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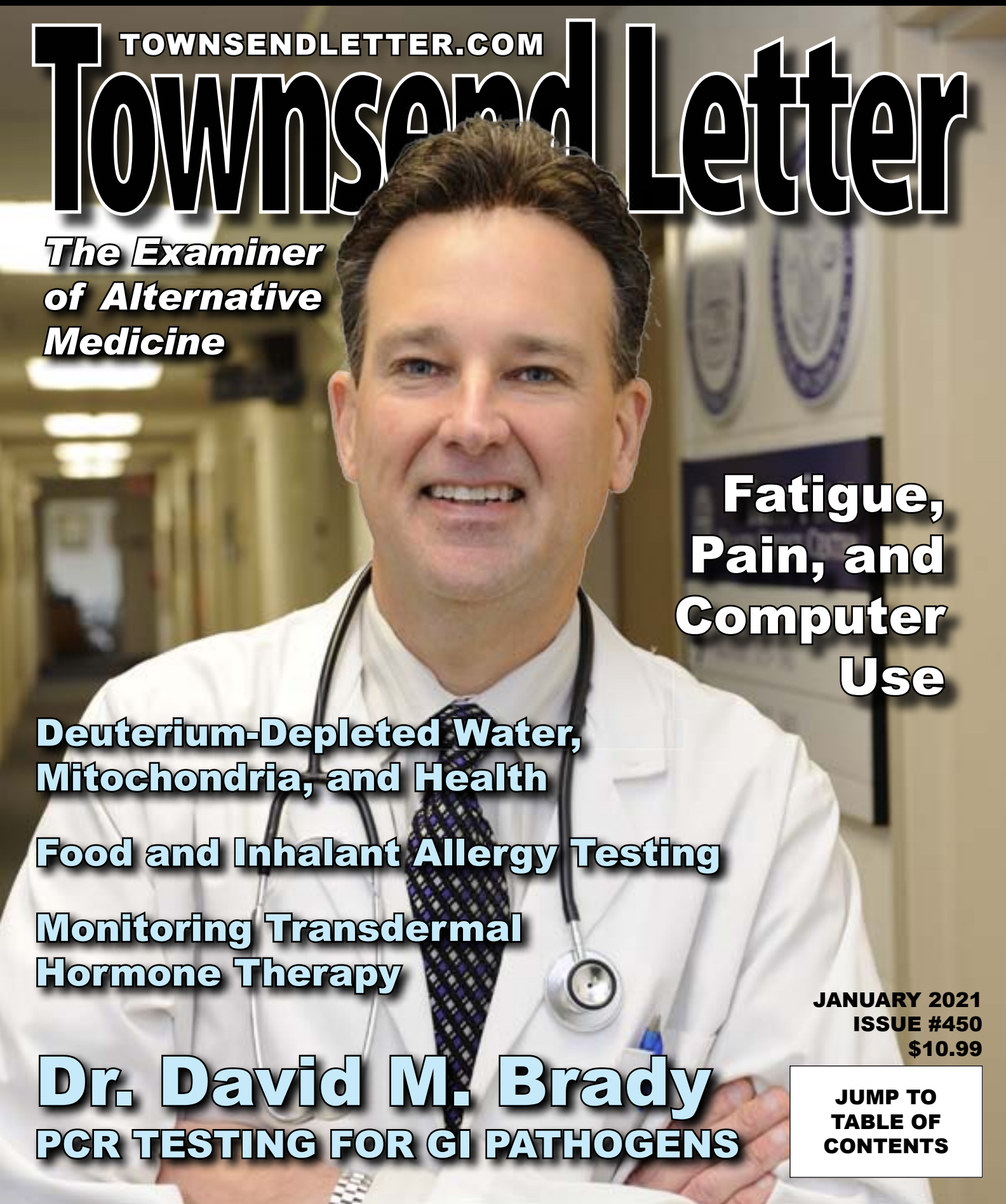

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From the Publisher

The Fragile State of COVID-19 Science

As this is being written a third surge of COVID-19 is developing in the US and Western Europe. Curiously, the pandemic is almost non-existent through most of Asia (except India) and Africa. Despite compliance with social distancing, masking, quarantine, and hand hygiene here and internationally, only in China and Southeast Asia has COVID-19 quiescence facilitated a return to normalcy. The uptick of hospitalizations in the central and mountain states is particularly worrisome given the approaching flu season expected to last for months. As the incidence of the Coronavirus leads to even greater numbers of cases, more lockdowns will be ordered threatening business survival and in-person education. The hope for a vaccine still appears months away – in other words, the public is expected to prevent the virus solely by social isolation and masking. There is no public health advocacy for the use of supplementation with vitamin D or C or any other nutrient or herbal. While hospital treatment has centered on drug therapies, including remdesivir and dexamethasone as well monoclonal antibodies, intravenous ascorbic acid remains largely unused.

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Letter from the Publisher

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The saga of the drug hydroxychloroquine in the treatment of COVID-19 during the past year demonstrates the fallibility of medical science. In May the *New England Journal of Medicine* and *Lancet* independently published reports based on the hospital records of nearly 100,000 patients treated with hydroxychloroquine for their COVID illness. Because these papers conclusively found that hydroxychloroquine offered no benefit for COVID-19, the World Health Organization cancelled all other studies of the drug. However, it was later revealed that a small company, Surgisphere, headed by one physician was responsible for pooling the data of nearly 700 hospitals in the midst of worldwide pandemic lockdowns. When Surgisphere was asked to produce the raw data from the hospitals, it was unable to do so. *NEJM* and *Lancet* promptly retracted the studies, but how did this fiasco pass through the peer reviewers? Even though hydroxychloroquine has not proven to be an effective drug in managing COVID-19, the shenanigans of a few rogue characters and the cluelessness of medical peer reviewers bodes poorly for COVID science.

The genomic structure of SARS-CoV-2 has created ongoing controversy. Originally in January 2020 a bat virus genetic sequence, RaTG13, was reported to be the genome of the virus causing illness in Wuhan patients. However, the viral genome identified as causing COVID-19, SARS-CoV-2, also sequenced in January was distinctly different from RaTG13. The latter's genetic sequencing is a match for as much as 95% of the former's genome. But 95% match is not a match. The human genome is a 99% match for the chimpanzee's – obviously that 1% mismatch makes humans different from chimpanzees. What would we expect from a 5-10% difference in viral gene sequences? Entirely differently behaving viruses. More bizarre yet, a researcher at the Hong Kong School of Public Health, Dr. Li-Meng Yan, is convinced that the virus was manufactured in a laboratory.[1] The technology for manipulating a genomic sequence to create a manufactured virus would indeed be the work of a 21st century Frankenstein and CRISPR disc-jockey combined; simple genetic engineering would result in numerous errors thoroughly disrupting viral replication. Still Dr. Li-Meng makes the case that genetic engineering is a possibility. More likely it is a recombination of viral RNA occurring zoonotically in nature giving rise to SARS-CoV-2.

Despite the repeated insistence by public health authorities that the incidence of COVID-19 cases will be dramatically reduced by the public's fastidious wearing of masks, there have been no published randomized controlled trials (RCT) demonstrating its effectiveness. None of the papers touting the value of wearing a mask in preventing infection meet the standards of a controlled trial. Without an RCT one cannot assert that "science" is determining public health policy. Instead, wearing a mask is, at best, a hypothesis that appears to be sound but remains unproven. Of note, a RCT of the effectiveness of wearing a mask in preventing COVID-19 was completed in Denmark in 2020.[2] However, the paper's lead author, Christian Torp-Pedersen at the North Sealand Hospital, stated to the Danish media that the *Lancet*, *NEJM*, and *JAMA* all rejected the paper for publication. Torp-Pedersen refused to disclose the outcome of the study until it was accepted for publication. On November 18th, the Danish RCT mask study was published in the *Annals of Internal Medicine*.[3] The conclusion was that wearing masks did **not** significantly reduce the infection rate of COVID-19, but there was slight reduction in infection in the mask wearers compared to non-mask wearers.

The US expended considerable energy in locking down businesses during the pandemic obliging workers to work from home – good for IT workers and professionals, not so good for entertainment, travel, tourist,

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Letter from the Publisher

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and hospitality workers. Meanwhile, Sweden opted not to shut itself down effectively letting life go on much as normal through the pandemic. While Sweden's case rate was higher than other European nations early in the pandemic, it has been better than other European nations and the US currently. Public health authorities in Sweden and the US embraced the same "science" in deciding how to approach the pandemic; however, if pandemic science were sound, Sweden should have experienced a much worse outcome than it had. Still, China's no-nonsense, absolute isolation and quarantine policies achieved far better results compared to Sweden and the US. Science appears unable to explain these geographic differences.

Perhaps the most fragile science of all is the testing for COVID-19. The rt-PCR test amplifies a segment of the viral genome of the SARS-CoV-2 virus. The test is touted to be highly specific – capable of distinguishing infection with other coronaviruses including a virus that causes the common cold. But that specificity has come into question. If a non-COVID-19 coronavirus has a partial sequence that matches SARS-CoV-2, the test amplifies the matching sequences resulting in a positive test. As much as authorities would like to claim otherwise, specificity is not 100% – at best it is 95%. Much more important is that a positive PCR test does not prove viral load and infection – how many well individuals without COVID-19 infection have had a positive test? Of course, many individuals are sick and do have a valid case of COVID-19, and not a few of these individuals become desperately ill requiring intensive care hospitalization. However, public health authorities treat every positive test as a COVID-19 case, an infection. There are no confirmatory tests to demonstrate infectivity. This has led to a wit calling the pandemic not a COVID-19 pandemic but a COVID-19 ***test*** pandemic.

Recently I was confronted with a situation involving a staff member who had been exposed through a chain of contacts to an individual with a positive COVID-19 PCR test. The individual who had tested positive was not ill. The following day the individual who had tested positive underwent repeat testing. The second test was negative. If rt-PCR testing has high specificity and sensitivity, how could it be positive one day and negative the next? Clinical information reported by the individual who had originally tested positive was that he remained well. My own rule of thumb is that if an abnormal test is repeated and the subsequent test returns normal, the normal test result is assumed to be correct. Admittedly a better approach would be to repeat the test a third time. However, it is very discouraging that there is no test to confirm infectivity. We are obliged to treat a positive PCR test as an actual case of COVID-19. As the above case illustrates this individual did not have COVID-19 illness. However, the positive test will be entered into the state registry and will be counted as one of the now nearly 10 million US cases.

While we await less fragile science that will enable us to prevent and treat COVID-19, we should remember that the disease poses the greatest danger in those patients who have underlying medical conditions. Mary Budinger argues that we can all reduce our risks for developing the coronavirus by giving up our diets of processed high-fat, salty, sugary foods and beverages. Her article available online only on www.townsendletter.com is titled, "COVID – A Wakeup Call for Our Love of Mac and Cheese." The science examining the effect of poor nutrition and junk food consumption on general health is extensive and sound. It makes sense this winter to take charge of one's health by cleaning up and regimenting one's diet.

Deuterium-Depleted Water

Over the years I have been asked to consider different forms of water that have been touted to alter and improve health. Some of the proprietary water formulations were simply added to the water bottle. Somehow the added formula changed the "structure" of the water or the "energetics" of the water. Other products provided the modified water in liter bottles to directly consume. The most highly marketed modified water was alkaline water. The theory here is that alkaline water would increase overall body alkalinity, which was touted to be important for reversing abnormal body chemistry thought to be detrimental to one's health. Alkaline water has become very popular and is now available for purchase from many commercial sources. While the different water products and modified water preparations appear promising to benefit health, the reasoning justifying their use always seemed difficult to understand and without adequate clinical evidence of effectiveness.

Evaluation of toxicity remains a field that is generally outside the purview of routine lab evaluation and clinical diagnosis. Integrative medicine and naturopathy have focused on increased toxic metal and chemical burdens. Such assessment is not part of mainstream diagnosis but is readily measured with specialized tests. It is not unusual for patients to show increased levels of lead, mercury, and other toxic elements as well as various petrochemical, pesticide, and plasticizer components. The detoxification of toxic metals and chemicals is a key component of integrative and naturopathic protocols.

However, one toxin that has largely gone undetected is the heavy water component, deuterium. Deuterium poses serious health dangers, especially if its consumption exceeds safety thresholds. It has been of considerable concern in military operations that armament containing deuterium pose a major risk for soldiers and civilian populations. Much more concerning, according to Victor Sagalovsky, is the chronic consumption of water containing sub-lethal levels of deuterium. Deuterium accumulation does not pose a risk of major poisoning; instead it shuts down optimal mitochondrial production of ATP. Compromised mitochondrial functioning is a key factor in nearly all pathology. Restoration of mitochondrial functioning may only be accomplished if the water being consumed has been depleted of deuterium – not a process that can be achieved through filtration or distillation.

In this issue Sagalovsky describes the basics of deuterium chemistry and how one can produce water that is deuterium-depleted. The potential health benefit of routine consumption of deuterium-depleted water provides a rationale for its use. Clinical studies are needed to demonstrate its effectiveness in treatment and prevention of disease.

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Letter from the Publisher

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Cover Story: Lab Diagnostics and Dr. David Brady

While medicine makes technological advances daily, it is remarkable how skimpy the annual comprehensive lab exam remains. For most individuals the yearly physical includes a metabolic profile and lipid profile. After age 50 a check for blood in the stool is advised together with a mammogram in women and a PSA in men. Typically, a preventive exam does not even include a CBC or UA. Of course, once an individual is symptomatic, more laboratory and imaging tests are ordered. Missing in the preventive exam are studies of hormones, inflammatory markers, viral and bacterial antibodies, toxic metal and trace element levels, stool microbiome assessment, food allergies, petrochemical and pesticide measurements, as well as organic acid testing. Why in 2020 are these studies not part of the routine annual exam? Of course, the obvious answer is cost. Insurance companies and Medicare are limiting medical diagnostics to the bare bone testing needed for making a diagnosis.

But the "Catch-22" is you are not justified for doing a diagnostic test unless you know the diagnosis and ICD-10 codes, limiting the testing that is permissible. How do you justify a CBC test if you don't know if the patient has anemia? How do you justify *Mycoplasma pneumoniae* Ab testing without knowing whether the patient already had a bacterial infection? Right, since you don't know the diagnosis, you can't justify the ICD-10 code, so the lab test will not be covered by insurance. Specialty diagnostic labs offer unique testing outside the scope of legion laboratories generally not covered by insurance. Perhaps one of the key services provided by naturopathic physicians and functional medicine practitioners is to offer patients laboratory testing not authorized in mainstream medicine. Without such assessments one would never know about one's mold toxicity or deficient methylation functioning.

Dr. David Brady discusses in this issue molecular methods for studying the stool microbiome, a dramatic leap from the conventional test of stool ova and parasite study. While O&P offers rapid study for organisms already suspected, quantitative and real-time PCR testing detects comprehensively all bacteria, fungi, parasites, and viruses, many of which were not suspected. Brady's article discusses the pros and cons of other methodologies, including standard PCR, metagenomic sequencing, metatranscriptomic sequencing, 16S sequencing, and laser "desorption" mass spectrometry. Lab testing has come a long way beyond microscopic exam of giardia and *Clostridia difficile*. While gastroenterology may limit itself to doing colonoscopies and Cologuard® testing, integrative practitioners can objectively evaluate the microbiome with the latest molecular methodologies.

Jonathan Collin, MD

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Shorts

briefed by Jule Klotter
jule@townsendletter.com

Data Collection

In 2003, Centers for Disease Control (CDC) published handbooks for medical examiners and for physicians that described a national standard for recording cause of death on death certificates. Under these guidelines, co-morbidities causing death are listed in Part 1. Initiating factors, such as recent infections, are listed in Part 2. As Henry Ealy and colleagues explain in their article "COVID-19 Data Collection, Comorbidity & Federal Law: A Historical Retrospective," the 2003 guidelines underwent a peer-review process and public comment period before being accepted, which is required by federal law.

Instead of following these established guidelines, CDC changed the guidelines for reporting deaths on March 24, 2020, without peer-review or public comment. CDC adopted the Council of State and Territorial Epidemiologists (CSTE) COVID-19 Position Paper. CSTE is an independent, privately funded organization. The new guidelines said COVID-19 should be listed in Part 1 of the death certificate for any person who died with confirmed (tested positive) or probable (clinical and epidemiological support for diagnosis) COVID – regardless of underlying disease. Co-morbidities were moved to Part 2.

Under the new March 24 guidelines, 161,392 deaths are attributed to COVID-19 (using CDC data through August 23, 2020). Using the 2003 guidelines and the same CDC mortality data, 9684 deaths are attributed to COVID-19.

The authors say, "If the data being reported was indeed compromised by the CDC's perplexing decision to abandon proven data collection and reporting practices in favor of untested methods, then all public health policies based upon these inaccurate data must be reexamined."

