weakness is due to a high protein diet. A high creatinine with a low BUN is probably due to the patient going to an

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extreme cutting out protein in the diet. The BUN/creatinine ratio is often listed on the metabolic panel. Normal range is generally 10 to 20, and creatinine should track with BUN as it requires protein to maintain muscle mass. If the patient has a very high or a very low ratio, it's good to find out why.

Along with a kidney-friendly diet, lifestyle, and continued care with their nephrologists, supplements offer adjunct support to slow the progression of chronic kidney disease.

Besides high BUN, there may be renal anemia due to a lack of erythropoietin. This will show with a low hemoglobin, hematocrit, and RBC. However, this only happens with advanced kidney disease after the creatinine has started to rise. If anemia occurs before this, suspect another cause. It is worth noting that dehydration will cause an elevation of hemoglobin and hematocrit, so the renal anemia may not be initially apparent.[4] It's good to note if there is a high or low MCV or an elevated RDW, to see if the patient is in need of B12 or iron. It may also be useful to run an iron panel, particularly if the patient has cut out all animal protein.

Another indicator with advanced kidney disease is an elevation of potassium. While healthy kidneys expel potassium in the urine, a very weak kidney is not able to do this, and potassium will rise. This may not be the case however, if the patient is consuming foods of low nutritional value and just doesn't have much potassium intake. Potassium sparing diuretics can also throw this number off. Surprisingly sodium usually stays in homeostasis as the body tightly regulates it. Sodium may even run low if there are adrenal or thyroid issues.

As the kidneys regulate the blood pH, expect to see indicators of renal acidosis. One should also expect to see a low CO2 level as the body becomes too acidic and the lungs try to compensate by expelling carbon dioxide. The kidneys maintain alkalinity of the blood by expelling metabolic acids in the urine. A urinary pH of 6.5 to 5.5 generally indicates that the kidneys are keeping up with this function. With advanced kidney disease, the kidneys are no longer maintaining the pH, and the urine will have a pH closer to 7.0. The patient is mostly passing water with the urine and acidic wastes are not being properly filtered out. (Extreme protein deprivation or extreme water intake may also cause a neutral urinary pH.[5])

With kidney trouble, expect to see a high blood pressure or a highly variable blood pressure. When the whole mechanism of blood pressure control is damaged in advanced renal disease, hypertension can be difficult to manage. Frequent checking at different times and in different settings is useful to see a pattern. The patient who is very troubled with their health concerns may have sympathetic dominance and "white coat" hypertension. It's helpful for the patient to have a self-inflating blood pressure monitor and keep their own log. (In practice, the units with a forearm cuff have appeared more reliable than those that attach at the wrist.)

Although these other indicators reinforce the seriousness of the patient's condition, the primary indicator is creatinine. When creatinine does rise, it often catches patients by surprise. Patients often tend to attribute this rise to some condition in the recent past and expect a quick fix. But usually the conditions were building for years, if not decades before trouble was apparent.

Most young adults start out with approximately 1 million nephrons in each kidney. Starting as early as age 18, these filtering units break down as part of normal aging. People may lose as much as 1% of their total nephrons in a single year. Usually this is not a problem as we have reserves in our kidney. But if there is a disease process causing progressive damage to the kidneys, this loss is accelerated. In the initial stages this isn't a problem. Some of the nephrons are lost, and the remaining functional nephrons just work harder to keep up with the demands of the body. This is a kidney in a state of hyperfiltration, with fewer and fewer nephrons working overtime.[6] This state can go on for years, and normal creatinine is maintained. There's no indication on the blood test that the kidneys are working hard to maintain filtration and keep up this creatinine.

Eventually the kidneys reach a point where they can't work any harder and the creatinine goes up. This may happen incrementally with the creatinine inching up a tenth of a point at a time or it may be a sudden jump. Patients may be in denial about the seriousness of the condition. They may have experienced acute kidney stress or dehydration that elevated the creatinine and, once the situation was addressed, the creatinine returned to its normal baseline. Now, they expect that once this situation is addressed that the kidneys will once again return to normal.

Some patients fail to grasp the progressive nature of chronic kidney disease. FSGS, focal segmental glomerulosclerosis, is a particularly difficult degenerative condition of the kidneys. A patient with FSGS asked me to uncover the cause of her high creatinine. Why would a patient with the most deadly form of nephrotic syndrome be asking this? She had had FSGS for 10 years and to her thinking it was okay; the creatinine was always normal, and her life was unaffected. No one had explained that the kidneys were not all right, and for 10 years there was a gradual, insidious breakdown of kidney tissue.

Once there is a critical loss in the number of functional glomeruli, histopathological changes take place, and the kidneys become scarred as excessive demands are placed on them.[7] Proteinuria is a hallmark of all types of nephrotic syndrome such as IgA nephropathy, FSGS, and lupus nephritis. But as the kidneys are damaged, even diabetic nephropathy and hypertensive damage will show some proteinuria as the kidney loses structural integrity.[8] Cardiovascular stress will also start to

become a long-term concern.

Besides chronic kidney disease, other conditions can put the kidneys in a state of hyperfiltration. Age-related kidney decline can happen in the absence of any pathology, with more nephrologists looking toward conservative care rather than dialysis for life extension.[9] Morbid obesity can also put the kidneys into a chronically overworked state of hyperfiltration. Although more muscle mass produces more creatinine, all metabolically active tissue produces wastes that must be handled by the kidneys. Hyperfiltration can also be the result of congenitally small kidneys or a low birth weight.[10] Another group facing hyperfiltration is kidney transplant donors. With a reduced number of glomeruli, supporting their single kidney becomes important.[11]

The kidneys' ability to recover from damage is limited. Scar tissue does not revert to functional tissue. Some patients have high expectations, believing the kidneys have an unlimited capacity for regeneration. Nephrologists are often skeptical of alternatives in kidney care, especially once there's been a critical loss of function. It's good for patients to understand that while we can't turn back the clock, we can optimize the function they do have and slow further damage.

A 2014 report from Stanford showed that kidneys are constantly remodeling in an adult and there is active cell division. This was a change from the previous idea that the kidneys were mostly static. This remodeling is likened to growth of a tree from the branches as each section of the kidney takes care of its own regrowth.[12] However, if the damage to the kidney is extensive enough, it would be similar to a tree stump and regeneration to a fully functional kidney would not be feasible. This may change with stem cell research, but at present time we do our best to support kidney health and delay the need for dialysis.

There is a myriad of kidney supplements on the market, but unfortunately most do nothing to support kidney filtration. A problem in the supplement industry is that all kidney problems are grouped together whether it be urinary tract infections, kidney stones, or hypertension and very few address kidney filtration at all. Some of the natural supplements that support the kidneys are well-known, but not supplements commonly associated with renal health.

Actual human trials on natural supplements is lacking, but we can take evidence from animal models. One approach is the 5/6 nephrectomy model. The lab animal has 5/6 of their nephron mass removed (1 whole kidney and 2/3 of the other kidney), leaving them with 1/6 of the original kidney mass. This creates the conditions of hyperfiltration, similar to a kidney patient operating on a fraction of the original nephron mass. All of the lab animals undergo the 5/6 nephrectomy and half of them receive treatment and half of them don't. Many natural substances tested with the 5/6 nephrectomy model show promise of supporting chronically overworked kidney and improving filtration. Along with a kidney-friendly diet, lifestyle, and continued care with their nephrologists, supplements offer adjunct support to slow the progression of chronic kidney disease.

Medicinal mushrooms have a long history of use for kidney ailments in Asia, with the cordyceps mushroom in particular proving useful. Cordyceps has been researched for use with IgA nephropathy, diabetic nephropathy, lupus nephritis, and post-transplant care. With the 5/6 nephrectomy model, cordyceps improved filtration, reducing serum creatinine and BUN. There was also less proteinuria, fibrosis, and sclerosis of the kidney tissue.[13]

Icariin, a constituent of the herb *Epimedium sagittatum*, was shown to significantly reduce creatinine, BUN, and uric acid in the 5/6 nephrectomy model. It also increased stem cells capable of repair.[14] Commonly known as horny goat weed (HGW), this herb is often found in "male enhancement" formulas, and in those formulas may be mixed with herbs like yohimbe that could raise blood pressure. Traditional Chinese medicine attributes reproductive function to the kidneys, and indeed many kidney patients note low libido. Horny goat weed may help with low libido, and a study from China on men on dialysis noted significantly improved sexual function with HGW supplements.[15]

Resveratrol helped preserve renal function and attenuated sclerosis in the 5/6 nephrectomy model. The results were attributed to both increasing cellular energy with mitochondrial support[16] and increasing nitric oxide.[17] Cardiac support from resveratrol is an added benefit to the kidney patient. Supplements can be helpful, and the patient can incorporate dark grapes and berries into the diet, both of which are low potassium fruits.

Hibiscus is a natural ACE inhibitor. Prescription ACE inhibitors are used to reduce proteinuria and lower stress on the kidneys, as well as lower blood pressure; and hibiscus demonstrates these benefits as well. In the 5/6 nephrectomy model, hibiscus lowered creatinine and BUN. There was also less damage to the kidney tissue in the lab animal that received hibiscus.[18]

Rehmannia glutinosa has been used for renal support in TCM. It's also part of formulas like Rehmannia 8 used for energy and a variety of health concerns. When Rehmannia was tested in the 5/6 nephrectomy model, there was a reduction in serum creatinine and proteinuria. The renal tissue showed fewer injuries as well, and Rehmannia slowed the progression toward renal failure.[19]

Salvia miltiorrhiza is typically characterized as an herb for cardiac support, but it's also useful for kidney support. When studied in the 5/6 nephrectomy model, one active component of this herb, Tanshinone IIA, helped reduce serum creatinine and angiotensin II.[20] Also known for its anxiolytic effect, *Salvia miltiorrhiza* may prove helpful for advanced kidney disease.

Another cardiac support supplement that may offer renal support is ubiquinol. In animal subjects with reduced renal mass under the conditions of salt loading, ubiquinol helped preserve renal

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function.[21] Results were attributed to the antioxidant properties of ubiquinol, but supporting the electron transport chain may have also played a role. As many renal patients are elderly and/or on statins, ubiquinol supplementation is often a good choice.

The bioflavonoid rutin also improved creatinine in the 5/6 nephrectomy model. Similar to quercetin and found naturally in buckwheat, apple skins, figs, and rooibos tea, rutin may improve kidney filtration and help protect the kidneys from tubular damage and sclerosis.[22] Rutin is often part of a bioflavonoid complex added to vitamin C but can be found by itself in capsules.

Adding to the long list of benefits of curcumin is supporting kidney filtration. The metabolite tetrahydrocurcumin, in particular, helps with renal fibrosis, hypertension, and proteinuria.[23] Nephroprotection is attributed to both antioxidant status and mitochondrial support.[24] Many kidney patients will also benefit from an improved lipid profile and blood sugar support.

As chronic insomnia is a huge struggle for many kidney patients, it is not surprising that melatonin makes this list of supplements that help filtration. It's hard to overestimate how disruptive chronic insomnia can be for kidney patients. Many kidney patients report years or decades of insomnia prior to overt kidney symptoms, while others only experience insomnia late in the progression of kidney issues. In lab rats with reduced renal mass, melatonin ameliorates oxidative stress, inflammation, proteinuria, and progression of renal damage.[25] It also helps nocturnal blood pressure, as uncontrolled hypertension can make sleep difficult.[26]

In conclusion creatinine and eGFR are the markers for kidney health, but there are some circumstances where these indicators are not reliable. Other indicators of kidney function such as BUN can also vary. Once kidney issues are identified, there are a variety of supplements that may offer support. The 5/6 nephrectomy model is commonly used to simulate the conditions of progressed renal disease and may be a first step to further research in this area. In practice, patients often respond to a combination of supplements for renal support. Sometimes there is a pronounced improvement in creatinine, but even just holding them at their current level is enough for most to keep the need for dialysis at bay.

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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.

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New Understanding of Autoimmunity Development Through T Helper Cell Regulation, Part 1

by Debby Hamilton, MD, MPH

Introduction

The prevalence of autoimmune disease continues to rise around the world. Estimates range from 32 to 50 million people in the US live with more than 80 types of autoimmune disease.[1] This prevalence means more people live with autoimmune disease than cancer and cardiovascular disease combined. As rates of autoimmune disease rise, it becomes increasingly important to understand the causative factors and the immune mechanisms underlying this change.

Over this time, our internal and external environment has continued to change. Our microbiome consists of many different commensal organisms that are critical for our immune system and overall health. With the changes in our food and environment, there has been a slow erosion of our microbiome contributing to the rise in autoimmune disease with the loss of immune tolerance. Toxins from pollution in our air to chemicals in our food have contributed to the accelerated loss of our microbiome from our lungs to our sinuses to our digestive tract.

Fortunately, the understanding of the intricacies of our immune system continues to advance. The past few years have given rise to added information about the T helper cells and their relationship to the development of autoimmunity. Specifically researching the role of elevated Th17 as one of the primary factors in autoimmunity development has changed our understanding. This elevation coincides with a loss of immune tolerance and an increase risk of infections, both contributing to a cycle of autoimmunity and inflammation.

Traditional Th1/Th2 Paradigm

In 1986, Mossman and Coffman identified two primary T helper cells and labeled them Th1 and Th2.[2] Specific cytokines would trigger the development of either Th1 or Th2 from naïve T cells. Th1 was induced by IFN-Y and Il-2 where Th2 was induced by Il-4. These two T helper cells once induced into their role stayed stable in those roles.

These two types of T helper cells also consistently played a different role in the immune system. Th1 cells were important in the fight against intracellular pathogens such as viruses. The development and maintenance of autoimmunity also seemed to arise from an increase in Th1 cells compared to Th2 cells. On the other hand, Th2 cells helped the body fight extracellular organisms including many of the classic bacterial infections such as strep and staph. An excess of Th2 also led to allergies and asthma.

The goal with the Th1 and Th2 paradigm was to have a balance of the two cells to prevent both autoimmune and allergic diseases from developing. They were also thought to be antagonistic so if one of the T helper subsets was elevated, the other was low. Autoimmune diseases were labeled as Th1 dominant conditions in general and allergies as Th2 dominant. With this concept, a patient could have either autoimmune disease or allergic disease alone where we know that many of our chronic patients have both. In theory, autoimmune patients with an elevated Th1 would be able to fight many chronic infections, including viruses, *Borrelia*, and *Mycoplasma* better than people with a normal Th1 immune response. As we learn more about our chronic autoimmune patients, we realize that many of these patients cannot fight these chronic infections, which counteracts the thinking behind the Th1/Th2 paradigm.

Discovery of Th17 Cells

In 2003, another T helper cell was identified and labeled Th17.[3] Both Th1 and Th17 share half of the same receptor leading to the difficulty in separating the two cells. The Th17 cells were also induced from naïve CD4 T cells by specific cytokines. Many of these cytokines are known as pro-inflammatory cytokines, including Il-23, Il-6, and Il-1. It appeared that a combination of cytokines was needed to induce Th17; and unlike Th1 and Th2, the role of Th17 could be either induced as pathogenic or protective. This induction was also fluid so the T helper 17 cell could change function depending on the environment.

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T Helper Cell Regulation

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Th17 cells play a critical role in first line innate immunity. These cells are induced along mucosal barriers when exposed to an antigen. Originally discovered in the lining of the digestive tract, they appear to be present along all hollow organs such as the sinuses, lungs, vagina, and bladder.[4] An antigen from the environment triggers the CD4 naïve T cells to be induced to form the Th17 cells. Release of specific cytokines such as TGFB, IL-6, and IL-23 promote Th17 development. If triggered by inflammatory cytokines, an elevation in Th17 cells was seen with the release of pro-inflammatory cytokines such as Il-17. Elevated Th17 cells once identified were found in various autoimmune diseases leading to a change in the Th1/Th2 paradigm.

Balance Between Th17 and Treg Cells

When there is dysbiosis along a mucosal lining such as the digestive tract, for example, this will trigger an increase in pathologic Th17 cells and a decrease in Treg cells.[5-7] This Th17/Treg cell imbalance leads to barrier disruption or "leaky gut." For integrative practitioners, the concept of a digestive barrier disruption is well known. Upon discovering the induction of Th17 in other organs, the idea of other leaky mucosal barriers is common. Th17 cells appear to be able to induce "leaky" lungs, sinuses, and blood brain barrier also. All these breaks in immune barriers trigger an inflammatory response in the body that can become systemic.

T regulatory or Treg cells are immunosuppressive in opposition to Th1, Th2, and Th17, which promote an immune response. Multiple mechanisms are involved in Treg cell immunosuppression including inhibitory cytokines, metabolic disruption of T-cells, cytolysis, and regulation of dendritic cells.[8] Development of Treg cells requires the transcription factor FOXP3 and the combination of IL-2 and TGFB. The major immunomodulating cytokines Treg cells release are TGFB and IL-10. TGFB is a critical cytokine for maintaining immune tolerance. The mechanism for developing immune tolerance is interfering with differentiation and survival of immune cells.[9] With a break in the mucosal barrier from infection or other antigen, Th17 cells are induced with a concomitant decrease in Treg cells resulting in a loss of immune tolerance.

Development of T Helper Cells from CD4 Stem Cells

CD4 stem cells can be induced into any of the T helper subsets.[3] Depending on what is triggering the immune system, different cytokines are released to increase the white blood cell response in the body. The cytokines then induce a subset of T helper cells. More than one T helper cell can be formed showing the complexity of our immune system. Transcription factors also influence the development of T helper subsets. Each of the four T helper cells have two specific transcription factors. Genetic mutations in specific transcription factors will decrease the production of the specific Thelper cell subset showing the importance of the role of this component. In a comparable manner to other transcription factors such as NFKB, some transcription factors such as Stat3 can increase inflammation in the body.

Mechanism of Development of Inflammation

Inflammation is a common term used in medicine, but many practitioners would have a difficult time explaining the precise details of the process. Everyone knows that chronic inflammation is damaging, but what is the exact mechanism of damage? It appears that one mechanism of inflammation development is through an ongoing innate immune system reaction. One of the first steps in innate immunity is the recruitment of neutrophils into the tissue. Neutrophils call in monocytes, which become macrophages to combat infection. Neutrophils are key for clearance of multiple pathogens including *Mycoplasma*, *B. pertussis*, *Candida*, *S. aureus*, and *Citrobacter*.[10] The macrophages are also supposed to remove old neutrophils from the tissue. If there are too many neutrophils or they are not removed in time, they release ATP and destructive molecules upon apoptosis that cause direct damage to the tissue. This in turn results

Summary of Th Cells Development and Function

	Cytokine Induced	Cytokines produced	Transcription factor	Normal function	Imbalanced issue
Th1	IFN-y	IFN-y	T-bet/STAT4	Intracellular infections	Poor immune function against viruses, Borrelia, Mycoplasma
Th2	IL-4	IL-4, IL-5, IL-13	GATA-3/Stat5	Extracellular infections, parasites	Allergies Asthma
Th17	IL-23, IL-6, IL-1, TGFB	IL-17, IL-21, IL-22	RORyt/Stat3	Extracellular bacteria, fungus at mucosal barriers	Autoimmunity
Treg	TGFB + IL-2	IL-10, TGFB	Foxp3/Stat5	Immune tolerance Immune regulation	Loss of immune tolerance, Immune dysregulation

in another influx of neutrophils causing a cycle for the development of chronic inflammation.

A neutrophil influx can be stimulated in multiple ways. One is the activation of NFKB transcription factor. This activation triggers the release of pro-inflammatory cytokines including IL-1B and TNF-alpha. If the cells in the tissue sense damage to the tissue, they will also release these two cytokines. Once IL-1B and TNF-alpha are released, they cause an influx of neutrophils into the tissue. Th17 cell elevation will also cause an increase in these pro-inflammatory cytokines leading to recruitment of neutrophils into the tissue.[11] A prolonged elevation of Th17 will lead to excessive neutrophil recruitment causing inflammation. Activation of the STAT3 transcription factor involved in Th17 cell production can also lead to influx of neutrophils and inflammation.

Developing and Maintaining Autoimmunity

Ideally our immune system would be balanced between the Th subsets. The immune system would respond to threats, promote the T helper cells needed for the antigen, and then have a resolution of the reaction. The problem with immune regulation for most patients is that the immune system and, concomitantly, inflammation is not turned off. The result is chronic inflammation and immune system imbalance. If there is elevation of Th17, there is often loss of immune tolerance and low levels of Treg cells. This leads to autoimmunity. In addition, Th17 and Th1 are antagonistic. With an ongoing elevated Th17, there is a decrease in Th1 cells. The Th1 cells are critical in fighting intracellular infections such as viruses. If there is an increase in infections, this will trigger an inflammatory response, which further triggers an increase in Th17, creating a cycle perpetuating autoimmunity. Since there is a balance between Th1 and Th2 cells, a decrease in Th1 results in an increase in Th2 cells resulting in more allergies. Increased Th2 and increased allergies is another source of inflammation continuing the cycle. In order to break this cycle,

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Diseases Associated with Elevated Th17 Levels

Supporting References for Th17 Elevation Chart

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treatment needs to target lowering Th17 and Th2 while increasing and balancing with increased Treg cells and Th1 cells.

The problem with immune regulation for most patients is that the immune system and, concomitantly, inflammation is not turned off. The result is chronic inflammation and immune system imbalance.

Types of Autoimmune Diseases with Elevated Th17

The rate of autoimmune disease continues to increase around the world. Research on Th17 has helped explain some of this prevalence. While autoimmune diseases were originally thought to be primarily Th1 dominant, new research and understanding of Th17 and its cytokines has changed this view (see graphic). Many of the common autoimmune diseases continue to find elevated Th17 and a dysregulated immune system including rheumatoid arthritis, multiple sclerosis, and Hashimoto's. Chronic inflammatory diseases such as asthma also have imbalanced T helper cells.

In integrative medicine, the concept of a broken mucosal barrier in the intestine is well known. Practitioners are taught to detect and treat the digestive tract and improve the microbiome. What is now being more recognized is that disruption of other mucosal barriers can also lead to autoimmune disease. The lungs and the sinuses appear to be common locations. Organs such as the bladder and vagina can also be an issue. The concept is that any hollow space in the body that is lined by epithelial cells forms a mucosal barrier. It is created to be the first line immune response to foreign antigens. The problem is when this first line immune barrier is broken, leading to loss of immune tolerance and development of inflammation.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common autoimmune disease that leads to systemic inflammation, destruction of the joints, and an increase in cardiovascular disease risk. Rheumatoid arthritis was traditionally seen as a Th1 dominant autoimmune disease. The discovery of Th17 has changed the understanding of the pathogenesis of the disease.

Although the disease is an autoimmune disorder of the joints, the disease does not appear to originate in the joints. Disruption of the mucosal barrier in the lungs and the digestive tract has both been linked to the development of RA.[12,13] When the intestinal microbiome of patients with rheumatoid arthritis has been evaluated, it appears that it is different compared to control subjects. Patients with RA tend to have a decrease in Bifidobacterium and Bacteroides bacteria with an increase in the Prevotella species.[13-15] This often creates intestinal hyperpermeability. The disruption of the mucosal barrier leads to loss of immune tolerance and induction of Th17 cells from naïve T cells through the inflammatory cytokines IL-6 and IL-23.[16] These Th17 cells travel in the blood stream to the joints where they instigate the autoimmune process. IL-17 has been associated with an increase in inflammation, influx of immune cells, and both cartilage and bone erosion in RA.[17]

Air pollution has been found to be another causative factor in the development of RA.[12] Diesel exhaust particles in air pollution when they are breathed into the lungs can cause the formation of Th17 cells through the activation of the aryl hydrocarbon receptor.[12] It is well known that other toxins such as the organophosphate pesticides trigger this receptor resulting in the development of inflammation.[18] The air pollution overall creates a pro inflammatory environment leading to high citrullination levels in the lungs, leading to the production of anti-citrullinated peptide antibodies.[12] Smoking is a known risk factor for RA.[19] As cigarette smoke contains multiple toxic chemicals, the mechanism appears to be the same with the development of inflammation, leading to the induction of elevated Th17 levels.

Multiple Sclerosis

Another common potentially debilitating autoimmune disease is multiple sclerosis (MS).

It is a neuroinflammatory disease characterized by recurrent demyelination leading to neurodegeneration. The initial insult in MS is disruption of the blood brain barrier (BBB).[20] This barrier is another example of a mucosal surface altered to allow for the increased development of Th17 cells. Why there is an altered blood brain barrier is not completely understood. The activated Th17 cells produce the cytokines IL-17 and IL-22, which disrupt tight junction proteins in the central nervous system endothelial cells that form the BBB.[20,21] Once through the BBB, the Th17 cells produce multiple pro-inflammatory cytokines such as (IL)-17, IL-6, IL-21, IL-22, IL-23, and tumour necrosis factor (TNF)-α contributing to the neuroinflammation present in MS.[21,22]

In an equivalent manner as RA, IL-17 appears to play a destructive role. It is a potent inducer of neutrophil recruitment into the CNS.[11] Neutrophils release toxic compounds that trigger recruitment of macrophages into the tissue and continue with immune system activation. Without removal by macrophages, they go through apoptosis releasing ATP and other compounds that cause tissue destruction. Elevated levels of IL-17 are found in MS plaques and the CSF of patients with MS, contributing to the neuroinflammation in the CNS.[23] In addition to the MS lesions, white blood cells of patients with active MS have higher IL-17 levels.[24] Severity of MS varies over a patient's lifetime with classic exacerbations and remissions. Higher levels of IL-17 are associated with worsening severity.[23] Understanding of the proinflammatory

continued on page 32 ➤

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T Helper Cell Regulation

➤ *continued from page 30*

role of Th17 releasing the destructive IL-17 leads to more options in terms of treatment targets including natural immune system modulators.

Hashimoto's Thyroiditis

Hashimoto's thyroiditis is a chronic autoimmune disease of the thyroid gland that has been increasing in prevalence. Even in children, many integrative pediatric providers are testing for and finding thyroid autoantibodies in our patients. With most autoimmune diseases, there appears to be an environmental and genetic combination of causes. Researchers have been looking at the gut microbiome and finding differences between patients with Hashimoto's and controls, with the Hashimoto's group having microbiome dysbiosis.[24] One study found significant differences in 27 distinct species between the two groups. The Hashimoto's group had decreased Bacteroides, like patients with rheumatoid arthritis, but also low levels of Prevotella which was elevated in RA patients.[26] In a comparable manner to other autoimmune diseases, elevated Th17 cells were found in both the blood and the thyroid of patients afflicted with this disorder.[27] Higher levels of Th17 cells correlated with increased severity of the disease and increased risk of ophthalmopathy.[27]

With an abnormal microbiome contributing to autoimmune disease, it naturally follows that having one autoimmune disease predisposes to other autoimmune diseases. This is true with Hashimoto's disease. Patients with this disorder often develop other autoimmune diseases such alopecia, vitiligo, type 1 diabetes, and celiac disease.[28] Interesting that a common association with RA is not seen. They are both seen to develop from an abnormal GI microbiome, but different abnormalities lead to similar elevations in Th17 but different clinical manifestations.

PANS (formerly called PANDAS)

PANS (Pediatric Acute-onset Neuropsychiatric Syndrome), which was formerly labeled PANDAS (Pediatric Acute-onset Neuropsychiatric Disorders Associated with Streptococcus), is a neurologic autoimmune disorder increasingly seen in children. The incidence appears to be increasing, but recognition in the mainstream medical community is still low. Classic PANS is seen in children with no history of behavior or developmental issues. The clinical symptoms arise abruptly with acute behavioral symptoms including rage, separation anxiety, OCD, and tics among others.

The neurologic autoimmune issue called PANDAS was first identified from *Streptococcus pyrogenes*.[29] The mechanism appeared to be an increase in pathogenic Th17 from multiple Group A strep infections.[30] The activated Th17 was made in the nasal associated lymph tissue (NALT) and then migrated into the olfactory bulb where it caused inflammation and damage to the blood brain barrier.[30] Once inside the brain it triggered neuroinflammation, including an increase in IgG cross reacting antibodies.[30] Group A strep is a common pediatric infection so there appears to be a genetic susceptibility toward an autoimmune response in certain children. Multiple infections appear to be a key factor also since an initial priming of the immune system was needed.[31]

Autism

Autism spectrum disorders (ASD) are increasingly being recognized as having significant immune dysregulation. This immune dysregulation includes autoimmunity, immune deficiencies, inflammation, allergies, and increased risk of infections.[32] Autoantibodies to the central nervous system play a role in the development and maintenance of ASD.[33] Because of these multiple immune system issues, the ratios and levels of the T helper cells have been investigated. Abnormal ratios of Th1/Th2/Th17 and T reg cells have been found.[33] An increase in Th17 cells with increased serum levels of the proinflammatory cytokines IL-17 and Il-6 are seen in children with autism.[33,34]

The question then becomes what is the origin of these differences? Each of the types of T helper cells have different transcription factors that induce the formation of these cells. Research has shown that children with ASD, compared to controls, have lower levels of Foxp3, which is a critical factor for Treg cell development.[32] If Treg cell development is lower, this will lead to lower immune tolerance and increase

Dr. Debby Hamilton, MD, MPH, is a pediatrician with experience in primary care, integrative medicine, research, speaking, and writing. Her education includes an undergraduate degree from Wesleyan University followed by a medical degree from Chicago Medical School, where she graduated with honors. She is board-certified in pediatrics, physician nutrition, and integrated/holistic medicine (AIHM), and has a Master of Science degree in Public Health (MPH). Dr. Hamilton founded Holistic Pediatric Consulting in Colorado in 2005. Her practice focused on treating children with chronic diseases such as autism and ADHD and preconception counseling based on her book, *Preventing Autism and ADHD: Controlling Risk Factors Before, During & After Pregnancy.* Her book led to her collaboration in the writing of *The Healthy Child Guide* through the Neurological Health Foundation. She has also contributed chapters for *Child Decoded*: *Unraveling Learning and Behavioral Disorders*. In 2017, Dr. Hamilton joined Researched Nutritionals. Her focus is managing and expanding Researched Nutritional's clinical research on the efficacy of nutritional supplements, working on protocol development, and promoting the education of healthcare professionals.

risk for autoimmune disease. The transcription factors RORγt^{+}, T-bet^{+}, and GATA-3^{+} were all elevated compared to controls, which correlates with an increase in Th17, Th2, and Th1 cells.[32] The question then becomes why the transcription factors are abnormal and is this the cause or the result of immune dysregulation?