Ealy H, et al. COVID-19 Data Collection, Comorbidity & Federal Law: A Historical Retrospective. *Science, Public Health Policy, and the Law.* October 12, 2020; 2:4-22.

PCR Ct Values and Clinical Practice

For months, public health agencies and the media have focused on the number of COVID-19 cases, defined by positive PCR tests. But how accurate are these tests? Do they reliably indicate infection? Reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) tests reverse transcribe viral RNA into DNA and then amplify/multiply the amount of nucleic acid. In an editorial commentary for *Clinical Infectious* Diseases, Michael R. Tom and Michael J. Mina explain, "…a fluorescence signal increases proportionally to the amount of amplified nucleic acid….If the fluorescence reaches a specified threshold within a certain number of PCR cycles (Ct value), the sample is considered a positive result." More cycles mean more amplification. Knowing how many cycles it takes before the test signals viral presence is important for interpreting results. A low Ct value indicates a high viral load in the sample: "The Ct value is inversely related to the viral load and every ~3.3 increase in the Ct value reflects a 10-fold reduction in starting material."

In their May 2020 commentary, Tom and Mina explain that knowing the cycle threshold helps to determine if a patient has a high viral load or a low viral load. High viral loads indicate that a person is infectious. The authors would like to see the Ct value–or at least a viral load range, such as high, medium, or low – reported in test results. But Ct value alone cannot indicate if a person is infectious because PCR does not differentiate between live virus and dead viral fragments that pose no threat. Consequently, clinical symptoms are important. Tom and Mina say, "Live virus is often isolable only during the first week of symptoms but not after day 8, even with positive RT-qPCR tests." Instead of relying on repeated testing, they suggest a "time-since-symptom-onset and time-since-symptom-resolution" approach in which the patient remains isolated for 10 days after symptom onset and three days after symptom resolution.

Three months after their commentary, *New York Times* journalist Apoorva Mandavilli wrote an article about cycle threshold and the PCR tests. She reported that most SARS-CoV-2 tests use up to 40 amplification cycles. A positive fluorescence signal after 20 cycles has a very different viral load than a positive signal after 39 or 40 cycles; yet both are treated as positive results. Laboratories and test manufacturers set the cycle threshold ranges – not the FDA or CDC. Mandavilli says that CDC has found "it is extremely difficult to detect any live virus in a sample above a threshold of 33 cycles."

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Shorts

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Simply lowering a test's Ct range reduces the number of positive results – and the lockdown measures and contact tracing associated with those results. As part of Mandavilli's article, New York's state lab provided data from July's test results. The lab reported 872 positive tests for the month, based on a threshold of 40 cycles. When the Ct threshold was reduced to 35, there were 497 positives (about 43% less). A Ct threshold of 30 cycles resulted in 323 positive cases (about 63% less). Epidemiologist Michael Mina told Mandavilli that he would set the threshold cutoff at 30 cycles or less. FDA is reportedly concerned that a lower cutoff would miss people who are newly infected and do not have a large viral load. Mina says that concern can be addressed by testing again after six or more hours to see if the Ct value (and viral load) has changed. Most COVID PCR tests now in use have a cycle threshold up to 40 cycles, according to Mandavilli.

Tom Jefferson and colleagues at the UK University of Oxford Centre of Evidence-Based Medicine are conducting an on-going review of studies that compare SARS-CoV-2 viability (by culturing samples) to Ct values. (Their review is a preprint "that has not been certified by peer review and should not be used to guide clinical practice.") The 29 studies in their fourth update show that greater infectivity is linked to testing of respiratory samples taken shortly after symptoms arise and to lower Ct values. High Ct values (weak positives) "are unlikely to be infectious." Five studies showed no culture growth in samples with Ct values of 35 or more.

It might be worthwhile to find out which PCR test your county or state is using and its Ct cutoff threshold.

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Mandavilli A. Your Coronavirus Test Is Positive. Maybe It Shouldn't Be. *New York Times.* August 30, 2020.

Tom MR, Mina MJ. To Interpret the SARS-CoV-2 Test, Consider the Cycle Threshold Value. *Clinical Infectious Diseases.* May 21, 2020.

Coronavirus Test Accuracy

During the pandemic, COVID-19 tests, according to FDA, are being approved under an Emergency Use Authorization (EUA): "An IVD [in vitro diagnostic] made available under an EUA has not undergone the same type of review as an FDA-approved or cleared IVD." As Jonathan Collin points out in this issue's "Letter from the Publisher," PCR tests amplify segments of the SARS-CoV-2 genome. Pathologist Sin Hang Lee, MD, director of Milford Molecular Diagnostics Laboratory (Milford, CT), says that CDC RT-qPCR test kits for SARS-CoV-2 use DNA probes that are only 25 bases long, which would not pass FDA's normal (non-EUA) requirement for nucleic acid-based molecular diagnostics for viral disease infections. He says, "Unconnected short DNA fragments may come from different sources in a complex human specimen." These fragments are not necessarily SARS-CoV-2 specific. Moreover, primers used in CDC test kits have reportedly given "false positive signals even in the absence of cDNA (no template control condition)."

Using Sanger sequencing (a tool approved by FDA to assess false test results), Lee tested 20 reference samples prepared by the Connecticut State Department of Public Health. The state lab had tested these samples using the CDC test kit to verify their accuracy. Reference samples are used by local laboratories to guide their development of their own SARS-CoV-2 PCR tests. Among the 10 negative reference samples, two tested positive. Among the 10 positive reference samples, three tested negative. FDA requires EUA tests to have 95% positive and negative agreement with the reference samples. Only 15 out of 20 samples (75%) that Dr. Lee tested were correct. "False-negative laboratory test results allow infected patients with mild clinical symptoms to spread SARS-CoV-2 among susceptible persons," says Lee. "False-positive test results may lead to placement of non-infected persons in the same isolation rooms with COVID-19 patients; eventually the non-infected individuals may become true-positive patients." Moreover, false positive results "can easily create unnecessary panic resulting in negative impacts on local economies."

CDC Coronavirus Test Kits Generate 30% False Positive and 20% False Negative Results – Connecticut Pathologist's Newly Published Findings Confirm. Business Wire. July 17, 2020.

FDA. Fact Sheet for Healthcare Providers. Molecular Laoratory Developed Test (LDT) COVID-19 Authorized Tests.

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Contact Tracing

In October 2020, United Airlines began testing a digital health pass that shows a passenger's COVID-19 test results (and, eventually, vaccine status) as part of a global pilot program, supported by the World Economic Forum and The Commons Project (Switzerland). The health pass is supposed to facilitate international travel during the pandemic as countries look for ways to restrict viral spread. COVID-19 test results are uploaded from certified labs to patients' smartphones. Those who are considered virus-free receive a verified QR (quick response) code on their smartphones that airline staff and border officials scan.

Mayo Clinic and Safe Health Group (Los Angeles, California) are working on HealthCheck, a smartphone and desktop app that also provides health status verification. They see HealthCheck as a way of permitting large gatherings with people who can verify that they have been tested or have received a coronavirus vaccine. Like the airline health pass, this app gives a QR code "to show your employer, your school, or to show before attending an event."

The American Medical Association (AMA), Centers for Disease Control (CDC), and Council of State and Territorial Epidemiologists (CSTE) are working on the eCR collaborative. The eCR collaborative seeks "to focus on COVID-19 reporting using electronic case reporting infrastructure that's in place to develop an eCR app that can be used by [electronic health record] vendors."

In each of these programs, access to transportation, work, education, and/or public gatherings are tied to coronavirus tests (and possibly other tests?) and vaccines. China already uses digital QR code health passes for public transporation.

Harvard lawyer and privacy expert Elizabeth M. Renieris along with pediatrician Sherri Bucher, MD, and Christian Smith,

an IT expert, believe that these digital health certificates "pose an unjustified interference with, and serious threat to, our fundamental human rights and civil liberties, in violation of the principles of legality, necessity, and proportionality." In their May 18 position paper, they say "these artifacts could interfere with our right to privacy; freedoms of association, assembly, and movement; our rights to work and education; and otherwise seriously limit our freedom and autonomy, even where not compulsory." They raise questions about legality, necessity, and proportionality. Are there precise legal guidelines for the use of this technology? Is the benefit of employing these certificates sufficient to justify the negative effects? Can the information be hacked? Will health passes actually reduce the spread of coronavirus? As I noted above, the accuracy of COVID-19 has been questioned. In addition, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, recently stated that the first coronavirus vaccines will not prevent infection; they will just lessen or prevent symptoms.

At this time, the World Health Organization advocates for proof of vaccination for just one vaccine-preventable disease: yellow fever. This severe, mosquito-borne, tropical viral disease has been studied for several decades. A vaccine has been in use for 80 years and gives lifelong immunity. The "Yellow Card" that verifies vaccination is required to travel to 40 countries/territories in sub-Saharan Africa and South America in an effort to keep the disease from spreading to non-endemic areas. This health certificate is not meant to prevent the spread of an infection that is already widely disseminated in the local population – nor does it affect daily life.

The authors say:

> …we would be skeptical of any solutions put forward by private sector actors, without significant public sector, civil society, and other stakeholder engagement. The prospect of severely curtailing the fundamental rights and freedoms of individuals through ill-thought-out plans for 'immunity passports' or similar certificates, particularly ones that would leverage premature standards and a highly experimental and potentially rights-infringing technology like blockchain, is beyond dystopian.

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Disclosure: The *Townsend Letter* publishes information about alternative medicine written by researchers, health practitioners, and patients. As a forum for the entire alternative medicine community, we present information discussing a wide variety of alternative and integrative medicine practices. In addition to publishing original research and literature abstracts and reviews, we encourage case studies and anecdotal reports. Detailed anecdotal reports are not viewed as proof but as possibilities that need further investigation. All authors are requested to submit their reports to other professionals for review.

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

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-Karen Russell, M.A., HHC Gerontologist and Holistic Health Counselor

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Rebecca Harder runs the Taos Hyperbaric Wellness Center, and Colon Care Hydrotherapy Clinic in Portland, and is the author of ***"Gastra Girl: Saving America One Colon at a Time"*** which is an inspiring compendium of holistic health articles on hyperbaric oxygen, ozone, far infrared saunas, vaccines, etc., and includes articles written by Paul Harsh, Dietrich Klinghardt, Sherry Tenpenny, and Russell Blaylock and others. Chapter 10 is entitled, "Why Infrared Saunas are an Absolute Necessity for Everyone." She intones, "I realized the Relax Sauna was head and shoulders above all the rest to recommend."

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Literature Review & Commentary

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

Widespread Use of Medications That Cause Weight Gain

A survey of 11,055 US adults participating in the National Health and Nutrition Examination Survey (NHANES) from 2013 to 2016 revealed that 23% had taken at least one drug during the previous 30 days that has obesity as a side effect. Drugs that are considered obesogenic include all glucocorticoids, beta-blockers, and antihistamines; and some antidepressants, antipsychotic agents, antidiabetic medications, and progestin-only oral contraceptives. The use of these drugs was more common among people who were obese than among those who were not obese. The author of this report suggested that the association may be "bidirectional," in that increasing use of obesogenic drugs may contribute to obesity, while at the same time, the more weight people gain, the more likely they are to need additional medications, particularly those that are obesogenic.

Comment: Obesity has become more common in the US during the past several decades. Approximately 36% of US adults are considered obese (body mass index ≥ 30 kg/m^2) and 69% are considered overweight or obese (body mass index ≥ 25 kg/m^2). While many factors contribute to excess body weight, the use of obesogenic drugs appears to be an important and often overlooked factor. Diet, exercise, and other lifestyle modifications are often effective in the treatment of conditions for which obesogenic drugs are prescribed (such as diabetes, depression, hypertension, and allergies). Moreover, these interventions may themselves help promote weight loss. Practitioners should be aware of the potential for medications to cause weight gain, and they should consider alternative treatments when appropriate.

Zoler ML. Nearly 25% of US adults take an obesogenic drug. *Family Medicine*. 2020(February):13.

Alpha-Lipoic Acid Promotes Weight Loss

Eighty-one overweight or obese adults (mean age, 39 years; mean body mass index [BMI], 34.6 kg/m^2) with elevated plasma triglycerides (100 mg/dl or higher) were randomly assigned to receive, in double-blind fashion, 600 mg of (R)-alpha-lipoic acid (R-ALA) or placebo once a day (30 minutes before breakfast) for 24 weeks. Participants were advised not to change their diet or physical activity. At 24 weeks, compared with placebo, R-ALA resulted in a small but significant decrease from baseline in mean BMI (-0.6 vs. +0.2 kg/m^2; p 0.004). Compared with placebo, R-ALA had no significant effect on triglyceride levels.

Comment: ALA is synthesized by humans and also occurs in small amounts in a wide range of foods. It functions as a cofactor for certain enzymes involved in mitochondrial energy production. In a study in rodents, ALA prevented the development of obesity by reducing food intake and increasing energy expenditure. ALA is commercially available as the R-isomer and as a racemic mixture of the R- and S-isomers. While R-ALA is the only isomer synthesized by humans and the only isomer that functions as a cofactor for mitochondrial enzymes, most clinical research has used racemic ALA. In previous randomized controlled trials, supplementation with racemic ALA in dosages of 300-1,800 mg per day resulted in modest weight loss in overweight or obese adults. Similar modest benefits were seen in the present study using the naturally occurring form of ALA.

Bobe G, et al. A randomized controlled trial of long-term (R)-alpha-lipoic acid supplementation promotes weight loss in overweight or obese adults without altering baseline elevated plasma triglyceride concentrations. *J Nutr*. 2020;150:2336-2345.

Severe Vitamin C Deficiency in Patients with Advanced COVID-19

Plasma vitamin C levels were measured in 18 patients (mean age, 59 years) in Barcelona, Spain, who were hospitalized with acute respiratory distress syndrome secondary to COVID-19 infection. Seventeen patients (94.4%) had undetectable vitamin C levels, and in the other patient the level was below normal.

Comment: Vitamin C plays a role in immune function and in maintaining tissue integrity, both of which are important factors in the body's response to infections. Vitamin C also has anti-inflammatory activity, which might help decrease the massive inflammatory response (cytokine storm) that is thought

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to contribute to morbidity and mortality in advanced cases of COVID-19. Vitamin C levels in leukocytes fall dramatically within 24 hours of the onset of a cold, to levels seen in people with scurvy.[1] This decline is presumably due to increased vitamin C utilization for implementation of tissue defense mechanisms.[2] Multi-gram daily doses of vitamin C, beginning at the first sign of illness, appear to be needed to prevent this decline from occurring. Similar declines in vitamin C levels have been observed in association with other types of infections. In patients with severe infections (sepsis), intravenous doses of more than 3 g per day are needed to normalize plasma vitamin C levels.[3] Anecdotal evidence suggests that intravenous administration of 1.5 g of vitamin C every six hours improves outcomes in patients hospitalized with COVID-19. A randomized controlled trial examining the effect of vitamin C against COVID-19 is currently being conducted in China.

Chiscano-Camon L, et al. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Crit Care*. 2020;24:522.

N-Acetylcysteine for Retinitis Pigmentosa

Thirty patients (mean age, 48 years) with moderately advanced retinitis pigmentosa received 600 mg (group 1), 1,200 mg (group 2), or 1,800 mg (group 3) of N-acetylcysteine (NAC) twice a day for 12 weeks and then three times a day, if tolerated, for 12 weeks. There were nine treatment-related gastrointestinal adverse events that resolved spontaneously or with dose reduction. During the 24-week treatment period, mean best-corrected visual acuity improved significantly by 0.4, 0.5, and 0.2 letters per month in groups 1, 2, and 3, respectively. Macular sensitivity improved significantly in group 3, but not in groups 1 and 2.

Comment: In retinitis pigmentosa, rod photoreceptors degenerate from one of many mutations, after which cones are compromised by oxidative stress. NAC has antioxidant activity and may therefore mitigate oxidative damage to cones. In a mouse model of retinitis pigmentosa, NAC increased cone function and survival. In the present study, treatment with NAC improved best-corrected visual acuity in patients with moderately advanced retinitis pigmentosa, presumably by improving cone function.

Campochiaro PA, et al. Oral N-acetylcysteine improves cone function in retinitis pigmentosa patients in phase I trial. *J Clin Invest*. 2020;130:1527-1541.

Biotin Interferes with Vitamin D Testing

The addition of biotin to serum samples at a concentration of 586 µg/L resulted in a false elevation of serum 25-hydroxyvitamin D by an average of 6.6 ng/ml, when biotin-streptavidin based assays were used. The presence of biotin did not affect the results when the assay method involved chromatographic steps or was antibody-based. At the time of this report, about 25% of labs were using a biotin-streptavidin based assay method for 25-hydroxyvitamin D.

Comment: Previous studies found that high-dose biotin can interfere with laboratory tests for thyroid function, testosterone, estradiol, progesterone, dehydroepiandrosterone (DHEA) sulfate, prostate-specific antigen, parathyroid hormone, luteinizing hormone, follicle-stimulating hormone, vitamin B12, and cardiac troponins (which are considered the gold standard for diagnosing acute myocardial infarction). The present study indicates that serum 25-hydroxyvitamin D should be added to the list of tests that may produce erroneous results in the presence of biotin. Patients receiving high-dose biotin (such as 2 mg per day or more) should be advised to discontinue the supplement for at least 72 hours before blood tests are done.

Carter GD, et al. Biotin supplementation causes erroneous elevations of results in some commercial serum 25-hydroxyvitamin D (25OHD) assays. *J Steroid Biochem Mol Biol*. 2020;200:105639.

More Vitamin D May Be Beneficial During Pregnancy

Six hundred twenty-three white pregnant women in Copenhagen, Denmark, were randomly assigned to receive, in double-blind fashion, 400 IU or 2,800 IU per day of vitamin D, beginning in week 24 of pregnancy and continuing until one week postpartum. Five hundred seventeen children were available for evaluation at six years of age. Compared with 400 IU per day, 2,800 IU per day resulted in significantly higher values for each of the following in the children: whole-body bone mineral content, whole-body-less-head bone mineral content, and bone mineral density of the head. The largest effect was in children whose mothers had pre-supplementation 25-hydroxyvitamin D levels below 30 ng/ml and among winter births. In post hoc analysis, the incidence of fractures was nonsignificantly lower by 38% with 2,800 IU per day than with 400 IU per day ($p = 0.08$).

Comment: This study found that 400 IU per day of supplemental vitamin D during pregnancy was not sufficient to promote optimal bone development in the children of Danish women. A previous study compared the effect of 400 IU and 4,400 IU per day of vitamin D during pregnancy in US women who had or whose partner had a history of asthma, eczema, or allergic rhinitis (which confers an increased risk of asthma to the offspring). In that study, the proportion of children who developed asthma or recurrent wheeze by 3 years of age was 20% lower in the high-dose group than in the low-dose group (24.3% vs. 30.4%; $p = 0.051$).[4] The average dietary vitamin D intake among US women is around 170 IU per day. Therefore, women in the low-dose group were consuming, on average, a total of around 570 IU per day, which is close to the current Recommended Dietary Allowance (RDA) for vitamin D of 600 IU per day during pregnancy. Based on the findings from these 2 studies, the RDA for pregnant women may need to be reevaluated.

Brustad N, et al. Effect of high-dose vs standard-dose vitamin D supplementation in pregnancy on bone mineralization in offspring until age 6 years: a prespecified secondary analysis of a double-blinded, randomized clinical trial. *JAMA Pediatr*. 2020;174:419-427.

Tocotrienol-Rich Vitamin E for Diabetic Neuropathy

Eighty Malaysian patients (aged 35-75 years) with type 2 diabetes and good glycemic control (HbA1c of 6-9%) were randomly assigned to receive, in double-blind fashion, tocotrienol-rich vitamin E (Tocovid; manufactured by ExcelVite; Malaysia) at a dose of one capsule twice a day or placebo for 12 weeks. Each Tocovid capsule contained 200 mg of tocotrienols (62 mg of d-alpha tocotrienol, 113 mg of d-gamma-tocotrienol, and 26 mg of d-delta-tocotrienol) and 92 IU of d-alpha-tocopherol. At eight weeks, compared with placebo, Tocovid significantly increased mean nerve conduction velocity of the median nerve, sural nerve, and tibial nerve, and significantly increased serum levels of nerve growth factor.

Comment: Increased oxidative stress, increased inflammation, and decreased levels of nerve growth factor are believed to play a role in the pathogenesis of diabetic peripheral neuropathy. Tocotrienol-rich vitamin E has antioxidant and anti-inflammatory activity and also increases serum levels of nerve growth factor. In the present study, tocotrienol-rich vitamin E increased nerve conduction velocity of three different peripheral nerves, which suggests that would be beneficial for preventing or treating diabetic peripheral neuropathy. I am aware of only one study in which vitamin E by itself increased nerve conduction velocity in patients with type 2 diabetes. In that study, 900 IU of vitamin E was given daily for six months.[5] The patients in the present study received a much lower dose of vitamin E (184 IU per day) for a shorter period of time. It is therefore likely that at least part of the improvement seen in the present study was due to the tocotrienols. It should be noted that the study was funded in part by ExcelVite, the manufacturer of Tocovid.

Ng YT, et al. The effects of tocotrienol-rich vitamin E (Tocovid) on diabetic neuropathy: a phase II randomized controlled trial. *Nutrients*. 2020;12:1522.

Intravenous Magnesium for Persistent Migraines (Status Migrainosus)

A retrospective study was conducted on 234 patients (mean age, 44 years) who received intravenous magnesium for status migrainosus between February 2014 and September 2016 at the headache clinic of the University of Southern California. Status migrainosus is defined as a migraine that lasts more than 72 hours. The usual dose was 2 g of magnesium sulfate in 50-100 ml of normal saline, given over 1-2 hours. Additional intramuscular injections for nausea (prochlorperazine, odansetron, or metoclopramide) or for refractory pain (ketorolac, dexamethasone, sumatriptan, or dihydroergotamine) were given as needed. Mean pain score (on a scale of 0-10, with 10 being the most severe) decreased from 5.56 before treatment to 2.75 after the magnesium infusion ($p < 0.001$). Fifty-four percent of the patients had clinically significant pain reduction, defined as a reduction of at least 30%. Forty-four percent of the patients who received magnesium did not require additional injections for pain. In patients who did not receive additional medications for pain, mean pain score decreased from 4.76 to 2.95 ($p < 0.001$), and 59% experienced at least a 30% reduction in pain.

Comment: As early as the 1930s, parenteral magnesium was mentioned as an effective treatment for migraine. More recently, numerous clinical trials have demonstrated that intravenous magnesium can decrease or eliminate migraine pain, often within 15 minutes or less. However, the effect of magnesium on status migrainosus has not been well studied. In this retrospective analysis, intravenous magnesium resulted in clinically significant pain relief in more than half of patients. The authors of this report concluded that intravenous magnesium may be useful as a cost-effective first-line treatment for status migrainosus.

Xu F, et al. Experiences of an outpatient infusion center with intravenous magnesium therapy for status migrainosus. *Clin Neurol Neurosurg*. 2019;178:31-35.

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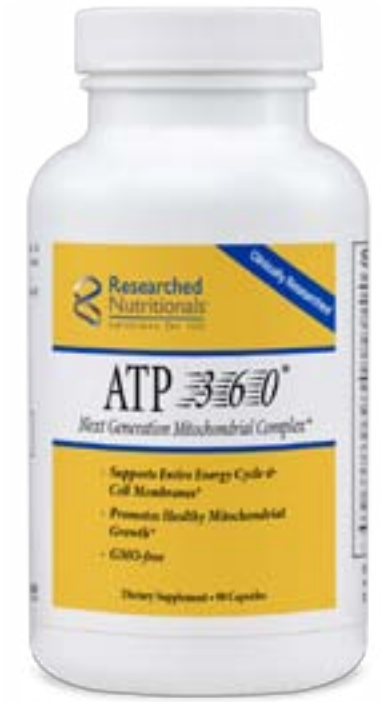

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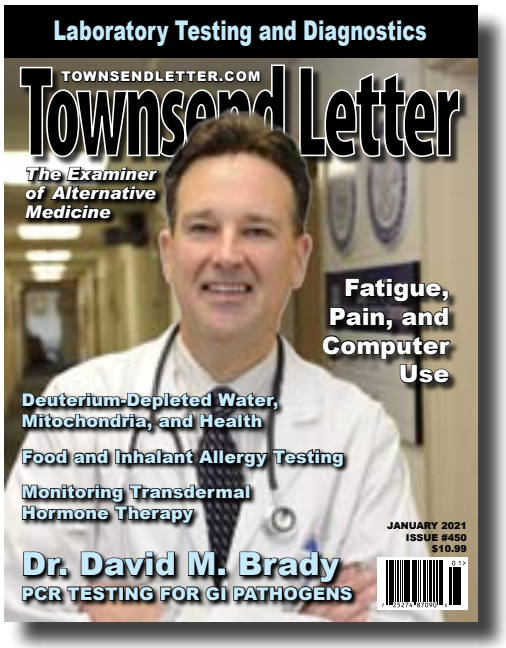

On the cover

Methodology Matters in Diagnostic Stool Testing

by David M. Brady, ND, DC, CCN, DACBN, IFMCP, FACN[1] and Cass Nelson-Dooley, MS[2]

Molecular Methods Revolutionize Diagnostic Testing

In 1885, the first microbe was cultured. In 1969, breakthroughs in anaerobic microbial culture helped further define the GI ecosystem. But in 2000, molecular techniques, or DNA analysis, sparked what was initially described as a renaissance in the laboratory and later called, the "molecular revolution."[1] These molecular methods, also used in the landmark Human Microbiome Project, made it possible to see at least 50 percent more microbes than had ever been seen before.[2-4]

Methods of Stool Testing Defined

Polymerase chain reaction (PCR) methodologies are DNA replication methods that make numerous copies of a target sequence of DNA in the presence of primers (short, single-stranded sequences of nucleic acids) and DNA polymerase (the DNA-replicating enzyme). PCR methods are targeted approaches for rapidly detecting, identifying, differentiating, and quantitating specific microbes and genes of clinical relevance.

- *Quantitative PCR (qPCR)* or real-time polymerase chain reaction (RT-PCR) is widely used in biomedical research as well as in clinical diagnostics to accurately identify and quantitate specific organisms or genes present in a sample. In qPCR, segments of DNA that are highly specific for selected targets are amplified (replicated many times). Colorimetrically labeled DNA probes (single-strand nucleic acid sequences designed to bind the amplified target gene) make it possible to quantitate the amplification process as it occurs, in real time (hence the name), yielding a quantitative DNA result.
- *Standard PCR* is similar to qPCR, except that it is not regarded as truly quantitative because the amplified DNA is quantified only at the final stage of the PCR process, making it impossible to determine the original true quantity of target DNA. It may instead be estimated by comparing it to a standard curve or by analyzing the quality and yield of PCR-products with gel electrophoresis.[5]

DNA or RNA sequencing methodologies determine the order of nucleic acids (adenine, cytosine, guanin, thymine) in a DNA molecule and count them.[6] They are untargeted approaches for obtaining a general, high-level profile of the microbes or genes present in the microbiome.

Metagenomic and metatranscriptomic sequencing-based approaches provide a general profile of the microbiome. Both approaches involve high-throughput methods for sequencing nucleic acids, followed by advanced computational analyses on the resulting data to identify microbes, and either individual genes (DNA/metagenomic sequencing) or transcripts (RNA/metatranscriptomic sequencing). Metagenomic approaches can be used to identify potential microbial functions, whereas metatranscriptomic approaches can be used to analyze gene expression patterns. These approaches can provide approximate, relative levels of organisms, genes, or transcripts but are not considered sufficiently accurate for true quantitation. The accuracy of any given sequencing technology may also depend on the numbers of reads used. Read length is the number of base pairs sequenced from a DNA fragment. Sequencing depth refers to the number of times a given sequence has been read. Higher numbers of reads, often found in research settings, produce more accurate results. Lower numbers of reads, which helps minimize costs in commercial settings, produce less accurate results. This is a very important factor, since sequencing methods with inadequate sequencing depth are unlikely to detect clinically relevant organisms present at low levels. Quantitative PCR, on the other hand,

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[2]*Health First Consulting, LLC, Lilburn, GA (USA); consultant at Diagnostic Solutions Lab, LLC (DSL)*

excels at accurate detection of low-abundance organisms (i.e., the important "needles in the haystack").

16S Sequencing is similar to other sequencing methods, but only a single gene, encoding 16S ribosomal RNA (16S rRNA), is sequenced. The 16S rRNA gene is common to almost all bacteria and archaea, which are bacteria-like organisms. Determining an organism's abundance when using the 16S gene is not as accurate as other sequencing methods because the 16S gene varies widely in copy numbers per genome.

Culture and Microscopic Methodologies

- *Culture + MALDI-TOF (Matrix Assisted Laser Desorption/ Ionization Time-of-Flight) Mass Spectrometry* relies on bacterial culture of the fecal specimen. The fecal specimen is plated with at least four growth medias under specific growth conditions to optimize microbial growth. Isolated microbial colonies are recovered and may be examined for phenotypic properties or screened with biochemical tests for specific identification. Isolated organisms are then identified using the MALDI-TOF MS, which is a proteomic method that measures ribosomal protein fingerprints of microorganisms, and they are then compared to a reference database.
- *Ova and Parasite Examination (O&P, Microscopy).* A routine O&P detects parasites and ova in fecal specimens using macroscopic and microscopic characteristics. Microscopic evaluation consists of a direct wet mount, concentration, and permanent-stain smear.

Fecal specimens are analyzed by a lab technician using a bright-field microscope. Accuracy is highly dependent on the expertise of the technician. Concentration methods, which are intended to increase the likelihood of finding ova, cysts, and larvae, can inadvertently reduce the numbers of cysts and ova in the sample. This may lead to underestimation of parasites in a stool specimen.[7,8]

Advantages of Quantitative Molecular (qPCR) Technology in Clinical Settings

qPCR is quickly becoming the standard for diagnostics due to the increased specificity, sensitivity, and reproducibility of PCR techniques. qPCR panels are able to rapidly detect and quantitate viruses, parasites, and anaerobic bacteria, which can be missed by traditional methods.[9,10] Government and private institutions around the world are incorporating it as "standard of care" in the testing of the GI microbiota. The FDA has cleared multiple molecular-based gastroenteritis testing panels, often used in hospital labs and focused only on a short list of pathogenic organisms associated with acute diarrhea and GI distress.[10] So, while there are many limited organism PCR diagnostic tests for gastroenteritis used in conventional medical settings for screening for common overt pathogenic organisms, an expanded panel that quantifies each pathogen and non-pathogen (including the clinically relevant commensal and opportunistic organisms) is a required tool to assess both the acute and chronic GI complaints that are commonly seen in ambulatory integrative and functional medicine clinics.

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qPCR technology provides the ordering clinician with true quantitative values, versus simply a positive/negative result. It helps differentiate trace levels of an organism from frank elevations indicative of active infection. The qPCR method provides absolute values – not relative levels – of each microbe. This information gives the clinician important clinical insight that allows them to create personalized treatment plans for even the toughest cases.

Each analyte on a quantitative (qPCR) stool analysis should be individually validated and should meet or exceed federal Laboratory Developed Test (LDT) and CLIA requirements. Before adding any organism to a report, the following analyses should be completed successfully:

- *Assay specificity* – the assay detects the intended organism and nothing else
- *Assay sensitivity* – the assay can measure accurately within a certain range of detection *(e.g. how low and how high the organism can be quantified)*
- *Assay variation* – if the same sample is tested multiple times, in different batches, on different days, the variation *(coefficient of variation, CV)* must be below 10%
- Reference range development
- Cross-assay comparison, when available.

According to CLIA standards, all organisms quantified by qPCR should have less than 15% CV or variation. This means that two identical samples, tested on different days, can only vary 15% from each other. Validation reports should be published internally, approved by laboratory leadership before adding any organism to a test panel, and reviewed during CLIA inspections. Generally, validated DNA positive controls from vendors such as ATCC are used to test molecular targets during assay validation. All lab assays and laboratory personnel should undergo proficiency testing, as required by CLIA. Proficiency testing is the analysis of unknown samples submitted by an authorized provider as a measure of external quality control.

All patient samples should be tested alongside control samples, standard samples, and endogenous controls to meet quality control requirements.

- Negative controls contain no target DNA.
- Positive controls contain a known amount of target DNA.
- Standard samples contain known concentrations of each target organism at serial dilutions. They should be run on a routine basis and used to establish a calibration curve with a coefficient of determination (R2) > 0.95.

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Figure 1. Comparison of Microbial Detection Methods

Stool Testing Methods	Fully quantitative	*Highly sensitive detection (Measures very low levels of organisms)*	Each analyte individually validated	Provides only clinically relevant organisms	Rapid turnaround time *(within days)*	Identifies bacteria, parasites, fungi, and viruses down to the strain level	Identifies genes involved in microbial function
qPCR / rt-PCR	+++	+++	+++	++	+++	+++	++
Standard PCR	–	++	++	++	+++	++	++
Shotgun Metagenomic Sequencing	–	+	–	–	–	++	+++
Metatranscriptomic Sequencing	–	+	–	–	–	++	+++
16S Sequencing	–	+	–	–	–	–	–
Culture + MALDI-TOF MS	–	–	+	+	+	–	–
Microscopy	–	–	+	++	+	–	–

Figure 2. Sample Reproducibility Data.