Children exposed to maternal immune activation in utero have an increased risk of developing ASD. Maternal exposure to influenza and other infections such as rubella also increases the risk of ASD in childhood. One of the mechanisms appears to be inflammation associated with increased Th17 and IL-17 in the mothers when pregnant.[35] Higher levels of IL-17 in pregnant women have been found to correlate with increased severity in ASD.[35] Research has shown in animals that blocking IL-17A signaling prevented ASD like behavior in offspring exposed to maternal immune activation.[35]

Summary

As the number of autoimmune diseases continue to escalate, it is critical for us to understand the immune mechanism that leads to this imbalance. Only by understanding how these diseases develop can we try to reverse this trend. Learning about the delicate balance in the T helper subsets is a good first step. The next step is to learn the natural tools we have as practitioners to support our patients. Next month, I will discuss the use of transfer factors and natural anti-inflammatory compounds to help balance our immune system.

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In Memoriam: Walter Crinnion, ND

by Jacob Schor, ND, FABNO

It is with sadness that we announce that our colleague Walter Crinnion passed away on Monday, March 11, 2019. By the time this comes out in print, those of you who knew him will have heard this news from other sources and read remembrances posted online. For those of you who didn't know Walter personally, you missed an opportunity. He brought a sense of underlying goodwill to our interactions. Even now, even in my sadness, he puts a smile on my face.

Many in the naturopathic profession met Walter when he taught at Southwest College of Naturopathic Medicine. He worked there as the Endowed Chair of the Department of Environmental Medicine from 2003 until 2013 until he was somewhat unceremoniously fired from his position. He took to describing himself as no longer a distinguished professor of environmental medicine, but instead as the 'extinguished' professor. Actually, Davis Lamson was the first to apply the term to Walter. Davis told me, "The term came from me, taken from an old situation at Iowa State when two very popular 'hippy' profs were canned. We were all in the same 'gang' together and one of them coined or stole the term, 'The Extinguished Professor's Club.' I used it for both Walter and Mona Morstein. Then I found myself in the same club."

Davis Lamson, ND, who taught oncology at Bastyr University for many years was also surprisingly released from employment at about the same time. I was lucky enough to be able to introduce both Walter and Davis at an OncANP conference and use the term twice. Perhaps in the context of writing this article, some may think using such a term is in poor taste. I never dreamed that I might end up using it in this context. I think Walter would appreciate the humor of being called 'extinguished.'

Davis and Walter both attended Bastyr University and graduated together in 1982 along with such notables as Pam Snider, Thomas Ballard, Peter D'Adamo, and others in that first class completing the program. Back then Bastyr students were lucky to have John Bastyr, ND, Bill Mitchell, ND, and Joe Pizzorno, ND, as teachers, and in Walter's case to leave school counting them as friends.

Davis tells me things about a classmate that I wish I had known. Walter was an accomplished bowhunter who supplied his family with wild game to eat while attending Bastyr. Davis was equally impressed that Walter had paddled down the Missouri River in Montana, not once but twice. This was a part of Walter that few of us got to meet. That's probably because, by the time we knew him, he was possessed by his single-minded mission to expose the health hazards of environmental toxicant exposures.

Walter recognized early on in his career that some weren't getting better and suspected that some of the illnesses he was seeing in patients were the result of environmental toxicity and needed to be treated as such. He became a student of William Rea, MD, a cardiothoracic surgeon in Texas who was a pioneer in the practice of environmental medicine. The more he learned how to diagnose and treat environmental illness, the more patients suffering from these exposures were drawn to his practice.

PubMed lists Walter Crinnion as the author of two dozen articles published in *Alternative Medicine Review*, each and every one about environmental toxins or how we might test and treat patients for exposure. Early articles were on organic food[1] and how to treat patients with sauna.[2,3] A pair of 2009 articles about pre- and post-urinary testing for heavy metal toxicity using DMSA set the standard for not just the naturopathic profession but for many others seeking to diagnose and treat this threat.[4,5]

Over the past 30 years, Walter Crinnion established himself as one of the foremost experts in the field of environmental medicine, not just for

the naturopathic profession but on a national and international level. He created the environmental medicine curricula at Bastyr University, University of Bridgeport College of Naturopathic Medicine, and the Southwest College of Naturopathic Medicine (SCNM). He held an endowed position at SCNM and was also adjunct faculty at George Washington University School of Medicine and Health Sciences as well as faculty at the University of Western States. He provided online training for licensed healthcare practitioners through SpiritMed Medical Education. He founded the Naturopathic Association of Environmental Medicine (now the National Association of Environmental Medicine), a member organization for providers in this field to set standards of care and offer education. He was the first member of our profession to brave the application process of the NANCEAC gauntlet hoping to win approval for all of his course offerings.

He used the Crinnion Opinion podcast and blog to keep his many followers informed about the latest information and protocols in the environmental medicine field. He wrote several books; *Clean, Green and Lean* was published in 2009. He co-wrote with Joe Pizzorno, ND, the textbook *Clinical Environmental Medicine*, published in 2019. He also blogged for the *Huffington Post*. He was the environmental medicine editor for the *Alternative Medicine Review* and on the editorial boards of the *Natural Medicine Journal*, the *New England Journal of Medicine*, *Pharmaceutical Biology*, *Science of the Total Environment*, and the *International Journal of Hygiene and Environmental Health*. It was an article of Walter's in the August 2016 issue of the *Natural Medicine Journal* on fine particulate air pollutants that triggered that journal's ongoing focus on air pollution. Dr. Crinnion wrote:

> Over the last 10 years, my review of the literature on the adverse health effects of air pollution resulted in a major change in my recommendations to patients who wish to have as much vitality in their lives as possible. For years my best health recommendations would include getting off sugar and white flour, reducing or eliminating red meats, eating organic as much as possible . . . exercising, meditating, and taking a small number of necessary supplements. My primary recommendation now? Invest in a high-quality air purifier for your bedroom.[6]

Walter's life ended far too soon. He leaves a loving family and friends plus hundreds of grateful patients and inspired students. He is survived by daughters Sara Hall (Josh), Joanna Oliver (Jeff), Rebecca Rathbone (Matt), and Kate Crinnion; grandchildren Scott and Joseph Rathbone; mother Virginia Crinnion; and sister Mary Padgett (William). His father, Walter P. Crinnion, and daughter, Marie, pre-deceased him. Walter lived in Phoenix, Arizona, with his daughter Kate.

An online post by Mona Morstein, ND, the third of the aforementioned trio of Extinguished Professors, expressed well how many of us feel:

> I've known Walter for decades, worked with him, respected him, learned from him, enjoyed hanging out in Montana with him. He was the proverbial One-Of-A-Kind guy – unique in his brilliance, his innovation, his knowledge, and his personality. He was the foundational pillar of environmental medicine and was remarkable in his willingness, his commitment, and passion for sharing that immense information with other physicians like myself. His legacy will live forever in our hearts, minds and our medical practices. Thousands and thousands of patients are better, healthier, and detoxed thanks to Walter's protocols.

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In Memoriam: Harvey Bigelsen, MD

October 13, 1940 – March 6, 2019

A great health warrior has passed. Dr. Bigelsen taught us not only great integrative medical practices from around the world, especially Germany, but also the political implications of pursuing innovative and traditional therapies, including homeopathy and isopathy.

Dr. Bigelsen hailed from Brooklyn, New York. He was noted as a math whiz kid from a young age and was captain of his football team at Midwood High despite his small stature. Harvey was accepted to medical school after three years of undergraduate study. He graduated from the State University of New York at Buffalo School of Medicine in 1965. He began his ophthalmology residency there and soon after was drafted in the army and deployed to Vietnam, where he was charged with triage of mass casualties. The horror of his experience left an indelible mark on his psyche and political perspective.

After Vietnam he completed his ophthalmology residency and started a practice in Princeton, New Jersey. When Einstein died, he donated his eyes to Harvey's senior partner. Harvey used to keep the eyes in his desk drawer for inspiration. Einstein's daughter was also his patient. He was noted by all for his physical resemblance to Einstein.

Dr. Bigelsen moved from Princeton to Arizona to work at the A.R.E. Clinic (Edgar Cayce) where he studied Cayce's medical readings. The modality he found most beneficial was osteopathy. Harvey realized he had not been taught anything about the structure of the body or its importance to health in medical school. To amplify the beneficial effects of neural therapy (procaine injections usually with additional complex homeopathic remedies), he insisted on osteopathic manipulations. His results were often dramatic.

Dr. Bigelsen was a co-founder of the Arizona Homeopathic Board of Medical Examiners to provide a political umbrella for doctors who employed alternative medical therapies. He was a founding board member of the American Holistic Medical Association and recipient of the 1986 Han Nieper Foundation award for person of the year, recognizing his work as the most influential physician for the advancement of natural medicine in the United States.

Harvey taught us about the dangers of working with Medicare. He was convicted of Medicare fraud for a $3,500 misbilling and was forced to surrender his Arizona license. They gave him the codes to use and then brought him up on code violations. He practiced in Mexico for a time and then in the Northern California area. His battles with medical authorities are legion and heartbreaking. In-depth reviews of his battles are available online; search "Medical Conspiracy in America by Harvey Bigelsen, MD."

He wrote four books including a *Holographic View of Dark Field Microscopy.* Darkfield anomalies which resembled a colon in his interpretation were related to colon pathology, thyroid to thyroid, liver to liver etc.

Our Powerful Introduction to Harvey

About 30 years ago, I (Gerber) was pursuing a homeopathic license in Arizona and thought it would be a good idea to introduce myself to the board members. Of course, we visited Dr. Bigelsen's clinic in Scottsdale. My wife and I had also booked a romantic weekend at the Enchantment Resort in Sedona, Arizona. My wife, Inge, developed a sore throat and tonsillitis with a large exudate. I asked Harvey for suggestions. He said let's use natural penicillin. I said what's that? Harvey said Notakehl, a homeopathic dilution of the original *Penicillium notatum* discovered by Sir Alexander Fleming in 1929 in Scotland, which had no side effects unlike regular penicillin. He diagnosed her on a Mitsubishi EAV machine and then injected her tonsillar pillars followed by a minor autoheme with one cc of her venous blood combined with the Notakehl, which he treated with laser light and injected it into her contralateral hip.

On the way to Sedona, she was highly febrile. I thought, "so much for the romantic weekend." The next morning on examining her throat, it was 90% better and she felt great. The following Monday, I called Harvey and said, "What was that miraculous stuff?" In the following six months, he introduced me to Sanum Isopathic remedies including Notakehl, Mucokehl, Recarcin, Nigersan, Fortakehl, Albicansan, Pefrakehl and many others. All these phenomenal remedies have been blocked by the FDA after 80 years of safe clinical practice in Germany.

We are eternally grateful to Harvey Bigelsen for introducing us to all these remedies and diagnostic techniques. Rest in Peace, Harvey.

Josh Bigelsen
Michael Gerber

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Pathways to Healing

by Elaine Zablocki

Major Delivery Organizations Implement Integrative Health

John Weeks

John Weeks has been active as a writer and organizer in integrative medicine for the past 35 years. Nowadays he serves as editor-in-chief of *The Journal of Alternative and Complementary Medicine: Paradigm, Practice and Policy Advancing Integrative Health* (*JACM*), and he continues as publisher/editor of The Integrator Blog.

Recently the journal published a remarkable issue titled "Multimodal Approaches in Integrative Health: Whole Person, Whole Practices, Whole Systems." These pages are the fruit of years of thinking, planning, and writing among dozens of like-minded peers. They describe research in many parts of the country, dealing with a wide range of conditions, in many clinical settings. This research demonstrates how effective integrative medicine can be in coping with the difficult challenges facing our healthcare system. (Thanks to a special grant from a philanthropic partner, the entire issue is posted online for us all to read and absorb.)

The conventional model of medical research generally looks at one isolated treatment, often a pharmaceutical, and compares it to another isolated treatment. Over the past 20 years integrative researchers have argued for studies of whole systems of care (such as Ayurveda or naturopathy or integrative and functional medicine) that use a combination of methods to support health. They have argued for "pragmatic research" to test the effectiveness of treatments in ordinary clinical practice with patients who often have more than one health problem. This issue of *JACM* reports on whole systems research in several settings.

When the editors put out a request for papers for this special issue, they found that many academic integrative medicine researchers are responding to the current opioid crisis and working to expand non-pharmaceutical treatment options in a dramatic way. In the past, the whole systems research movement has generally published theoretical papers about the benefits of this approach, together with small-scale examples. "We were surprised. For this issue we received many papers that were in a different category altogether," Weeks says. "People are working in many different environments to actually implement integrative models. Now we are doing what people have envisioned over so many years and doing it on a large scale. These papers are documenting the models, challenges and processes."

Sharing Details, Sharing Questions

The *JACM* special issue includes many articles with specific examples of collaborative efforts to develop whole systems treatments for a wide range of conditions. For example, "Whole Systems Within Whole Systems: The Oregon Health Plan's Expansion of Services for Back and Neck Pain" discusses the transition to an integrative method of pain treatment that includes acupuncture, chiropractic, massage, yoga, and non-pharmaceutical protocols. "This is an examination of work by people who are in the trenches, figuring out what are the barriers and how to get through those barriers," Weeks says.

The special issue also includes two articles on work underway at the Veterans Administration. One is a research article, and the second is a commentary from Tracy Gaudet, MD, and Ben Kligler, MD, of the VA's Office of Patient-Centered Care and Cultural Transformation. "When you read this commentary, you'll be in touch with the best thinking in the United States about how to transform conventional medicine to care that is concerned with whole health." Weeks says. "In order to do this, we need to ask different questions. In the past, our model for healthcare was, the patient comes in with a chief complaint, and the physician gives them a drug. Now we need to ask ourselves, what is health? And how can we support whole health?"

The current opioid crisis offers an opportunity to transform responses to chronic pain in the United States. Organizations are ready to explore non-pharmacological approaches to pain, and the VA and the Defense Department are leading the way. "The umbrella of non-pharmacologic approaches goes beyond physical therapy and psychology," Weeks notes. "It extends to the broader array of integrative approaches such as mind-body, yoga, chiropractic, acupuncture, and so on. Both the VA and DoD have an affirmative response to these methods because they are focused on connecting clinical services delivery to the whole health of the soldier."

In a more focused whole systems clinical intervention, the article on "Intervention Development Process for a Pragmatic Randomized Controlled Trial: The Thoracic Peri-Operative Integrative Surgical

Care Evaluation Trial" documents the way a multidisciplinary committee of naturopathic doctors, medical doctors, PhDs, and others worked together to develop a protocol for a trial of naturopathic approaches. "They worked together analyzing the evidence to prioritize different kinds of interventions, in order to find out what whole systems approaches would be most effective to support people with that cancer," Weeks says.

The Future of US Healthcare

Ideas that used to be visionary suggestions are now proving themselves in real world, large-scale deployment. We can see how integrative medicine has matured over the past 20 years.

The future of healthcare will clearly be a major theme in the upcoming US election. Democratic candidates are putting forward a range of proposals to dramatically reshape the healthcare system. "The most important thing at this time is for the integrative health community to take part in the dialogue and seek to influence this discussion at every turn," Weeks says. "Support candidates. Write letters to the editor. When you're offered a chance to comment on a proposal, step forward and take advantage of that opportunity. When a candidate holds a meeting in your city, show up and talk with them."

Several organizations are collaborating on proposals for improved healthcare. "At this time the best voice for our field is the Integrative Health Policy Consortium (IHPC), as it has been over the last 15 years," Weeks says. "IHPC is working in collaboration with key organizations such as Integrative Medicine for the Underserved and the Academy of Integrative Health and Medicine, and with most of the professional associations. IHPC serves as a central focal point. Thanks to its work, we now have a bipartisan Integrative Health and Wellness Caucus in Congress."

I asked Weeks to suggest the most effective ways people who support integrative medicine can communicate with candidates and legislators over the coming months. He pointed us back to the two articles on the Veterans Administration in the *JACM* special issue. "Read those articles and be ready to explain what this work means," he said. "Most politicians and elected officials have no idea of the way complementary practitioners have been integrated into these very large systems. One way to talk about these issues is to just describe what the Veterans Administration and Department of Defense are doing in order to offer the most effective care to the people they serve. Focus on the value of non-pharmacologic, integrative practices and practitioners, which will create a new model for chronic pain treatment. They will get us out of the crisis precipitated by our penchant for simplistic pharmaceutical solutions."

Resources

The Integrator Blog News & Reports: http://www.johnweeks-integrator.com/posts/

The Journal of Alternative and Complementary Medicine: Paradigm, Practice and Policy Advancing Integrative Health. Multimodal Approaches in Integrative Health: Whole Person, Whole Practices, Whole Systems. March 2019. https://www.liebertpub.com/toc/acm/25/S1

"Integrative Medicine and Single Payer: What Might We Expect?" by John Weeks. https://www.johnweeks-integrator.com/uncategorized/integrative-practices-and-practitioners-and-single-payer-what-might-we-expect/

Integrative Health Policy Consortium: www.IHPC.org

Elaine Zablocki is the former editor of CHRF News Files.

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Shorts

briefed by Jule Klotter
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More Censorship

Editors of Elsevier's *Pharmacological Research* withdrew a 2018 study, "Cognition and behavior in sheep repetitively inoculated with aluminum adjuvant-containing vaccines or aluminum adjuvant only," from publication. A letter from the publisher to senior author Lluís Luján asserted that the paper was not retracted, "'which implies wrongdoing,'" according to journalist Celeste McGovern. The study reported distinct behavioral changes in sheep who received aluminum-containing vaccines or aluminum adjuvant alone, compared to those receiving a saline placebo.

The withdrawal occurred after behind-the-scenes complaints about methodology. Usually, questions and comments about a study are posted in a letter to the editor and the study's authors publicly respond. Dr. Luján responded to the complaints, which he deemed 'misleading' and 'spurious'. The journal's statistical editor reviewed the study's raw data and did not recommend withdrawing the paper. In email correspondence from Elsevier, "'concerns from the readership' morphed into 'a signed note of concern from a reader,'" writes McGovern. The identity of this reader was never revealed. Dr. Luján refused to withdraw the study himself, so the editors did it.

This 2018 study is one in a series of studies investigating a disturbing and mysterious outbreak that developed in Spanish sheep in 2009, after widespread vaccination for bluetongue, a non-contagious, viral illnesses transmitted by midges (tiny flies). The animals became unusually nervous and disoriented. Some began biting wool off others in the flock and eating it. Some were lethargic. Others had seizures and died. With winter cold, animals lost weight, looking emaciated, and developed muscle tremors. Spanish veterinarians and researchers investigated all possible sources for the malady, searching for pathogens and environmental toxins in food and water. Some farmers reported that their sheep developed these odd symptoms after bluetongue vaccination. Dr. Luján could not believe it at first: "'But it was just too much coincidence.'" In medical literature, he found studies on autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and was struck by the similarity to the sheep's malady.

In 2013, Luján and his team published a paper describing post mortem findings from 64 sheep with "ovine ASIA." The animal bodies displayed thickened nerves on their backs, abdomens, and legs. Evidence of brain inflammation and 'severe neuron necrosis' was found. Aluminum (Al) was present in the nerve tissue. The researchers were able to induce the disease with aluminum-containing vaccines.

In 2018, Luján's team published a placebo-controlled experiment with 84 male neutered lambs that were divided into three groups; one group was given commercial aluminum-containing vaccines, the second got an equivalent amount of aluminum adjuvant, and the third got a saline placebo. The animals received 19 subcutaneous injections within 15 months. Their *Veterinary Pathology* article reported that "[a]ll of the vaccine and 92.3% of the adjuvant-only lambs presented injection-site granulomas...." The number of granulomas was higher in the vaccine group. Most troubling was the high aluminum content in the lymph nodes of the vaccine group: vaccine group (median 82.65 μg/g), adjuvant-only (median 2.53 μg/g), control (median 0.96 μg/g). Scanning transmission electron microscopy revealed aluminum (Al) in the macrophages belonging to animals in both treatment groups but not the saline control group: "In these two groups, Al-based adjuvants induce persistent, sterile, subcutaneous granulomas with macrophage-driven translocation of Al to regional lymph nodes."

In another 2018 study, published in *Frontiers in Immunology*, Spanish researchers used RNA sequencing to investigate aluminum hydroxide's effect on the immune response. They compared vaccinated sheep to sheep injected with this widely used aluminum adjuvant. They found the adjuvant, in itself, increased expression of inflammatory cytokines, NF-Kβ family genes, and apoptotic genes. In addition, aluminum affects DNA repair. The authors state: "...these experiments demonstrate that aluminum containing adjuvants are not simply delivery vehicles for antigens but can also induce endogenous danger

signals that can stimulate and modulate the immune system."

The withdrawn *Pharmacological Research* study focused on changed behavior caused by the aluminum-containing vaccines. The researchers assigned 21 unvaccinated, neutered Rasa Aragonesa lambs (known to be a gregarious breed) to one of three groups. The food, water, and pens for each group were identical, and all lambs received 16 injections in 12 months. Group A (control) received phosphate-buffered saline; Group B received aluminum adjuvant (equivalent to vaccine content; 70.861 mg), and Group C received commercial aluminum-containing vaccines. The animals were tested in summer and winter for cognitive changes (maze test, open field test, and novel object test). During the testing period, a video camera recorded behavior in the pens for 12 hours/day on seven consecutive days. The recordings were later analyzed by a blinded researcher.

The cognitive tests showed no significant differences between the groups. Behaviors, however, were significantly different. Lambs in groups B and C spent more time standing than the placebo group. During the winter test period, lambs in Groups B and C showed more aggressive interactions, fewer affiliations, and stereotypies – that is, repetitive movements (such as rubbing against the wood pen) for no apparent reason. In contrast, aggressive behavior and stereotypies were consistently low in Group A in both summer and winter. In addition to behavior changes, cortisol levels during winter were significantly higher in the two treatment groups compared to the control. Unlike groups B and C, the placebo group's median cortisol level had significantly decreased from its summer level. The researchers could not say whether the more pronounced behavior changes observed in winter were due to the cold weather, the greater number of inoculations that had occurred by that point, or both.

The authors wrote: "In our opinion, all these behavioral changes exhibited by the Vaccine and Adjuvant-only lambs in our study are of outmost importance, as they are the first scientific explanation of some of the previously observed behavioral changes in flocks....Indeed, these changes can be undoubtedly detected by veterinarians and farmers in field conditions but they have never been scientifically linked to vaccination and/or Al inoculations."

Dr. Luján told McGovern that aluminum in animal vaccines has been known to cause other problems, such as cancer in cats. When veterinary researchers removed Al from cat vaccines, the incidence of cancer at injection sites "all but disappeared." Clearly, it is possible to make vaccines safer. Unfortunately, Dr. Luján and other veterinarians have found that oversight and public health agencies do not want to hear about the problems with aluminum-containing vaccines: "One colleague told him that every time he reported ASIA symptoms to oversight agencies, his complaints were ignored."

Elsevier's withdrawal of this study is not the only example of attempts to censor information about aluminum toxicity. Aluminum expert and toxicologist Christopher Exley, a professor of bioinorganic chemistry (Keele University, UK), was one of the authors of the *Veterinary Pathology* article. Since finding extremely high levels of aluminum in the brains of people with diagnosed autism, funding from government sources has disappeared; he now relies on private sponsors. He turned to GoFundMe for donations. In keeping with the clampdown on vaccine debate, GoFundMe deleted his account in April 2019, and returned the money to his donors. For those interested, it is still possible to support research on aluminum via a link on Keele University's website.

Asin J, et al. Cognition and behavior in sheep repetivitely inoculated with aluminum adjuvant-containing vaccines or aluminum adjuvant only. *Pharmacological Research.* 2018. Available at www.iisaragon.es with supplemental material.

Asin J, et al. Granulomas Following Subcutaneous Injection with Aluminum Adjuvant-Containing Products in Sheep. *Veterinary Pathology.* 2018;1:11.

McGovern C. Anatomy of a science study censorship. March 20, 2019.

Varela-Martinez E, et al. Molecular Signature of Aluminum Hydroxide Adjuvant in Ovine PBMCs by Integrated mRNA and microRNA Transcriptome Sequencing. *Frontiers in Immunology.* October 23, 2018.

Medium-Chain Fatty Acids Repel Insects

Medium-chain fatty acids (C8:0 to C12:0) found in coconut oil repel biting flies, bedbugs, ticks, and mosquitoes, according to a 2018 report by a team of entomologists and US Department of Agriculture scientists. After testing the various fatty acids in whole coconut oil, they found that only caprylic acid (C8:0), which comprised about 6.85% of their tested coconut oil, capric acid (C10:0), comprising about 7.33%, and lauric acid (C10:0), comprising about 52.68%, had a noticeable repellent effect. Coconut oil, itself, was not effective in repelling biting flies. Much of this study focused on finding a natural repellent for biting flies that afflict US livestock, causing over two billion dollars in losses. The researchers say, "Coconut oil's lack of repellency suggests that the large bulky nature of the triglyceride structure may play a role in determining the repellency properties...." The effectiveness and longevity of these compounds were as good as or better than DEET's. The pesticide DEET is considered the gold standard insect repellent but has been linked to multiple health problems.

In laboratory tests, the researchers found that a compound of these three fatty acids repelled stable flies, horn flies, and bed bugs more effectively than DEET. Moreover, the fatty acids had over one week of activity while DEET's effect began to decline by day 3. Coconut fatty acids and DEET, at concentrations of 0.05 mg/cm^2, showed basically the same ability to repel lone star ticks; and, at concentrations of >0.4 mg/cm^2, the coconut fatty acids had the same repellent activity against yellow fever mosquitoes as DEET.

Researchers have investigated other natural options for repelling biting insects, including essential oils such as catnip oil, citronella, and palmarosa; but their effectiveness wanes within hours, and some have toxicities of their own. This investigation of coconut fatty acids suggests that a non-toxic, effective insect repellent is possible for animals and humans alike.

Zhu JJ, et al. Better than DEET Repellent Compounds Derived from Coconut Oil. *Scientific Reports.* 2018;8:14053.

Proton-Pump Inhibitors and Kidney Damage

Proton pump inhibitors (PPIs), such as Nexium, Prevacid, and Prilosec, have largely supplanted histamine H2-receptor

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antagonists (H2RAs; e.g., Tagamet, Pepcid, Zantac) as the preferred treatment for gastric ulcers, esophagitis, and acid-related disorders. Initially recommended for short-term use, PPIs are often used long-term; and their perceived safety has led to over-the-counter availability. Concerns have arisen about possible kidney damage with long-term PPI use.

A 2019 study, led by Tigran Makunts, found evidence of an association between PPI use and kidney damage. For this study, the researchers used data from the FDA Adverse Event Reporting System (FAERS), a post-marketing surveillance system that collects reports of possible adverse drug effects that are voluntarily submitted by healthcare practitioners, pharmacists, patients, and lawyers. Makunts et al sifted through over 10.3 million adverse effect reports, submitted from January 2004 to March 2018, to isolate 42,537 reports in which PPIs were used as monotherapy and 8,309 reports in which only H2RAs were used. They used the data to perform an odds ratio analysis, comparing adverse event frequency in the two types of medications. They also looked at frequency of adverse events for each of the five PPIs that appeared in adverse effects reports: omeprazole (Prilosec; n=7,749), esomeprazole (Nexium; n=27,053), pantoprazole (Pantoloc; n=3,651), lansoprazole (Prevacid; n=3,360), and rabeprazole (Aciphex; n=724).

Compared to patients using only H2RAs, those on PPI monotherapy were more likely to report chronic kidney disease (OR 28.4, 95% CI [12.7, 63.5]), acute kidney injury (4.2 [2.8, 6.3]), end-stage renal disease (35.5 [5.0, 250.0]), renal impairment of unspecified type (8.0 [5.0, 13.0]), and kidney stones (2.8 [1.3, 6]): "The composite renal ADR frequency was 5.6% of the total PPI 'monotherapy' ADRs reports and 0.7% for H2RA 'monotherapy' reports (8.6 [6.6, 11])."

In addition to kidney damage, the researchers also found an increase in electrolyte abnormalities among PPI users. Patients on PPI monotherapy were more likely to report hypomagnesemia (OR 78.5 [11, 560]), hypocalcemia (25.5 [6.4, 100]), hypokalemia (6.3 [1.6, 15]), and hyponatremia (2.2 [1.1, 4.6]). The authors note that hypomagnesemia (low magnesium blood levels) is listed as a rare side effect on the package inserts; but it may be subject to detection bias. Unlike calcium, potassium, and sodium, magnesium levels are not routinely measured. Makunts et al say, "It may be prudent to monitor magnesium levels in patients with ongoing PPI therapy and other risk factors for hypomagnesemia."