In the analysis below using a commercially available stool panel using an entirely qPCR-based method, one patient's specimen was extracted for DNA and run eight different times by qPCR. All CVs were below 6.5%, indicating that assay variation was low. Cq is the quantitation cycle, or the result, from qPCR. Lower Cq values indicate higher starting copy numbers of the target DNA.

Target Organism	CV	Quantitation Cycle (Cq)							
Blastocystis	**6.31**	10.76	10.22	12.4	10.78	10.72	10.95	10.27	10.54
Bacillus	**1.09**	13.53	13.52	13.51	13.3	13.31	13.53	13.76	13.41
Faecalibacterium	**1.01**	23.82	23.79	23.97	23.95	24.11	24.45	24.03	24.39
EHEC (eae)	**1.98**	24.56	24.51	25.79	25.53	24.75	25.33	24.74	25.46
Enterococcus faecium	**0.70**	15.45	15.5	15.43	15.34	15.15	15.3	15.37	15.36
Morganella	**2.01**	22.83	22.33	23.27	23.54	23.8	23.33	23.29	22.84
Proteus spp.	**1.57**	25.47	25.42	25.15	24.44	25.01	25.39	24.83	24.58
Proteus mirabilis	**2.56**	23.79	25.47	24.81	24.07	23.61	23.97	24.15	24.72
Pseudomonas spp.	**4.08**	18.86	19.81	18.87	20.06	20.66	19.06	20.99	19.99
Pseudomonas aeruginosa	**1.87**	25.13	24.84	25.6	24.72	25.5	25.35	24.31	25.6
Salmonella enterica	**1.54**	25.32	25.45	25.33	24.42	25.41	25.58	25.52	24.92
Staphylococcus aureus	**3.84**	25.84	25.62	24.17	25.62	23.19	25.12	24.28	25.69
Streptococcus spp.	**3.07**	30.89	29.9	30.28	31.37	29.42	30.28	31.83	32.07

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- Endogenous controls are target organisms detected in most clinical samples.

These quality control measures allow multiple checkpoints in the assay to verify adequate nucleic acid extraction and proper amplification. If results for positive or negative controls, standard samples, or endogenous controls are abnormal, or if results are questionable for any other reason, DNA should be re-extracted, and the assay should be repeated. All patient results should be reviewed at multiple levels of laboratory management.

Discussion

The molecular revolution in stool testing is here, and it is here to stay. Culture methods have severe limitations, including within the laboratory and in sample transit. Culture methods are simply unable to truly quantitate microbes or analyze many anaerobic GI microbes at all. Within the molecular realm there are various options. DNA and RNA sequencing methods, including the most common 16S approach, offer the ability to test for a wide array of organisms at higher taxonomic level in a cost-effective manner, but lack the ability to quantitate and report to the clinician just how much of anything is actually present in a specific patient. These sequencing techniques are most appropriately used in research settings where the goal is the look across a wide array of organisms and to determine their relative populations to one another within a subject's sample. This is why test results for 16S sequencing and metagenomic and metatranscriptomic sequencing-based methods are reported as a percentage of the total DNA found, versus an absolute quantitative amount of organismal DNA found. When the goal is to test a large number of samples within a cohort of subjects and typify the microbial composition of their guts, regardless of if the organisms found may be considered clinically significant or not, then sequencing is the logical choice. The usual intention is to then apply big-data number crunching to the resulting data-set in an attempt to determine what is typically seen in a specific population of subjects, such as those with rheumatoid arthritis, diabetes, obesity, or a host of other diseases, versus controls. Both 16S and metagenomics/metatranscriptomic sequencing methods are beneficial in a research setting when exploring the breadth of the microbiome and uncovering new species, without quantifying the exact amount present.

However, if the goal is to use the test diagnostically on an individual subject and then apply that information to make clinical decisions, then the most appropriate methodology is PCR, and a quantitative method such as qPCR is ideal and preferred. This is generally performed on a curated target list of clinically relevant organisms where the clinician is provided information not only of what is present, but how much of each organism. A laboratory's selection of clinically relevant targets (organisms) is of utmost importance to maximize the utility of the panel in clinical practice. Further, the rapid turn-around of PCR methods is conducive to a clinical setting, whereas culture-based methods or sequencing methods can take weeks or months, respectively. A well-designed panel of qPCR targets helps to determine if an infection is present, including more acute diarrhea-producing pathogenic infections. It can also detect more subtle findings of dysbiosis of commensal and/or opportunistic organisms, which often produce chronic GI complaints of gas, bloating, distension, abdominal cramping, occasional diarrhea, and other symptoms that often lead to a diagnosis of irritable bowel syndrome (IBS) or functional bowel disorder (FBD). While all microbiological methods have merit and can be used to build on our understanding of the human microbiome, molecular methods – and especially qPCR methods – offer the practitioner the most sensitive, specific, clinically relevant, and rapid results when addressing acute and chronic gastrointestinal illness in a clinical setting.

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Radically Changing Your View of Water

by Victor Sagalovsky

Health and medical professionals are astounded when they first hear about a ubiquitous, yet barely acknowledged water molecule, that can be every bit as toxic as heavy metals. This remarkable story chronicles the 60 years of scientific investigation into the biology of deuterium that is finally coming to the forefront of health and medicine.

Hidden in plain sight is a small percentage of water molecules containing deuterium – a rarely mentioned isotope of hydrogen. It is one of three hydrogen isotopes, the others being protium and tritium. But there's nothing new about deuterium – it goes back to the beginning of the universe. Only now is its significance in the *biology of all living things* being recognized and understood worldwide.

The Cosmic Beginning

In the first fractions of a second following the Big Bang, 13.8 billion years ago, was the creation of protons and neutrons followed by their interaction with electrons. The result was the most overwhelmingly abundant element in the universe, hydrogen, as its three isotopes: protium, deuterium and tritium.

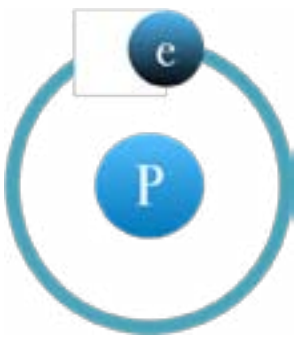
Over billions of years of the expansion of the Universe, the first elements were generated in the sustained fusion of stars and supernovas and distributed throughout vast space. Element attracted element...cosmic dust formed...then asteroids comets, planets and moons....

The elements hydrogen and oxygen chemically reacted, generating interstellar H2O – liquid water, water vapor, and ice (first, a protium or deuterium H-isotope joined to oxygen forming OH, then another H-isotope joined the OH, forming H2O). Eventually, about 4.5 billion years ago, a long-lasting event known as the Late Heavy Bombardment brought most of the water to Earth in the form of icy comets and asteroids (some water was generated by chemical reactions within the crust of the Earth).

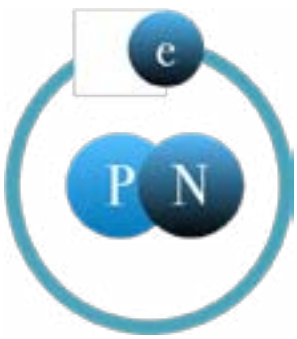
Back on Earth

Deuterium is present in virtually all water on Earth. There are about six drops (150 ppm of deuterium-containing water molecules in each liter of water. There are noteworthy anomalies in Nature due to the meteorological redistribution of the protium and deuterium H-isotopes. The most significant example is the deuterium content of snow and ice in Antarctica – 89 ppm, nearly half the deuterium level of the Earth's water sources, including the oceans.

Fast forward more than 13 billion years to 1932 when Harold C. Urey and his colleagues Ferdinand G. Brickwedde, and George R. Murphy at Columbia University proved the existence of deuterium as a stable H-isotope with a mass of 2 (the protium H-isotope has a mass of 1). Deuterium had gone undetected by physicists perhaps because it only made up 0.0149% of all hydrogen in the universe. Some suspected the existence of this twice-as-heavy H-isotope as early as 1913. Urey was hot on its trail. ➤

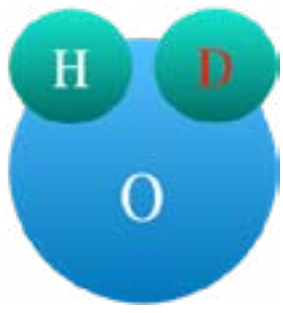


Light Hydrogen
Protium, "H"



Heavy Hydrogen
Deuterium, "D"

Light Water H2O



Heavy Water HDO

Your View of Water

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Ushering in the Atomic Age

In 1934 Dr. Urey won the Nobel Prize in chemistry for this monumental discovery of deuterium that would usher in the atomic age. Concentrated deuterium (in the form of heavy water) was the missing piece needed for nuclear reactors and the making of atomic bombs. Because of deuterium, our world would never be the same.

While the 1930s brought a paradigm shift in physics, much was the same with biology. In 1929, ATP (adenosine triphosphate), the fuel of *all life,* was discovered. This came 39 years after the discovery of mitochondria, the powerhouse of the cell in which ATP is generated. In 1937, some of the mysteries of mitochondria were unraveled, especially the mechanisms of ATP production. But science would have to wait another 60 years before the detrimental effects of deuterium on ATP production and the *biology of all living things* would be understood.

Shortly after Dr. Urey proved its existence in 1933, his mentor, Gilbert N. Lewis, a professor of chemistry at Berkeley University, was the first to create pure heavy water using the electrolysis of water. Professor Lewis was also the first to observe that when concentrated heavy water was frozen, it sank instead of floated like normal water. He also observed how it strongly delayed the reproduction of microbes and retarded the growth of germinating seeds.

Between 1933 and 1939 there were 216 published English language studies on the biological effects of deuterium, all arriving at the same observation: that heavy water was an impairment on key biological processes. The experiments replacing normal water with just 30% heavy water caused bacteria, plants, and animals to die in a matter of days.

As World War II approached, heavy water became increasingly difficult to obtain for further study as countries were hoarding production in preparation for making nuclear reactors and atomic bombs. Biological research on deuterium was thus stifled and gradually faded away until the 1950s.

The Modern Chapter on Deuterium Begins

About the same time that Francis H.C. Crick and James D. Watson announced the double-helix structure of DNA in 1953, a gerontology and genetics graduate student named Gennady D. Berdyshev at the University of Tomsk in Siberia (Soviet Union) was urged to investigate a very peculiar anomaly concerning lifespans of the Soviet population. While the average percentage of centenarians in all of the Soviet Union was about 8 per one million, in certain mountainous areas of Siberia there were an astounding 324 centenarians per one million. Furthermore, most of this population of Altai and Yakutia enjoyed great health and vitality well into their old age. Knowing that these regions were supplied with glacial melt water from high altitudes, he was motivated to investigate this factor as a possible common denominator of health and longevity of their inhabitants. Scientists focused on the possibility that some unique and unrecognized water characteristic might be involved – a mystery hidden perhaps in ancient glacial ice.

The first experiments consisted of mining permafrost at a depth of 20 meters and melting water that had existed as ice for 300 million years. In the lab, they observed how this water stimulated cell division and slowed down cellular aging. When the institute could no longer pay for the extraction of ancient ice, they evaluated Siberian snow from their own vicinity and to their surprise it had the same effects. The theory of deuterium-depleted water was beginning to take shape.

The experiments done by V.M. Muhachev at the Tomsk University in 1959 to 1960 convinced his colleagues that even a small dose of deuterium distorted the chemistry of hydrogen bonding and inhibited sub-molecular processes. By 1960 Berdyshev had enough information to conclusively link the health and longevity of the Yakuts and the Altaians with the consumption of glacial melt water. The researchers from Tomsk further discovered that ancient ice, high latitude mountain snow, and glacial runoff were 15-20% depleted in deuterium compared to what became known as the Vienna Standard Mean Ocean Water (VSMOW), which is 155.76 ppm of deuterium-containing water at the equator. In 1966 Rodimov and his biophysics department chair, I.V. Toroptsev, were allowed to publish their work in English for the benefit of researchers and scientists everywhere. With their groundbreaking findings in *Biological Role of Heavy Water in Living Organisms*[1] they put Tomsk University on the map, becoming the very first scientists to show how water depleted in deuterium had a positive biological effect. Considering that deuterium had only been discovered 30 years before, this was a monumental breakthrough. Possibly, one of the great secrets of health and longevity had just been revealed!

Coincidentally around the same time, one of the greatest discoveries in biology was taking shape by Paul D. Boyer, a molecular biologist at UCLA. He discovered that tiny protein nano-motors within the mitochondria, sitting at the end of the Electron Transport Chain (ETC) provided a key step in producing ATP. These protein assemblies, spinning at a rate estimated to be 9000 RPM, have the structure and function of an electro-mechanical motor, complete with rotor, stator and magnetic field. Boyer christened these nanomotors "ATP Synthase." But, it would be another 40 years, and the turn of the millennium, before deuterium's damaging effect on ATP Synthase would be discovered.

Human Blood Serum Constituents, mmol/l
Note: There is 3 to 5 times more serum deuterium in the body fluids than other key constituents.

Calcium: 2.2 – 2.7	Magnesium: 0.8 – 1.2
Potassium: 3.5 – 5.1	Glucose: 3.3 –5.1
Deuterium: 12 -14	

Biological Effects of Deuterium

By the 1960s it was clear that deuterium, having twice-the-mass of its lighter isotope protium, could be responsible for profound biological and biochemical effects. After all, no other element on the periodic table has isotopes differing in mass to this extreme degree. An understanding of how deuterium functions at the cellular level was now on the horizon.

While Russian scientists were doing their research and making quiet breakthroughs, Americans were also hot to blaze a deuterium trail. It was 1963 when John F. Thomson of the medical research division of Argonne National Laboratory in Chicago wrote the definitive 152-page treatise entitled "Biological Effects of Deuterium."[2] In 1966, the work of his colleagues Joseph J. Katz and Henry L. Crespi reinforced the biological implications of deuterium, noting in "Deuterated Organisms Cultivation and Uses,"[3] that deuterium affects the shape of proteins and the replication of DNA. Laboratory mice experiments were conducted in which their normal body water was altered in the percentage of heavy water, yielded the following observations:

- *Experiment #1*: Laboratory mice body water was increased in concentration of heavy water to 30%. It proved to be fatal to the mice in a matter of days.
- *Experiment #2*: Laboratory mice body water was depleted in deuterium by 30% (105 ppm) and resulted in significantly increased lifespan.

Nearly a decade later in 1974, again at Argonne National Labs, British scientist T.R. Griffiths, at the 2nd International Conference on Stable Isotopes, proposed the theory that deuterium might be the primary cause of aging. In *Possible Roles of Deuterium in the Initiation and Propagation of Aging and Other Biochemical Mechanisms and Processes,*[4] he reported that deuterium, being twice as heavy, more electronegative and having different atomic binding properties than regular hydrogen, interfered with DNA replication. Because DNA repair enzymes contain deuterium in a position that is normally occupied by protium, they have a potential for triggering DNA replication and repair errors. The following year, in 1975, J.D. Gleason and I. Friedman, replicating the Russian findings on plant growth, published the first American study on using deuterium depleted water to increase the growth of grains. This small but significant publication in *Nature*[5] magazine paved the way for a new generation of scientists to try and understand more deeply the function of deuterium in the biology of all living things.

Maintaining Health and Slowing Down Aging

When the Hunza people of northern Pakistan were investigated for their robust health and increased longevity, it was determined that the deuterium content of their water, from the glaciers of Mt. Ultar, was about 133 ppm, a deviation of 16% from the 155 ppm global reference for equatorial ocean water. A 16% reduction may not seem significant, however there are two factors that are in play. One is that the Hunza population is provided with this deuterium depleted water from birth to death and their vegetable, grain and fruit produce, as well as the animals they raise also are depleted in deuterium. Two, Griffith had reason to postulate that the adverse biological effects of deuterium is "proportional to the square of the concentration." This is the reason why researchers report that even a small depletion of deuterium has a significant biological benefit.

By the 1990s pivotal research was being furthered in Romania and Hungary. W. Bild and colleagues at the Romanian University of Medicine and Pharmacology showed that mice exposed to a sub-lethal dose of 8.5 grays of radiation had a greater survival rate on deuterium-depleted water. Mice consuming water that was reduced to 30 ppm of deuterium had a 61% survival rate whereas the control group consuming plain tap water (150 ppm) had a survival rate of only 25%. The test group also maintained normal white blood cell and red blood cell platelet counts as compared to the control group which did not. The same two groups of unfortunate rodents were also infected with pneumonia and the test group showed an intensification of immune defenses not seen in the control group. The scientists concluded that mice with lower levels of deuterium in their systems would benefit from fewer cell division errors and more effective repair of radiation-damaged DNA. It was proof yet again that deuterium-depleted water had some unknown and seemingly magical positive biological effect. Note: These animal tests were carried out for the sole purpose of evaluating the effects of deuterium depletion for patients undergoing chemotherapy.