The lack of comprehensive medical records is a stated limitation of this study, and the reports can only indicate an association – not causality. The authors note that FAERS/AERS reporting "does not represent the population incidence" because reporting is voluntary, which suggests that many adverse events may not be reported. People with compromised kidney function might consider using an H2RA, if possible. At the very least, renal function and electrolytes need to be monitored if PPI use extends beyond the authors' recommended four-to-eight weeks.

Doctors Deny That PPIs Can Cause Kidney Damage. Peoples Pharmacy. April 8, 2019.

Makunts T, et al. Analysis of postmarketing safety data for proton-pump inhibitors reveals increased propensity for renal injury, electrolyte abnormalities, and nephrolithiasis. *Scientific Reports.* 2019;9:2282.

Benefits of a Short Forest Bathing Program

Taiwan researchers tested the effects of a two-hour forest bathing program on 128 middle-aged and elderly people, age 45-86 years (mean 60.0 ± 7.44), 46.1% of whom (n=59) reported chronic illnesses such as diabetes, hypertension, and heart disease. The experience – in groups of 12 – took place in a valley, planted with Japanese cedar and giant timber bamboo 40 to 90 years ago and surrounded on three sides by mountains. While walking 2.5 km (about 1½ miles) through the forest, participants were guided to use their four senses to see the scenery, listen to birds and running streams, smell the wood, and feel the surfaces of leaves and trees. Pulse rate, systolic and diastolic blood pressure, and heart rate variability (to indicate sympathetic-parasympathetic nervous activity) as well as psychological measures were taken before and after participation in the program.

Participants' pulse rate and blood pressure (systolic and diastolic) decreased significantly after the program, "which indicated physiological benefits from stress recovery." There was no statistically significant change in autonomic nervous activity. In addition, all negative mood scores ("tension-anxiety," "anger-hostility," "fatigue-inertia," "depression-dejection," and "confusion-bewilderment") significantly decreased, and the positive measure for "vigor-activity" increased. Chia-Pin Yu et al say, "Although some studies have suggested that longer forest bathing programs have a more beneficial effect, the present study clearly demonstrated that among middle-aged and elderly individuals, the short forest bathing program was associated with stress recovery."

The authors state that the lack of possibly confounding variables (e.g., socio-economic status, lifestyle habits, etc) is a limitation of the study. I also wonder how this type of sensory exercise compares to a simple hike in the woods or walk around a city park. Simply being in a natural environment has many stress-relieving and health-promoting effects, as Kurt Beil, ND, explained in his July 2018 article for *Townsend Letter.* Or is mindful attention to sensory input a key part of the benefits?

Beil K. Forest Bathing: Immersion in the Healing Power of Nature. *Townsend Letter.* July 2018;78-82.

Yu C-P, et al. Effects of Short Forest Bathing Program on autonomic Nervous System Activity and Mood States in Middle-Aged and Elderly Individuals. *Int J Environ Res and Public Health.* 2017;14:897.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Vegan Diet Decreases Inflammation

One hundred patients (mean age, 61 years) with angiographic evidence of coronary artery disease were randomly assigned to consume a vegan diet or the American Heart Association (AHA)-recommended diet for eight weeks. The AHA diet emphasizes vegetables, fruits, whole grains, nuts and seeds, low-fat dairy products, poultry, fish, and legumes. The vegan and AHA diets were designed to be as similar as possible, with the only difference being plant-based vs. animal-based protein. Participants in both groups were provided with groceries, tools to measure dietary intake, and diet counseling. The primary endpoint was high-sensitivity C-reactive protein (CRP). After adjustment for baseline concentrations, the mean CRP level was significantly lower by 32% with the vegan diet than with the AHA diet ($p = 0.02$). The degree of reduction in body mass index and waist circumference did not differ between groups.

Comment: CRP is a marker of inflammation, and a high CRP concentration is an independent risk factor for cardiovascular disease. The results of the present study suggest that consumption of a vegan diet can decrease CRP levels. This effect may be due in part to the fact that cooking of animal foods results in the formation of relatively large amounts of pro-inflammatory advanced glycation end products (AGEs). The production of AGEs is much less when plant foods are cooked. Plant-based diets also tend to be higher than omnivorous diets in various nutrients that have an anti-inflammatory effect, such as vitamin C and magnesium.

Shah B, et al. Anti-inflammatory effects of a vegan diet versus the American Heart Association-recommended diet in coronary artery disease trial. *J Am Heart Assoc*. 2018;7:e011367.

Whole Grains Decrease Inflammation

Sixty overweight or obese Danish adults at risk of developing metabolic syndrome (as indicated by the presence of at least one of the following: dysglycemia, low HDL-cholesterol level, or hypertension) were randomly assigned to consume whole grains or refined grains for eight weeks. After a six-week washout period, each person consumed the alternate diet for an additional eight weeks. Mean intake of whole grains was 179 g per day during the whole-grain period and 13 g per day during the refined-grain period. Compared with refined grains, whole grains significantly decreased the mean concentration of two markers of inflammation: C-reactive protein ($p = 0.003$) and the interleukin-6 ($p < 0.01$). Mean body weight decreased by 0.2 kg with whole grains and increased by 0.9 kg with refined grains ($p < 0.001$ for the difference in the change between diet periods), although mean energy intake did not differ significantly between diet periods.

Comment: Previous observational studies have found that higher intake of whole grains is associated with a lower risk of developing cardiovascular disease. The results of the present study suggest that the protective effect of whole grains is due in part to a reduction in inflammation. Whole grains are also higher than refined grains in various cardioprotective nutrients, including magnesium, vitamin B6, copper, and chromium.

Roager HM, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial. *Gut*. 2019;68:83-93.

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Magnesium Improves Cognitive Function in People with Cirrhosis

Twenty-nine patients with compensated liver cirrhosis (83% of whom had abnormal cognitive exam results consistent with minimal hepatic encephalopathy) were randomly assigned to receive, in double-blind fashion, 520 mg per day of magnesium oxide or placebo for eight weeks (Note: this was 520 mg per day of elemental magnesium, according to a personal communication from one of the study authors). At baseline, 10% of the patients had hypomagnesemia and one-third had low levels of intracellular magnesium (measured using a buccal mucosal swab). Initial serum and intracellular magnesium levels correlated positively with cognitive performance. At the end of the treatment period, the mean score on a test of long-term memory was significantly better in the magnesium group than in the placebo group ($p = 0.03$).

Comment: Hepatic encephalopathy is characterized by various neuropsychiatric abnormalities that occur in patients with cirrhosis. Minimal hepatic encephalopathy is a subclinical phase of hepatic encephalopathy in which there are no overt symptoms, but there are minor changes in coordination, attention, and visuomotor function. The results of the present study suggest that magnesium deficiency is common in patients with compensated liver cirrhosis and minimal hepatic encephalopathy, and that magnesium supplementation may improve cognitive function in these patients.

Cohen-Hagai K, et al. Magnesium deficiency and minimal hepatic encephalopathy among patients with compensated liver cirrhosis. *Isr Med Assoc J*. 2018;20:533-538.

Low FODMAPs Diet for Inflammatory Bowel Disease and Celiac Disease

Forty-one patients with celiac disease who were on a gluten-free diet, 30 patients with inactive inflammatory bowel disease (16 with Crohn's disease, 14 with ulcerative colitis), and 56 patients with irritable bowel syndrome (IBS) were studied. All patients were experiencing symptoms suggestive of functional bowel disease (such as bloating, diarrhea, flatulence, abdominal pain, and constipation). The patients were taught how to follow a low FODMAPs diet for three months. There were no changes in medications or lifestyle habits during the study. Symptoms were assessed at baseline and after one and three months with the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS). The mean IBS-SSS score improved significantly ($p < 0.001$) in each of the three groups. In the patients with celiac disease on a gluten-free diet, the mean score improved by 38% after one month and by 65% after three months. In the patients with inactive inflammatory bowel disease, the mean score improved by 33% after one month and by 65% after three months. In the IBS patients, the mean score improved by 47% after one month and by 70% after three months.

Comment: Patients with celiac disease or inactive inflammatory bowel disease frequently have symptoms related to coexisting functional bowel disease, such as bloating, abdominal pain, and flatulence. These symptoms are also common in patients with IBS.

"FODMAPs" is an acronym for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. FODMAPs include fructose, lactose, sorbitol, fructans (e.g., fructooligosaccharides and inulin), and galactans (also called galactooligosaccharides; e.g., raffinose). Foods restricted on a low-FODMAPs diet include lactose-containing foods, foods with added fructose, foods which naturally contain fructose in excess of glucose (e.g., apples, pears), fructans-containing foods (e.g., wheat, artichokes, onions, garlic, and leeks), sorbitol-containing foods (e.g., stone fruits), and raffinose-containing foods (e.g., legumes, lentils, cabbage, and Brussels sprouts).

The present study confirms the results of previous studies demonstrating that a low-FODMAPs diet can improve IBS symptoms. The new study also showed that this diet can improve functional bowel symptoms in people with celiac disease who are on a gluten-free diet and in those with inactive inflammatory bowel disease. Details on how to follow a low-FODMAPs diet are available on the Internet.

Testa A, et al. Beyond irritable bowel syndrome: the efficacy of the low FODMAP diet for improving symptoms in inflammatory bowel diseases and celiac disease. *Dig Dis*. 2018;36:271-280.

Precaution with Intravenous Vitamin C

A 54-year-old man with metastatic prostate cancer and glucose-6-phosphate dehydrogenase (G6PD) deficiency developed severe hemolytic anemia and acute renal failure after receiving 30 g of vitamin C intravenously, followed by 60 g four days later. The patient also received zinc, magnesium, methylcobalamin, and glutathione (presumably intravenously, although the route of administration was not specified), Symptoms appeared within 2 days after the first infusion, and included syncope and severe fatigue. He required multiple blood transfusions and 10 days of hemodialysis. Renal function recovered, and the patient was discharged after 21 days of hospitalization.

Comment: There have been two previous case reports of acute hemolysis induced by high-dose intravenous vitamin C in patients with G6PD deficiency. In both of these previous reports, the hemolysis-inducing dose was 80 g. One of the patients who suffered hemolysis from that dose had previously received 40 g of intravenous vitamin C three times a week for one month, with no evidence of hemolysis.[1] The present case report suggests that as little as 30 g of intravenous vitamin C can cause severe hemolysis in some patients with G6PD deficiency. The patient in this report also received zinc, magnesium, methylcobalamin, and glutathione (presumably intravenously, although the route of administration was not specified). I am not aware of evidence

that any of these substances can cause hemolysis in people with G6PD deficiency, but it is possible that one or more of them increases the effect of vitamin C in these individuals.

High-dose intravenous vitamin C is contraindicated in people with G6PD deficiency, and patients should be tested for this condition before receiving such treatment. While the hemolytic effect of vitamin C in patients with G6PD deficiency is presumably dose-related, it is not known what dosage of intravenous vitamin C would be safe for these individuals. Numerous practitioners administer 1-5 g of vitamin C intravenously as a component of the Myers cocktail without first testing for G6PD deficiency. Among the many thousands of patients who have received this treatment, there have been no reports of severe hemolytic episodes. However, it is possible that minor episodes of hemolysis have gone unrecognized.

Rees MJ, et al. Massive oxidative haemolysis and renal failure caused by high dose vitamin C. *Med J Aust*. 2018;209:248-249.e1.

Soy Extract for Menopausal Hot Flashes

One hundred thirty-six perimenopausal and post-menopausal Caucasian women with at least seven hot flashes per day were randomly assigned to receive, in double-blind fashion, a soy germ extract (providing 100 mg per day of isoflavone glycosides) or placebo for 12 weeks, followed by 12 weeks of open-label treatment with soy germ extract. The mean number of hot flashes fell to a significantly greater degree with soy than with placebo (43.3% vs. 30.8%; $p < 0.001$ for the difference in the change between groups). During the open-label phase, both groups had a 68% decrease in the number of hot flashes. Soy germ extract was more effective for women with severe symptoms at baseline than in those with less severe symptoms.

Comment: Genistein and daidzein are isoflavones present in soy that have weak estrogenic activity. Among the many controlled trials that have been conducted, most but not all found that consumption of isoflavone-rich soy protein or isoflavone supplements significantly decreased the frequency and/or severity of hot flashes and improved other symptoms related to menopause (such as impaired cognitive function and mood disorders). Treatment regimens that have been used in clinical trials included 50-120 mg per day of soy isoflavones for six weeks to six months, 20-60 g per day of isolated soy protein for 6-12 weeks, and one-half cup per day of soy nuts divided into three or four portions spaced throughout the day for eight weeks. The results of the present study indicate that an extract of soy germ is also beneficial.

Imhof M, et al. Soy germ extract alleviates menopausal hot flushes: placebo-controlled double-blind trial. *Eur J Clin Nutr*. 2018;72:961-970.

Another Benefit of Folic Acid Supplementation During Pregnancy

One hundred nineteen healthy pregnant women (aged 18-35 years) in Northern Ireland who had taken 400 µg per day of folic acid during the first trimester were randomly assigned to receive, in double-blind fashion, 400 µg per day of folic acid or placebo during the second and third trimesters. Thirty-nine children of those women were assessed at six-to-seven years of age. Compared with the placebo group, the folic acid group scored significantly higher on measures of emotional intelligence and resilience, as determined by median scores on the Resiliency Attitudes and Skills Profile, the Strengths and Difficulties Questionnaire, and the Trait Emotional Intelligence Questionnaire Child Short Form.

Comment: Folic acid supplementation is recommended in the periconceptional period as a means of preventing neural tube defects and certain other birth defects. The potential importance of continuing folic acid for the entire pregnancy has not been as well studied, although it may increase the duration of gestation and the birthweight of the infants.[2] The results of the present study suggest that folic acid supplementation throughout pregnancy, as compared with only during the first trimester, may improve the psychological and social development of the children.

Henry LA, et al. Folic acid supplementation throughout pregnancy: psychological developmental benefits for children. *Acta Paediatr*. 2018;107:1370-1378.

Increasing Water Intake Prevents Recurrent Cystitis

One hundred forty healthy women (mean age, 35.7 years) with recurrent cystitis (3 or more episodes in the previous year; mean, 3.3) who had been drinking less than 1.5 L of fluid per day (mean, 1.1 L per day) were randomly assigned to drink, in addition to their usual fluid intake, 1.5 L per day of water (water group) or no additional fluids (control group) for 12 months. During the study, the mean number of cystitis episodes (1.7 vs. 3.2; $p < 0.001$) and the mean number of antimicrobial regimens used to treat cystitis episodes (1.9 vs. 3.6; $p < 0.001$) were each significantly lower by 47% in the water group than in the control group. Mean urine volume increased by 1.4 L per day in the water group and by 0.1 L per day in the control group. The mean number of voids per day increased by 2.4 in the water group and decreased by 0.1 in the control group.

Comment: Increased fluid intake is often recommended as a preventive measure for women with recurrent cystitis, but there is little research demonstrating such an approach is beneficial. The present study found that increasing water intake is indeed effective for preventing recurrent cystitis in premenopausal women who drink low amounts of fluid.

Hooton TM, et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: a randomized clinical trial. *JAMA Intern Med*. 2018;178:1509-1515.

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On the cover

The Skin as Exposome: An Underappreciated Route of Entry for Toxicants

by Anne Marie Fine, NMD

As the research body of evidence between the major role of toxicants and chronic disease continues to grow, the contributions of personal care products applied to and sprayed around the skin are often overlooked. There is persuasive evidence that even low-level toxic exposures cumulatively contribute to chronic diseases, making it even more likely that the single exposure model of toxicology is more the exception rather than the rule. Certain ingredients in personal care products have been found to be endocrine disruptors, neurotoxins, carcinogens, and skin sensitizers. Daily exposure to these products, even if the exposures are considered small dosages, must be considered in evaluating overall body burden of toxicants.

This article seeks to provide an integrated understanding of the totality of exposome factors in human health by focusing on the contributions of personal care products via dermal absorption.

The Skin Exposome

The exposome as a concept and definition has been around for more than ten years. The exposome consists of external and internal factors and their interactions, affecting a human individual from conception to death.[1] It acts on the human genome and is the environmental trigger to the expression of certain genes. However, the exposome of human skin has not received major attention both for effect on the skin itself and for effects on the body through dermal absorption. The skin plays a particularly important role in environmental exposures because it is first and foremost a barrier organ that is subjected to lifelong exposure to a large variety of environmental factors, while acting as a portal to absorb or excrete certain compounds. For this reason, I am expanding the definition of the skin exposome to encompass not only sun exposure, sleep, stress, cigarette smoking, air pollution, nutrition, but also cosmetics and personal care products.

The skin is the body's largest organ, accounting for more than 10% of total body mass. And while its role as an organ of excretion is well-known, an opposite function, that of an organ of absorption is not at all well-known.

Dermal absorption of chemicals depends on the integrity of the skin barrier function, lipophilicity of the compound, with low molecular weight chemicals with good solubility in both water and fat penetrating the skin more readily, and temperature of the skin, with higher temperature allowing more absorption. Compromised barrier function of the skin also results in increased dermal absorption of chemicals, which can lead to the entry of larger molecules such as proteins, inorganic metal compounds, or nanoparticles. Solvents are one class of chemicals that has been shown to reduce barrier function of the skin by damaging lipid and protein structures of the stratum corneum. Many personal care product formulations contain dermal penetration enhancers such as alcohol and propylene glycol, which also carry certain ingredients deeper into the dermis. Medicines, including topically applied hormones or nicotine aids, can also be driven into the skin dermally through patches or creams, which typically contain a penetration enhancer.

The ability of dermally applied ingredients to penetrate the skin and reach the circulatory system has been established. Certain ingredients from personal care products such as parabens, phthalates, and BPA have been

found not only in maternal serum, but in cord blood of newborns, amniotic fluid, and breastmilk.[2] We can no longer pretend that the skin is an impenetrable barrier. However, the internet and some self-proclaimed "experts" commonly promote the idea that 60% of what is applied to the skin is absorbed into the bloodstream. This derives from a single study in 1984,[3] which demonstrated that an average of 60% of solvents from drinking water were absorbed dermally via bathing. However, this study cannot be extrapolated to apply to all substances applied to the skin, because as previously discussed, differences in molecular composition and solubility affect absorption.

In one study of healthy men, it was demonstrated that after applying a body lotion containing 2% each butylparaben, diethyl phthalate (DEP), and dibutyl phthalate (DBP), the butyl paraben was detectable in the serum after only one hour, and in urine with a peak value 8-12 hours later.[4] The main phthalate metabolites, monoethyl (MEP) and monobutyl phthalate (MBP), were found in the serum as well.

Bisphenol A (BPA) is another chemical compound that easily and quickly enters the systemic circulation. While it is felt that BPA exposure is largely due to oral ingestion from consuming food or water stored in plastic containers or cans lined with BPA, studies have also demonstrated dermal absorption through thermal receipts that are coated in free BPA.[5]

More recent evidence now points to dermal absorption through ambient air exposure as a meaningful exposure pathway for phthalates, in addition to the expected mechanisms of oral absorption and dermal application.[6]

Due to the short half-lives of some of these chemicals found in personal care products, simply removing them and substituting products that don't contain the problematic substances has shown good results in reduction of urinary metabolites in remarkably short periods of time. For example, the Hermosa study was an interventional study of adolescent girls that demonstrated significant reductions in urinary levels of parabens, triclosan, and phthalates, over a three-day period of substituting personal care products that did not contain those chemicals.[7]

Endocrine Disruptors

Endocrine disrupting chemicals (EDCs) alter hormonal signaling, affect developing reproductive systems, and disrupt mammary development.[8] Often the impact of endocrine disruptors is highest at times of greatest developmental growth, such as in utero, puberty, and pregnancy. Epidemiological data show increases in incidence and prevalence of diseases associated with endocrine disrupting chemicals such as breast, prostate and testicular cancers, diabetes, obesity, and decreased fertility over the last 50 years.[9] Endocrine disruptors in personal care products include parabens, phthalates, and triclosan.

Paraben esters act as estrogen agonists, androgen antagonists, inhibitors of sulfotransferase enzymes, and have genotoxic activity.[10] Recently, parabens were shown to impair human sperm motility, enhance the generation of mitochondrial ROS, and stimulate the formation of oxidative DNA adducts.[11] While parabens have never been formally classified as a carcinogen, they have been shown to enable multiple hallmarks of cancer, including resistance to cell death, sustained proliferation, evasion of growth suppressors, invasion and metastasis, genome instability, and deregulation of energy metabolism.[12] Parabens have been found in 99% of breast tissue samples and can stimulate sustained proliferation of human breast cancer cells at concentrations measurable in the breast.[13]

Phthalates are a group of chemical compounds consisting of high molecular weight phthalates and low molecular weight phthalates. The low molecular weight phthalates are found in personal care products as dimethyl ➤

Table 1: Epidemiological studies on semen quality and endocrine disruptors including phthalates, BPA, PCB, and DDT/DDE

Compound	Study design	Sample size and subjects	Age	Concentration	Semen quality	First author (year)
PHTHALATE						
DEP	Cross-sectional	300 Healthy males	29	0.64–3.11 µg/mL	↓Concentration	Pant et al. (21)
DBP	Cross-sectional	300 Healthy males	29	0.18–1.65 µg/mL	↓Concentration, motility	Pant et al. (21)
DBP	Cross-sectional	300 Healthy males	28–29	13.47 µg/mL	↓Motility, viability	Pant et al. (22)
DEHP	Cross-sectional	300 Healthy males	28–29	5.73 µg/mL	↓Motility, viability	Pant et al. (22)
MEP	Cross-sectional	168 Male partners of sub-fertile couples	36	175.5ng/mL	No relationship	Duty et al. (23)
MEP	Cross-sectional	463 Male partners of sub-fertile couples	36	180 ng/mL	No association	Hauser et al. (24)
MEP	Cross-sectional	45 Male partners of sub-fertile couples	35	121.9 ng/mL	↓Concentration	Wirth et al. (25)
MEP	Cross-sectional	269 Males from infertility clinic	32	153.6 µg/mL	No relation	Jurewicz et al. (26)
MBP	Cross-sectional	168 Male partners of sub-fertile couples	36	16.1 ng/mL	↓Concentration, motility, morphology	Duty et al. (23)
MBP	Cross-sectional	463 Male partners of sub-fertile couples	36	17.3 ng/mL	↓Concentration, motility	Hauser et al. (24)
MBP	Cross-sectional	45 Male partners of sub-fertile couples	35	26.9 ng/mL	No association	Wirth et al. (25)
MBP	Cross-sectional	463 Male partners of sub-fertile couples	36	8.0 ng/mL	No association	Hauser et al. (24)

JengHA. Exposure to Endocrine Disrupting Chemicals and Male Reproductive Health. *Front Public Health*. 2014; 2: 55.

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phthalate (DMP), diethyl phthalate (DEP), dibutyl phthalate (DBP), and diisobutyl phthalate (DIBP). High molecular weight phthalates such as di(ethylhexyl) phthalate (DEHP) are a ubiquitous type of plasticizers used in a wide range of consumer products including toys, food packaging, cosmetic products, and medical equipment. DEHP represents a particular public health concern because 100% of the US population have measurable levels of this endocrine disrupting compound. Phthalates have been found to be associated with significantly earlier menopause in women, decreased couple fecundity, low birth weight, preterm birth, altered placental methylome and transcriptome, and pregnancy loss.[14]

In men, phthalates have been associated with altered semen parameters as noted in Table 1.[15] In addition to potential contributions to the deterioration of sperm quality, phthalates have also been found to be associated with anatomical abnormalities in male fetuses such as shorter anogenital distances, a marker for potential reproductive problems.[16,17]

Phthalates also join other environmental exposures that increase the odds of diabetes. Women who were in the third and fourth quartile of phthalates had nearly twice the odds ratio of developing diabetes than women in the first quartile.[18] Phthalates during pregnancy also were associated with a higher risk for higher weight gain and glucose intolerance, which are both risk factors for gestational diabetes.[19]

While phthalate exposure through ingestion, inhalation, and dermal contact are considered important routes of exposure for the general population, recent research has uncovered a new exposure: ambient air.[20] This adds another layer of complexity upon the concept of avoidance, as even if a person scrupulously avoids the use of phthalates from cosmetics and plastics, simply being in the vicinity of other phthalate emitters puts that person at risk. This has been borne out by a recent study that examined 23 cosmetics, four perfume, and nine clothing department clerks for changes in urinary phthalates pre and post-shift. Post-shift urinary levels of mono-2-ethylhexyl phthalate (MEHP- a metabolite of DEHP) and monomethyl phthalate (MMP-a metabolite of DMP) were significantly higher for the cosmetics and perfume clerks than for the clothing clerks. Median levels of air diethyl phthalate (DEP) in cosmetics (1.77 $\mu g/m^3$) and perfume (1.75 $\mu g/m^3$) groups and di-(2-ethylhexyl) phthalate (DEHP) in perfume group (6.98 $\mu g/m^3$) were higher than those in clothing group (DEP: 0.89; DEHP: 2.16 $\mu g/m^3$). Over half of cosmetic (70%) and perfume sale clerks had exceeded cumulative risk of phthalate exposure for anti-androgenic effect. The authors concluded that cosmetic and perfume workers had increased risks of reproductive or hepatic effects for DBP and DEHP exposure and suggest that not only inhalation but dermal exposure through ambient air is important route of phthalate exposure for cosmetics and perfume workers.[21]

Originally registered as a pesticide by the EPA, triclosan is a chlorinated aromatic compound that has been used as an antimicrobial agent since the 1970s. It has widespread use in consumer goods like anti-bacterial soaps, kitchen utensils, toys, bedding, and clothing, making it easy to see how 75% of people tested have been exposed.[22] In personal care products, it enjoyed a near monopoly on the antimicrobial soaps for home use that came into fashion in the 1990s. The FDA banned triclosan for use in antimicrobial hand soaps in 2016 due to concern about its estrogenic and androgenic activities in vitro, and adverse effects reported on reproductive function in rodents and aquatic species, as well as not being found to be any more effective in neutralizing bacteria than plain soap and water. However, triclosan can still be found in other consumer products such as toothpaste. In more recent findings, triclosan is now being found in indoor air, with concentrations varying according to location; office space was the most contaminated, followed by apartment space, house space, and day nursery space.[23]

Neurotoxins

Lead and aluminum are the primary neurotoxins found in personal care products. The FDA conducted a study that found lead in 100% of all the lipsticks, with tested levels up to 7.19 ppm.[24] (See Table 2)

Lead from lipstick poses harm because exposure is due to ingestion; after all, lipstick commonly winds up on teeth

Table 2: FDA Analyses of Lead in Lipsticks – Expanded Survey

The following results for lead content in 400 lipsticks were obtained by Frontier Global Sciences, Inc., under a contract with the US Food and Drug Administration (FDA). The lipsticks were purchased from retail stores between February and July 2010.

Sample #	Brand	Parent Company	Lipstick Line / Shade # / Shade	Lot #[a]	Lead (Pb)[b] (ppm)
1	Maybelline	L'Oréal USA	Color Sensational / 125 / Pink Petal	FF205	7.19
2	L'Oréal	L'Oréal USA	Colour Riche / 410 / Volcanic	FE259	7.00
3	NARS	Shiseido	Semi-Matte / 1005 / Red Lizard	OKAW	4.93
4	Cover Girl Queen Collection	Procter & Gamble	Vibrant Hues Color / Q580 / Ruby Remix	9139	4.92
5	NARS	Shiseido	Semi-Matte / 1009 / Funny Face	9DLW	4.89
6	L'Oréal	L'Oréal USA	Colour Riche / 165	FF224	4.45

or the food that the woman is eating, which is why lipstick is commonly applied several times per day. As no level of lead has been proven to be safe in children according to the CDC, pregnant and breastfeeding women are a particularly vulnerable population.[25] The CDC reports that even low levels of lead in children's blood have been shown to affect IQ, attention span, and academic achievement.

Aluminum is widely found in anti-perspirants and is considered a neurotoxin and metalloestrogen.[26] It has been found in breast tissue and fluids at higher levels than in blood. Over time, breast cancer incidence in the upper outer quadrant of the breast has increased, leading to questions of whether or not aluminum-containing underarm cosmetics may be contributing to this phenomenon.[26] In one small study analyzing nipple aspirate from women with and without cancer, significantly increased aluminum and pro-inflammatory and chemoattractant cytokines were found in the women with cancer, suggesting that aluminum accumulation in the breast may be a possible risk factor for breast cancer.[27] In a recent case control study, the use of underarm cosmetic products containing aluminum salts multiple times per day commencing prior to age 30 had a significant increase in breast cancer risk (OR of 3.88 (95% CI 1.03–14.66)).[28]

Carcinogens

Several agents listed by the IARC as Group 1 carcinogens can be found in personal care products: formaldehyde, 1-4 dioxane, and ethylene oxide.[29] For the most part, these are found as contaminants in formulations except for formaldehyde, which is either intentionally added to formulations such as certain hair-straightening products, or released slowly into a product from a formaldehyde-releasing preservative system. Because of this fact, they will not be explicitly listed on a label as "formaldehyde," making it important to know how to determine its presence.

In the case of formaldehyde-releasing preservative systems, the chemicals that are listed on the label slowly release formaldehyde over time, which preserves the product. The health concerns with formaldehyde releasers include direct toxic effects and contact dermatitis for many users. In fact, the American Contact Dermatitis Society awarded formaldehyde its dubious honor of being the 2015 contact allergen of the year. Twenty of all cosmetic products, including 17% of stay-on products and 27% of wash-off products contain formaldehyde releasers. These formaldehyde-releasing preservative system chemicals include the following:

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- Quaternium-15,
- Dimethyl-dimethyl (DMDM),
- Hydantoin,
- Imidazolidinyl urea,
- Diazolidinyl urea,
- 2-bromo-2-nitropropane-1,3-diol (bronopol),
- Sodium hydroxylmethylglycinate.[30]

Both 1-4 dioxane and ethylene oxide are by-products of the ethoxylation process, which is a method used to make certain agents less harsh by reacting them with ethylene oxide. This process can result in small amounts of 1-4 dioxane and residual ethylene oxide in the product. You will not know if this appears in the product of question because these are an unintentional byproduct of the ethoxylation process and may or may not be present at all since some companies use vacuum stripping to remove them. However, if the label contains the following chemicals that have been subject to the ethoxylation process, then the contaminants might appear in the final product:

- Sodium laureth sulfate,
- Polyethylene,
- Polyethylene glycol (PEG),
- Polyoxyethylene,
- Polysorbate,
- Or any ingredient with "xynol," "ceteareth," or "oleth."[30]

Conclusion

When assessing the entirety of the exposome that affects human health, it is important to consider the invisible sea of synthetic chemicals being applied to our patients' bodies every day. Consumer awareness about human health concerns associated with various ingredients used in personal care products is increasing markedly. This has placed considerable demand on the companies that formulate these products to produce safer products even in the face of regulations that have simply not kept up with the science. Indeed, other countries are already adhering to the Precautionary Principle and formulating safer products for their people through the lens of stricter regulations. As we evaluate our patients' toxic body burden with appropriate attention paid to the daily use of myriad personal care products, we can identify problematic exposures and make well-informed suggestions for replacement products.

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Dr. Fine has been published in peer-reviewed medical journals, Thrive Global, and popular magazines alike. She is featured regularly on health podcasts, TV, and radio shows. Dr. Fine is also the international bestselling author of *Cracking the Beauty Code: How to program your DNA for health, vitality, and younger-looking skin,* a book that synthesizes her knowledge of skin aging, gene-environment interactions, and environmental medicine. She is also the founder and CEO of IAMFINE®, an integrative beauty and wellness brand that empowers women to take control of their health and beauty.

For more information see www.drannemariefine.com.

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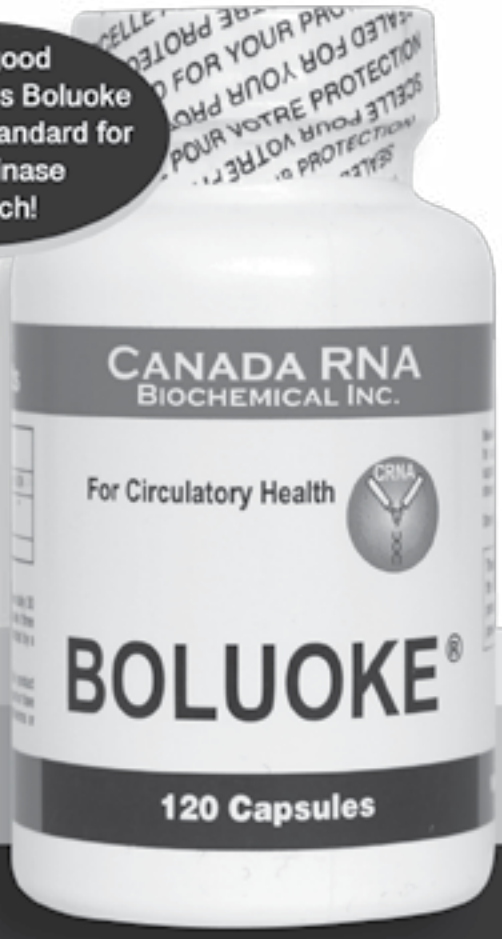

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One Cure for Nasal Polyps: A Case Report

by Jonathan Wright, MD

Originally appeared in *Green Medicine Newsletter* (January 2019)

An otherwise healthy woman in her 60s (we'll refer to her as Audrey) started to notice mild breathing obstruction in her sinuses, "kind of like starting to catch a cold." There was no fever, mucous discharge, or any other symptom indicating infection. The problem gradually worsened; she felt "totally congested" and developed a snore which became worse and worse. She needed two pillows under her head to sleep at night.

She visited an ENT physician who looked as far as possible into her sinuses, then ordered a "CT scan." At follow-up, she was told she had "a bad case of nasal polyps," and that the scan showed her sinuses were "almost totally clogged" by the polyps, with only an occasional "clear air pocket" showing on the x-ray. She was advised to have surgery to remove the polyps.

She asked the ENT physician if surgical removal of all the nasal polyps would permanently eliminate the problem. She was advised that at the very least her breathing would be a lot better for a while, but often the polyps return. She asked how often polyps return and was told "ultimately, more than half the time." She declined surgery and started searching online for causes and alternative treatments. Unfortunately, all the websites she visited kept repeating that the cause of nasal polyps is unknown, citing allergic rhinitis, asthma, aspirin allergy, sinus infections, "something stuck in the nose."[1]

The Cause of Nasal Polyps Has Been Found

Fortunately, researchers at universities in Poland,[2] Iran,[3] Croatia,[4] India,[5] and again from Iran[6] have determined the actual cause of nasal polyps. (Also, fortunately, their reports were printed in English, so I could read them!)

The cause of nasal polyps was first disclosed in 2011 in the titles of the Polish and Iranian research reports, and repeated in the 2012, and two 2016 research reports:

- Poland (2011) "Detection of Helicobacter pylori and cagA gene in nasal polyps and benign laryngeal diseases."
- Iran (2011) "Helicobacter pylori-DNA in nasal polyp tissues in comparison with inferior nasal turbinate tissues: A case control study in Tehran, Iran."
- Croatia (2012) "The significance of Helicobacter pylori in patients with nasal polyposis."
- India (2016) "Detection of Helicobacter pylori in Nasal Polyps."
- Iran (2016) "Helicobacter pylori in nasal polyp formation: A case-control study in Tehran, Iran."

The consensus is obvious: Nasal polyps are caused by an infection with the bacteria *Helicobacter pylori*! It's also obvious why polyps return in the majority of those who have their polyps surgically removed: surgery can't possibly remove a bacterial infection!

Many *Green Medicine Newsletter* readers likely are aware that *Helicobacter pylori* (often termed "*H. pylori*") is the cause of stomach ulcers, and that "modern medicine" (in this case, an ironic term) treats *Helicobacter pylori* with patent medicines, such as a combination of two antibiotics and a patented "acid blocker," a combination often called "triple therapy." So why isn't this – or a version of it – used by "modern medicine" against nasal polyps? Although it can't be said (or written) for certain, it's quite possible that much of "modern medicine" isn't even aware of the nasal polyp research cited above!

A Psoriasis Treatment to Target *H. pylori*

Is there a better, more targeted treatment against *H. pylori* than "modern medicine's" routine "triple therapy"? This better *H. pylori* remedy was developed in the early 1990s by dermatologist Stephen Smith, MD, but not as treatment for *H. pylori*, but as a remedy for psoriasis. Dr. Smith published research[7] demonstrating its effectiveness in 1997. (That this treatment works by killing *H. pylori* only became obvious years later.)

The research reported in 1997 used the earliest form of Psorizide® (nickel dibromide) or a placebo. Patients suffering with psoriasis took either Psorizide® first and then the placebo, or the placebo first, then Psorizide®. (The patients were not informed of which one they were taking at any time; for the technically inclined, this is termed "double-blind, crossover" research.)

When using Psorizide®, psoriasis was cleared to a significantly greater degree than when the placebo was used.

As Dr. Smith tells us, it "felt like a brick wall" trying to get FDA "approval," so – because homeopathy was legalized "federally" in the 1930s and exempted from FDA jurisdiction – Dr. Smith switched to homeopathic formulations containing nickel sulfate 1x, potassium bromide 1x, and fumaric acid 1x (Psorizide Forte®)[8] or nickel sulfate 1x, potassium bromide 1x, and zinc bromide 4x (Psorizide Ultra®).[9]

Psorizide® in its various forms had helped many individuals consulting at Tahoma Clinic to either clear or significantly improve their psoriasis.

In 1997, there was no research available that linked either psoriasis or nasal polyps with *H. pylori*. Research linking psoriasis and *H. pylori* appears to have started – as did the proof of Helicobacter (also called "H. pylori) causing stomach ulcers – with single cases. One case was reported[10] in a "letter to the editor" in 2007, with before and after photographs. It was titled "Complete remission of palmoplantar [palms of the hands, soles of the feet] psoriasis through Helicobacter pylori eradication: a case report."

In this case report, a 35-year-old man was described (and photographed) with this severe form of psoriasis. He had been given a "breath test" (routinely used in "modern medicine" for diagnosis of *H. pylori* infection) which was found to be positive for *H. pylori* infection. He was given the usual (for "modern medicine") *H. pylori* (often called "triple therapy") treatment of amoxicillin and clarithromycin along with a stomach acid blocker, omeprazole. After six weeks of this treatment, the psoriasis started to fade; a year later, the psoriasis was completely gone. (The researchers did not state whether the treatment noted above was used for the entire year.)

Another single case was also reported[11] in another "letter to the editor" published the next year. Titled "Clearance of chronic psoriasis after eradication therapy for Helicobacter pylori infection" (and accompanied by photographs), the letter described a 48-year-old woman with "severe and extensive" psoriasis affecting her everywhere except her face and scalp for "at least" the prior fifteen years. She also had been diagnosed with *H. pylori* infection.

She noticed a major improvement in her psoriasis starting just two weeks after beginning treatment for *H. pylori*. (The authors of the "letter to the editor" were careful to point out that she took no other treatment for psoriasis during that time.) They concluded: "There is no doubt that our patient's psoriasis has improved after the eradication of the *H. pylori* gastric infection."

Since these case studies were published, there have been many conflicting reports about *H. pylori* and psoriasis. In 2018 a "meta-analysis" of this topic was published.[12] (A "meta-analysis" is not original research; it's a comprehensive review of all available previously published research reports and reviews.) Although the reviewers could not determine exactly how *H. pylori* is related to psoriasis, they concluded: "This meta-analysis has shown an increased *H. pylori* infection in patients with psoriasis."

2 + 2 = 4

Nasal polyps might be cleared with Psorizide, and they were! My math skills have always been weak (just ask my math teachers). However, from time to time it seems to me that 2+2 does equal 4, so in this circumstance putting together the 2007 case reports of clearance of psoriasis with "triple therapy" for *H. pylori*, along with the 2011 through 2016 reports that nasal polyps are infested with *H. pylori*, it seemed obvious that if Psorizide® might kill the *H. pylori* associated with psoriasis, it might also kill the *H. pylori* associated with nasal polyps, and clear them too. And likely (as Dr. Smith's interview and my own experience observes) there would be many, many fewer adverse effects than with "triple therapy."

Audrey listened patiently while all of that was explained and decided she'd rather try the Psorizide®; and if that didn't work, she might consider the "triple therapy," which – if it happened – we agreed should be reduced to "double therapy" without the acid blocking medication. "Don't think there's any acid produced in my nose, or anyone else's either," she observed.

During the first week or two of Psorizide® use, she didn't notice any difference in her breathing. The third week she started having nosebleeds lasting for a few minutes or longer. After that she continued to have heavier and more frequent nosebleeds once or twice weekly. Many appeared to contain not only blood but also bits and pieces of pinkish tissue. Then the surprise: a heavier nosebleed containing blood and bits of tissue and an entire nasal polyp! Not kidding: she took a picture of it with her cell phone and showed me!

As the nosebleeds continued, she "looked at the bright side," saying, "I'm reducing my heart attack and stroke risk with these nosebleeds, I don't need to donate blood until after the nosebleeds have stopped for a while!"[13] (She also kept track of her blood count and serum iron – *not* serum ferritin – to make sure she didn't become actually anemic, which despite the once or twice weekly nosebleeds, she didn't.)

After almost a month of this, she couldn't help but notice that she was breathing more easily. After two months, she was breathing significantly better; and the nosebleeds had diminished in frequency and quantity, tapering to once weekly and then stopping altogether after approximately three months. She was breathing freely, no longer snoring at all, and was able to "sleep flat" without pillows if she wanted to do that. As a precaution, she ➤

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tapered the treatment to nothing over the next few weeks, has had no more problems breathing, and no recurrence at all of nosebleeds in the last two years.

How Does Psorizide® Kill *H. pylori*?

At present, there's no verified "mechanism of action" (scientese for "how the **** does this work") for how Psorizide® kills *H. pylori*. There's at least one clue though: *H. pylori* likes nickel! No, not kidding, *H. pylori* really does! According to one authority: "It [nickel]…. is an essential element and critical for the pathogenicity of *Helicobacter pylori.* Nickel is essential for the activity of two of *H. pylori*'s essential enzymes, urease and hydrogenase. Several studies revealed that these enzymes are important for colonization of the host gastric mucosa."[14] [In English, nickel is essential for *H. pylori* to invade the cells lining the stomach, and (presumably) nasal polyps.] Another research report[15] tells us that *H. pylori* bacteria store nickel inside themselves to help them invade tissues!

While nickel is very important for *H. pylori*, bromide appears to be detrimental to this bacteria. As Dr. Smith says in the interview, Israeli researchers had reported that in individuals successfully treated for psoriasis at the "Dead Sea" in Israel, serum bromide levels were significantly higher after treatment than before treatment. It's just a thought – not proven at all – that *H. pylori* likes nickel so much that it gobbles the nickel and bromide together, and the bromide kills the *H. pylori*.

Facts are that Psorizide® has both the nickel that *H. pylori* likes a lot and the bromide which appears to kill it. Perhaps the other natural components (zinc, fumaric acid, sulfate) in the other homeopathic forms of Psorizide® contribute to killing it too! Only time and further research will tell us.

For now, Psorizide® – Psorizide Forte®, specifically, for Audrey – has cleared one case of nasal polyps, and no signs or symptoms of them have returned in the two years since they departed via nosebleeds rather than being removed surgically.

If you have nasal polyps, you might consider showing this article to your physician. If you're a physician, this treatment for nasal polyps – which appears to treat the cause – might be worth considering for your patients with nasal polyps! And of course, warn them of potential nosebleeds while the polyps – and the *Helicobacter pylori* that research has reported nasal polyps to contain – are departing.

The author has no financial connection with the product Psorizide® or the company which manufactures *Psorizide®*

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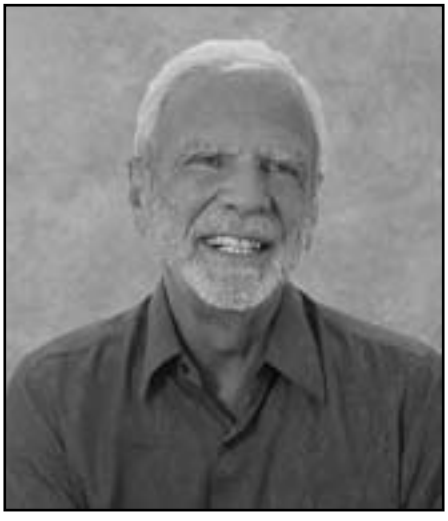

A Harvard University and University of Michigan graduate, Dr. Jonathan V. Wright, MD (Hon. ND), was also awarded an honorary ND by Bastyr University (1993). He continues to be a forerunner in research and application of natural treatments for healthy aging and illness. He has taught natural biochemical medical treatments since 1983 to thousands of physicians in the USA, Europe, and Japan. He was the first to develop and introduce the use of comprehensive patterns of bio-identical hormones (including estrogens, progesterone, DHEA and testosterone) in 1982 and directed the development of tests to ensure their safe use. Other accomplishments include originating successful natural treatment for elimination of childhood asthma, developing natural treatment to stop vision loss and/or improve vision in the majority of individuals with "dry" macular degeneration, pioneering the use of aldosterone to reverse age-related hearing loss, discovering the effects of iodine on estrogen metabolism and cobalt on steroid detoxification, and popularizing the use of the natural sugar D-mannose for elimination of 85-90% of urinary tract infections. He also originated effective natural treatment for seborrheic dermatitis, allergic and viral conjunctivitis, Osgood-Schlatter's disease, and treatment that improves bone density in the large majority of those with osteoporosis. Dr. Wright serves as medical director of Tahoma Clinic in Tukwila, Washington (www.TahomaClinic.com).

Intravenous Vitamin C Sensitizes Pancreatic Cancer to Radiation Therapy

by Heather Wright, ND, FABNO

A landmark paper on using intravenous vitamin C concurrently (IVC) with chemotherapy and radiation treatments for pancreatic cancer was published in December 2018. This paper summarizes a series of studies conducted by senior author Joseph Cullen at the University of Iowa and colleagues.[1] There were three parts to this research by Cullen's team:

1. In vitro vitamin C treatment increased toxicity of radiation therapy to pancreatic cancer cells more than radiation therapy alone. Secondly IVC plus radiation damaged healthy jejunal cells less than radiation alone. This suggests that the combination may increase anti-tumor effect while protecting healthy cells.
2. In mice who grew pancreatic tumors and received radiation treatment, they tested intraperitoneal injection of vitamin C and looked at the impact on nearby jejunal tissues compared with control mice who received radiation alone and found that the mice treated with vitamin C had less damage to nearby jejunal tissue demonstrated by reduced villous blunting, loss of crypt cells, and collagen deposition. It was found that radiation created heavy damage to mitochondrial structures in jejunal epithelial cells, which was partially inhibited by ascorbate treatment.
3. In the human clinical trial, they evaluated the safety and potential efficacy of IVC combined with radiation treatment and gemcitabine chemotherapy for patients with locally advanced pancreatic cancer compared to matched historical controls who received gemcitabine and radiation but not IVC. The study also assessed the maximal tolerated dose (MTD) of IVC in participants.

In the human study, IVC was administered during radiation therapy while participants received ongoing treatment with gemcitabine. Fifteen subjects were enrolled in the experimental group, and 19 subjects were selected from the records of the hospital to be used as historical comparators. Blinding and randomization were not described. All the patients in the study received similar gemcitabine and radiation therapy. All of the patients had pancreatic adenocarcinoma. Patients initially received one test dose of 15 g IVC before proceeding to the dose cohort of 50 grams of IVC, which was given daily, while gemcitabine was given weekly for six weeks and radiation was given via 25-28 treatments for a total of 50 Gy. Interestingly, this is the first study to actively infuse IVC during radiation 'beam on' time. For this, patients were started on IVC in the infusion area then transported to the radiation area for their treatment and then they returned to the infusion area to complete the drip.

The IVC doses for each patient were escalated from 50 grams to 75 grams and then to 100 grams in a two-stage design for participants who tolerated it well without dose limiting toxicity, defined as vomiting resulting in hypokalemia, febrile neutropenia, intra-abdominal hemorrhage, or severe weight loss. Serious adverse events related to the IVC were also considered a dose-limiting toxicity.

Of the sixteen patients enrolled in the study, two withdrew and fourteen patients completed the study. In the ascorbate group there were eight females, and six males with a median age of 59. In the comparator group there were six females, and 13 males with a median age of 63. All the participants in the IVC treatment group had received prior chemotherapy while only two of the control group had. More people in the control group had higher performance scores, fewer smoked, and more were diagnosed with earlier stage disease and node negative disease than those in the treatment group. Thus, the comparator group could have had an advantage and possibly be expected to have better outcomes compared to those patients in the IVC treatment group.

While the stated primary purpose of this study was to assess the safety and toxicity of the combination of IVC, gemcitabine, and radiation treatment, our attention is drawn to the secondary objectives, which were to ascertain a maximum tolerated dose of vitamin C and to understand any effect the combined treatment had on patient prognosis. Though the study was not powered to prospectively assess differences in survival, the investigators hypothesized that the patients receiving treatment with IVC would be no worse off than those receiving the chemoradiation alone. The median overall survival of the 14 patients receiving IVC-gemcitabine-radiation was reported to be 21.7 months. The authors compared this to 12.7 months in the University of Iowa's institutional average for patients receiving the same treatment without IVC, however did not report survival data for the 19 historical comparator subjects selected. Also, these

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survival values did not meet statistical significance (p=0.08). The median overall survival of the treatment group as reported is better than n=74 patients in the E4201 trial, which compared outcomes of locally advanced pancreatic patients receiving gemcitabine with or without radiation therapy reporting statistically significant survival benefit for the combined approach.[2] In terms of progression-free survival (PFS) in the Cullen study, the IVC-treated group median was reported to be 13.7 months, which the authors compared to the University of Iowa's institutionally treated median of 4.6 months and was also compared to subjects in the ECOG-E4201 trial (11.1 months).

Three adverse effects were attributed to IVC: dry mouth, thirst, and transient blood pressure elevations. One patient had a grade 3 transient blood pressure elevation due to hypovolemia and withdrew. Another patient withdrew due to chronic back pain attributed to prolonged sitting during the IVC infusion and radiation. One of the patients in the IVC treatment group receiving the 100 g dose experienced transient hypertension resolving within 30 minutes after infusion. A second participant at the 100 g dose level, who did not have a baseline history of hypertension, developed post-infusion hypertension that did not resolve within 30 minutes post infusion. This was considered possibly a dose-limiting toxicity of IVC, and the patient resumed the study in the 75 g dose cohort without further complication.

Other adverse events included anemia, leukopenia, decreased lymphocyte count, decreased ANC, and decreased platelet counts, which were all consistent with known effects from gemcitabine and radiation therapy.

Hemoglobin levels remained stable in the IVC patients but fell significantly in 13 out of the 19 'controls' (p<0.01). Oxidative injury assessed via plasma F_2-Isoprostane levels showed a significant decrease in the IVC-treated patients (p=0.02) but did not change in controls (p=0.88). Further, one in 13 patients in the IVC group (7%) had grade 3 anemia whereas six subjects (18%) in the comparator group had grade 3 or 4 anemia.

Two subjects in the treatment group became resectable following trial completion (both were initially borderline resectable) and were alive at follow-up 44 and 35 months from diagnosis.

One of the reasons this study by Cullen is so important is that it suggests vitamin C can potentially act synergistically with pro-oxidant therapies such as chemotherapy and radiation to add anti-tumor effect while also acting as an antioxidant protecting the surrounding tissue.

Plasma vitamin C levels in the treatment group averaged 15 mM at the 50 gram/day dose (n=17, 95% CI 13-17 mM), 20 mM for the 75 g dose (n=37, 95% CI 9-21 mM) and 20 mM for the 100 g dose (n=32, 95% CI 19-22mM). Increasing the daily dose of vitamin C above 75 g/day did not significantly increase plasma levels. As has been determined in other studies, the maximum tolerated dose of IVC was found to be 100 grams per infusion with 75 g selected as a recommended dose for future phase II trials. Six participants entered the 75 g dose cohort receiving IVC over 120 minutes, and five moved up to the 100 g dose cohort receiving IVC over 180 minutes.

Cullen and his research team at the University of Iowa are working to assess the effect of adding vitamin C to treatment in several other cancer types. In addition to pancreatic cancer, they are running research trials on lung cancer and glioblastoma. A $9.7 million grant from the National Cancer Institute is helping fund their research.[3]

Cullen's phase I pancreatic clinical trial adds further confirmation that IVC is safe and well tolerated in humans when given alone or in combination with chemotherapy.[4-7] The unique and exciting part of this study is that chemotherapy and radiation were combined with daily IVC in 50-100 g doses, which appears to be safe in patients with resectable pancreatic cancer. This study's protocol is also unique in that the vitamin C was infused during the actual radiation treatment.

The protocol used in Cullen's study reflects an overall change in treatment strategy that's occurred over the last few years. For pancreatic cancer patients not initially eligible for surgery, a combination of chemotherapy and radiation is now thought to improve survival and the chances of becoming resectable. More research on IVC, gemcitabine, and radiation – while safe – will still have a way to go before oncology teams would potentially implement this approach. Larger well-designed studies are needed.

Of the two patients in the Cullen study who went on to get surgery, both had received FOLFIRINOX as first line treatment that had been discontinued due to progression of disease before they entered the Cullen trial.

Although most people think of vitamin C as an antioxidant, the mechanism of action against cancer is thought to be pro-oxidant. We think vitamin C action varies with concentration. At blood concentrations obtained through IV administration, vitamin C can increase generation of hydrogen peroxide in the tissue space, where a pro-oxidant effect is thought to trigger apoptosis in cancer cells that are deficient in catalase (which protects normal cells such as red blood cells from damage by hydrogen peroxide). Thus, the strategy used in the Cullen study is of particular interest as the anti-cancer effect of radiotherapy is also understood to be pro-oxidant and the combination of IVC and radiation may have either additive or synergistic pro-oxidant actions as seen in the vitro and vivo portions of Cullen's study as well as in other studies.

Regarding plasma levels of ascorbate, the authors selected the study doses based on pre-clinical and human data reporting synergy between gemcitabine and IVC in doses sufficient to generate high millimolar plasma concentrations (10-15 mM) predicted to have anti-tumor effect.

The plasma ascorbate levels for the 50 g dose level averaged 15 mM (n=17, 95% CI 13-17), significantly lower than seen at the higher doses of 75 g and 100 g (p<0.05). The take-home for the clinician is that doses of 50-100 g are safe. Cullen's study also confirmed that dosing by weight in kilograms allows predictable plasma concentrations but tells us that a

cap at 75 g might make sense for future studies as higher doses do not raise plasma levels further.

A sweet spot may exist at this 75 g dose between potential benefit and risk of adverse events. The main thing though was that higher doses were not associated with increased plasma levels.

In patients with advanced disease and poor performance status where a top priority is to support quality of life and do no harm, I recommend lower doses, 30 – 50 g. While higher doses are reported safe, the side effects associated with high osmolarity fluids and high total fluid volume could be cause for concern.

If vitamin C is given to boost quality of life or replete suspected vitamin C or antioxidant deficiency, these lower dose IVC infusions could make sense as supportive care; giving 20-30 g at intervals of every few days or weekly might be helpful.

This study provided IVC infusions during radiation treatment for a total of 50 to 50.4 Gray in 25-28 fractions, meaning IVC was given every day for up to 28 days. In terms of performance status, 11 out of 14 patients in this study who received IVC plus chemoradiation had Karnofsky scores that remained stable, while two increased, one decreased, and there were two patients who withdrew from the study. The average Karnofsky score for participants was reported to be 86 ±2 (SEM). This is good; 80-100 is the top tier for performance status.

The mild adverse events reported by Cullen et al are similar to those reported in other studies and are typical to what is seen in clinical practice: thirst, dry mouth, and transient blood pressure and/or urinary changes resolving soon after infusion completion. It is not uncommon to also see dizziness, hypotension, urinary urgency, chills, and/or cramping pains. While there are reports of hypotension in the literature, Cullen et al report they did not observe this symptom. Instead they report that five participants experienced transient blood pressure elevations at least once in the course of the study which resolved within 30 minutes after IVC treatment. One patient was admitted for what ultimately turned out to be esophageal spasm yet subsequently completed the trial in the 75 g dose cohort without further issue.

Normally we expect that patients receiving chemotherapy and radiation treatment will develop anemia to the degree that it impacts quality of life and may disrupt treatment. The Cullen study reports that hemoglobin levels in the experimental group remained stable (p=0.44). In contrast the controls were reported to have significant decreases in hemoglobin over the course of treatment (p<0.01). In non-oncology settings, several studies report low doses of IVC may elevate hemoglobin in anemia.[8,9] In a study of 40 patients on hemodialysis, it was found that IVC given as 3 g twice weekly was equally effective as erythropoietin in raising hemoglobin (p=0.076).[10]

This new strategy of treating patients with chemo and radiation prior to surgery ➤

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is the subject of a series of recent studies that will encourage oncologists to change the routine.

The results of this study are extremely encouraging. Two participants out of 14 became eligible for surgery, underwent resection, and at 44 months and 35 months post diagnosis were without evidence of recurrence.

Previous studies providing IVC to oncology patients have reported benefit to quality of life and reduction in side effects of standard cancer treatment approaches.[11-14] The studies have been small and with considerable heterogeneity. Some of the drawbacks of the studies on intravenous vitamin C are use of historical controls or lack of controls, lack of randomization and/or control groups, participants with primarily advanced incurable disease, and lack of power to analyze overall survival.

Possible vitamin C deficiency isn't talked about much in the IVC clinical trials. People with cancer and smokers have higher levels of inflammation and vitamin C deficiency when compared to healthy volunteers or non-smokers. Antioxidant and anti-inflammatory effects of IVC have been reported in oncology and non-oncology trials.[15] The difficult question that often arises is, how does an antioxidant like vitamin C interact with pro-oxidant cancer treatments? One of the reasons this study by Cullen is so important is that it suggests vitamin C can potentially act synergistically with pro-oxidant therapies such as chemotherapy and radiation to add anti-tumor effect while also acting as an antioxidant protecting the surrounding tissue.

To start to look at this further in humans, Cullen measured plasma F_2-Isoprostanes as a marker of systemic lipid peroxidation or oxidative stress. These levels dropped significantly in those who received IVC but not in the comparator group.