The growing reported evidence from researchers, along with the work of Hungarian Nobel-prize winner Albert Szent-Györgyi, inspired the work of Gábor Somylai, a doctor and molecular biologist. In 1991 he engaged in the most extensive clinical trials of the physiological benefits of deuterium depletion ever conducted. His findings were published in 1998 in the paper "The Biological Effects of Deuterium Depletion"[6] and his 2001 book *Defeating Cancer.*[7] Somylai's double-blind clinical trials first demonstrated that deuterium-depleted water was free of any side effects and, that the survivability of his test group on deuterium-depleted water was significantly better than those cancer patients in the control group. He also showed that consuming deuterium-depleted water was an excellent complementary adjuvant to conventional radiation and chemotherapy. Between October 1992 and the spring of 1999, Dr. Somylai and his team administered some 350,000 liters of deuterium-depleted water (DDW) to approximately 1,200 patients, generating over 12,000 pages of documented records. His groundbreaking work put Hungary on the map as an important center for research on the emerging health science of deuterium depletion.

By the beginning of the 21st century, it was well understood among researchers that consumption of deuterium-depleted water (DDW) protected DNA from damage – but it was not understood how. It was only a matter of time until this mystery would be solved. In 2006, Russian chemist Igor A. Pomytkin and his colleague O.E. Kolesova published the study "Relationship

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between Natural Concentration of Heavy Water Isotopologues and Rate of H_2O_2 Generation by Mitochondria."[8] They were able to show that whatever cellular mechanism is susceptible to heavy water deuterium damage and, in turn, is protected by deuterium-depleted water (DDW) was located within the mitochondria. Scientists now understand that mitochondria have an inherent biological strategy for keeping cellular water free of deuterium – as the water inside the inner membranes of mitochondria has 60-70% less deuterium than extracellular water.

The Great Biological Discovery

The following year, 2007, marked the occasion of the most monumental discovery in the short history of deuterium science. Abdullah Olgun, PhD, a medical doctor, biochemist, and pharmacologist from the Department of Biochemistry and Clinical Biochemistry at Gülhane School of Medicine in Ankara, Turkey published the paper "Biological Effects of Deuteronation: ATP Synthase as an Example."[9] His pioneering research showed for the first time how deuterium caused its damage in Complex Five of the electron transport chain, inside the ATP Synthase nano-motor. Dr. Olgun determined that roughly every 15 seconds a bare *heavier* deuterium nuclei (a proton – neutron pair), impinges upon the fast spinning nano-motor, causing it to jam, stutter and ultimately self-destruct. Dr.Olgun further explained in his paper "Deuteronation and Aging,"[10] published the same year in the *Annals of the New York Academy of Science*, that mitochondrial damage resulting from deuterium is one of the primary causes of physical aging. The mystery of how deuterium damaged life was finally revealed! The Nobel Prize worthy significance of Abdullah Olgun's findings may be hailed as one of the greatest biological discoveries of the 21st century and the absence of recognition of his achievement stands as a careless oversight in the annuls of science.

At that time of Dr. Olgun's groundbreaking discovery, few scientists realized the gravity of his breakthrough. One notable person that did was Anton Chernopiatko, a Russian businessman, scientist and deuterium-depletion enthusiast who also co-authored with Pomytkin the 2015 study "Deuterium Content of Water Increases Depression Susceptibility: The Potential Role of a Serotonin-Related Mechanism."[11] Having embraced the importance of deuterium depletion from an early age, a lifelong quest was ultimately put into action. Chernopiatko, now having definitive proof of the role of deuterium as a biological Trojan horse, took it upon himself to advance deuterium-depleted water production technology beyond laboratory and research purposes and construct a factory to produce it on a commercial scale.

Victor Sagalovsky is the co-founder of Litewater Scientific. He is an author, scientist, and teacher. Currently, Victor has directed his efforts to advancing the health, anti-aging, and longevity benefits of deuterium depletion and the production and distribution of Litewater DDW.

Whereas Berdyshev in the 1990s had created an industrial process for reducing deuterium by 30-40% using a refrigerated process, it was around 2003 that the first vacuum-assisted fractional-distillation rectification column, exclusively for the production of deuterium-depleted water, was developed at the Institute of Fine Chemical Technologies in Moscow. This efficient process could remove 95% or more of the heavy water deuterium. In 2012, Chernopiatko began construction of a plant in the Russian countryside commercializing the technology developed at the Institute in Moscow. Five years of advanced engineering, trial and error, and good old elbow grease yielded the first dedicated facility in the world to continuously produce 90%+ deuterium-depleted water (DDW).

It is 2020; the mechanisms of deuterium and how to remove it are well understood. Nevertheless, the awareness of this colossal discovery is still in its infancy. Four international conferences on deuterium depletion in Budapest have provided a place for scientists to present their work. One scientist keen on advancing the work is Laszlo Boros, MD, and professor at UCLA who is leading the charge in the new field of deutenomics. The objective of this new science is to understand how deuterium is managed by biological systems. According to Dr. Boros, "The structured water pool of the (cellular) cytoplasm can thus be considered as a 'deuterium scavenging water tank' that absorbs deuterium from carbohydrates and amino acids in order to protect mitochondrial ATPase nanomotors from breaking, among other functions!"[12]

The New Age of Deuterium Depletion

As of this writing, there are three primary producers of deuterium-depleted water, Preventa in Hungary, Qlarivia in Romania, and Vividi in Russia, which is offered in the United States by *Litewater Scientific* under their "Litewater" brand. This exclusive deuterium-depleted water (DDW) is notable for its 94-97% reduction of deuterium – the lowest in the world. Only time will tell how this new scientific revelation of deupletion (deuterium depletion) will impact health and longevity of mankind. So far, the science and its application to health and medicine show much promise.

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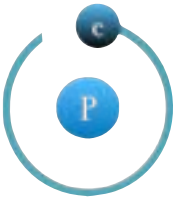
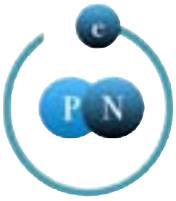
Deuterium in Water

The Explanation, the Risks, the Solutions

"Reducing the total body burden of deuterium may be the most significant health optimization, anti-aging, and longevity strategy known."



Light Hydrogen
Protium, "H"



Heavy Hydrogen
Deuterium, "D"

Light Water H_2O

Heavy Water HDO

It has been more than 60 years since the initial Russian discovery of the damaging biological effects of deuterium - found in ALL water sources on Earth and EVERY food we consume.

Mainstream health and medical professionals have been unaware of this health compromising phenomenon which has been hiding in plain sight.

Litewater Scientific is here to help you learn about this rapidly emerging health science which some refer to as the most profound biological discovery of our time. Shall we begin?

So, what is deuterium?

Designated as "D", it is one of the three isotopes of hydrogen - the simplest element. But "D" is *twice as heavy* as the more abundant common form, "H". This factor makes deuterium a biological toxin.

Both H and D combine with oxygen to form water molecules, predominantly H_2O and HDO. There are about 6 drops (150 ppm) of deuterium-containing water molecules in every liter of water on Earth.

Currently there are no hard and fast rules on characterizing deuterium ppm levels. However, water with less than 130 ppm typically qualifies as "deuterium depleted" or "light water".

Why is the deuterium in water and foods so damaging to living things?

Because of its high mass, deuterium routinely disables the most critical cellular functions - including ATP production and DNA replication. This occurs every moment from conception to death.

How can we avoid these life-long harmful health effects of endogenous deuterium?

- *First* and foremost, regular consumption of deuterium depleted water (DDW). This healthy habit gradually flushes deuterium from your body.

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Expansion of Visceral Adiposity and Cardiometabolic Disorders: Focused Laboratory Testing

by David Quig, PhD

In 2018 the CDC reported that in the US 60% of adults and 20% of children and adolescents were obese or overweight (BMI>25).[1] Cardiometabolic disorders have increased at disturbing rates, and visceral fat deposition is a central factor. Lifestyle choices regarding diet and physical activity are certainly in play. However, modifications of caloric intake and energy balance alone appear insufficient to overcome the extensive influence of the gastrointestinal (GI) microbiota on the initiation and progression of metabolic and cardiovascular complications. The GI microbiota are pivotal factors in the regulation of chronic low-grade inflammation, glycemic control, endothelial dysfunction, and associated cardiometabolic comorbidities. Research-based advances in diagnostic testing have led to the availability of highly focused laboratory tests to evaluate GI dysbiosis and serum-based cardiometabolic risk factors.

Lab tests can detect metabolic and GI disruptions before overt cardiometabolic illness occurs.

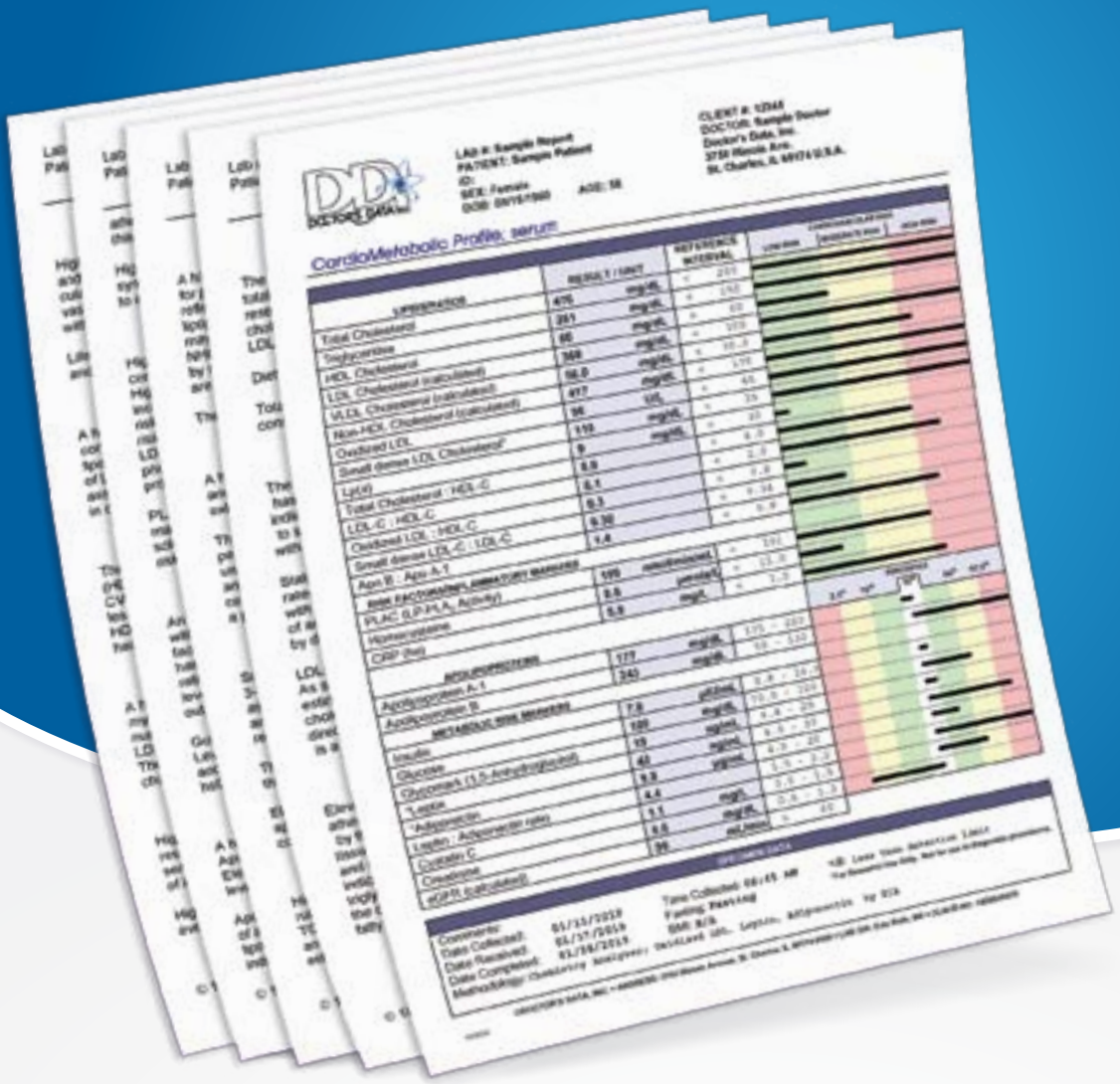
Obesity has increased at an alarming rate among adults, and excess adiposity is also more prevalent among children and adolescents.[2] Obesity is associated with cardiometabolic risk factors, including dysglycemia, dyslipoproteinemia, sterile endotoxemia, and low-grade inflammation. Specifically, abdominal visceral fat (VAT) is a strong independent predictor of mortality, and it has a central role in pathogenesis of metabolic syndrome (MetS) and coronary artery disease (CAD).[3] The extent of fat deposition in the three primary types of depots is correlated, but VAT is very different from subcutaneous fat with respect to release of fatty acids immediately to the liver and pancreas and pathogenic sequelae.[4] Further, macrophages amass more extensively in VAT and release pro-inflammatory cytokines and reactive oxygen species that result in systemic low-grade inflammation, disrupted adipokine metabolism, and insulin resistance.[5,6] Low-level systemic elevations of gut microbiota-derived bacterial lipopolysaccharides (LPS) augment infiltration and activation of macrophages and accentuate the release of pro-inflammatory cytokines.[5,7,8] Intestinal barrier disruption and high abundance of LPS-rich Proteobacteria (phylum), Enterobacteriaceae (family), and Shigella and Escherichia (genera) are common with inflammatory conditions such as obesity, type-2 diabetes mellitus, inflammatory bowel disease, and high-fat diets.[9-11] In contrast, normally abundant commensal species such as *Faecalibacterium prausnitzii*, *Bifidobacterium spp*., *Eubacterium rectale,* and *Akkermansia muciniphila* are diminished. That loss of commensals begets increased inflammation and intestinal permeability (paracellular).[12,13] Such an inflammatory microbiota profile is readily detected and characterized via a highly focused PCR-based dysbiosis test.[11]

An abundant and diverse microbial community is essential for the maintenance of the intestinal barrier function and normoglycemia. Adequate intake of soluble fiber and GI eubiosis provides a balanced abundance of short-chain fatty acids (SCFA) that regulate several aspects of host metabolism related to adiposity and MetS.[14,15] Butyrate and propionate stimulate proliferation of enteroendocrine L-cells and their release of glucagon-like peptide-1 (GLP-1). GLP-1 regulates post-prandial glycemic control and satiety and attenuates LPS-induced inflammatory pathways in VAT.[14] Butyrate and acetate stimulate β-oxidation of fatty acids in lean tissues and the constant secretion by Goblet cells of mucins that constitute the critical mucus barrier gradient.[16] The status of colonic SCFAs can be indirectly assessed via a stool specimen.