More patients in the IVC group also actually completed treatment, meaning they received all of their prescribed chemo and radiation rather than having dose reductions or stopping treatment. This is something I believe happens more often in patients receiving integrated cancer care. With lower side effects, less damage to peripheral tissues, and improved overall outcomes, the people using integrative therapies may actually be more adherent to standard cancer treatment regimens and this may support better outcomes overall. Specifically, in this Cullen trial, 14 subjects were enrolled to receive the combined therapy, and eight (57%) received GEM as prescribed in six cycles with all 14 (100%) receiving the prescribed radiation dose. This is a better rate of therapy completion than typically seen. For example, in the ECOG 2011 study, only 29% of patients completed all cycles of chemotherapy and almost a quarter did not complete radiation therapy.[16]

As a clinician, I advocate for the use of intravenous vitamin C as a reasonable and rational approach for supportive care in integrative oncology and consider doses between 15 g and 75 g on an individual basis finding them to be well tolerated by people who have been carefully screened.[17] Many naturopathic doctors have experience with the safe delivery of IVC to oncology patients and thus make excellent points of referral and coordination for patients seeking integrative care with this modality. The Oncology Association of Naturopathic Physicians (https://oncanp.org/about-oncanp/) is the specialty organization of naturopathic oncology providers. Members have expertise in integrative cancer treatment coordinating natural therapies with standard oncology care.

Heather Wright is a naturopathic doctor with 12 years of experience working in hospital-based integrative oncology teams. Dr. Wright graduated from Bastyr University in 2005 after completing post-baccalaureate pre-medical studies at Tufts and Northeastern Universities. Dr. Wright has special expertise in pancreatic cancer and has co-authored and conducted clinical trials as well as participated in consortium work in the field of pancreatic cancer.

Dr. Wright is currently president of the Oncology Association of Naturopathic Physicians (OncANP.org) and serves as research director for KNOWoncology.org, a knowledge translation project summarizing human level data in integrative oncology. Dr. Wright sees clients at CAMAcenter.com in Philadelphia, Pennsylvania, and also uses teleconsultation services.

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Joint Hypermobility Syndrome and Complex Illness: The Extracellular Matrix Connection

by Michael McEvoy, www.MetabolicHealing.com

Joint hypermobility syndrome (JHS) is a significantly under-reported clinical phenomenon. Individuals with JHS frequently present with a complex array of symptoms and conditions. These often include postural orthostatic tachycardia syndrome (POTS), mast cell activation syndrome (MCAS), neurological symptoms, heart rate changes, blood pressure fluctuations, chronic pain, frontal, temporal and occipital headaches, visual disturbances, blood clotting abnormalities, vascular and circulatory conditions, bruising, organ prolapse, bowel disorders, esophageal, cardiac and pyloric valve abnormalities, autoimmune conditions, chiari malformation, cranial cervical instability, intracranial pressure changes, disturbances of cerebrospinal fluid, dura matter abnormalities, post-traumatic stress disorder (PTSD) and sensory processing disorders, anxiety, depression, and gynecological issues such as polycystic ovary syndrome (PCOS) and endometriosis.

The etiologies of the complex symptom presentations that are associated with JHS have been explored to a limited extent. By understanding these etiologies, it is possible to develop therapeutic interventions for individuals suffering with these conditions.

Loss of Extracellular Matrix (ECM) Function

"Strictly speaking, the cell concept is only a morphological abstraction. Seen biologically, it cannot be accepted without the vital environment of the cell," says Alfred Pischinger, MD, in his book *Matrix & Matrix Regulation: Basis for a Holistic Theory in Medicine.*

It can be argued that the extracellular matrix (ECM) is the most overlooked aspect of human physiology, yet one that may hold the key to unravelling the complexities of chronic disease. Joint hypermobility syndrome, such as EDS (Ehlers-Danlos syndrome), explicitly implicates disruptions to the normal functions of the ECM. The ECM is a vast and complex network – comprised of collagen, proteins, polysaccharides, and electrolyte fluids – with the following essential functions:

- To provide the structural scaffolding for cells and organs,
- To modulate cell-to-cell communication,
- To modulate the life cycle of cells,
- To create a yin/yang balance between cell survival and cell death,
- To modulate growth factor and cytokine function and signaling,
- To regulate stem cell function, and
- To provide the proper fluid balance and pressure gradients in various tissue compartments.

Regulation of Growth Factors

With the loss of normal ECM function, a number of pathological processes and complex symptoms prevail. Cells maintain their adhesion to the ECM through surface interfaces such as integrins and basement membrane laminins. Cells that lose their adhesion to the ECM undergo a form of cell-programmed death.

A number of critical growth factors bind to and are activated by the ECM. These include VEGF-A and VEGF-B (vascular endothelial growth factor A & B), FGF-2 (fibroblast growth factor-2), IgF (insulin growth factor), HGF (hepatocyte growth factor), PDGF-BB (platelet-derived growth factor BB), EGFR (epidermal growth factor) and TGFß-1 (transforming growth factor ß-1).[1] Insufficient collagen and proteoglycans in the ECM will directly impair the function of these important growth factors, leading to a number of adverse, downstream effects.

VEGF-A is the primary operator in angiogenesis and is critical in neuronal function, wound repair, endothelial cell function, and in the delivery of oxygen to tissues. Individuals with JHS frequently suffer from organ and vascular fragility, skin bruising, epilepsy, and neuropathy as well as chronic pain. Domains located within the TNXB gene have been found to regulate the maturation and function of VEGF-A, VEGF-B, and TGFß.[2,3] Mutations and deletions of TNXB will impair the function of these critical growth factors and increase the probability of vascular, endothelial, and neuronal conditions. Mutations and deletions of the TNXB gene (tenascin-X) lead to a form of hypermobile EDS.

TGFß-1 is a critical cytokine growth factor that requires a functional ECM for activation. Since the 1980s it has been known that forms of EDS and Marfan syndrome frequently feature higher blood levels of TGFß-1.[4,5] Among its

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myriad number of functions, TGFß-1 is a potent pro- and anti-inflammatory cytokine, activating certain mature T-cells (including anti-inflammatory T-regs) and is necessary for cell growth and proliferation, neuronal refinement, synaptic pruning, as well as stem cell differentiation. TGFß is also a key regulator of the gut and is released by numerous GI cells, such as dendritic cells and epithelial cells.[6]

The loss of normal function of TGFß-1 due to ECM dysfunction may in part explain the higher frequency of autoimmune and rheumatic diseases seen among those with JHS, as well as the frequency of gastrointestinal symptoms and gynecological conditions such as endometriosis.[7] Endometriosis in particular has a pathophysiology that directly involves aberrant TGFß-1 and VEGF-A signaling.[8,9]

Brain structural abnormalities and associated anxiety disorders in JHS have been observed.[10] TGFß signaling is critical for axonal function in the developing brain,[11] including neurite development in the hippocampus, as well as for stem cell differentiation and function during embryogenesis. Mouse studies have found that the inactivation of TGFß receptors in the mid-hind brain regions result in enlarged midbrain.[12] Aberrant TGFß signaling in the developing brain, due to inadequate ECM function, may provide a hypothesis for the brain structure abnormalities observed in EDS and JHS, as well as the associated amygdala volume differences, anxiety, and emotional processing disturbances seen among those with JHS.[10]

From the therapeutic side, CBD (cannabidiol) has been shown useful for JHS individuals suffering with anxiety. This may in part be explained by the fact that the amygdala is rich in endocannabinoid receptors. LDN (low dose naltrexone) has reportedly been used for emotional processing therapies with varied success. Pharmaceuticals such as losartan and VIP (vasoactive intestinal polypeptide) have been used to lower high levels of TGFß-1.

IgF-1 (insulin growth factor-1) regulates the activities of growth hormone (GH). Very few conditions feature elevations in IgF-1, but EDS and JHS are among these.[13,14] IgF-1 is a potent promoter of type 1 and 3 collagen biosynthesis, as well as of the ECM-essential enzymes lysyl oxidase and lysyl hydroxylase.[15] What is critical to understand is that integrins (adhesive proteins that attach cells to the ECM) are centrally involved in the activation of IgF-1.[16] Among those with JHS, this implicates poor utilization of IgF-1 and the associated loss of cellular adhesion to the ECM as a focus for this growth factor's elevations.

Additional attention should address the need to support and optimize collagen turnover. Sodium ascorbate has shown to be useful in JHS, as vitamin C plays a decisive role in collagen and ECM synthesis and remodeling.

Idiopathic intracranial hypertension (IIH) is one of the most complex conditions associated with JHS and EDS. Individuals with IIH frequently suffer from cerebrospinal fluid leaks, severe headaches, visual field defects, palsy of cranial nerves, tinnitus, intracranial noises, and papilledema. The literature reports the association between IIH, elevated IgF-1 levels, and growth hormone therapy (as a trigger for IIH).[14,17] The somatostatin analogue drug octreotide (which inhibits growth hormone & IgF-1) was shown to significantly improve the symptoms of IIH in a case study of a patient with JHS.[14]

Therapeutically speaking, the modulation of growth factors presents a challenge because of underlying ECM structural defects. One of the overall adverse effects of growth factor dysregulation is related to loss of mTOR signaling. mTOR (mammalian target of rapamycin) is an intracellular protein that regulates numerous pathways related to cell growth, autophagy, immune cell modulation, and the inflammatory process. mTOR signaling has been detected in matrix-producing fibroblast cells and is highly responsive to growth factor activation. Insufficient amino acids have been shown to shift the mTOR program towards an inflammatory state through the activation of NF kappa-ß, whereas increased amino acids shift to a cell survival state via STAT1 genes.[18] One potential therapy in addition to mTOR-responsive amino acids (glutamine, arginine, leucine) could be the phospholipid phosphatidic acid (PA). Not only does PA promote mTOR, it behaves similar to growth factors and has been shown to increase the ECM constituent hyaluronic acid.[19] mTOR needs to be kept in balance with a related protein, AMPK. Experimental, injectable peptides such as BPC-157 are reportedly improving tissue recovery processes and may hold significant potential for JHS-related ECM dysfunction.

Additional attention should address the need to support and optimize collagen turnover. Sodium ascorbate has shown to be useful in JHS, as vitamin C plays a decisive role in collagen and ECM synthesis and remodeling. Maintenance of proper hydration and electrolyte balance is also crucial.

Polysaccharides are the fundamental sugars that serve as the basis of glycoproteins in the ECM, and various polysaccharide-containing supplements have been attempted with varying degrees of success. These include aloe vera, lion's mane, and maitake mushroom, as well as brown algae and red algae. In some cases, polysaccharides seem to reduce joint hyperextensibility. There have been isolated case reports of rapid tissue healing phases induced by sulfated polysaccharide-containing red algae, notably in JHS-associated bowel conditions. Aloe vera polysaccharides have been reported in some instances to improve bruising symptoms, rosacea, reduce hyperextensible joints, and some evidence suggests alteration of clotting factors.

MCAS, the ECM, and Joint Hypermobility

The fact that mast cell activation syndrome (MCAS) is commonly seen in JHS and EDS is no surprise.[20] Mast cells are clustered abundantly throughout loose connective tissues. Mast cells are most notable for their ability to degranulate and release histamine via IgE-mediated responses, although this is only a part of the story.

Mast cells are also reservoirs of heparin, an ECM proteoglycan that acts as an anticoagulant. Significantly, mast cells are integral to the normal function and repair processes of the ECM. The fact that mast cells have the ability to release fibroblast growth factors and heparin-binding epidermal growth factors (as well as to stimulate these in nearby fibroblasts) is significant because it illustrates the intrinsic relationship between mast cells and ECM-producing fibroblasts. Moreover, histamine acts to up-regulate the fibroblast growth factor-7 receptor via H1 receptors, while tryptase (an enzyme that is released with histamine and is associated with MCAS) has been shown to stimulate fibroblast growth factor-2 from fibroblasts.[21]

Is it possible that MCAS is actually a coordinated attempt to increase the production of collagen and ECM constituents? Is this a repair process gone wrong among those with JHS and EDS? What's clear is that the study of MCAS must take into consideration the relationship between mast cells, fibroblasts, and the conditions of the ECM environment.

While medications such as ketotifen, cromolyn sodium, and supplements such as quercetin have been useful at controlling MCAS symptoms, these substances don't address the cross talk between mast cells and the ECM environment. The ECM glycosaminoglycan chondroitin sulfate holds promise for MCAS, as it has been shown to be a potent inhibitor of connective tissue mast cells.[22] Evidence has shown that Nrf2 pathway activation may be a key intracellular modulator of mast cell degranulation.[23] Two recent case studies demonstrated stabilization of MCAS symptoms and associated control of histamine liberation with Nrf2 pathway activation using Nrf2-promoting supplements.

Environmental Toxins and the ECM

If individuals have a compromised ECM, they may be more prone to the destructive effects of toxins, certain drugs, and infections. Various pathogens including viruses, Lyme, mold, and bacteria lead to the infiltration of pro-inflammatory metalloproteinases (MMPs), which incite a breakdown of the ECM, leading to the infiltration of inflammatory cytokines and immune cells.[24] This process is likely a significant contributing factor to the collagen

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deficiency complications among those with JHS due to their already weak ECM. Numerous case study reports among those with JHS and EDS identified fluoroquinolone antibiotics as being pivotal to patients' downward spiral into chronic illness; these drugs incite destructive effects on the ECM and connective tissue.[25]

cytokines IL1ß and IL18 and the activation of downstream cytokines such as NF kappa-ß and IFN-γ. Inflammasome activation is a significant contributing factor to autoimmune disease, including rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's)[27] as well as inflammatory bowel diseases such as Crohn's.[28]

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Positively charged, cationic toxic metals (such as aluminum, mercury and cadmium) may find their way to the ECM, where they attract to the negatively charged anionic sulfates in ECM glycosaminoglycans (GAGs). Stephanie Seneff's postulation that the herbicide glyphosate replaces glycine is highly relevant because glycine is the primary amino acid in collagen. The collateral damage of the metalloproteinase/toxicity-removal process is the degraded fragments of ECM constituents such as hyaluronic acid, teanscin-c, decorin, biglycan, and aggrecan.[26] These ECM fragments are known as DAMPs (damage associated molecular patterns). DAMPs trigger toll and NOD-like receptors (TLRs and NODs) and stimulate inflammasomes in macrophages, setting the stage for autoimmune processes.

Inflammasomes and Autoimmune Disease

Inflammasomes are intracellular protein complexes located within immune cells such as tissue macrophages. Inflammasomes are sensitive to a number of toxic and pathogenic stimuli such as PAMPs (pathogen associated molecular patterns), toxins (aluminum, cadmium, mercury, silicon dioxide, asbestos) as well as DAMPs. Inflammasome activation generates pro-inflammatory

The association between EDS, JHS, pain disorders, and rheumatic diseases is well established. A study of 66 women with fibromyalgia identified 27% as having joint hypermobility.[29] A study of 100 patients diagnosed with rheumatoid arthritis (RA) found 18% had joint hypermobility. All were female, and hypermobile patients had higher levels of PGE2 prostaglandins and IL-8.[30] A study of 81 patients diagnosed with SLE (systemic lupus erythematosus) found 48% had joint hypermobility, compared to 15% of the control group.[31] A study of 83 patients with inflammatory bowel disease and 67 healthy controls investigated the presence of JHS. Joint hypermobility was identified in 70.7% of Crohn's disease patients, compared to 25.4% of healthy controls.[32]

From clinical observations, many other autoimmune conditions frequently feature JHS but are significantly under-reported in the literature. From a therapeutic side, it is imperative to reduce the toxic burden in JHS patients.

In addition to the benefits of whole food, elimination-type diets for autoimmune conditions and targeting GI function, inflammasome activity can be curtailed through ß-hydroxybutyrate, a ketone. Research also finds that activating the AMPK protein can reduce expression of inflammasome activity. This can be accomplished in many different ways, such as through caloric restriction, exercise, and through supplements such as berberine, lipoic acid, and resveratrol.

Hypermobility Syndrome: Chronic Pain and Headaches

Chronic head and neck pain is common in JHS. Causes include chiari malformation, dura matter abnormalities, intracranial pressure, and CSF leaks.

Chiari malformation is a structural condition where the cerebellum protrudes into the spinal canal. A theory postulated by Driscoll suggests, in some cases of EDS, increased CSF pressure in the subarachnoid space (an area between the brain and the dura matter) can increase the prevalence of chiari; and by reducing this pressure, chiari can be reduced.[33] This intracranial pressure not only creates pain, it contributes to dysautonomia, CSF leaks, and papilledema (swelling of the optic nerve). The drug acetazolamide has been shown to improve this buildup of pressure. Already discussed is the potential use of the drug octreotide, in cases where IIH is caused by elevated IgF-1. Pain among those with JHS can be influenced by temperature, altitude, and barometric pressure. Upper cervical chiropractic care, cranial osteopathy, craniosacral therapy, CBD, and herbs like *Mitragyna speciosa* have been useful in managing some of these complications.

It has been observed that dystonia exists in roughly 66% of EDS patients.[34] Dystonia is characterized as involuntary muscle contractions that cause writhing and twitching. The cause of dystonia in EDS and JHS is linked to hypoperfusion and/or low oxygen levels. This is supported by the fact that dystonia has improved with oxygen therapies, as well as compression therapy.[34] Low doses of the drug L-DOPA (180 mg daily) have been shown effective in controlling dystonia in EDS.[34] Those who responded well to the L-DOPA treatment had an 82% improvement in dystonia symptoms and 59% of those had dramatic improvements. Dopamine at lower concentrations is a known vasodilator. Dopamine promotion therapy can be supported through natural products

such as the combination of *Mucuna pruriens* and vitamin B6, or tyrosine and B-6.

Genetics and Associated Comorbidities

Genomic variations of the RCCX gene cluster on chromosome 6 are likely a significant factor in the etiology of many patients with JHS and the associated comorbidities. The genes that comprise RCCX are very significant and confer powerful effects throughout the body.

The RCCX gene cluster on chromosome 6 has been described as the most complex region within the human genome because many anomalous events occur in this region: unequal crossover, non-allelic homologous recombination (NAHR), duplications of genes, pseudogenes, overlapping gene regions, retroviral and transposon insertions, and intergenic recombination.

Briefly, the RCCX gene cluster consists of the following genes:

- TNXB (tenascin-X) is an anti-adhesive glycoprotein in the extracellular matrix. Deficiencies of TNXB cause a form of EDS that is associated with JHS and skin hyper-elasticity. New TNXB research finds associations with organ prolapse and bowel diseases.
- CYP21a2 makes adrenal hormones cortisol and aldosterone, which are critical in the stress response and in salt balance. Variations of CYP21a2 are linked to CAH (congenital adrenal hyperplasia), hirsutism, PCOS/ ovarian cysts, PTSD, abnormal stress response, and possibly psychiatric illness.
- C4 is central to the complement, innate immune system. C4 also is involved in the synaptic pruning process in the brain. Genetic variations and deficiencies of C4 are found in many types of autoimmune diseases: lupus, RA, celiac, Crohn's, ankylosing spondylitis, Grave's, and type 1 diabetes. Variations of the C4 gene have also been observed in autism and schizophrenia. The C4 gene contains an endogenous retrovirus, HERV-K. This retrovirus is known to be expressed in neurological diseases and in cancer.
- STK19's (formerly known as RP1) function is unknown.

Gene sequencing for RCCX is not yet commercially available. The RCCX genes can be thought of as a domino effect: when one gene is affected, they all are. Individuals with JHS plus comorbidities associated with RCCX (congenital adrenal hyperplasia, C4-associated autoimmune disease, PCOS, family history of mental illness) may very well have inherited an undesirable genotype.

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Postbiotic Metabolites: The New Frontier in Microbiome Science

by Ross Pelton, RPh, PhD, CCN

Scientific Director, Essential Formulas

The human microbiome is now known to be relevant to virtually every branch of science, medicine, and human health; and microbiome science is evolving rapidly. The purpose of this article is to summarize the history of the human microbiome and to introduce readers to postbiotic metabolites, which is the new frontier in microbiome science.

Louis Pasteur (1822-1895) was the first microbiome scientist. Pasteur made breakthrough discoveries regarding vaccination, microbial fermentation, and pasteurization. Pasteur's medical discoveries enabled him to create cures for many of the world's major killer diseases during his time including rabies, anthrax, tuberculosis, cholera, and smallpox. Consequently, Pasteur became known, respected, and loved throughout the world; and he was the first scientist to become an internationally known "global rock star."

Pasteur's accomplishments are absolutely mind-boggling. A modern-day equivalent would be if one scientist today single-handedly created cures for cancer, heart disease, diabetes, and Alzheimer's disease. However, Pasteur's accomplishments also ushered in the widespread belief that germs are the cause of diseases, which initiated the germ theory of disease.[1] This resulted in a century of bacteria-phobia and gave rise to the era of antibiotic drugs. However, during the past several decades, the over-prescribing of antibiotics has resulted in microbiome destruction, weakened immune systems, and the rise of deadly antibiotic-resistant "superbug" infectious diseases.

Elie Metchnikoff (1845-1916) was a Russian-born scientist who developed an interest in the study of beneficial microbes. In 1888, Metchnikoff traveled to Paris to meet Pasteur and ask Pasteur's advice regarding some difficulties he was experiencing with his research. Pasteur was impressed with Metchnikoff and invited him to stay, setting him up with his personal laboratory. In 1904, Metchnikoff was promoted to deputy director of the Pasteur Institute where he remained for the rest of his highly productive career. In 1908, Metchnikoff won the Nobel Prize for medicine for his discovery of phagocytosis and its importance to the immune system.[2]

At the Pasteur Institute in the early 1900s, Metchnikoff became increasingly interested in human health and longevity. He learned that Bulgaria had a disproportionately high number of healthy elderly citizens. He conducted a study and compiled statistics from 36 countries, which led him to discover that Bulgaria had more people who lived to be 100 years of age than any of the other 36 countries he surveyed.

Metchnikoff believed that the aging process resulted from the activity of "bad" bacteria that produce toxic substances in the intestinal tract. According to Metchnikoff, these toxic compounds were responsible for what he referred to as "intestinal auto-intoxication," which caused the physical deterioration and breakdown associated with aging.

And then, Metchnikoff had a tremendous intuitive insight that made him the "Founding Father of Probiotics." Metchnikoff believed that the long healthy lifespans of Bulgarians was related to their daily consumption of fermented milk products like yogurt and kefir. He knew the bacteria responsible for the fermentation of milk produced lactic acid, which created an acidic environment in the GI tract. He theorized that the lactic acid created a slightly acidic environment, which, suppressed the growth of toxin-producing bacteria. The net result was a reduction of "intestinal auto-intoxication," which resulted in better health and longer life.

In 1907, just two years after making his landmark proposal that the ingestion of *Lactobacillus bulgaricus* was responsible for the health and longevity of Bulgarians, Metchnikoff published his findings in his book titled, *The Prolongation of Life: Optimistic Studies*.[3] Consequently, Metchnikoff is also credited as the founding father of the life extension movement.

The Modern Era of Microbiome Science

The human microbiome refers to the organisms (bacteria, fungi, and viruses) that reside in and on our body. When I

use the term microbiome in this article, I am limiting its scope to the bacteria that reside in the gastrointestinal tract.

The Human Genome Project, which cost an estimated $3 billion, was a 13-year (1990-2003) project that resulted in the first successful sequencing of the human genome. Scientists hoped that sequencing the human genome would lead to cures for many of today's chronic degenerative diseases. That goal was a complete failure; sequencing the human genome never led to successful treatments for any diseases.

However, one great benefit that emerged from the Human Genome Project was the development of incredible technology that allows scientists to sequence genomes rapidly and at a vastly reduced price. For example, in January 2017, Illuminia, which is the world's leading producer of next-generation sequencing technology, announced that their new NovaSeq™ could sequence a genome in one day for only $100.[4] From 13 years and $3 billion to one day for $100. How's that for rapid scientific advancement!

The incredible power and speed of the new gene sequencing technology were partly responsible for the government's funding of the Human Microbiome Project (2007-2012).[5] Subsequently, the Human Microbiome Project resulted in the publication of over 350 studies, which are viewed as the "birth" of the modern era of microbiome science. In May 2016, the Obama administration committed to continue supporting microbiome scientific research by funding the National Microbiome Initiative. This program is sponsored with $121 million in funding from federal agencies and an additional $400 million from non-government institutions.[6]

The Genome Complexity Conundrum

When scientists successfully sequenced the human genome, they discovered that humans have about 23,000 genes, which is substantially fewer than they expected. This finding initially caused scientists to shake their heads in disbelief and created a situation that became referred to as the "genome complexity conundrum."[7]

The challenge was due to the following facts. Whereas humans have about 23,000 genes, the common rice plant (*Oryza sativa*) has about 45,000 genes. This led scientists to scratch their heads and say or think, "If we humans are as complex and evolved as we think we are, how can it be that we only have half as many genes as the common rice plant?"

The answer to the genome complexity conundrum began to emerge when scientists discovered that the intestinal tract of most humans is home to an estimated 100 trillion bacteria. A human harbors from 500-1,000 different species of bacteria and these bacteria contain over 3.3 million non-repeating genes. This means that over 99% of the DNA in your body is the DNA of your bacteria. This explains why humans can "get by" with only 23,000 genes. Bacteria utilize the information contained in their vast amount of DNA to produce compounds that are responsible for directing and regulating a great deal of the functioning of the human body. This explains why it is so critically important for people to learn how to create and maintain a healthy microbiome. Your bacteria are involved, either directly or indirectly, in the regulation and control of much of what happens in your body.

This realization has also resulted in a new understanding of what it means to be human as scientists began to realize that we are not just the product of our human genes. Instead, we are a bacteria-controlled superorganism. We are not just "us"…we are "us" plus "them."

Postbiotic Metabolites: The New Frontier in Microbiome Science

As scientists started to realize how incredibly important our probiotic bacteria are in the regulation of health, they began looking for mechanisms. How and why are probiotic bacteria capable of regulating so much of our human biological functioning?

Probiotic bacteria are amazingly complex little chemical manufacturing plants. Their metabolic processes enable them to digest and ferment the fibers in foods, which results in the production of a wide range of health-regulating compounds that known as "postbiotic metabolites."

In the new frontier of microbiome science, much more emphasis is being focused on identifying the compounds that various strains of bacteria produce, learning to understand the health-regulating effects of these compounds, and discovering which strains of bacteria are more efficient at producing these health-regulating compounds.

A PubMed search reveals that "postbiotics"[8,9] and "postbiotic metabolites"[10] are terms that are used with increasing frequency in the title of scientific studies. In *The Mind-Gut Connection*, respected author and microbiome scientist Emeran Mayer, MD, states that our bacteria utilize the information in their millions of genes to transform the food people eat into "hundreds of thousands of metabolites."

A pronounced shift is taking place in microbiome science. Until recently, a large portion of scientific research was devoted to isolating, identifying, and naming different species of bacteria. In the new frontier of microbiome science, much more emphasis is being focused on identifying the compounds that various strains of bacteria produce, learning to understand the health-regulating effects of these compounds, and discovering which strains of bacteria are more efficient at producing these health-regulating compounds.

Balance and Diversity: Critical Factors for Microbiome Health

Diversity refers to how many different strains of bacteria are present in the intestinal tract. Numerous human clinical trials report that a more diverse microbiome equates to better health.[11,12] Scientists estimate that a healthy human microbiome contains approximately 1,000 different species of bacteria.[13] On the other hand, low bacterial diversity in the intestinal tract can contribute to various diseases such

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as obesity[14] and inflammatory bowel disease.[15]

The Fiber Gap: America's #1 Nutritional Deficiency

Fiber is the required food for your probiotic bacteria. A recent article titled "The Fiber Gap and the Disappearing Gut Microbiome: Implications for Human Nutrition" discusses how low fiber diets are affecting people's microbiome and ultimately, their health. The authors of this study report that an alarming **90% of children and adults in America DO NOT consume the recommended amount of daily dietary fiber**.[16] Scientific studies provide convincing evidence that the microbiome is the very foundation of health.[17,18] It is becoming alarmingly clear that the Standard American Diet, known as the SAD diet, is more than just SAD, it is killing people.[19]

It's not enough to only take probiotics, you must learn to feed your probiotic bacteria well. Non-digestible carbohydrates and fibers are the "food" that your probiotic bacteria require. Different species of probiotic bacteria thrive on different kinds of fibers that are present in different kinds of plant-based foods. Eating a more diverse fiber-rich diet is the way to develop and maintain a more diverse microbiome. If your probiotic bacteria are not supplied with a diverse, fiber-rich diet, they will not thrive and survive.

The quantity of fiber in the daily diet is not the only fiber issue. A diversity of fiber-rich foods is required to promote the growth of a diverse microbiome. How many different kinds of colored, fiber-rich fruits and vegetables are you feeding your probiotic bacteria today?

Many people now take probiotics, which is confirmed by the dramatic increase in sales within this category. In 2005, sales of probiotics in the United States was $764 million.[20] In 2014, probiotic sales reached $1.41 billion, and from 2014 to 2017, sales nearly doubled to $2.14 billion.[21] However, since the vast majority of Americans are not consuming high-fiber diets, it can be assumed that many people are not getting much benefit from the probiotics they are taking.

For an easy way to increase the diversity of fiber-rich foods in your daily diet, I suggest you watch my 8-minute YouTube video which teaches people how to save an enormous amount of time making salads that contain a wide variety of fiber-rich vegetables. Just Google: Ross Salad Buzz.