Obesity is associated with an entanglement of cardiometabolic risk factors, including dyslipoproteinemia, dysglycemia, low-grade inflammation, and endothelial and renal dysfunctions. Beyond a dated lipid profile, lipoprotein-related cardiometabolic risk considerations include the serum levels of triglycerides and non-HDL cholesterol, and the levels and ratios of apolipoproteins A-I and B. Also, very important are the levels of the specific low-density lipoprotein (LDL) culprits, oxidized LDL, small dense LDL, and Lp(a), which are independent of total LDL cholesterol. The potential cardiometabolic effects of high-density (HDL) and low-density (LDL) lipoproteins are not well predicted based upon the traditionally measured lipoprotein cholesterol levels.[17] Higher apolipoprotein B (apoB) levels, lower HDL-associated apolipoprotein A1 (apoA1), and a higher apoB/apoA1 ratio have strong predictive value with respect to cardiometabolic risk and outcome.[18,19] A high level of oxidized LDL (Ox-LDL) is a strong independent risk factor for CAD.[20] In the CARDIA study Ox-LDL was also associated with

continued on page 30 ➤

CARDIOMETABOLIC PROFILE



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➤ *continued from page 28*

incidence of MetS, and its components of abdominal obesity, hyperglycemia, and hypertriglyceridemia.[21] Fasting triglyceride levels are not recognized as an independent risk factor for CAD, but mechanistically very low density lipoprotein (VLDL) triglycerides have a pivotal role in an atherogenic lipoprotein profile. An expanded VLDL triglyceride donor pool initiates formation of atherogenic small dense LDL (sdLDL) particles via the activity of the plasma lipid transfer protein.[22] Subsequent hydrolysis of the acquired LDL core triglycerides results in sdLDL. The sdLDL more readily infiltrate the endothelium where the antioxidant-poor sdLDL are susceptible to oxidation by macrophages in the arterial wall.[23,24] The LDL-like Lp(a) is also associated with atherogenesis as it is taken up in an unregulated manner by macrophages, and appears to have distinct prothrombotic and proinflammatory properties.[25,26]

The activity of macrophage-derived lipoprotein-associated phospholipase A_2 (PLAC) provides important information regarding vascular inflammation and plaque instability.[27] Oxidized lyso-phospholipids and fatty acids released by PLAC activity on the surface of LDL particles contribute to oxidation of LDL (Ox-LDL) and endothelial inflammation. Concomitantly elevated serum levels of PLAC activity and CRP are associated with greater risk for coronary and stroke events.[28]

Excess VAT, MetS, and CAD are conditions associated with altered adipokine metabolism. Adiponectin is an abundant adipocyte-derived adipokine that effectuates anti-inflammatory, anti-oxidative, antidiabetic, and vascular protective mechanisms. Excess VAT and MetS are associated with decreased expression of adiponectin, hypoadiponectinemia, and higher levels of opposing leptin.[6,29,30] A high leptin-to-adiponectin ratio coupled with elevated hsCRP has strong predictive value for CAD.[31,32]

Serum insulin and dysglycemia may be assessed directly in the fasted state, and time averaged glycemic control over the past two to three months is indicated by serum levels of HbA1C. However HbA1C levels do not provide information regarding maximal hyperglycemic episodes that are independently associated with CAD and renal damage in type 2 diabetics.[33] Beyond HbA1C, an abnormally low serum level of 1, 5-anhydroglucitol (Glycomark™) provides specific information regarding daily hyperglycemic episodes over the past one to two weeks. Renal dysfunction associated with cardiometabolic disorders may be thoroughly assessed via serum cystatin C, creatinine and estimated GFR. The level of cystatin C is an excellent inversely related indicator of diminished glomerular filtration, and predictor of subclinical CAD in diabetics.[34,35]

The prevalence of excessive adiposity among youth and adults will likely have significant long-term cardiometabolic consequences. Early detection of metabolic disruptions and clinical intervention are paramount towards stemming the tide of the epidemic. The GI microbiota and its net metabolism have a central role in the initiation and progression of metabolic and cardiovascular complications. Comprehensive stool analysis inclusive of a highly focused PCR-based dysbiosis test facilitates confident identification of a dysfunctional microbial community. Modern research-based laboratory testing provides clinicians with more specific serum-based metabolic biomarkers that have high predictive value for cardiometabolic disorders. Such a complete kit may also fulfill the monitoring and motivational needs of clinicians.

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David Quig, PhD, received his BS and MS degrees in human nutrition from Virginia Tech and a PhD in nutritional biochemistry from the University of Illinois. After a five-year stint as a research associate studying lipid biochemistry and cardiovascular disease at Cornell University, he worked as a senior cardiovascular pharmacologist for seven years with a major pharmaceutical company. For the past 22 years, David has served as the Vice President of Scientific Support for Doctor's Data, Inc. He has focused on toxic metals, methylation and amino acid metabolism, the clinical application of the biochemistry of endogenous detoxification, and the influence of the gastrointestinal metabolome on health and sustained adverse conditions. David regularly speaks at national and international medical conferences and has facilitated and co-authored an array of studies, spanning exposure and retention of environmental toxicants, nutritional status, and gastrointestinal dysbiosis.

Topical Therapy with Estradiol, Progesterone, and Testosterone and Their Distribution in Saliva, Capillary Blood, Serum, and Urine

by David T. Zava, PhD

The use of saliva and finger-prick capillary blood (dried blood spot – DBS) for testing sex steroid hormones (estradiol – E2, progesterone – Pg, testosterone – T) was developed out of the need to circumvent some of the problems and inconveniences of collecting venipuncture blood. Comparison of saliva and capillary DBS has shown that when these hormones are produced endogenously, they show excellent correlation with serum/plasma tests,[1,2] and to some extent urine sex steroid metabolites.

While the quantitative equivalencies of saliva, capillary blood, and serum/plasma are excellent when hormones are produced endogenously, we and others[2,3] have shown that with topical (percutaneous) delivery of sex hormones, saliva and capillary DBS levels of hormones are strikingly different from conventional venipuncture serum and urine levels of the supplemented hormones. Topical steroid hormone therapy with increasing dosage results in very little, or only a very slight, dose-related increase in conventional venipuncture serum or urine metabolite levels of the dosed hormone (Tables 1-3). In striking contrast, topical dosing results in a relatively linear dose-dependent escalation of hormone in saliva and capillary blood DBS. In fact, saliva and capillary whole blood levels for the sex hormones delivered topically no longer show quantitative equivalence and often exceed serum levels by as much as 10-to-100-fold.[2]

Because topical sex hormone therapy at physiological dosing has little impact on venipuncture serum or urine levels of the dosed hormones but raises salivary and capillary blood levels to high physiological levels, this has led to the question of what topical dose (physiological or pharmacological) is more effective and appropriate for achieving physiological levels of hormones in *tissues*. It also begs the question: why are saliva and capillary blood levels so much higher, and serum and urine levels so much lower, with conventional pharmacological dosing of topical E2 and Pg in women and topical T in men, as seen in Tables 1-3?

Most noteworthy and often unappreciated is that *physiological* dosing with the sex hormones, meaning that the dose used topically is equivalent to the amount of sex hormone produced daily by the ovaries, testes, and/or adrenal glands (see Table 4), leads to physiological levels in saliva and capillary blood (see Tables 1-3), but has little effect on increasing serum or urine levels from low menopausal/andropausal to healthy levels seen in young females and males (Table 4).

While physiological dosing of topical E2 (0.1-0.5 mg) and Pg (10-50 mg) in postmenopausal women and topical T (5-20 mg) in older men (>50 y/o) raises the capillary blood and saliva levels to physiological levels seen in healthy premenopausal women (Table 4) and in younger men, little change is seen in serum or urine levels until dosing approaches ➤

Table 1. Saliva, DBS, Serum, Urine with Topical Estradiol (E2) – ZRT Database.

	Saliva pg/mL	DBS pg/mL	Serum pg/mL	Urine µg/g Cr
Postmenopause (no E2)	0.8 (<0.5-1.3, N=28974)	30 (<10-49, N=1654)	9, 10, 10	(0.15-0.75)
0.1	1.7 (N=529)	60 (N=69)		
0.2	2.6 (N=332)			0.86
0.25	3.4 (N=625)	95 (N=109)	29, 25, 28	0.93
0.30	3.9 (N=239)			
0.50	4.3 (N=1117)			
1.0	6.8 (N=1208)	231 (N=99)	32, 30	
2.0	11.6 (N=985)	307 (N=80)	68, 68, 82	0.85
3-5	14.7 (N=585)	364 (N=40)	102, 161	1.02
Premenopause - Follicular	(0.5-1.7)	18-58		
Premenopause - Luteal	(1.3-3.3)	43-180		0.78-1.79
0.05 mg Transdermal Patch	1.3 (0.8-2.1, N=4782)	50 (31-78, N=369)		0.94 (0.46-1.77, N=55)

Refs: 2,4-10

high physiological or pharmacological amounts (Tables 1-3).

At the peak of the luteal phase (about days 19-21 of the menstrual cycle) where daily Pg production by the ovaries ranges from about 5-30 mg, venipuncture serum and fingerstick capillary blood (DBS) Pg levels are quantitatively nearly equivalent at about 5-25 ng/mL, with saliva about 1-2% of blood levels at about 50-300 pg/mL, and urine pregnanediol, a surrogate for Pg, levels are about 500-2000 µg/g Cr (Table 2). To achieve premenopausal luteal physiological ranges in postmenopausal women with topical Pg therapy only requires physiological dosing (10-30 mg) when measuring saliva and capillary whole blood[2,15] (Table 2). Even at pharmacological dosing with topical Pg, serum and urine never even reach physiological levels.[2,3,11,15]

Even with pharmacological topical sex hormone dosing, serum and urine levels of E2 in women and T in men rarely increase even to within mid-physiological ranges. Pharmacological dosing with E2 (>1-5 mg) in postmenopausal women, and T (>50-200 mg) in hypogonadal men[16], only increases serum and urine E2 and T from low to mid-physiological levels (Tables 1 and 3).

When T is synthesized endogenously by the testes at about 3-7 mg/day, serum/plasma and capillary blood levels of T in healthy men are quantitatively near equivalent (optimal range about 400-800 ng/dL), and salivary levels are at about 2% of serum/capillary blood T levels (optimal range about 80-160 pg/mL). When topical T is used in hypogonadal men (serum T <300 ng/dL) at FDA-approved pharmacological dosing (50-200 mg), it distributes into saliva and capillary blood at very high levels, with saliva and DBS levels of T about 10-to-20-fold higher (median ranges about 800-2500 pg/mL in saliva and 3000-7000 ng/dL in DBS – Table 3). In sharp contrast, this pharmacological dosing only increases T to mid-physiological range of about 400-600 ng/dL in serum, as reported by others.[13] In parallel with serum, urine levels rise only slightly with pharmacological T dosing.

In sharp contrast to pharmacological dosing (50-200 mg), topical dosing more in the physiological range of about 5-20 mg of T has little to any impact on serum/plasma or urine levels of T, but increases capillary blood T from hypogonadal to mid-range levels seen in healthy young men (500-800 ng/dL) (Table 3). The lack of a significant increase in serum and urine

Table 2. Saliva, DBS, Serum, Urine Progesterone (Pg) with Topical Pg Therapy – ZRT Database.

Body Fluid Tested Units of Measurement	Saliva pg/mL	DBS ng/mL	Serum ng/mL	Urine µg/g Cr
Baseline (no Pg Therapy)	20 (N=64404)	0.3 (N=2684)	<1	115 (N=180)
5-15	444 (N=13340)	11.1 (N=862)		214 (N=19)
20-30	510 (N=33113)	14.1 (N=2551)	<1	173 (N=76)
40-60	708 (N=21913)	18.1 (N=1785)	1-3 [ref #11]	161 (N=55)
80-120	1016 (N=8907)	27.4 (N=632)	<1 [ref #2]	303 (N=25)
150-250	1282 (N=2111)	20.2 (N=203)		429 (N=12)
Optimal Reference Range	100-300	10-30	10-30	1000-2000
Reference Range - ZRT	75-270	3.3-22.5	3.3-22.5 2-20 [ref #12]	579-1710

Refs: 2,8,11,12

Table 3. Saliva, DBS, Serum, and Urine Testosterone (T) with Topical T Therapy – ZRT Database.

Body Fluid Tested Units of Measurement	Saliva pg/mL	DBS ng/dL	Serum ng/dL	Urine µg/g Cr
Baseline (no T Therapy)	73 (N=34654)	281 (N=5901)	287 (N=4)	13 (N=233)
5-20	310 (N=3969)	1173 (N=1080)	241 (N=5)	14 (N=33)
25-<50	593 (N=2741)	2000 (N=639)	230 (N=1)	37 (N=7)
50-75	1153 (N=3223)	2884 (N=737)	286 (N=1)	26 (N=15)
80-120	1672 (N=1731)	5323 (N=451)	*	57 (N=4)
150-250	2692 (N=832)	6959 (N=155)	173 (N=2)	23 (N=3)
Optimal Reference Range	100-250	500-1200	500-1200	
Reference Range - ZRT	56-221	400-1200	400-1200	3.8-14.2

Refs: 13,14. *Insufficient Data

Table 4. Expected Synthesis of Estradiol (E2) and Progesterone (Pg) in Women and Testosterone (T) in Men vs. Median Serum Levels.

Patient status	mg E2/day	Serum E2	mg Pg/day	Serum Pg	mg T/day	Serum T
Premenopausal						
- Early Follicular	65-100	40-60	< 1	< 1		
- Mid Follicular	100-160	60-100	< 1	< 1		
- Ovulatory	320-3640	200-400	1-2	1-3		
- Luteal	100-300	100-200	10-30	3-30		
Menopause	18	5-20	< 1	< 1		
Male	30-60	25-45	< 1	< 1	3-7	300-1200

Ref: 7

levels of topically delivered sex hormones to physiological ranges (Table 4) at physiological dosing (i.e., about 50-300 µg E2 and 5-30 mg Pg in women and 5-20 mg T in men) (Tables 1 and 3), has resulted in justification of dose escalation of FDA-approved and compounded products to amounts that are 10-to-20-fold higher (i.e., 500-5000 µg E2 and 100-300 mg Pg in women and 50-200 mg T in men) than levels of these hormones that are produced daily by the gonads of healthy young women and men (Table 4).

These data suggest that at least for topical E2 and Pg in women, and topical T in men, serum and urine underestimate by at least 10-fold the amount of topically delivered hormones distributed to the salivary gland and capillary beds of the fingertip, which are likely representative of other tissues throughout the body.

In support of the concept that saliva and capillary blood levels of hormones with topical physiological dosing more accurately represent tissue uptake and response than serum blood or urine levels, studies have evaluated target tissue levels of hormones and tissue response to the topical delivery of the sex hormones E2 and Pg in human breast and uterine tissues.[8,17] Chang and coworkers looked at the levels of E2 and Pg in breast biopsies and tissue response (increase or decrease in mammary cell proliferation) following topical E2 (1 mg) and Pg (25 mg) application directly to the breasts of women.[8] Mammary tissue levels of hormones, determined by breast biopsy following therapy with topical E2, Pg, or placebo showed a 100-fold increase in breast tissue E2 and Pg and marked Pg inhibition of E2-stimulated mammary cell proliferation. Not surprisingly *serum* levels of E2 and Pg in these women showed no significant change from patients treated with topical E2 and Pg vs a placebo topical cream. Similar results have been reported for physiological dosing of Pg (30 mg) that protected the uterus from overstimulation by conjugated estrogens and transdermal E2.[17,18] These data are in line with studies[2,3] and Tables 1-2, showing that physiological doses of topical E2 and Pg raise salivary and DBS levels of E2 and Pg to high physiological levels but have little impact on serum or urine levels of these hormones.

Topical Therapy

Topical hormone delivery is often described as a "first-pass" type of delivery meaning that it circumvents the liver when it first enters the bloodstream and in doing so does not induce steroid binding proteins (SHBG, CBG, and TBG) or increase clotting factors. However, as we and others have found, in the context of topical hormones "first-pass effect" is more likely a misnomer because even with continued long term use, topically delivered hormones never increase to any significant extent in serum or urine, or affect liver synthesis of hormone binding globulins, in contrast to what is seen when the liver is exposed to high levels of circulating estrogens with other forms of estrogen therapy (e.g., oral, intramuscular/subcutaneous, pellet, troche, sublingual). Based on the evidence that progesterone never accumulates in serum or urine with prolonged therapy[2] (Table 2), a more appropriate description for topical sex hormone therapy, at least for progesterone, would be a "no-pass effect." ➤

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What is the evidence that topically delivered hormones might transmigrate through the skin into the lymphatics instead of the blood vascular system? From pharmacokinetic studies[2] we know that when a steroid hormone is delivered as a cream or gel to the surface of the skin, it takes about two-to-six hours before it peaks in saliva or capillary blood from the fingertip, and then begins to slowly decline to baseline within 12-36 hours. If hormones were passing from the skin into the blood vascular system directly, levels in serum and capillary blood would be near equivalent as seen for endogenous production of these hormones, and salivary levels would be about 2% of blood levels,. They are not. Saliva and fingerstick blood represent hormones present in the interstitial fluid of capillary beds. Venipuncture blood serum and urine are more representative of hormones outside the capillary beds and interstitial tissue.

These clues and emerging research into topical sex hormone delivery into different body fluids strongly suggest that the sex steroids mostly are not being delivered to tissues by the blood vascular system, but instead point to another system of delivery, the most likely of which is the lymphatics, as elaborated by others.[3,15] If correct, this might suggest that topical hormone therapy will be more beneficial for tissues with high lymphatic infiltration, such as the reproductive tissues (breasts, uterus), brain, and immune system, all targets for female hormone therapies. It might also mean that tissues with less lymphatic infiltration, such as the bones and skeletal muscle,[19] would receive less hormone and be affected less. If so, *topically* delivered sex hormones such as E2 and Pg would be less effective in promoting bone growth in postmenopausal women suffering from osteoporosis, and T would be less effective in increasing muscle mass in men and women suffering from sarcopenia caused by androgen deficiency.