Balance is also a critical factor in healthy microbiome. Unfortunately many people who purchase probiotics have the mistaken understanding that more is better. It is now common to see products claiming to be superior because they contain 50 billion bacteria or even 100 billion bacteria per dose. The fact is, massive doses of just one or several strains of probiotic bacteria does not promote microbiome balance; they actually work against balance, and this is why. Probiotics that deliver very high doses of just one or several strains of bacteria can cause the immune system to trigger an alarm reaction. The authors of one study made the following statement in their conclusion, "Probiotics can be ineffective or even detrimental if not used at the optimal dosage for the appropriate purposes."[22]

Balance and greater diversity are imperative because these factors result in the production of a broader range of postbiotic metabolites. Some of their benefits include reduced inflammation, regulating the acid/base balance in the GI tract, directly fighting pathogens, regulating digestion, absorption of nutrients, detoxification, regulating the immune system, gut-brain communication, and much much more. Remember, in *The Mind-Gut Connection*, Dr. Meyer stated that your bacteria would produce "hundreds of thousands of metabolites." This is why postbiotic metabolites are now becoming the new frontier in microbiome research.

A Microbiome Analogy

The "goal" in an automobile manufacturing plant is the production of vehicles such as cars, trucks, SUVs and vans. The workforce in an automobile manufacturing plant consists of hundreds of employees with a wide variety of skills and talents. However, the skills and abilities of this workforce are largely ineffective unless they have the thousands of parts that are required to produce different kinds of vehicles.

Similarly, in your microbiome, you have between 500 to 1,000 species totaling an estimated 100 trillion bacteria that function as the workforce. However, your probiotic "workers" must have available a wide variety of fiber-rich foods (the parts) in order to create the desired end products, which are the postbiotic metabolites. Probiotic bacteria are primarily a "workforce," and their "job" is to build/create postbiotic metabolites.

Dysbiosis

Dysbiosis is generally considered to be an imbalance between the good and bad bacteria in the intestinal tract. However, dysbiosis is more than just bad bacteria. In dysbiosis, the gastrointestinal environment or the microbiome ecosystem has become upset and damaged. In addition to bacterial imbalance, the acid/base balance is usually far too alkaline, the cells that line the GI tract are highly inflamed, the protective mucous layer can be compromised, the gut barrier is damaged and allows intestinal permeability, and cell-to-cell communication and gut-brain communication is dysfunctional. Ideally, the best way to fix gut dysbiosis problems is to address the whole microbiome ecosystem.

The Microbiome Ecosystem's Two Pieces

Postbiotic metabolites are the compounds that control and regulate the microbiome ecosystem. There are two pieces to this puzzle. Probiotic bacteria AND fiber-rich foods are needed to produce postbiotic metabolites. And, a wide diversity of probiotic bacteria AND a wide diversity of fiber-rich foods are necessary in order to have a wide

diversity of postbiotic metabolites produced.

Reestablishing the Microbiome Ecosystem

Most people take probiotics to address dysbiosis-related intestinal problems. However, for probiotics to be effective, those bacteria need access to high-fiber foods in the GI tract. Then, the bacteria have to begin the process of breaking down the foods so they can access the fibers and start the process of converting fibers into postbiotic metabolites. This process takes time.

Confounding the process is the fact that the ingested probiotic bacteria are likely entering into a very hostile environment that is highly inflamed, 10 to 100 times too alkaline, and overrun with "hostile" pathological bacteria. As an analogy, consider the problem of sending Eskimos to fight in the Sahara Desert, or desert nomads to fight in freezing Alaska. They will have great difficulty being effective.

The Benefits of Fermented Food

Fermentation is a process in which bacteria break down sugars, carbohydrates and fibers in foods and convert them into alcohol and organic acids. Fermentation has been used by humans for thousands of years as a method to preserve foods. Over time, people realized that fermented foods also conveyed health benefits.

Until recently, people thought the health benefits from fermented foods such as sauerkraut, kimchi, miso,and tempeh were due to the ingestion of probiotic bacteria contained in the fermented foods. However, it is becoming clear that the food preservation properties AND the health benefits from fermented foods are primarily due to the postbiotic metabolites produced by the bacteria during the fermentation process.[23]

Several metabolites produced during fermentation are classified as short-chain fatty acids (SCFAs) such as acetic, propionic, and butyric acid. These small molecular weight acidic compounds are postbiotic metabolites that play a critical role in food preservation because they create a slightly acidic pH which inhibits the growth of pathogens.

Recent human clinical trials have revealed strong associations between consumption of fermented foods and improved health for conditions such as obesity,[24] type 2 diabetes,[25] hyperlipidemia,[26] hypertension,[27] osteoporosis,[28] and depression.[29] These studies emphasize that an individual's probiotic bacteria and the postbiotic metabolites they create have important effects far beyond just gut health.

Most people take probiotics to address dysbiosis-related intestinal problems. However, for probiotics to be effective, those bacteria need access to high-fiber foods in the GI tract.

Directly Ingesting Postbiotic Metabolites = FAST ACTION

As mentioned previously, it takes time for ingested probiotic bacteria to locate fibers, break them down and produce postbiotic metabolites. A faster and more effective way to address dysbiosis-related problems is to ingest postbiotic metabolites.

When ingested orally, postbiotic metabolites immediately begin asserting their health-promoting activities such as readjusting the acid/base level, reducing inflammation, accelerating the growth of healthy new cells in the lining of the GI tract, "fighting" and killing pathological bacteria, and re-establishing healthy gut-brain communication. This circumvents the time-consuming process of probiotic bacteria needing to locate fibers and begin producing postbiotic metabolites.

Metabolomics and Metagenomics

Metabolomics and metagenomics are two scientific disciplines that are barely twenty years old. These relatively new fields of science are developing very fast, in large part, due to the fundamental importance of the microbiome.

Metabolomics is the branch of science that identifies small molecule metabolites in biological systems, such as the postbiotic metabolites produced by bacteria in the gastrointestinal tract. Rapid advances in metabolomics have resulted in the discovery of thousands of bacteria-produced small-molecule metabolites, or postbiotics.[30]

Microbes run our world. The new science of metagenomics is unlocking the secrets of our microbial planet. Metagenomics, defined as the *genomic analysis of microorganisms*, is discovering the genes in bacteria that are responsible for the production of postbiotic metabolites.[31]

A couple of terms that are synonymous with postbiotic metabolites are microbial metabolites and bacterial metabolites. In a review article titled "Bioactive Microbial Metabolites," the author states that as of 2002, over 22,000 bioactive secondary metabolites are published in the scientific literature.[32] And, in *The Gut-Mind Connection*, Dr. Mayer noted that we will ultimately learn that bacteria probably produce hundreds of thousands of metabolites.

Postbiotic Metabolites

Some of the better known postbiotic metabolites include the following:

a. B-vitamin synthesis (biotin, cobalamin, folates, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, and thiamine)[33]
b. Vitamin K[34]
c. Short-chain fatty acids (SCFAs): acetic, propionic and butyric acid.[35]
d. Glutathione: synthesized by *Lactobacillus fermentum* ME3.[36]
e. Antimicrobial peptides (AMPs)[37]
f. Phenyllactic acid[38]
g. D-amino acids[39]
h. Hydrogen peroxide[40]
i. Volatile organic compounds (VOCs)[41]
j. Phytoestrogens: Equol, enterolactone, enterodiol.[42]
k. Urolithin A and urolithin B[43]
l. Fulvic acids[44]

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It is beyond the scope of this article to attempt to name and list the health-regulating effects of thousands of microbial metabolites/postbiotic metabolites that been identified to date.

Dr. Ohhira's Probiotics®: Directly Delivering Postbiotic Metabolites

Dr. Ohhira's Probiotics is a fermented food product that is produced utilizing a multi-year fermentation production process under cleanroom conditions. The initial process takes place in large 80-gallon fermentation vats. Dozens of different kinds of organically grown foods (vegetables, fruits, seaweeds and mushrooms) are shredded and added to the fermentation vats along with 12 strains of probiotic bacteria. Then the bacteria are allowed to ferment/digest the high-fiber prebiotic foods they have been supplied with for a period of three to five years, which results in the production of a wide range of postbiotic metabolites.

There are two versions of Dr. Ohhira's Probiotics. The Original Formula undergoes three years of fermentation. The final product is a thick, dark-colored paste-like substance that is encapsulated and is sold at the retail level in fine health food and vitamin stores throughout the United States.

The Professional Formula originates by transferring paste from the 80-gallon vats after the initial three-year fermentation cycle into different containers for an additional two years of anaerobic fermentation. Over 99% of your microbiome consists of anaerobic bacteria that reside in your large intestines and colon. Thus, the additional two years of anaerobic fermentation results in the production of larger amounts of the postbiotic metabolites from the anaerobic bacteria. The Professional Formula is primarily marketed to healthcare professionals.

Dr. Ohhira's fermentation production system simulates nature. Humans ingest food into our digestive tract where bacteria convert the food into a wide range of health-regulating postbiotic metabolites. Dr. Ohhira created an external system that allows probiotic bacteria to function like they do in the GI tract, which results in the production of postbiotic metabolites.

Recent research conducted by an independent laboratory in Japan reported that Dr. Ohhira's Probiotics contain over 400 different postbiotic metabolites.[45] This explains why Dr. Ohhira's Probiotics has achieved a reputation for rapidly improving dysbiosis-related intestinal symptoms. When taken, the postbiotic metabolites immediately begin to initiate healthy changes in the intestinal microbiome ecosystem.

Because postbiotic metabolites have such wide-ranging health-regulating effects, postbiotic metabolites are now being recognized as a new frontier for the pharmaceutical industry. Drug companies recognize that medications based on postbiotic metabolites will be more stable and have far fewer side effects because they are based on compounds that are naturally produced in the body.[46]

Postbiotic metabolites are now being recognized as a form of communication in the body. A recent article titled "Human Microbial Metabolites as a Source of New Drugs," in the journal *Drug Discovery Today*, reviews the rapidly emerging science about how postbiotic metabolites communicate with the immune system and various organs in the body to regulate many aspects of human health.[47] The mechanisms behind these health-regulating effects involve what scientists call "cross-talk" between the probiotic bacteria-produced metabolites and receptors on cells throughout the body.

Many gastrointestinal problems can be improved and/or resolved by increasing the quantity and the diversity of postbiotic metabolites in the microbiome. One method involves two actions:

a. Adopt a healthy plant-based, fiber-rich diet. The dietary fibers will "feed" your beneficial probiotic bacteria which will enable them to grow and proliferate
b. Eliminate the high fat, high sugar, processed foods that alter the microbiome ecosystem and promote the proliferation of pathological bacteria.

However, if your microbiome is unbalanced, it is important to realize that consuming high-fiber foods doesn't guarantee fast results because you have a deficiency of probiotic bacteria present. It takes time for your reduced population of beneficial bacteria to process dietary fiber and create postbiotic metabolites, which will begin to shift the microbiome ecosystem back to a healthy state.

A much faster method of resolving intestinal problems is to ingest post-biotic metabolites directly. As mentioned previously, each dose of Dr. Ohhira's Probiotics delivers over 400 postbiotic metabolites. Thus, Dr. Ohhora's Probiotics deliver a balanced microbiome formula that contains probiotics, prebiotics and most importantly, a multitude of postbiotic metabolites. This is why Dr. Ohhira's Probiotics work fast and effectively to improve many intestinal problems. This is the Dr. Ohhira's Difference!

I want to make an analogy between NASA's mission control center, which regulates our space flights and your microbiome. Many scientists and engineers work in NASA's mission control center. However, it is the hundreds of computers making millions of computations per second that control our space flights. The scientists and engineers are critically important, and the system wouldn't work or even exist without them. However, it is the computers that are the master regulators of space flights.

Similarly, your probiotic bacteria are critically important for the functioning of your microbiome ecosystem. However, it is the multitude of postbiotic metabolites that are the "mission control center" that send millions of biochemical signals, which influence every organ system. Postbiotic metabolites are the master health-regulating compounds in the body. This

is why postbiotic metabolites are the new frontier of microbiome science.

In closing, I want to emphasize that the most critical factor in creating and maintaining a healthy microbiome is a healthy plant-based, fiber-rich diet. If you don't feed your probiotic bacteria well, they won't thrive and survive. When people consume high sugar, high fat, processed foods, they promote the growth of pathological bacteria that can cause many health problems. Remember, when you eat, you are not just eating for yourself, you are feeding 100 trillion guests. This is why a healthy diet is the most significant factor for a healthy microbiome and a healthy life.

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Those Measles Outbreaks: Thoughts Out of Season

by Richard Moskowitz, MD

Before the current measles hysteria gets even further out of hand, a little common sense might help us think more carefully before rushing to take action that won't work and will actually do harm. Refusing unwanted medical treatment is a basic human right that all civilized nations have sworn to uphold, with the sole possible exception of a dire and imminent threat to the public health, which a few localized measles outbreaks, numbering no more than a few dozens or hundreds of cases, decidedly are not.

All of these outbreaks are typical of those that have occurred ever since the vaccine was introduced, and others just like them will undoubtedly continue to occur even if the drug industry's well-funded campaign succeeds in vaccinating everybody. Yet, Washington State and New York's Rockland County have declared public health emergencies on the basis of them, and several other states are considering doing the same, while the news media have enthusiastically joined in, with editorials and Op-Eds in the *New York Times,*[1] the *Boston Globe*,[2] the *River*,[3] and other major outlets, as well as talk shows on NPR and other radio stations – all well-meaning but repeating the same alarmist fears and exaggerations as if they were settled truths and citing these modest outbreaks as ample justification for eliminating personal-belief exemptions from the states that still honor them. A clear violation of the First Amendment, the latest and most ominous example is Congressional pressure on Facebook and other social media (including Amazon) to censor postings that dare raise doubts or questions about vaccines or their mandates.

On the other hand, these politicians and journalists have simply taken on faith the information and unspoken subtexts that prominent doctors and public health authorities are feeding them. Unfortunately, what they're being told is not only bad ethics but also bad science, based on assumptions that are flatly contradicted by current research, and violate basic human rights and moral values that we still profess to hold dear.

Often assumed to be self-evident without even having to be stated, much less proved, their bottom-line assumptions are really two postulates that depend on each other to support them – namely, 1) that these small outbreaks of measles and other infectious diseases that we vaccinate against are initiated and propagated by unvaccinated individuals; and 2) that vaccines are not only miraculously safe but also uniformly effective in rendering people immune to these diseases without having to contract them, so that only the unvaccinated are still susceptible and thus capable of transmitting them to others.

But you can't have it both ways. For if these postulates were really true, if the immunity conferred by the measles vaccine were truly comparable to the absolute, lifelong immunity that results from coming down with and recovering from the actual disease, then the unvaccinated would pose no threat to anyone but themselves, based on a free choice of their own making, such that those taking the vaccine would have nothing to worry about. Conversely, if vaccinated individuals are indeed at risk of acquiring the disease from the unvaccinated, then the vaccine is clearly ineffective to that extent; and whatever it does offer cannot be a genuine or reliably effective immunity.

In any case, there's plenty of good scientific evidence that both of these assumptions are simply false. The vast majority of cases of measles, mumps, and other vaccine-preventable diseases in both past and recent outbreaks, typically between 75 and 95%, have been in *vaccinated* individuals.[4] Much the same is true of recent mumps outbreaks in the United States, where typically 95-100% of the cases have been vaccinated.[5]

So even if all non-medical exemptions were eliminated and virtually everyone were vaccinated, as the proposed new laws would require, similar outbreaks would undoubtedly continue to occur. In other words, the so-called immunity conferred by vaccines is a trick, a counterfeit of the real thing; and "herd immunity," the stated goal of the mandates, customarily tied to a vaccination rate of 95% or more in the case of measles, is a chimera of wishful thinking that vaccination simply cannot achieve, in contrast to the natural disease, regarding which public health experts have long known that large-scale outbreaks no longer occur when at least 80% of the population have already contracted and recovered from it.[6] *That,* and only that, is herd immunity: to expect a vaccine to achieve an even higher level, with no outbreaks at all, is pure fantasy, not hard science or even plausible reasoning.

Moreover, scientists have also demonstrated that individuals receiving vaccines made from live viruses, like measles, mumps, rubella, chickenpox, rotavirus, oral polio, and some versions of influenza, regularly "shed" them and

are thus contagious for many weeks afterward.[7]

Regarding the resurgence of whooping cough in recent years, numerous studies have further shown that the increasingly large and frequent outbreaks of the disease are likewise being spread by vaccinated individuals, even though the bacterium is no longer alive, in part through natural selection for vaccine-resistant strains,[8] as has been documented in the case of other non-living vaccines (HiB, pneumococcus, and possibly injectable polio) as well.[9] In short, the entire rationale of vaccinating as many people as possible, and the bullying and resentment of parents who choose not to vaccinate that always accompanies it, is not only cruel and misplaced but helps to create and propagate the very diseases that the vaccines were designed to eradicate.

Rather than simply accepting the fact that vaccines have at best a partial and limited efficacy, we are allowing the CDC and the drug industry to play on our fears to the extent of inflating these small, localized outbreaks of measles into the dreaded semblance of a looming public-health emergency, posing a serious threat to society, justifying forced vaccination of everyone, even against their will if necessary, and thereby nullifying our co-authorship of and ongoing allegiance to the Nuremberg Code of Human Rights and the Helsinki Declaration governing Biomedical Research, both of which insist upon the right of every patient and every experimental subject to give informed consent to all medical and surgical procedures, and explicitly forbid administering them by force.[10]

Although one could imagine a genuine public health emergency that might justify and even require temporarily waiving such rights, such as a large-scale bioterrorist attack or the rapid dissemination of a deadly plague, that is precisely what these small, localized outbreaks of ordinary childhood diseases are not. The truth is that there is no emergency, that we vaccinate purely as a matter of long-term health policy, and that most of the diseases that we vaccinate against were 1) already rapidly declining, thanks to improvements in sanitation, water quality, and other aspects of public health (pertussis, diphtheria, tetanus);[11] 2) ordinary diseases of childhood that most people contracted and recovered from without complications or sequelae (measles, mumps, rubella, flu, rotavirus, chickenpox);[12] 3) or caused by mutant strains of organisms that are part of our normal flora and only occasionally cause invasive disease (HiB, pneumococcus).[9]

Measles is indeed a perfect test case of the vaccination concept, as the most highly contagious of them all, with an attack rate approaching 100% in susceptible individuals; and the measles vaccine has in fact reduced the annual incidence of the disease in the United States from about 400,000 cases to less than 10,000, surely an impressive and historic achievement, no matter how it was done or why it was thought necessary. But inasmuch as these small, localized outbreaks are still occurring, and will undoubtedly continue do so in the future, no matter what we do, the CDC surely owes us a more convincing explanation than the impossible dream of "herd immunity" for why they don't simply declare victory and let it go at that.

So, for all of these reasons, contrary to what we're being told, the science is far from being settled when it comes to vaccine effectiveness. Even that much would be enough to deflate the myth that vaccine mandates are necessary. But it's not the only reason, or even the most important one. Vaccine safety is even further from being settled, to put it mildly, and for very good reasons. In the first place, many studies have shown that children who come down with and recover from acute febrile infections like measles, mumps, rubella, chickenpox, and influenza are much less likely to develop chronic autoimmune diseases and cancer later in life than those merely vaccinated against them.[13]

Still other studies link the risk of death, hospitalization, and other serious adverse reactions most closely, not to any particular vaccine or vaccines, but rather to the total number of vaccines given, both simultaneously at the same visit[14] and cumulatively over the patient's lifetime.[15] In other words, these worst outcomes cannot be simply written off as idiosyncratic aberrations or genetic mutations of certain hypersensitive individuals but are rather built into some essential feature of the vaccination process itself.

These findings are already more than sufficient to question, if not discredit, the almost universal reverence accorded to the concept of vaccination, not to mention the blank check that allows and even incentivizes the drug industry to develop, market, and ultimately mandate more and more vaccines, based on the assumption that vaccines are safe and effective across the board, that they save vast sums of money from not having to care for patients suffering with these diseases, and that it is therefore okay and even desirable to pile on as many doses of as many different vaccines as the traffic will bear, often for no better reason than that we have the technical capacity to make them.

It is the same assumption that allows and even blesses the drug industry to conduct its own safety studies without genuine placebo controls of unvaccinated individuals;[16] that limits adverse effects to those appearing within a few hours or days of the shot,[17] thus automatically excluding the chronic diseases from consideration; that gives the lead investigator unlimited authority to determine whether a reported adverse reaction is or is not vaccine-related, according to criteria that are never specified;[18] and that allows the CDC to insist that vaccines are uniformly safe and effective without conducting independent studies of its own, even though Congress has legislated and the Supreme Court has upheld that they are "unavoidably *unsafe,*" in order to shield the manufacturers from liability for the deaths and injuries they cause,[19] a free ride granted to no other industry.

In short, these assumptions are not science, but merely *scientism,* a reverent, quasi-religious faith characterized by dogmatism *in the name of science,* which stifles the critical thinking, questioning, and doubting of allegedly settled truths that real science requires, and helps explain why the news media refrain from reporting deaths or injuries from vaccines without having to be told, and why most physicians offer up their own children for the same vaccinations they administer to their patients. The late Richard Feynman, Nobel Laureate in Physics, sums it up admirably:

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> [In science] we must leave room for doubt, or there is no progress and no learning. There is no learning without having to pose a question, and a question requires doubt. Before you begin an experiment, you must not know the answer, [or] there is no need to gather any evidence; and to judge the evidence, you must take all of it, not just the parts you like. That's a responsibility that scientists feel toward each other, a kind of morality.[20]

Which brings me to my final point, that if vaccination and vaccines were indeed safe and effective across the board, then the thousands upon thousands of parents who have no doubt that their children were maimed or killed by them and must live with that existential reality every day of their lives must be either lying, ignorant, or stupid, and thus perhaps even deserve to have their stories ignored and dismissed out of hand by the medical community, the news media, and the public at large. Yet their suffering, whatever may have caused it, surely cries out at the very least for caution, restraint, and simple compassion for the viewpoint of those whose lived experience is so tragically different from that of everyone else privileged enough to be ignorant of or somehow unmoved by their loss.

As a family physician who has cared for many of these children over the years, I can say with complete assurance that the vast majority of their parents are by no means ignorant or credulous "anti-vaxxers" or hostile to science. Quite the contrary, in fact: they are often well-educated, have devoted their lives to unraveling the mystery about what really happened to their kids, and ask no more than that vaccines be made as safe as possible, based on careful investigation by independent scientists unaffiliated with the drug industry. After more than fifty years in the trenches, I can also attest that the instinctive, practical sense of caring parents is often a far more accurate and trustworthy guide to the truth about what caused the specific tragedies that they have had to endure than any preformed, generic pronouncement that pre-empts any need to consider the details of their actual, lived experience.

Finally, the widespread and indeed almost universal reverence accorded to vaccination, based on the catechism that vaccines are not only safe and effective but also among the supreme achievements of modern medicine, has impelled me to write with a sense of urgency and foreboding at this critical moment in our history when the time-honored rights of patients to refuse unwanted medical treatment and to make such decisions on behalf of their children are being challenged as never before. I will feel well rewarded if my words, my reasoning, and the commingled sadness, fear, and outrage I have long felt about this subject will promote a healthy debate and elicit more of the rigorous scientific work that still remains to be done.

Given the legitimate doubts and fears surrounding their use, the simplest and wisest solution would be to make the vaccines optional, that is, available to all those who want them, once fully apprised of their risks, so that exemptions will no longer be required. For if vaccines and vaccination are truly as safe and effective as the CDC and the industry have been insisting, it shouldn't be that difficult to convince the public to give them to their children most willingly, without needing mandates to impose them by force.

Until that happens, the most pressing issue before us is to preserve the frail remnant of personal liberty embodied in the few remaining exemptions that most citizens in our democracy have long been rightly proud of, and that the influential and well-funded drug industry has always been eager to take away. My fervent hope and heartfelt plea is that good common sense will prevail and the American people will be sufficiently aroused to not let that happen.

Richard Moskowitz, MD, has practiced as a family medicine physician since 1967. Patient education and advocacy, holistic medicine, and classical homeopathy are integral to his practice. He has written numerous articles and several books, including *Homeopathic Medicine for Pregnancy and Childbirth*, *Plain Doctoring: Selected Writings, 1983-2013,* and *Vaccines: A Reappraisal.* He lives and practices in the Boston, Massachusetts, area.

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Stem Cell Therapy as a New Paradigm in Osteoarthritis Treatment

by Peter A. Fields, MD, DC

Osteoarthritis remains the most common joint disease in the world, representing a major cause of disability and an enormous financial and economic burden. Oftentimes, those with degenerated joints end up needing surgical repair or joint replacement. Regenerative orthopedics is growing in popularity in the medical world as an alternative to surgery. Since surgery comes with many disadvantages, regenerative treatments, like stem cell therapy, offer a way to alleviate pain and restore cartilage in osteoarthritis treatment, providing an exciting way to repair joints in a non-surgical manner.

Osteoarthritis: The Disease and Its Progression

Osteoarthritis is a chronic disease that debilitates the articular joints, developing through a sequence of events that has, at its core, a loss of joint cartilage and is characterized by chronic pain, joint stiffness, structural damage, and bone remodeling through the progressive loss of cartilage. The disease process affects other joint structures and eventually will lead to joint space narrowing and bony overgrowth, progressing until joint movement becomes noticeably restricted. Bony overgrowth with the appearance of bone spurs or osteophytes, detected by x-ray, has become the criterion for diagnosing advanced osteoarthritis or radiographic osteoarthritis.

Many people do not realize what occurs before the cartilage loss. Osteoarthritis almost always begins with unresolved ligament weakness or injury. The weakened and lax ligaments allow for abnormal motion in the joint. With each movement the joint makes, time after time, the joint wears down and becomes damaged.

Joints are composed of two bones covered with articular cartilage. In a healthy joint state, strong ligaments hold the bones together and, along with healthy cartilage, enable the bones to glide evenly over one another when the joints are in motion. When the ligaments are weak from injury, the bones will glide over one another in an uneven manner, prompting one area of bone to bear additional weight on the articular cartilage when the joint is stressed. This unbalanced distribution amplifies with ongoing joint stress, destabilizing the joint and weakening the ligaments further. The increase in abnormal weight distribution inside the joint results in a breakdown of the articular cartilage. With reduction in articular surface, the joint loses its smooth gliding motion and movement becomes limited. Muscles will tense in an effort to stabilize the joint, since the ligaments are now unable to do their job; but they too will eventually weaken, spasm, produce "knots," and elicit painful trigger points. Bone loss develops as the unstable bony surfaces continue to rub roughly and unevenly, leading to joint space narrowing, exposure of the underlying subchondral bone, and precipitation of a process of bone remodeling in which the subchondral bone thickens. This accumulated or thickened bony overgrowth is called osteoarthritis.

Articular cartilage has no blood supply and therefore tends to heal slowly and imperfectly. Cartilage also lacks a neural network and *does not elicit pain itself.* The pain in osteoarthritis occurs from the pressure on the subchondral bone after the loss of cartilage tissue and from the stress on the tendons and ligaments of the joint.

Treatment Options for Osteoarthritis

Over the years, many medications and procedures have been tried to relieve the pain and symptoms of osteoarthritis, but there is still no cure. Exercise, medications, physical therapy, and lifestyle modification may provide symptom relief, but they are unable to regenerate the joint. Icing the joint and the use of nonsteroidal anti-inflammatory medicines (NSAIDs) to decrease the swelling will unfortunately inhibit the natural inflammatory

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response and normal healing mechanism of the body for soft tissue repair. NSAIDs reduce the body's ability to repair and hasten the osteoarthritic process. There are, however, treatments available that stimulate the regenerative processes in the joint and facilitate repair of the joint.

One regenerative technique that has shown success is stem cell therapy, a non-surgical treatment capable of repairing the joint and supplying the affected joint with chondrogenic (cartilage forming) bone marrow-derived mesenchymal stem cells (BMSC). Stem cells have been shown in research to speed up and enhance bone and cartilage repair in osteoarthritic joints.[1] Injecting these cells into the degenerated joint supports the development of cartilage. Since surgery comes with many disadvantages, stem cell therapy to repair defects of articular cartilage provides an exciting treatment option. Additionally, research findings demonstrate evidence of the reduction in the usual progressive destruction of articular cartilage in osteoarthritic disease by mesenchymal/bone marrow stem cells. Bone marrow stem cells appear to suppress inflammation and release growth factors that combat osteoarthritis and the degenerative process, enabling healing mechanisms to repair articular cartilage and relieve the chronic pain of oseoarthritis.[2]

Gold Standard in Stem Cell Therapy

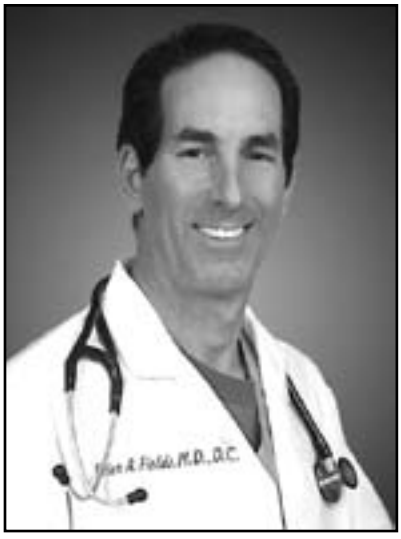
In our practice, we use the Gold Standard in Stem Cell Therapy, which combines several different regenerative treatments to effectively repair osteoarthritic joints. The treatments are non-surgical, requiring basically no down time and allowing the patient to stay active. There is also no extended time off work necessary. Regenerative orthopedic therapies are reparative and effective non-surgical alternatives. We comprehensively treat the entire joint with multiple injections of the platelet-rich plasma portion of the blood, progenitor cells from adipose (fat), plus bone marrow. These regenerative treatments, along with dextrose prolotherapy in and around the involved joint, offer benefits in terms of pain relief, regenerative properties, and cartilage repair for people affected by osteoarthritis. Dextrose prolotherapy is a technique that is used to aid the body in healing by prompting creation of new collagen. Various trials and studies have shown the effectiveness of dextrose prolotherapy in treating osteoarthritis, as well as ligament and tendon injuries.[3-5]

Since these regenerative treatments are effective at repairing ligaments and tendons, treatment earlier on in the process has the potential to prevent damage and help to avoid the lifestyle adjustments that often transpire with the disease. In many cases, prolotherapy alone is sufficient to bring the pain relief and repair needed. When cases of degeneration are advanced, we turn to the Gold Standard in Stem Cell Therapy integration of prolotherapy with components of blood, fat, and bone marrow. Many clinics use only one or two of these procedures, but we have discovered that this combination acts as an amazing regenerative solution to reverse the damage of osteoarthritis on the joint.

Dextrose prolotherapy involves the injection of a hypersmolar dextrose solution into an injury site to elicit localized inflammation, which is the first step in healing the damaged area. The dextrose solution acts as a proliferant via the induction of local inflammatory and wound healing cascades, including fibroblast cells that make collagen. With the addition of the Gold Standard in Stem Cell Therapy, the goal is to enhance the effects of hypertonic dextrose prolotherapy and improve treatment outcomes in patients with advanced arthritic conditions. All solutions are centrifuged and concentrated to get a solution with the most concentration of stem cells. The Gold Standard in Stem Cell Therapy is a great proliferant solution for regeneration that addresses the whole joint.

What Is the Expected Outcome?

Patients treated with the Gold Standard in Stem Cell Therapy report



Peter A. Fields, MD, DC, The Athletic Doc®, is a world-renowned expert in the field of regenerative orthopedics (non-surgical joint and spine repair). Dr Fields is the director of the OrthoRegen in Santa Monica, California, which is one of the largest practices in the world dedicated solely to regenerative orthopedics.

Dr Fields has appeared on national TV as a regenerative medicine expert as well as several TV and radio stations in the Los Angeles area. He lectures on regenerative orthopedics at various conferences around the world on these techniques and also writes a column on orthopedic/sports medicine for a national magazine. In addition, Dr Fields is a clinical instructor with the Hackett-Hemwall Foundation, the largest teaching organization for prolotherapy.

Dr Fields is a very active and competitive triathlete, having completed ten full Ironman Triathlons as well as nine 70.3 (half) Ironman Triathlons and over 40 other triathlons. In addition, he recently climbed Mount Kilimanjaro (19,341 feet) in Africa. He has had his back and shoulder treated by these techniques and avoided surgery. In other words, this doc walks his talk!

significantly decreased pain, remarkable gains in function and quality of life, boosted exercise ability, increased range of motion, as well as losses in stiffness and crepitus. These regenerative therapies are safe and effective treatment options for osteoarthritis, with the potential to slow down the progression of osteoarthritis while promoting the regeneration of articular cartilage. The treatment is essentially a new paradigm in the treatment of osteoarthritis and one that decreases the need for surgical joint repair and replacement.

Not a One-Shot Magic Cure

All stem cell treatments are not alike, so it is important to do your homework. Treatments are advertised that may involve just one injection of stem cells, and one injection is most likely insufficient to adequately repair the injured joint. Without comprehensive repair of the joint, sufficient pain relief may not occur. The joint injury that eventually results in osteoarthritis, as noted earlier, involves multiple joint structures. The ligaments that were injured when the cycle of abnormal joint motion began, all need to be treated. The degeneration and breakdown of cartilage that is present in osteoarthritis transpires over time. If one ligament is injured, there's a huge likelihood that other ligaments or soft tissue are also injured. A comprehensive treatment is necessary to strengthen, repair, and stabilize all involved ligaments and structures of the joint to prevent destructive forces from continuing the breakdown of cartilage common in osteoarthritis. *A single injection is simply not comprehensive enough to reverse the damage affecting the entire joint.* In our practice, we address these unnatural hypermobile forces with a multi-injection technique called comprehensive regenerative orthopedics.

Osteoarthritis is a challenging condition to treat, but regenerative injection therapies, such as stem cell therapy, offer an effective way to meet the challenge, have been proven to effectively activate cells for regeneration and repair in the degenerated osteoarthritic joint, and offer the potential for enhancing the quality of life of individuals with the disease.

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Letter to the Editor

Re: Geomagnetisim and Food Allergy

I commend Dr. Zamm and the *Townsend Letter* for the publication of "Why Food Allergy Occurs – An Electronic Mystery Story" in the April 2019 issue.

The hypothesis that geomagnetism in association with solar wind polarizes secretory IgA as a molecular gatekeeper that affects the absorption of gut nutrients vs antigens is insightful.

It makes eloquent sense that amino acids and glucose, which are non-allergenic nutrients, would easily pass through the polarized secretory IgA biofilm in the small intestine, or respiratory system. Larger molecules, such as gluten, and other antigens would not pass the healthy polarized mucus barrier.

This biochemical and energetic force field effect, from earthing and solarizing geomagnetism, would also influence leaky gut. The bipolar phospholipid layers of all cell membranes, and the cell junctures of epithelium such as respiratory, digestive, and skin would similarly respond.

This hypothesis may further explain the empirical evidence of nature cure, via earthing, and nature immersion therapy, etc.

As other content, in this April issue demonstrates, our indoor generation might experience less allergy if we lived more in nature. It's basic to biochemistry. Old Nature Cure sanatoriums effectively treated the ill on this basis. For example, dew walking, sun bathing, and hydrotherapy all have electronic, or energetic polarizing effects on all living organisms.

Be well, live well, enjoy life in harmony with the earth and sun.

Dr. Brent B. Mathieu
www.greenmanhealth.com
www.voxhumri.com

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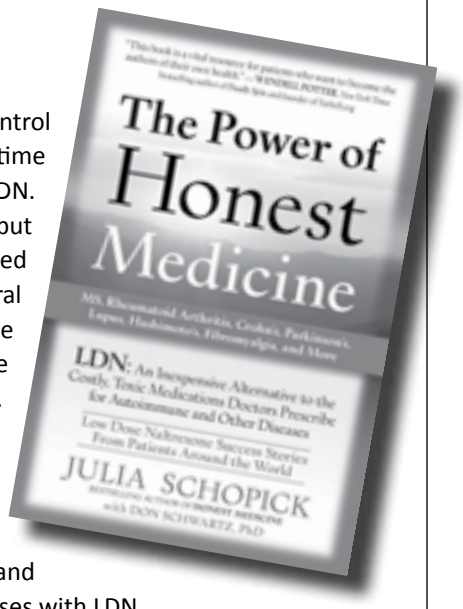
Low-Dose Naltrexone for Autoimmune Disease and Cancer

review by Burt Berkson, MD, MS, PhD

The Power of Honest Medicine: LDN, an Inexpensive Alternative to the Costly, Toxic Medications Doctors Prescribe for Autoimmune and Other Disease*s* by Julia Schopick with Don Schwartz, PhD
Innovative Health Publishing, Oak Park, Illinois; www.HonestMedicine.com
Softbound; 2018; 292 pp; $16.95



The Power of Honest Medicine: LDN, an Inexpensive Alternative to the Costly, Toxic Medications Doctors Prescribe for Autoimmune and Other Diseases is an intelligent tour through the science and day-to-day use of low-dose naltrexone (LDN) by doctors and patients. Well-respected author Julia Schopick (with Don Schwartz) describes an effective way to control several examples of autoimmune disease with the use of LDN in this well-written book. Through personal stories by patients and effective explanations by the author on the use of this amazing agent, I found this book easy and captivating to read.

Naltrexone was first approved in the 1980s as a prescription drug to reverse the effects of opiate poisoning. Low-dose naltrexone is a very low dose of naltrexone and has been found to be effective in treating several diseases including systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, Parkinson's disease, certain cancers, etc.

I first learned about LDN about 20 years ago when a man presented to my clinic, using a walker, and who appeared very ill. He told me that he had rheumatoid arthritis and prostate cancer metastasized to his bones. He said that an oncologist at a well-respected cancer hospital in Texas told him that there was no effective treatment for his disease and that he should receive palliative therapy at a hospice.

The man asked me if I would prescribe some narcotic tablets to help him with his pain, so he could get his wife with senile dementia admitted to a nursing home. Then he asked me if I had ever heard of Dr. Bihari in New York. I answered no. He told me that he had heard that Bihari was effectively treating metastatic cancer *and* autoimmune disease.

I advised him to go see Dr. Bihari. Maybe he could help him. He answered that Dr. Bihari was just in a little office. "If he was any good wouldn't he be associated with a large medical center?" I answered that if he could cure cancer, he might put a large cancer clinic out of business since they treat cancer and do not often cure cancer.

I did not see the gentleman for three years. I thought he had died. Then one day he appeared in our clinic complaining of a sinus infection. The man looked healthy and was standing straight and did not have the use of his walker. He told me that he saw Dr. Bihari and that his rheumatoid arthritis and prostate cancer became under control with a drug, that at that time cost only $15 a month: LDN.

I was very skeptical, but curious, and prescribed it to myself and several patients. It had no side effects and helped me sleep comfortably. Many of my patients reversed their lupus, dermatomyositis, autoimmune hepatitis, rheumatoid arthritis, and other autoimmune diseases with LDN.

Then I started prescribing it for cancer with the addition of intravenous alpha lipoic acid and observed the same remarkable results with several stage 4 cancer patients. Check "Berkson BM" in Google Scholar or PubMed, and Google "Berkson, National Cancer Institute." You will find some very amazing information there. My colleagues and I published the first peer-reviewed publications on the reversal of stage four cancers in patients using LDN plus alpha lipoic acid.

In this exceptionally good book, Ms. Schopick describes the remarkable results people with autoimmune disease are having using LDN and the problems that many patients have persuading their doctors to prescribe this efficacious agent. The book is logical and methodical and provides a plan for the use of LDN for several autoimmune illnesses.

I genuinely enjoyed reading this book, and I would recommend it to doctors, patients, and anyone who wants a good read about a drug that is effective and almost completely ignored by the medical establishment.

Burton M. Berkson, MD, MS, PhD
Founder, the Integrative Medical Center of New Mexico, Las Cruces
Adjunct professor, Oklahoma State College of Medicine, Tulsa
Former professor, Rutgers University, and Chicago State University
Author: *The Alpha Lipoic Acid Breakthrough*
Co-author:
Syndrome X (the first book on metabolic syndrome)
All About the B Vitamins
User's Guide to the B-Complex Vitamins

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Bastyr University San Diego Clinic: Student Case Reports

edited by Baljit Khamba, ND, MPH

Fourth-year interns at Bastyr University are actively developing their clinical skills through treating patients at the school's clinic. They engage their didactic skills in rigorous case taking, examinations, evaluation, and a naturopathic-focused treatment plan under the supervision of their attending doctor. The interns are able to gain experience in areas such as mental health, mind-body medicine, oncology, hydrotherapy, physical medicine, out-reach community care, IV treatment, biofeedback, and so on. Each one of these opportunities presents a prime opportunity for the students to enrich their knowledge about conditions and approaches to care. In efforts to fortify their understanding, the students write case reports under the supervision of Dr. Baljit Khamba in their course "Advanced Case Studies." By completing these reports, future practitioners gain a valuable skill that they can then utilize once they graduate.

Craniosacral Therapy for Stress-Related Dysautonomia

by Kim Love

Abstract

The aim of this case report is to elucidate the validity of craniosacral therapy as a treatment for dysautonomia due to chronic stress. A patient presented to the Bastyr University California clinic with multiple chronic infections, autoimmunity, neurological disturbances in the form of full body tremors, and dysautonomia. The underlying chronic stress and inflammation from the infections and autoimmunity, along with the dysautonomia, were treated using eleven 20-to-40-minute sessions of craniosacral therapy (CST). CST has been studied for use in reducing autonomic nervous system dysfunction as well as improving heart-rate variability (HRV), which is a measure of parasympathetic nervous system function.[1] With this particular patient, the goal was to improve his sympathovagal response and reduce sympathetic overload by using CST to upregulate the parasympathetic system. After 11 sessions of treatment, the patient subjectively reported feeling much lighter, more joyous, and stated he had more vitality overall. The tremors reduced in frequency and in strength, and were more subclinical, according to the patient. Overall, CST is a useful modality for reducing dysautonomia due to chronic stress.

Introduction

Dysautonomia, specifically with sympathetic dominance, has been linked to many age-related autoimmune and metabolic immune-mediated inflammatory diseases (IMIDs), including rheumatoid arthritis (RA), Sjogren's, inflammatory bowel syndrome (IBS), type I diabetes, and psoriatic arthritis, to name a few.[2] The pathogenesis of this condition is related to the effects of chronic stress/inflammation on the central nervous system. According to Bellanger and Lorton, "Unresolvable immune stimulation from chronic inflammation leads to a maladaptive disease-inducing and perpetuating sympathetic response in an attempt to maintain allostasis."[2] For patients suffering from dysautonomia, regular daily activities can be very difficult. Normal anoxious stimuli can provoke extreme reactions and perpetuate the cycle of sympathetic overload.

The problem with dysautonomia is that the conventional medical world does not have any treatments that can restore balance to the overall autonomic nervous system. Their treatments are largely related to treating the underlying autoimmune condition or chronic infection or other diagnosis along with palliative symptom-based drug therapies. Instead of focusing solely on the autoimmunity, the chronic infection, or the other "diagnoses" the patient may have, the hypothesis that this case report aims to address is that improving or strengthening the parasympathetic nervous system through

craniosacral therapy is a more effective root-cause holistic treatment approach to dysautonomia that results from underlying chronic stress. Once the sympathovagal response has been restored, the body can now focus on fighting the infection or reducing chronic inflammation that underlies most autoimmune conditions and chronic infections.

CranioSacral therapy (CST) has been shown in the literature to improve heart rate variability (HRV), to increase the activity of the parasympathetic nervous system, and to improve the sympathovagal response in patients experiencing subjective discomforts.[1] Furthermore, CST has been shown to reduce sympathetic dominance after an acute 5-minute laboratory induced stressor compared to no treatment.[3] The subjects in the Fornari et al study who received CST after receiving a stressor had marked improvement in parasympathetic tone and a much lower overall cortisol response compared to the control group who did not receive any treatment after the stressor.[3]

Case Description

JG is a 46-year-old Caucasian male who presented to Bastyr University California (BUC) clinic in November of 2016 with two main concerns: neurological disturbances and irritable bowel symptoms. He described the neurological disturbances as full body tremors with a left frontal lobe migraine triggered by certain beaches, food, or mold exposure. He also experiences brain fog, bilateral tinnitus, and unstable gait (falling to the left) along with his tremor. With the tremor episodes, he also experiences dysarthria and inability to formulate sentences. He reported personality changes that resemble autism. Cholestyramine would clear his mind for one hour after taking it. He had a recent MRI that was clear, and his neurologist diagnosed him with migraine with vestibular disturbances.

He described his irritable bowel symptoms as abdominal discomfort in the form of tightening and cramping, along with pain, in the LLQ (lower left quadrant). He also reported feeling "moody" after eating certain foods and will regularly get diarrhea after the cramping and pain. He had eliminated soy, eggs, gluten, corn, seeds, nuts, nightshades, and high oxalate foods as they all exacerbated the abdominal pain. Butyrate supplementation improved his symptoms along with certain probiotics. Some probiotics upset his stomach.

His review of systems was positive for occasional heart palpitations, Raynaud's in the hands in a cold environment, undigested food in his stools, the inability to extend his arms fully or to flex his fingers fully, enlarged DIPS/PIPS (finger joints) for the past 20 years, left elbow inflamed, dry flaking skin on the face, dandruff on the scalp, anxiety after eating too much sugar, and rhinitis after exposure to mold.

Pertinent past medical history included a positive Lyme diagnosis, RA, and Sjogren's. He tested positive for Lyme disease in 2016 with a positive western blot for IgG and IgA antibodies to *Borrelia burgdorferi.* He also had a diagnosis of RA from 1990, colitis in 2017 by colonoscopy, and Sjogren's by anti-SSA in 2016. He had a spinal fusion surgery when he was a young adult for his RA.

Pertinent social history included self-reported emotional and physical abuse from his father as a child. He was married with no children.

Current medication list included monolaurin (which he took for immune support), butyrate, fish oil, Migrelief (a botanical medicine extract of feverfew for migraine relief), Mucinex, cholestyramine.

Medication	**Dosage**
Monolaurin	600 mg QD
Sodium butyrate	800 mg QD
Omega-3 Fish oils	2 grams QD
Migrelief	PRN for headaches
Fexofenadine HCL (Mucinex)	600 mg capsule PRN
Cholestyramine	PRN for mold exposure

Pertinent physical exam findings included a blood pressure of 110/65; a pulse of 69 bpm; oral temperature of 98.1 degrees Fahrenheit. His general appearance was well groomed, but he appeared fatigued. He had hypometric rapid eye saccades to the left with fatigue after 3 saccadic eye movements; hyperactive bowel sounds in the LLQ and LUQ, hypoactive bowel sounds in the RUQ; tenderness to palpation in the LLQ and McBurney's point, along with a tight diaphragm on palpation. His left arm was stuck in flexion, with an inability to fully extend it; his left lateral epicondyle was enlarged and inflamed around the joint; his PIPS/DIPS were inflamed bilaterally. He had reduced flexion and extension on bilateral wrists. He had decreased sensation ➤

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to pinpoint on his left anterior ankle; his gait was stable, but he had reduced arm swing bilaterally; his heel to toe was stable. He experienced sweating and marked irritability after exposure to a loud noise. His judgment and insight were intact, and his mood was forlorn.

Current lab tests also showed high antibody titers to EBV and HHV6.

Lab Test	Result
EBV titres	IgG Early Ag - 26.9
	IgG Ab VCA >600
	IgG nuclear Ag >600
HHV6 titres	4.89

Potential diagnoses included Lyme disease, RA, Sjogren's, and mold exposure. Dysautonomia due to chronic stress was the working diagnosis due to his reaction to noise with sweating and irritability, his history of abuse as a child, his autoimmune conditions, as well as his chronic infections.

Treatment was eleven weeks of 20-to-40-minute sessions of craniosacral therapy performed once per week by one student clinician.

Outcome was measured by subjective patient reports and objective student clinician observations. The patient reported feeling stronger with more overall vitality. He stated he felt more emotionally clear and was able to reconnect with his spirituality. He stated he was able to reconnect with family and friends in a way that he had not been able to in many years. He stated he experienced less anxiety with leaving the house (for fear of having a tremor). He reported less brain fog, less anger, and more joy than he has felt in the last 20 years. He reported experiencing the tremors more subtly and with less frequency; additionally, the tremors appeared more subclinical and did not reach their full potential.

The student clinician observations included a much lighter and more joyous demeanor. The patient smiled for the first time and cried what he called "tears of joy" after the eighth treatment. The patient reported looking forward to each weekly treatment and was distraught when the student clinician informed him that the quarter was coming to an end and he would start receiving treatments from a different clinician. Unfortunately, he stopped coming to the clinic and refused to receive craniosacral therapy from a different student clinician.

Kim Love is a fifth-year medical student at Bastyr University California. She is a mother to a fun-loving, energetic three-and-a-half year old and the wife to a wonderful US Marine. She herself is a former Marine and has a passion to one day serve the military community with naturopathic medicine and all that it has to offer. She loves traveling, spending time outdoors, camping, and being with family.

Discussion

In an exhaustive review of the literature on both PubMed and Embase using the search term "craniosacral therapy," only three research studies specifically looked at the autonomic nervous system (ANS) effects of craniosacral therapy. For these studies, the ANS outputs were measured using HRV. In one research study, compared to a placebo, a single session of craniosacral therapy induced a faster recovery of HRV, an increased parasympathetic activity, and a reduced sympathetic output after an acute mental stressor.[3] Another study demonstrated improved HRV and sympatho-vagal response after only two 30 minute CST sessions in patients who were stressed, anxious, or weak. Compared to the control group who received only a rest period of 30 minutes, the patients who received the CST treatment had significant improvement in their HRV and in their parasympathetic nervous system tone as measured by HRV parameters taken from EKG readings.[1]

Limitations include the practitioner to practitioner variability with the CST treatments, the difficulty in standardizing subjective reported outcomes, the limited number of test subjects in the research studies, and the limited number of research studies specifically on CST and dysautonomia. More research on the use of CST as a therapeutic modality for treating underlying chronic stress that results in dysautonomia is certainly needed and warranted. This is a simple, yet profoundly impactful therapy that may provide help for patients with multiple autoimmune conditions and multiple chronic infections by reducing the underlying chronic stress and sympathetic dysregulation.

For patient JG, HRV measurements were not taken; therefore, the sympatho-vagal response was measured subjectively using patient reports of experiencing fewer neurological tremors that reduced in severity. Other measurements included subjective patient reports of feeling more joyous and less anxious overall. If the patient were to be treated again, it would be ideal to include more objective outcomes with the use of HRV measurements.

Conclusion

CST can be an impactful therapy for a 46-year-old male patient experiencing neurological tremors, sweating from noxious stimuli, and overall hypersensitivity to his surroundings which all fit under the umbrella of dysautonomia due to chronic stress. After eleven CST weekly sessions, he reported more joy in his life, less frequency of the tremors, and the ability to reconnect to his friends, family, and spirituality.

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Calendar

Please submit an announcement of your event 90 days in advance.
Event publication must be limited to 25 words or less. Multiple event listings require paid advertising.
Contact calendar@townsendletter.com for details.

MAY 25-26: KOREN SPECIFIC TECHNIQUE (KST) in Stockholm, Sweden. Locate and release physical and emotional stresses. Also, **JUNE 14-16** in Denver, Colorado; **SEPTEMBER 13-15** in Detroit, Michigan. CONTACT: www.korenspecifictechnique.com; phone 267-498-0071.

MAY 30-JUNE 1: INSTITUTE OF FUNCTIONAL MEDICINE ANNUAL INTERNATIONAL CONFERENCE – Stress, Pain, and Addiction in San Antonio, Texas. CONTACT: https://aic.ifm.org/

MAY 31-JUNE 2: 48th ANNUAL INTERNATIONAL ORTHOMOLECULAR MEDICINE TODAY CONFERENCE in Vancouver, Canada. Sessions on orthomolecular oncology, immunology, and general medicine. CONTACT: https://isom.ca/event/omt2019/

MAY 31 – JUNE 3: MEDICINES FROM THE EARTH HERB SYMPOSIUM in Black Mountain, North Carolina. CEs available. CONTACT: 541-482-3016 or www.botanicalmedicine.org.

JUNE 7-9: LDN 2019 CONFERENCE in Portland, Oregon. CONTACT: https://www.ldnresearchtrust.org/conference-2019

JUNE 7-9: COLLEGE OF NATUROPATHIC DOCTORS OF SASKATCHEWAN HEALING SKIES CONFERENCE in Saskatoon, Saskatchewan, Canada. CONTACT: http://sanp.ca/healing-skies-conference.html

JUNE 12: HIGH-DOSE OZONE AND UBI TRAINING @ SOPMed Conference in San Diego, California. CONTACT: https://sopmed.org/workshops/

JUNE 13-15: 5th ANNUAL SOCIETY FOR PROGRESSIVE MEDICAL EDUCATION CONFERENCE (SOPMed) in San Diego, California. CONTACT: 517-242-5813; https://sopmed.org/

JUNE 14-16: 4th HRI INTERNATIONAL HOMEOPATHY RESEARCH CONFERENCE in London, United Kingdom. CONTACT: https://www.hrilondon2019.org/

JUNE 21-22: THE GREAT PLAINS LABORATORY, INC. presents GPL ACADEMY PRACTITIONER WORKSHOPS in Minneapolis, Minnesota. Organic acids testing, toxic chemical testing, and mycotoxin testing, among others. CONTACT: http://www.GPLWorkshops.com

JUNE 22-29: ALLEN COLLEGE OF HOMOEOPATHY SUMMER SCHOOL in Chelmsford, Essex, United Kingdom and online. CONTACT: https://homoeopathy-course.com/images/pdf/reasons-to-join-summerschool.pdf

JUNE 28-30: THEORETICAL AND PRACTICAL COURSE IN NEURAL THERAPY in New York, New York with David Vinves Catalonia, MD (Spain). Organized by Dr. Gurevich. CONTACT: www.HolisticMD.org; 516-674-9489.

JUNE 28-30: 14th ANNUAL JOINT HOMEOPATHIC CONFERENCE – Homeopathy and Brain Health in Baltimore, Maryland. CONTACT: https://www.homeopathycenter.org/2019-joint-american-homeopathic-conference

JULY 12-13: THE GREAT PLAINS LABORATORY, INC. presents GPL ACADEMY PRACTITIONER WORKSHOPS in Boston, Massachusetts. Organic acids testing, toxic chemical testing, and mycotoxin testing, among others. CONTACT: http://www.GPLWorkshops.com

AUGUST 15-17: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS 2019 ANNUAL CONVENTION in Portland, Oregon. CONTACT: https://www.naturopathic.org/

AUGUST 15-18: 10th ANNUAL INTEGRATIVE MEDICINE FOR MENTAL HEALTH (IMMH) CONFERENCE in San Diego, California. CMEs available. CONTACT: https://www.immh2019.com/

AUGUST 22-25: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING For Doctors, Dentists & Health Professionals: Detecting Parasites, Dental & Fungal with Simon, Yu, MD, in St. Louis, Missouri. **CONTACT:** 314-432-7802; http://www.preventionandhealing.com/pah-training.php

SEPTEMBER 4-7: 20th ANNUAL FALL CONFERENCE ON INTEGRATIVE MEDICINE IN WOMEN'S HEALTH in Napa, California. CONTACT: http://www.symposiamedicus.org/

SEPTEMBER 6-8: EMFC 2019 – DIAGNOSIS AND TREATMENT: EFFECTS OF ELECTROMAGNETIC FIELDS EXPOSURE in Santa Cruz, California. CONTACT: https://emfconference.com/

SEPTEMBER 12-15: 17th ANNUAL RESTORATIVE MEDICINE CONFERENCE in San Diego, California with Tieraona Low Dog, MD. CONTACT: https://restorativemedicine.org/conferences/2019-annual-conference/

SEPTEMBER 20-22: NEURAL THERAPY HANDS ON in New York, New York with David Vinves Catalonia, MD (Spain). Fascia, ANS, palpation, autonomic ganglia. Organizer Dr. Gurevich. CONTACT: www.HolisticMD.org; 516-674-9489.

SEPTEMBER 20-29: KLINGHARDT IMMERSION WEEK – Injection Techniques, Neural Therapy, and Autonomic Response Testing Workshops in Kenmore, Washington. CONTACT: 908-414-0769; info@klinghardtacademy.com; www.klinghardtacademy.com

OCTOBER 10-13: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE FALL CONFERENCE – Fatigue: A Complex Diagnosis and Treatment Dilemma in Louisville, Kentucky. CMEs available. CONTACT: http://www.aaemconference.com/fall/

OCTOBER 12-14: FIELD CONTROL THERAPY® (FCT) INTENSIVE TRAINING with Savely Yurkovsky, MD, in White Plains, New York. CONTACT: 914-861-9161; http://www.yurkovsky.com

OCTOBER 23-27: INT. COLLEGE OF INTEGRATIVE MEDICINE (ICIM) – Healthy Parents, Healthy Children in Toronto, Ontario. CONTACT: https://icimed.com/

OCTOBER 25-26: ANNUAL MICROCURRENT CONFERENCE in Scottsdale, Arizona. CONTACT: http://microcurrentconference.org/

OCTOBER 25-27: ADVANCED APPLICATIONS IN MEDICAL PRACTICE (AAMP) FALL EVENT – Integrated Oncology at the Next Level in Seattle, Washington. CONTACT: 954-540-1896; https://aampconferences.com/

NOVEMBER 1-2: SCIENCE, SPIRIT & CLINICAL PEARLS, NHAND 19th ANNUAL CONFERENCE in Nashua, New Hampshire. **Call for Abstracts is OPEN through May 31st**. CONTACT: https://www.nhand.org/call-for-abstracts/; conference@nhand.org

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Curmudgeon's Corner

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

Joking About Cancer

Granted that having cancer is no laughing matter for anyone involved: not the patient, not the doctor, nor the caregivers. Yet, with every new patient who comes to see me, there is an unwritten goal, a challenge that I set for myself: "How quickly and how often can I get them to laugh out loud?" Not just chuckle, but a loud laugh, loud enough to justify an interrupting knock on the door and a head poked in questioning, "Are you guys working in here or just having a good time?"

This has been part of my new patient routine for years, and it takes me a moment to back up and remember how this habit got started so I can explain this peculiar patient care strategy.

My interest in laughter goes back to a 2001 letter to the editor of *JAMA* from Hajime Kimata. Kimata, an allergist in Japan, wrote to describe the first of a series of studies he performed on the effects of laughter. Kimata gave credit to Norman Cousins for giving him the idea for his research and went on to describe a simple study.