That the breasts and uterus are heavily infiltrated by lymphatics and the brain by the glymphatic system is consistent with the effectiveness of physiological sex hormone replacement therapy in these tissues and for physiological (10-30 mg) Pg dosing being able to counter the growth-promoting actions of estrogens in the breasts[8] and uterus[17,18] without raising serum levels of Pg (Table 2). Glymphatic delivery of Pg and Pg metabolites such as allopregnanolone to the brain would also explain how physiological (10-30 mg) topical Pg might help reduce anxiety, create calmness, and promote sleep as seen with higher dose (100-300 mg) oral progesterone.[20] Because topical Pg does not raise serum levels of Pg, very little research effort has focused on percutaneous Pg therapy for benefits of insomnia; however, recognition that the brain glymphatic system might facilitate transport of topically delivered Pg would spur new interest in the use of physiological topical Pg for insomnia.

In men topical T even at high dosage has much less impact on muscle development relative to other forms of T therapy that increase *serum* levels of T (e.g., im/sc injections, pellets). This is attributed to poor absorption of topical T. However, topical T at pharmacological dosing (50-200 mg) does have a significant impact on brain function as it relates to activation of dopamine receptors and well characterized actions of dopamine to increase aggression, pleasure-seeking activities, and risk-taking behaviors.[21]

In summary our results presented in Tables 1-3 derived from tens of thousands of female and male patients who have used different doses of topical E2, Pg, and T and tested saliva, capillary blood, serum, and urine metabolite levels of these hormones, reveal that serum and urine provide a less accurate means to monitor topical hormone therapy but are fine for measuring endogenous hormones, or sex hormones delivered by most other methods (e.g., transdermal patch, oral, troche, pellet, or im-sc injection).

Saliva or capillary whole blood (DBS) testing provides a more accurate picture of topical doses needed to achieve physiological levels of these hormones in the capillary beds that are nourishing tissues. Continued use of serum or urine for establishing dosing regimens of topically delivered hormones could, and likely will over time, lead to excessive tissue exposure, which could down-regulate (tachyphylaxis) sex hormone receptors and diminish tissue response to the hormone, thereby leading to hormone deficiency symptoms which the hormone therapy was meant to alleviate.

Dr. Zava earned his PhD in biochemistry and has extensive experience researching hormones and breast cancer. He established ZRT Laboratory in 1998 to provide health care practitioners and patients with a deeper understanding of the role hormones play in wellness, and remains a strong advocate of wellness through preventative health. He is the co-author of *What Your Doctor May Not Tell You About Breast Cancer* and the author of many peer-reviewed articles.

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Longevity, Cardiovascular Disease, and Taurine

by Pushpa Larsen, ND

Japan enjoys the second longest life expectancy in the world at 85.03 years, exceeded only by Hong Kong with a life expectancy of 85.29 years, a difference of about three months.[1] Japan also has the lowest rate of cardiovascular mortality with a mere 31 deaths from ischemic heart disease per 100,000 people.[2] (In comparison, Canada ranks 16th and the US 46th in longevity, and have 86 and 110 deaths form ischemic heart disease per 100,000 people, respectively.) In 1982, a Japanese researcher, Yukio Yamori, proposed to the World Health Organization a worldwide epidemiological study to investigate the relationship of diet with hypertension and cardiovascular mortality. The original study was accomplished over a period of 20 years and eventually included 61 populations in 25 countries. Over 14,000 participants, evenly divided between males and females and ranging in age from 48-56, participated.[3-6]

The CARDIAC study (**CAR**diovascular **DI**sease and **A**limentary **C**omparison) used the 24-urine taurine level as a marker for seafood intake. One of the most interesting findings was the comparison of Japanese Okinawans still living in Okinawa and those who had emigrated to Brazil, of which there were two populations studied: Okinawans living in Sao Paolo close to the southeast coast of Brazil, and Okinawans living in Campo Grande, more than 600 miles inland. Of the Japanese, Okinawans have the longest life expectancy and the lowest mortality from cardiovascular disease. Both Brazilian populations of Okinawans had substantially lower taurine levels than Japanese Okinawans. This is not surprising as the Brazilian diet has considerably more roasted meats and less seafood than a traditional Japanese diet. Taurine levels were lowest in Okinawans living in Campo Grande – far from a source of fresh seafood – who ate fish on average only once every two weeks. The lifespan of this population was a stunning 17 years shorter than Okinawans living in Japan, *"an effect related to the very high IHD mortality. Low fish consumption and reduced T intake appeared to increase IHD."*[4]

Taurine Basics

Taurine, more formally known as 2-aminoethanesulfonic acid, is chemically a very simple compound: $C_2H_7NO_3S$. It is ubiquitous in the tissues of most mammals and is particularly high in cardiac and skeletal muscle as well as the brain, the retina, and other neural tissue. Its effects on cells is both wide-ranging and profound. Its name hails back to ox bile, *Bos taurus*, from which it was first isolated.

Taurine is classified as a conditionally essential amino acid. It does not participate in the formation of proteins and does not meet the technical definition of an "essential" amino acid, in that it can be synthesized in the body. It is synthesized from methionine and cysteine in the pancreas, liver and other tissues, albeit at fairly low levels. Humans do, however, retain taurine in the tissues in greater amounts than some other species and do not often develop the overt deficiency symptoms seen in cats and foxes.[7] The main source of taurine is dietary and a lack of taurine in the diet can have severe repercussions on health, as seen in the Campo Grande population of Okinawans. Ripps and Shen, in their review of its functional properties, assert that taurine is *"undoubtedly one of the most essential substances in the body."*[8]

Mechanisms and Actions

Taurine has a number of functions that result in cytoprotection. These are summarized well by Shaffer, et al. as displayed in Table 1. These mechanisms include antioxidant actions, improvement of energy metabolism, modulation of gene expression, mitigation of endoplasmic reticulum stress, neuromodulation, quality control and detoxification, calcium homeostasis, and osmoregulation. This last is a particularly important cytoprotective function of taurine. All cells are sensitive to fluctuations in volume that can lead to cell death if not properly regulated. The uptake and release of taurine allows cells to maintain a normal volume in the face of osmotic stress from other sources. The osmoregulatory function is important for cell survival in all types of cells. [7,9]

Taurine has been shown to mitigate mitochondrial oxidative stress induced by a wide array of substances, including "ozone, nitrogen dioxide, bleomycin, amiodarone, arsenic, iron, Adriamycin and catecholamines."[7] Taurine seems to also hinder oxidative stress by protecting antioxidant enzymes from the effects of reactive oxygen species (ROS) generated by the mitochondria. There are a number of conditions in which the body's inability to deal with ROS overproduction is a contributing factor. Among these are cardiovascular disease, renal injury induced by diabetes,

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inflammatory diseases, lipid peroxidation of photoreceptors in the eye, reperfusion injury, and several neurological diseases, all of which may be improved with taurine.[8] Taurine does not directly scavange free radicals other than HOCl, which is thought to help limit myocardial damage. However, taurine may help regulate the generation of ROS in the mitochondria, which can slow down the series of events leading to an apoptotic cascade.[9]

The various mechanisms by which taurine exerts its benefits could fill (and has filled) several articles and is beyond the scope and intention of this one. What is striking is that taurine's many actions affect cells of all types, which suggests that a taurine deficiency could lead to a wide range of symptoms. For example, quality control and detoxification, by which the body restores or eliminates damaged cells and organelles, decreases in taurine-deficient cells. Taurine regulates crucial ratios that help stabilize some membranes, affecting their fluidity as well as transport activity and the activity of enzymes associated with the membranes. Because of the broad effects of a taurine deficiency, it follows that taurine as a therapeutic may have similarly broad applications.

Table 1. Cytoprotective Actions of Taurine

Antioxidation
Anti-inflammation by neutralization of hypochlorous to produce taurine chloramine
Diminishes superoxide by conjugating with uridine of $tRNA^{Leu(UUR)}$ in mitochondria
Generates ATP by encoding mitochondrial ND6 protein
Prevents mitochondrial membrane permeability and apoptosis
Benefits mitochondrial disease, MELAS by providing substrate for taurine conjugation
Energy Metabolism
Activates complex I and NADH sensitive enzymes by reducing NADH/NAD+ ratio during glycolysis
Restores fatty acid oxidation by increasing PPARalpha levels
Conjugates bile acids to facilitate lipid absorption by intestines
Gene Expression
Changes transcription profile of metabolism-related genes
Modulates genes to induce longevity
Changes transcription factors
Modulates protein phosphorylation and cell signaling
Endoplasmic Reticulum (ER) Stress
Attenuates ER stress by improving protein folding
Ameliorates stroke brain injury by inhibiting ER stress
Protects neurons in stroke and Alzheimer's disease
Neuromodulation
Protects CNS by agonizing GABAA , glycine and NMDA receptors
Decreases seizures by binding with GABAA receptor
Protects against seizures by elevating glutamic acid decarboxylase
Quality Control
Protects cardiomyocytes by activating ubiquitin-proteasome system and autophagy
Attenuates toxin-mediated autophagy
Ca^{2+} Homeostasis
Protects heart and brain during MI and stroke by diminishing Ca^{2+} overload
Taurine loss during ischemia-reperfusion protects heart by reducing hypoxia-induced Ca^{2+} overload
Taurine depletion leads to cardiomyopathy due to reduced activity of SR $^{Ca2+}$ATPase
Protects brain neurons during epilepsy by inducing Ca^{2+} binding proteins
Protects neurons against glutamate excitotoxicity by reducing glutamate-induced elevation of $[Ca^{2+}]$
Osmoregulation
Serves as an organic osmolyte

Adapted from Schaffer, S., & Kim, H. W. (2018, May 1). Effects and mechanisms of taurine as a therapeutic agent. Biomolecules and Therapeutics. Korean Society of Applied Pharmacology. https://doi.org/10.4062/biomolther.2017.251

Taurine and Cardiovascular Disease

Taurine levels in myocardial cells is species dependent. Species with the fastest heart rates have higher levels of taurine. This has led some researchers to speculate that taurine is somehow associated to the heart's workload. Taurine is especially important in heart failure.

Congestive Heart Failure. The reduced contractile ability characteristic of heart failure is related to a set of conditions that are taurine dependent. Taurine-deficient hearts exhibit a loss of myofibrils thought to be related to increased apoptosis due to the lack of the regulatory effects of taurine. Taurine-deficient hearts are also less sensitive to calcium, an essential element in muscular contraction. Taurine is also important to the phosphorylation of a phosphoprotein found in the sarcoplasmic reticulum, phospholamban. When phosphorylated, increased Ca^{2+} uptake by the SR results in relaxation of the heart muscle.[9]

Taurine has been approved for the treatment of congestive heart failure in Japan for several years. In addition to relieving breathlessness with exertion and fluid retention, it can also reduce or completely eliminate the need for CHF drugs such as digoxin. Although increasing diuresis and improving contractile force are beneficial, perhaps the most important effect of taurine on CHF has to do with inhibition of norepinephrine and angiotensin II. These molecules decrease the contractile ability of the heart by increasing afterload pressure and other effects. Taurine has been found to

increase exercise capacity of CHF patients and may prolong lifespan.[7]

Hypertension. Taurine has proved to be effective in preventing hypertension from developing in several animal models. Various factors have been identified, including decreases in oxidative stress, sympathetic tone, and inflammation, combined with improved kidney function and Ca^{2+} homeostasis.[7] Two human clinical studies also found benefits from taurine for hypertension. Katakawa reported improved endothelial function which he attributed to taurine's effects in reducing oxidative stress.[10] In a study by Sun, 120 prehypertensive patients received 1.6 grams of taurine per day, or placebo, for a period of 12 weeks. Patients receiving taurine had decreases in both systolic and diastolic BP, compared to patients in the placebo wing of the trial, who experienced no decrease in BP. The higher the initial blood pressure, the greater improvement was seen with taurine supplementation.[11.]

Atherogenesis. Taurine has several beneficial effects on vascular tissue, which inhibit or reverse the atherosclerotic process. These include inhibition of apoptosis, inflammation, and oxidative stress, as mentioned above. Taurine can also reverse intima medial thickening and arterial stiffness, which probably account for some part of improvements in blood pressure.

Taurine inhibits proliferation of vascular smooth muscle cells in culture. Smooth muscle cell proliferation is a part of the cascade of events leading to intimal media thickening and the development of atherosclerotic plaques. Taurine is also important to the health of vascular endothelial cells, decreasing apoptosis and protecting them through its anti-inflammatory and anti-oxidant activity and the modulation of intracellular calcium. Dysfunction in endothelial cells cultured from smokers was attenuated by the addition of taurine, which upregulated the expression of NO synthase.[12]

Stroke. Stroke is a leading cause of death and disability. A main contributor to neuronal death during stroke is the large accumulation of glutamate in the synaptic clefts as glutamate uptake is compromised by lack of ATP to glutamate transporters. This ultimately results in influxes of Ca2+, compromised mitochondrial function and the generation of ROS, all of which contribute to cellular distruction.[13] Taurine helps protect cells from the toxic effects of excess glutamate by reducing the overload of calcium and reducing oxidative stress.[7]

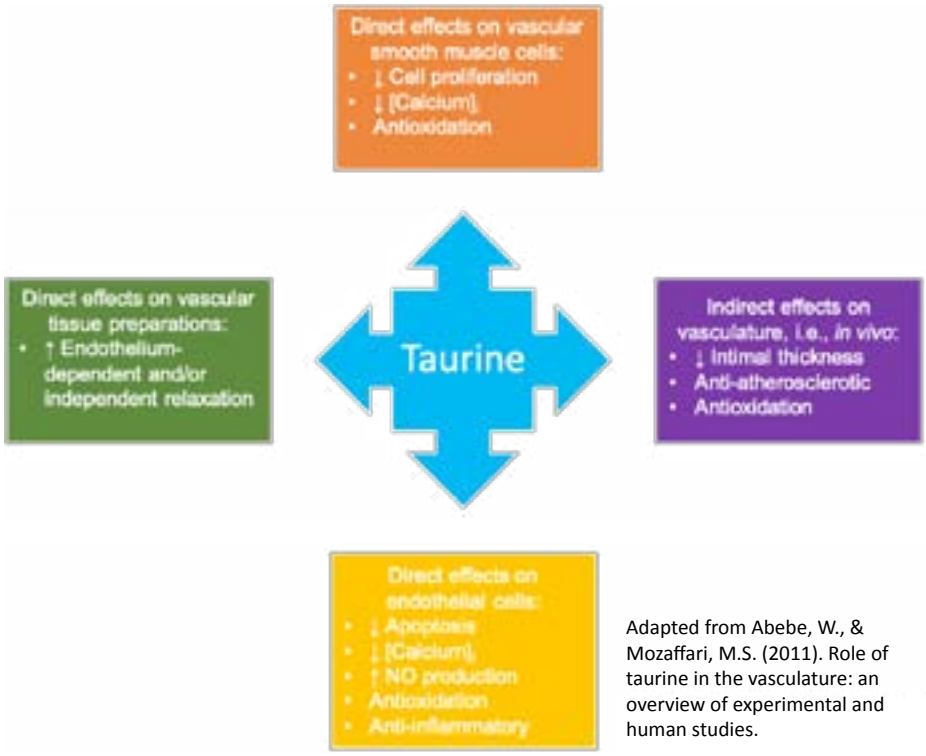
What Else Is Taurine Good For?

This article is focused on the cardiovascular benefits of taurine, but if we are considering longevity, it is worth mentioning a few other conditions in which taurine can be useful. A lack of taurine contributes to a broad range of pathologies, including renal dysfunction, pancreatic βcell dysfunction, and decreased vision to the loss of photoreceptors in the retina.[8] Supplemental taurine reduces markers for inflammation in obesity and may improve lean body mass.[7]

Diabetes. Schaffer and Kim assert, "There is overwhelming evidence that taurine therapy reduces pathology associated with diabetes, obesity and the metabolic syndrome."[7] Patients with Type I diabetes have low plasma and platelet taurine levels.[7] Taurine decreases advanced glycation end products (AGE) and lipid peroxidation in the kidney, thus improving diabetic nephropathy. [8]

Mitochondrial Disease. MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) is a mitochondrial disease that shares characteristic symptoms with taurine deficiency.[13] Supplementing MELAS patients with taurine has been helpful. In one such case a 29-year-old woman who had no response to standard pharmaceutical therapy for epileptic and stroke-like episodes, had a complete cessation of these events shortly after starting on oral taurine. In a second case, a 21-year-old male was diagnosed with MELAS and put on anticonvulsant therapy that did little to decrease his stroke-like episodes, which included visual loss and sensory aphasia. Upon starting taurine supplementation, the episodes ceased. In both cases the patients' serum levels of taurine increased by 5- and 10-fold, respectively.[7] Schaffer reports that taurine therapy also returns mitochondrial respiratory function to normal in these patients.

Taurine and the Eye. All ocular tissues contain taurine, although the retina has the highest levels.[8] In a normal retina, the concentration of taurine is at least 10 times that of any other amino acid.[8] Taurine is required for the survival ➤



Adapted from Abebe, W., & Mozaffari, M.S. (2011). Role of taurine in the vasculature: an overview of experimental and human studies.