Everyone, of course, (or at least those of a certain age) had heard of Norman Cousins and his book, *Anatomy of an Illness*. Cousins was the editor of the *Saturday Review* from 1942 to 1972 and, in that era of national media, was a household name. On retiring he joined the faculty of UCLA where he taught ethics and medical literature, in particular the connection between attitude and health.

When Cousins was diagnosed with ankylosing spondylitis in 1964, he came up with a method of self-treatment; he induced himself to laugh by watching *Candid Camera* TV shows. Every household in America knew this story, and so the idea of using laughter as medicine is forever connected with Norman Cousins.

Humans begin laughing spontaneously in response to triggers during early infancy. Laughter isn't something we happen to learn when young. Laughter is an ancient skill. People have been more or less the same in an evolutionary sense for the past 200,000 to 300,000 years. We are descended from a line of hominids, "homos" of various models, that go back 2-3 million years. All of them knew how to laugh.

It's not just humans that laugh; laughter's a trait shared by other apes and even some mammals. If that comes as a surprise, search online for "laughing dogs" and take a look. Evolutionary biologists are pretty sure that laughter goes back millions of years; our ancestors were laughing long before we were even human. Current theory suggests that the evolutionary origins of laughter can be traced back at least 10 to 16 million years to the last common ancestor of humans and modern great apes.[1]

Laughter is not a learned behavior but rather a fundamental communication skill deeply ingrained in our DNA. We are hardwired to laugh.

Laughter serves, at least in part, a deeply social function. Current theory suggests that laughter evolved from a pattern of quick, shallow panting breaths that mammals, particularly primates, use during 'play behavior.' This breathing pattern communicates both playfulness and safety. Laughter says something to the effect, "This wrestling is just a game. We're having fun. There is no need to be afraid. We are playing."[2]

Play allows for the development and learning of complex physical skills, in particular, hunting, fighting, and social cooperation. During play, laughter encourages both cooperation and competition. Play and the shared communication through laughter, strengthens positive bonds between individuals. Laughter prolongs how long either children or chimpanzees will play. Laughing directly triggers conscious and unconscious positive emotional responses in both those who are laughing and also in those who just hear laughter.

In Kimata's first *JAMA* report, 26 patients with atopic dermatitis, all who were allergic to dust mites (and most of whom were also allergic to cedar pollen and cat dander), were studied. After going 72 hours with no medication, they underwent skin prick tests before and after viewing *Modern Times*, the old, rather funny, Charlie Chaplin movie. The resulting wheals triggered by the skin prick tests were measured. A similar procedure was repeated before and after a control-video of the same length featuring weather

information. The wheals were significantly smaller after watching Chaplin and the effect lasted for hours, actually for days. The weather show had no effect on wheal size.[3]

Kimata performed a series of other studies on laughter effects that were published over a nine-year period. Most of these laughter studies used Charlie Chaplin as the therapeutic intervention; though in time, Mr. Bean was substituted. Kimata went on to show that laughter helped kids with eczema sleep better,[4] reduced the symptoms of bronchial asthma,[5] improved erectile dysfunction,[6] and so on.

The study in this series that impressed me the most was one on laughter changing fecal polyamine levels. Kimata knew that atopic dermatitis symptoms were aggravated by certain bowel bacteria and followed fecal polyamine levels for a week in 24 patients watching humorous movies nightly. Regular doses of laughter increased *Lactobacilli* and *Bifidobacterium* levels while decreasing *Staphylococcus aureus* and *Enterobacterium*. Watching non-humorous films had no effect.[7] (Think of the patients who you've tried to change their gut biome: the tons of probiotics etc. and how slow and frustrating that process can be. These changes happened in a week.) Kimata conducted a dozen or so studies, and then something kind of sad happened.

Kimata was awarded the IgNoble prize in 2015. For those of you who don't recognize this prize by name, the IgNoble prize is awarded "… to celebrate … trivial achievements in scientific research." It's kind of a joke, an award that makes fun of how stupid some research studies sound to lay-people.

Kimata won the prize for a study that, instead of laughter, looked at the effect of kissing.[8] For all of his interest in laughter, it seems that Kimata did not think this prize was funny or at least didn't see the humor in it. We have not seen any new research come from Kimata since then.

Kimata may have stopped publishing, but in the last decade others took over the laughter research. PubMed now lists nearly a hundred clinical trials looking at the effects of laughter on health. Along the way, Richard Wiseman set up an online experiment to collect jokes and rank them. As a result, we know the world's funniest joke (with the caveat that reactions and ranking vary by nationality and time of day)[9]:

> A lady, she's carrying a little baby, gets on the bus. The bus driver, looks at her, looks at the baby and says, 'Lady, that's the ugliest baby I've ever seen.' The woman is horrified and plops herself into a seat. The fellow sitting next to her looks at her distraught expression and asks, 'Did that bus driver just insult you?'
>
> She nods 'yes.'
> 'Did you say anything back to him?'
> She shakes her head no.
> 'You can't let him get away with this. If you don't speak up for yourself and keep this hurt inside, it will make you sick, you'll get cancer. You should go tell him off. Will you do that?'
> She nods, 'Yes, I don't want to get cancer.'
> 'Here now, he's slowing for a bus stop, you go tell him what you think. I'll hold that monkey.'

I've continued to follow this laughter literature closely over the years. I wanted my patients to laugh more. As one study summed it up:

> Humor and jokes reduce anxiety and stress (for patients and doctors). Humorous people have a more realistic, flexible and less fearful behavior. Humor helps to overcome negative experience. Humor can help the patient to gain new views towards the disease and a healthy distance towards occurring symptoms. Humor improves the relationship between patient and doctor.[10]

Studies told us that laughter improves immune function in cancer patients, something that they all come wanting to improve.[11] Laugher specifically reduces stress during chemotherapy.[12] It may reduce radiation dermatitis in breast cancer treatment.[13] Laughter reduces anxiety, stress, and depression in cancer patients.[14] All these are good things to happen.

I wanted my patients to laugh…. It seemed like a good idea, and I started telling them that laughter was good for them.

Then came the Guillermo paper in 2013. Lise Alschuler ND, past president of the Oncology Association of Naturopathic Physicians (OncANP.org), wrote a nice review of this study for the *Natural Medicine Journal*.[15] She did a great job of translating some rather complex biochemistry into understandable English for us. Simply put, ovarian cancer cells appear to be activated by stress hormones. This was shown in cell culture experiments, animal experiments, and then in human data.[16] It seems that ovarian cancer cells thrive and spread in the presence stress hormones.

This idea that cancer thrives on stress was emphasized by several other studies that came out about the same time reporting that betablocker drugs might have a role in slowing cancer growth. These drugs block stress hormones from triggering cancer cells to grow. (See *Townsend Letter*, August/September 2014; http://www.townsendletter.com)

In August 2018, a meta-analysis was published that examined the effects of betablocker use on cancer prognosis. Examining data on 319,006 patients, the authors reported, "beta-blocker use is associated with improved survival among patients with ovarian cancer, pancreatic cancer, and melanoma." Using these stress-blocking drugs improved cancer specific survival by 22%.[17]

I wasn't about to put all my patients on betablockers; but in my mind, laughter struck me as the next best thing. Laughter clearly reduces stress hormones.[18] I wanted my patients to laugh. Laughter seems to be the most natural antidote to stress. As I wrote, laughter is hardwired into our nervous systems and to me seems like a safer choice.

There's a 2013 study that I refer to as the 'apple on the desk' study. Conducted with elementary school kids, 218 nine-year-olds were divided into three groups. The kids in two of the groups were subjected to attempts to increase their fruit consumption while the third group was left alone to be a control group. Kids in the first group went through a year-long educational curriculum about healthy lifestyle choices and how to make better food choices. They had a total of 29

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quarter-hour lessons taught by their own teacher once a week divided over the entire school year. The second group had no educational training. Instead their teacher simply brought a healthy snack for herself to class three times a week and ate it sometime during the day.[19] See why I call it the 'apple on the desk' study?

The children who took part in either of the experimental interventions significantly increased their fruit consumption compared to the control group, eating about 2 to 2.5 servings per day. At one-year follow up though, only the kids whose teacher had eaten the fruit continued to eat more fruit, about two servings per day. Those who had sat through the educational curriculum had gone back to eating one serving a day, the same as their starting level and the same as the control group.

This study strongly suggests that modeling the behaviors we want to see in our patients is more effective than 'teaching them about doing what we want.'

A sticker on my desk reminds me to, "Eat the apple." In other words, model the behaviors you want to see your patients adopt. If I want my patients to laugh, I get them to laugh. I tell them jokes. I make them laugh. I laugh with them.

Those of you who have read the Harry Potter books will remember the boggarts. A boggart, for those of you who haven't read the books, is a shapeshifter that lurks in dark spaces. It has no definite form but quickly takes the shape of that which the person who encounters it fears the most.

The Boggart-Banishing Spell (pronounced, "*Riddikulus*") is used to defend against a boggart. The spell makes the creature assume a humorous form thereby counteracting its ability to terrorize. A boggart can't scare you if you are laughing at it; boggarts are defeated by laughter.

My goal is for patients to learn to joke about the worst thing that may ever happen to them. Cancer is their boggart….

Not everyone has read Harry Potter, so I may fall back on quoting medical journals:

> Laughter provides a physical release for accumulated tension. Humor and laughter can be effective self-care tools to cope with stress…. Laughter provides an opportunity for the release of uncomfortable emotions that, if held inside, might create biochemical changes that are harmful to the body. Humor turns an event that might cause suffering into a less significant occurrence.[20]

Patients are often desperate for the opportunity to laugh and joke about their situation. It's just they are too shy to do so in front of their doctor; and we, the doctors, are too proper to do so. Cancer is such a serious disease after all. We frown if they make light of it. Yet at the same time, cancer is such a great punchline.

If you listen carefully to your patients, they will slip in little half-jokes into their conversation. Tentative jokes to test you, to see how or if you will respond to them or not. By testing the waters this way, they are asking if it is okay to joke about their situation and whether you will be on their side in helping them reduce the stress and discomfort. I've found that all I need do initially is respond affirmatively. To their quiet "ha-ha" I respond with a nod, a half smile and a "ha." After a few rounds of this, they lengthen their laugh to a "ha-ha-ha," and I meet them with a "ha-ha." It doesn't take much. Soon we are trading jokes.

While cancer is a great punchline, Death is the all-time winner punchline that powers the best jokes. Cancer can be the worst, most tragic thing that ever happened in our lives; but with practice we can reframe it. Maybe it's never going to be the best thing, but at least we can joke about it and reduce the stress.

It's how we choose to see it.

It's like the logo on the FedEx trucks. You can see the logo two ways. Either it reads "Fed Ex," or it's an arrow. People have a choice what to see.

It's like that with cancer. We can see the disease as a tragedy, or we can see the joke it makes of life. We get to choose.

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Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, MSW
www.healthyhomeopathy.com

Travel Smart and Stay Healthy…Naturally!

Just Back from Brazil!

Bob and I just returned from northeast Brazil where our homeopathic self-care home medicine kit was a godsend; of course, the kit is at the top of our "Don't Leave Home Without It" list. Those 50 little vials of white pellets have saved us and the thousands of folks who have slipped those handy one-pound kits into their packs and suitcases. In Brazil, where we attended a retreat in one of the most beautiful parks in the world, Chapada Diamantina, others asked for our help with diarrhea, sinusitis, and bee stings. And we used various remedies ourselves at least a dozen times over the course of three weeks.

We had never before heard of Chapada Diamantina, where plentiful diamonds were mined, and crystals abound. But it is being discovered, mainly by European trekkers, as a natural treasure of pristine pools, enormous waterfalls, and caves with the bluest of waters for swimming. The two main towns are Vale da Capao and Lencois, both gateways to countless natural adventures with relatively few tourists, especially if you start your hikes by 9 AM or so, which is highly recommended in any case given the temperatures that soar above 90°. We had originally planned a three-day trek, but after realizing how hot it was likely to be, we opted for day hikes, which turned out to be a wise decision. Even with our safari-style hats covering our necks, I still got a serious sunburn on my shoulders and upper back!

How to Find the Best Homeopathic Kit for You!

- Potency: Most of the available kits contain 30C potency remedies. I definitely don't recommend anything lower, even if you did find it. If you are a homeopath or are very certain of your acute and first-aid prescriptions, you could consider a 200C kit. But, over 20 years and thousands of kits sold, we have never been tempted to make kits higher than 30C. And, though we do have a multi-potency kit with potencies of 200C, 1M, and sometimes 10M, we use it mainly as our homeopathic pharmacy away from home when we are in Chile. We have found our 30C remedy to be fine. Of course, you need to choose the right remedy!
- Number of remedies: It has never made sense to us to offer a 36-remedy kit. Ours has contained 50 remedies from the beginning. We chose carefully which remedies to include and they go along with our two books: *Homeopathic Self Care: The Quick and Easy Guide for the Whole Family* (nearly 500 pages covering 70 conditions) and *The Savvy Traveler's Guide to Homeopathy and Natural Medicine* (233 pages, 68 conditions). The kit weighs one pound; the book is very lightweight and compact. You do *not* want to find yourself out on the trail or the road knowing just which remedy you need but not having it in your kit. The additional 14 remedies can make a big difference. That's why we included them.
- Why take our or another book and kit with you on your travels? I apologize for being blunt, but it is a no brainer. We talk about trip savers and life savers in these books. The probability of your using these remedies and of needing the book to figure out when and how is very high. On the off chance that you don't injure yourself or get sick on a particular trip, someone else around you will. I am talking about *seventy* (70!) conditions covered by a mini-medicine chest with few, if any, side effects! Safe for you, your kids, your pets, your friends, and travel buddies who just happen to hear that you might be able to help them! And let me discourage you from just taking the book (no kit) or just the kit (no book). Unless you happen to be me/us (who *wrote* these books!), there is no way to remember all of that information.
- And if you don't believe the remedies in the kit could work, just try the *Arnica* the next time you get a bruise or a sprain. Then tell me what happens!
- How about putting together your own kit? You could, but why do so when remedies in kits cost $2 each maximum, most last a lifetime, and, you can always contact the manufacturer for a replacement remedy, such as *Arnica.*
- One other thing: If it were me and you plan to use this or a similar kit at home as well as on the road, get *both* of our books mentioned above. The large book is full of charts, icons, and even some quizzes, to *teach* you how to self-treat for acute problems. And our travel book is packed with practical info about how to stay healthy on the road – everything from protecting your skin and your stuff to purifying your water. Plus, it's a fun travelogue to entice you to visit destinations.

To buy our kit/books: I am thrilled to report that our recently hacked website (!) is now fixed. Purchase through our website: https://healthyhomeopathy.com/product-category/kits/ or call Sandy at our office; leave a message at 360-322-4996. You can also buy from Amazon (search Homeopathic Remedy Kit: 50 commonly used remedies by NCHM).

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We have had significant challenges the past year listing our kit on Amazon, which was surprising to us after years of successful kit sales. Apparently, it is available again there. If you do buy it there, we would be very grateful if you could write us a review to help us move back to an earlier page!

Other Travel Items

So, I will assume that you have your homeopathic travel kit covered, and I will focus instead on other items that you may not have thought to carry with you.

1. *Sunscreen*: We cover this in depth in *The Savvy Traveler's Guide to Homeopathy and Natural Medicine: How to Stay Healthy Wherever You Go!* In a nutshell, there is considerable controversy as to whether the chemicals common to many sunscreens, especially retinyl palmitate, may, in fact, *cause* skin cancer. Now that's a scary thought! Your safest bet is to stay current with the Environmental Working Group's website, www.ewg.org, which publishes ongoing research on the safest sunscreens for the whole family. The bottom line is to use that messy white cream containing zinc oxide. Not attractive, but it does the job. Our recent favorite has been a Badger sunscreen, widely available.
2. *Sun hats*: We took several day hikes, one of which was six hours round trip with no shade. It must have been 90-plus° and we baked. We had thought ahead to take our lightweight, safari-style hats with the extra material in the back to cover the neck and upper back. These are also invaluable when you are on the water for hours at a time, as we were while ferrying and boating to the tropical island of Boipeba.
3. *Chill Outs*: These handy, little, lightweight brainstorms go around your neck to keep you cool (at least cooler) in excessive hot, dry heat. They go by many names, including Australian Cool Snakes. You need to leave them soaking for half an hour or more in a sink filled with cold water before putting them on. They contain water-absorbing crystals which cut the heat. Given the extreme dryness on our Brazilian hikes, we dipped them into streams at every opportunity to keep them moist.
4. *Battery-Operated Fan:* This is something I rarely use, but that is because we largely avoid going to hot, humid places. I found it handy this time on a stuffy ferry boat, though the better solution was riding outside in the open breeze. It is also invaluable in small spaces filled with tobacco smoke. Fortunately, with the increased awareness over the years, that rarely happens – a far cry from those buses in Nepal and elsewhere years ago filled with the locals smoking and no opening windows. We try, on long bus rides, to sit by an opening window, but that isn't always an option. And there are lots of buses where the A/C isn't working or strong, but the windows don't open.
5. *A Quick, Healthy, Non-Melting Snack:* We are not vegan and gluten-free like a number of contemporary travelers, especially millennials. But we want to carry along something delicious and nutritious in a pinch. Trying out the local delicacies is a great idea, but we try to stuff some protein bars in our luggage for those hypoglycemic moments! Our latest fave is the Peanut Butter Chocolate Chip Zing Bars. Besides being yummy and easy to pack, they don't melt like some of their chocolate-covered bars. They're also handy to tuck into a PFD (personal flotation device) while kayaking!
6. *Ear Plugs:* I can happily recommend the thick, blue ear plugs that are touted as the best ever. We got ours online from www.earplugsonline.com. The true test has been during Zumba classes here in Chile where the music is turned up to an ear-splitting volume! They passed the test with flying colors. How Latinos can endure years of Zumba classes with the music turned up to "full" without going deaf by their early 20s, I will never know.
7. *Bug Repellant:* Again, I refer you to the *Savvy Traveler* (Bugs Be Gone, page 48), but there may be even more recent products and info. We avoid DEET at all costs. We have not yet been to southern Africa and may relent, but I still equate DEET with poison. Permethrin sprayed on clothing (I haven't tried the clothing sold with infused Permethrin because I use my travel clothing year after year) did work years ago on our Alaska kayaking trip, but it is messy. temporary, and a hassle. Needing to purchase a new hiking shirt, I did a bit of research yesterday on whether blue does in fact attract more mosquitoes. It seems that any dark color calls to the buggers, blue or not. There are a number of good aromatic products containing citronella and eucalyptus, but we avoid them because they can antidote homeopathic remedies. I prefer to only use repellant when absolutely necessary, even though mosquitoes love me. We were told prior to our Brazil retreat to put on sunscreen preventively whenever we went out, and it turned out that I got maybe one bite in a week and never needed to use the small, backpacking size vial of repellant that I had picked up at REI.
8. *Bug Hat:* This is something we picked up prior to a trip to Ayer's Rock in the middle of Australia, where the black flies swarm on your back in droves. It looks like a regular baseball cap, but it has a net that rolls up into a little snapped compartment above the visor. They were a godsend at the time, but we've rarely used them since.
9. *Hand-washing supplies:* Forget the travel clothesline…. I've always managed to find places to hand the few clothes I wash out in a pinch. But what is invaluable is either a small container of Dr. Bronner's liquid soap (my standby) or of a different alternative sold with backpacking supplies like Campsuds. Personally, I love the minty smell of Dr. B's, and it takes literally a few drops per sink load. And don't forget one of those flat, universal sink stoppers since many hostels/hotels/guest rentals do not have drain plugs for bathroom sinks. I forgot mine on our first stop in Brazil and missed it the rest of the trip.
10. *Immune Support:* We recommend two supplements to our patients (available from our office) – Immune a Day and Olive Leaf Relief. I carry about 20 capsules of each in my purse wherever I go. At the first sign of a scratchy throat (my tell-tale indicator of a cold coming on), I take two of each one every two hours. I'd say about 80% of the time, it stops the cold in its tracks. You may have a different immune support of choice, whatever works! But take it often and immediately!
11. *Foot care shoes and products:* We learned about the Compeed brand (from the UK) of products when we prepared to hike the Camino de Santiago de Compostela (35 days) three years ago. We are about to hike a shorter version (12 days), of the Camino Portugués, and we plan to do our same daily routine. In addition to dozens of specialized blister and other foot-saving items, we used the deodorant stick lubricant for feet religiously every morning before hiking and will do so again. It is much less messy and healthier than Vaseline and works quite well preventively. Last time I suffered from toe numbness for three months post-Camino despite having what I considered great, broken-in hiking shoes. This time we are using Altra wide-box shoes with special REI-fitted insoles to hopefully avoid pressure on the toes and nails.

12. *Anti-Theft Protection:* Rumor has it that Brazil is a hotbed of theft, especially San Paolo and Rio. The lovely Brazilian Wwoofers (Willing Workers on Organic Farms) who stayed with us for a month this past November warned us about being especially careful during our travels there. We went online to find some chilling videos of the stealthy, remarkably quick young Brazilians who can snatch cell phones, packs, and wallets in the flash of an eye. I remember one agile jumper who grabbed a phone out of the hand of a passenger on a bus that happened to be stopped in the street! Having had my purse stolen outside a Chilean airport a year ago when I was attending to our golden retrievers (which contained my US and Chilean cell phones, external hard drive, cash, and more – though, thankfully, *not* passports and credit cards which were in my money belt), I did *not* want to be a target again. So, Bob and I bought special RFID (non-hackable) wallets and passport sleeves. We bought cheap decoy wallets to surrender in a pinch. We had (uncomfortable and not very useful) thigh money belts made by our Chilean seamstress. And, probably the most effective prevention, we were ultra-watchful about using a cell phone/camera. The only other thing that may have been useful is to buy one of those daypacks that foil theft (we used our small day-hiking packs with water bladders). No thefts at all in Brazil, but we were robbed in Chile just before leaving on our trip! The thieves made off with our Patagonia jackets and my tried-and-true backpacking clothes (!!) and would have taken more (they had our TV unplugged and my Zumba shoes ready to go) had we not come home unexpectedly! One last reminder: during our three weeks in Brazil, two were in places without cash machines! And there were no places to change money. That's a good thing to check out in advance!

Healing with Homeopathy

Happy, Safe Travels!

Part of the wonder and surprise of travel is not knowing what is around the corner. But travel smart and safe. There are many unpredictable predicaments that can arise. A close friend fell on a sidewalk on Kauai a week ago and ended up in a Seattle hospital with a fractured cervical vertebra! As we age, we need to remember to take extra care of ourselves on a daily basis with diet, supplements, prevention on all levels, to hopefully extend our fruitful travels long into our golden years. My travel heroine is a good friend from Whidbey Island, Meg Petersen, who is still hiking in Nepal into her mid-nineties! She may need a Sherpa, but so would I!

Judyth Reichenberg-Ullman and Robert Ullman are licensed naturopathic physicians, board certified in homeopathy. We have written eight books on homeopath, including *The Savvy Traveler's Guide to Homeopathy and Natural Medicine: Tips to Stay Healthy Wherever You Go*, as well as *Mystics, Masters, Saints and Sages – Stories of Enlightenment*. We also have an app: Natural Travel Doctor. Apple version: https://tinyurl.com/l7song8 and Android: https://tinyurl.com/m7cnexh**.** We are more passionate than ever about homeopathy, and we never seem to tire of traveling.

We practice in Edmonds, Washington, and by Skype. The Edmonds office address has changed, as you will see on our website. We live on Whidbey Island, Washington, and in Pucón, Chile. Visit our website www.healthyhomeopathy.com. Please friend us on Facebook at Healthy Homeopathy. Unfortunately, we have been recent victims of Chinese computer hacking, but, hopefully, our site will be recovered and back up very soon! Call us at 425-774-5599 or email us at drreichenberg@gmail.com or drbobullman@gmail.com.

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Editorial

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was significantly higher with DCC (41.8% vs. 20.6%; p = 0.01), but there was no difference in the proportion of infants with symptomatic polycythemia or in those who required partial exchange transfusions.[8]

Experts Now Recommend Delaying Cord Clamping

In January 2017, the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists issued a new set of recommendations regarding the timing of umbilical cord clamping. The report stated:

> Delayed umbilical cord clamping appears to be beneficial for term and preterm infants. In term infants, delayed umbilical cord clamping increases hemoglobin levels at birth and improves iron stores in the first several months of life, which may have a favorable effect on developmental outcomes. There is a small increase in jaundice that requires phototherapy in this group of infants. Consequently, health care providers adopting delayed umbilical cord clamping in term infants should ensure that mechanisms are in place to monitor for and treat neonatal jaundice. In preterm infants, delayed umbilical cord clamping is associated with significant neonatal benefits, including improved transitional circulation, better establishment of red blood cell volume, decreased need for blood transfusion, and lower incidence of necrotizing enterocolitis and intraventricular hemorrhage…. Given the benefits to most newborns and concordant with other professional organizations, the American College of Obstetricians and Gynecologists now recommends a delay in umbilical cord clamping in vigorous term and preterm infants for at least 30-60 seconds after birth.[9]

These new recommendations seem to validate (albeit belatedly) the wisdom of Mother Nature. That is, if the cord continues to pulse for a period of time after delivery, it may be doing so for a reason; and it may be unwise to interfere with the placenta's attempt to give the baby one final gift. There is still no agreement on the optimal timing of cord clamping, which has varied between one minute and five minutes in various studies. There seems to be something inherently logical about the midwives' practice of waiting (if possible) until the cord has stopped pulsing.

Alan R. Gaby, MD

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Delaying Umbilical Cord Clamping: A Traditional Practice Whose Time Has Come

Thirteen years ago, I wrote an article in the *Townsend Letter* suggesting that many infants could benefit if obstetricians would adopt a practice that is common among midwives – delaying the clamping of the umbilical cord after the baby is born. More than a decade later, the mainstream obstetrical community has finally acknowledged the importance of giving newborns extended access to the placental blood supply.

At the time a baby is born, the placenta contains a relatively large amount of blood. If the cord is allowed to remain open, much of this blood is delivered to the baby through the umbilical cord. The volume of this placental "transfusion" amounts to approximately 40 ml of additional blood per kg of body weight.[1] This blood provides about 75 mg of extra iron, an amount sufficient to meet the baby's iron needs for more than three months. Iron deficiency is one of the most common nutritional problems during the first year of life. In addition to being a component of hemoglobin, iron is essential for brain development. A deficiency of iron during this critical period can result in impaired myelination in the central nervous system[2] and permanent impairment of brain function.[3] In addition, cord blood is rich in stem cells, which are capable of differentiating into oligodendrocytes (which play a role in myelin formation).[2] Moreover, the delivery of highly oxygenated fetal hemoglobin from the placenta to the baby may have a favorable effect on the infant's health in the early postnatal period.

Midwives have traditionally delayed cord clamping until the cord stops pulsing, or for at least three minutes after delivery. Obstetricians, on the other hand, have traditionally clamped the cord almost immediately, so that the baby can be assessed, weighed, and readied for whatever emergency interventions might become necessary. The reluctance of obstetricians to delay cord clamping has also been due to a concern that doing so could increase the risk of neonatal hyperbilirubinemia. When I wrote my article in 2006, there was evidence that delaying cord clamping can decrease the prevalence of iron deficiency and iron-deficiency anemia at six months of age.[1] However, as of 2012, the official position of the American College of Obstetricians and Gynecologists was that the evidence "is insufficient to confirm or refute the potential for benefits from delayed umbilical cord clamping in term infants…."[4]

Since that time, a number of studies have provided additional evidence about the benefits of delaying cord clamping. Some of those studies are described below.

New Research

In a study of 540 late preterm and term infants born in Nepal who were at high risk of iron deficiency, delaying cord clamping significantly decreased the prevalence of anemia and significantly improved measures of neurodevelopment at 12 months of age.[5,6]

Seventy-three infants born in the US at term were randomly assigned to delayed cord clamping (DCC; mean, 2.87 minutes) or immediate clamping (ICC; mean, 28 seconds). In patients who underwent cesarean delivery, milking of the cord five times was the proxy for DCC. At four months of age, the mean serum ferritin concentration was significantly higher in the DCC group than in the ICC group (96.4 vs. 65.3 ng/dl; $p = 0.03$). In addition, infants in the DCC group, as compared with those in the ICC group, had greater myelin content in brain regions associated with motor, visual, and sensory processing/function (indicating better functional development of the brain).[7]

One hundred thirteen small-for-gestational-age infants born in India at 35 weeks of gestation or later were randomly assigned to delayed cord clamping (DCC; at 60 seconds) or early cord clamping (ECC; immediately after birth). At three months of age, the median serum ferritin level was significantly higher with DCC than with ECC (86 vs. 50.5 ng/ml; $p = 0.01$). Fewer infants had iron deficiency with DCC than with ECC; (23.6% vs. 47.7%; $p = 0.03$).The proportion of infants with polycythemia

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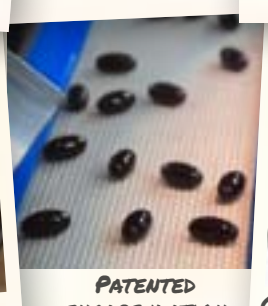
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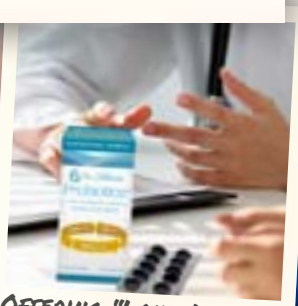
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