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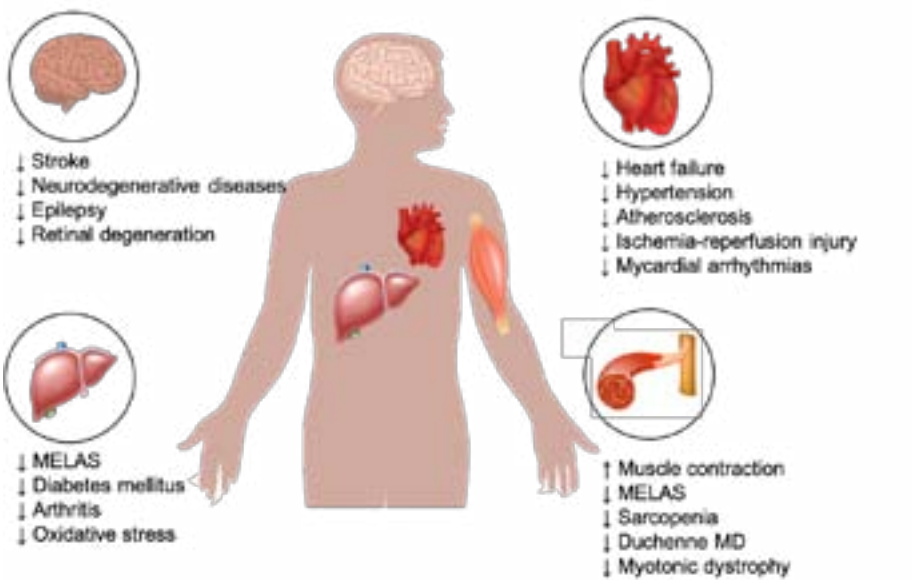
of retinal ganglion cells.[7] Taurine also protects rod outer segments from photic damage.[8] Severe degenerative changes to photoreceptors are common in animals that do not synthesize adequate levels of taurine, including cats, monkeys, and humans, if they do not get adequate dietary taurine.[8]

Of these criteria, taurine lacks only the identification of a post-synaptic receptor.[8]

Sarcopenia. Taurine is a common ingredient in nutritional formulas intended to improve sports performance and muscle development, and there are a number of studies that show improvement in exercise performance with taurine supplementation. Less researched, but germane to the issue of longevity, is whether sarcopenia in older



Adapted from Schaffer, S., & Kim, H.W. (2018, May 1). Effects and mechanisms of taurine as a therapeutic agent. Biomolecules and Therapeutics.

Taurine in the Brain. No brain region that has been tested fails to contain or uptake taurine: "At each of these sites, there is evidence of taurine's ability to ameliorate certain forms of neuropathology."[8] Taurine is a weak agonist of the $GABA_A$, glycine, and NMDA receptors.[7]

While taurine does seem to have some mild anticonvulsant effects, those effects are inconsistent.[8] In human clinical trials, about one third of patients had a reduction in epileptic seizures with taurine administration.[7]

Interestingly, taurine meets all criteria but one for the definition of being a neurotransmitter. Those criteria are 1) the enzymes and biochemistry necessary for biosynthesis exist in presynaptic neurons; 2) it is released by presynaptic depolarization and affects post synaptic cells, and the mechanism for doing that is calcium-dependent; 3) its action is terminated by degradation or re-uptake, and there is an antagonist; and 4) there is a specific receptor on post-synaptic cells.

men and women can be reversed or slowed with the use of taurine. Taurine plays a role in regulating two pathways involved in the degradation of muscle proteins and myocyte death, the calpain pathway and the capsase pathway. Both are calcium-dependent and taurine's regulatory effect on intracellular calcium concentrations helps keep these pathways in check. Taurine also appears to influence protein catabolism in aging muscle via the stimulation of inhibitory pathways.[14]

Dietary Sources of Taurine

Taurine is most abundant in shellfish such as scallops, oysters, clams, mussels, prawns, and octopus. It is also high in many saltwater fish. Taurine levels in freshwater fish were not found, but one source suggested that fresh had a higher capacity for synthesizing taurine than saltwater fish, so presumably fish of any kind would provide decent levels of taurine. Red meats contain some taurine, although significantly less than fish and shellfish. Best meat sources of taurine are dark meat of turkey and chicken. Dairy products and eggs contain relatively little taurine and one researcher found no detectable levels on taurine in legumes, nuts, or vegetables.[15]

Taurine levels in vegetarians and vegans are generally much lower than for omnivores.[16] In one study, plasma taurine levels in vegans were about 78% of the control values, and 24-hour urine taurine values were only 29% of control values. The difference between plasma and urine values becomes important when you are measuring taurine levels in your patients.

Testing for Taurine: Reference Ranges and Expected Ranges

I work for a lab that does taurine testing and was involved with the development of the taurine reference ranges. We chose to collect a 24-hour sample and report our results in µmoles/24 hours. The strong epidemiological research that assessed taurine levels worldwide used this collection period and unit of measure, and we wanted to be able to compare results, not to a "normal" population, but to what the research had demonstrated were healthy levels of taurine – the point at which cardiovascular disease mortality actually starts to drop. The results were very clear in the research. For men, that point is when they reach 24-hour urine taurine values of 2000 µmol/24h or more. Once taurine levels fall below 1000 µmol/24h in men, cardiovascular disease mortality rises steeply. For women, the steep rise begins when taurine levels fall below 750 µmol/24h.

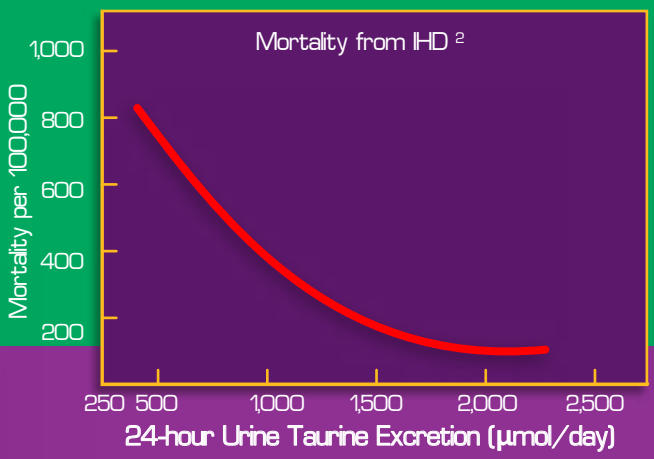
Laboratories, including ours, usually develop a reference range based on collecting samples from a large group of "normal" individuals. The ends of the reference range are determined by calculating the standard deviation setting the range between two standard deviations on either side of the mean. That is a perfectly acceptable method to use for most applications, but there is a very real problem in using that method to assess taurine levels.

A "normal" population of individuals in the United States (or Canada) is probably not eating much fish or seafood. There will be some exceptions to this, but for most people, fish once every couple of weeks – like the Campo Grande population

continued on page 40 ➤

Did you know that your patient is at higher risk of dying from heart disease if they have low 24-hour urine taurine?

In studies of 41 population samples from 25 countries, comprising more than 3,900 men and women, researchers found the highest mortality from heart disease in populations with the lowest 24-hour urine taurine levels.[1]



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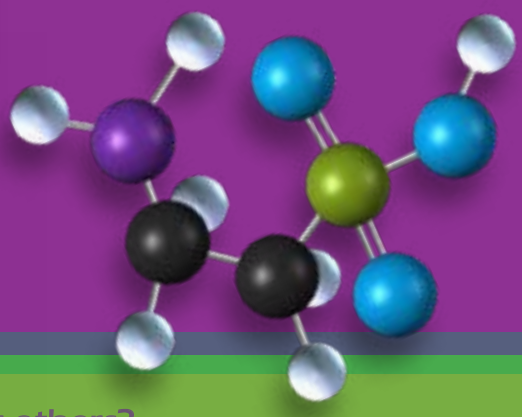
Taurine



Why should you choose the MVL taurine test over others?

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- Urine taurine results compared to established cut-off values for men and women reported in published research studies
- Excellent agreement with published research so that patients with results below cut-off values can be identified as being at higher risk for cardiovascular disease
- Experienced in-house physicians available for consultation on testing for your patient, interpretation of results and treatment options

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1. Yamori, et al. *Journal of Biomedical Science* 2010, 17(Suppl 1):S21
2. Adapted from Yamori, et al. *Adv Exp Med Biol*; 2009:13-25.

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Taurine

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– is probably closer to the norm. So if we set a reference range based on that norm, a patient with very low taurine values could easily be within the normal reference range. Since the purpose of this test is to assess cardiovascular mortality risk in order to better treat our patients, knowing that they are "normal" is not that useful. Remember, the US ranks 46th in longevity and has more than three times the number people dying from heart disease as Japan. Rather than using a "normal" reference range, we chose to use an "expected" range, in which the patient's values are measured against what the expected levels would be in a healthy – or in this case, lower risk – population.

A second thing to consider is whether plasma levels can be "translated" to urine values for the purposes of assessing risk. Aside from the differences in collection, methodology and units of measure, the difference between plasma and urine values is dramatic, as seen in the study of taurine levels in vegans. Urine values when compared to the control group told a much different story than plasma levels. This underscores the importance of using a 24-hour urine sample to measure against the expected urine range for a *low risk* population.

Supplementing with Taurine

What if your patient doesn't like fish, or is allergic to fish? Or what if they are a committed vegan? Is supplemental taurine as beneficial as taurine obtained from eating seafood? Yamori, et. al., in their 1996 study, reported taurine levels in a Tibetan population which ate no fish or other meat because of their religious beliefs. This population also tended to eat a high amount of salt. As a result, about 40% of the population had high blood pressure, which was double the world average of 20% for hypertension prevalence. Many of these individuals, who ranged in age from 48-56 (or fairly young by today's standards), had severe hypertension, with systolic values over 200 mmHg. Yamori and his team did an intervention study with this group in which each person took 1 gram of taurine, in their tea, three times a day for a total of 3 grams of supplemental taurine daily. Within two months, subjects experienced a significant drop in both systolic and diastolic blood pressure.[3]

Three grams a day, in divided doses does seem to be a pretty typical dosing regimen for taurine. Taurine is a very inexpensive supplement and is available in capsules as well as powders that can be added to smoothies. It is also a common ingredient in so-called energy drinks or sports drinks. A 250 mL can of a popular energy drink contains 1000 grams of taurine. However, energy and sports drinks containing taurine may also include 90-300 mg of caffeine, as well as sugar or aspartame, and should not be considered a useful source for this nutrient in most cases.

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IgG Sensitivity Testing and Inflammation: Where and How Do IgE/IgG4 Fit?

by Andrea Gruszecki, ND

Introduction

The testing of immunoglobulin G (IgG) has been common in functional, naturopathic, and alternative clinical practices for years.[1] New research is shifting the conventional medical perspective on IgG measurements, and human studies are proving that IgG-immune system interactions can result in chronic, delayed, inflammatory reactions.[2,3] An improved understanding of the inter-relationship between various IgG immunoglobulin subclasses and IgE highlights the necessity of separate assessments for IgG subclasses 1-3 and IgG4. One of the likely reasons that it has taken so long for the science to catch up to clinical practice is that the early research was unable to differentiate the function and contribution of each individual IgG subclass during immune system activation. It is now clear that the use of total IgG ($_{tot}$IgG) in the evaluation of chronic inflammatory antigen (allergen) reactions is no longer appropriate. IgG subclass four (IgG4) is associated with immediate IgE-mediated reactions and has protective, anti-inflammatory properties, unlike the other potentially pro-inflammatory IgG 1-3 subclasses. The clinical management of IgG4/IgE differs from the management of the other IgG subclasses. To fully discern the nature of the immune system's response to foods and environmental antigens, and to provide proper patient care, IgG4 must be evaluated independently from IgG 1-3, and not as $_{tot}$IgG.[4]

IgG4, IgE and Immediate Hypersensitivity Reactions

Antigens are good inducers of IgG1, IgG4 and IgE. Type I immediate hypersensitivity reactions (or anaphylaxis) typically occur after antigen sensitization, when IgE antibodies are formed against the antigen. With additional exposures, the IgE binds to receptors on mast cells and basophils, which release histamine and pro-inflammatory mediators. Mast cell and basophil activation via IgE receptors cause the symptoms associated with type I sensitivity.[5] In patients with IgE-mediated allergy symptoms, increased production of allergen-specific IgE antibodies is observed, but often, there may be low production or lack of allergen-specific IgG1 and IgG4 antibodies due to acquired or inherited subclass deficiencies.[6] Approximately 2.5% of the general population has an IgG subclass deficiency which results in lower IgG levels and may exacerbate type I IgE reactions and symptoms.[7]

In the majority of individuals, IgG4 antibodies are induced by T-regulatory cells and are formed following repeated or long-term exposure to an antigen. IgG4 may become the dominant subclass during chronic exposures, raising IgG4 levels.[8] IgG4 antibodies can prevent IgE reactions through several mechanisms[3]:

- IgG4 can bind with receptors on mast cells and basophils, blocking IgE access. Unlike IgE, IgG4 binding does not promote the release of histamine or pro-inflammatory cytokines by basophils or mast cells.
- IgG4 induces the secretion of tolerant, anti-inflammatory cytokines from T-regulatory cells, reducing local and systemic reactivity.
- Circulating antibodies may be bound into complexes with IgG4. IgG4 is unique in that it often dissociates into two separate, smaller, monovalent antibody

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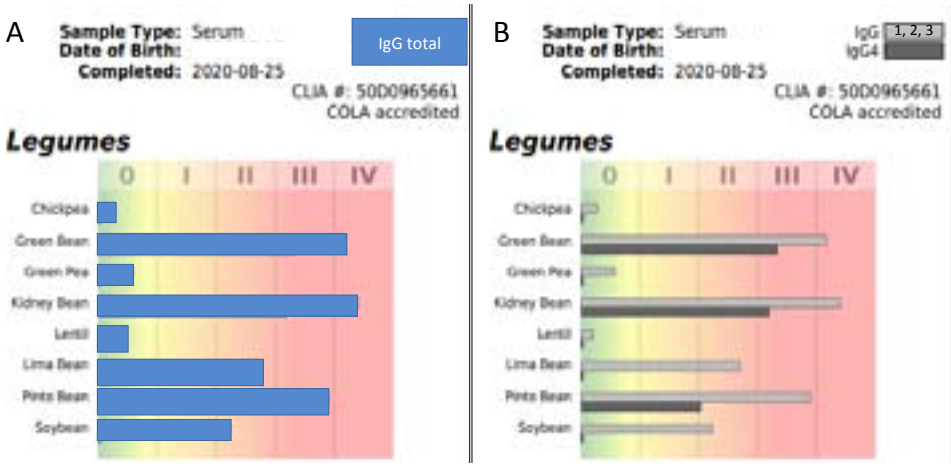
Figure 1. Which foods should be re-introduced? The results in figure A give no indication that certain legume reactions are IgE/IgG4-mediated. IgE-mediated foods should be avoided because their re-introduction may risk a Type I hypersensitivity reaction (anaphylaxis). The results in figure B clearly indicate that the re-introduction of green bean, kidney bean, and pinto bean may be contraindicated.



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"chains." The monovalent IgG4-antigen complex is small enough to be filtered and excreted by the kidneys before it deposits into tissues.

- IgG4 receptor binding may prevent pro-inflammatory, antigen-specific IgG1 and IgG3 "priming" of mast cells and basophils that carry both IgG and IgE receptors.

IgG and Hypersensitivity Reactions

Both complement activation and hypersensitivity reactions require multiple cell signals to manifest either tolerance or proinflammatory reactions. There are three types of hypersensitivity reactions mediated by immunoglobulin-antigen (Ig) interactions. Traditionally, type I immediate hypersensitivity has been considered IgE-mediated, while type IV hypersensitivity is considered an antibody-independent process.[5] The remaining two types of hypersensitivity have different mechanisms, but both types can be mediated by IgG 1-3 complement activation.

Type II hypersensitivity causes IgG antibody-mediated cell damage when normally tolerated environmental antigens are bound by IgG antibodies to the surface of circulating blood cells such as platelets or red blood cells.[9] The coated cells become targets for white blood cells, and the bound antibodies can either activate natural killer cells and cytotoxic T-cells or induce pro-inflammatory complement cascades that destroy the coated cells.[10] Immune system T-cells program antibodies for type II reactions during a first exposure, and reactions may then occur with subsequent exposures. Type II hypersensitivity can be involved in autoimmune reactions against cell surface proteins or extracellular matrix proteins if the environmental antigen is chemically similar to body tissues.[3] Classical type II reactions begin within 24 hours of exposure; these reactions commonly occur due to medication use, or as a response to infections (fungal, bacterial, viral). Medical conditions associated with type II hypersensitivity include loss of platelets (immune thrombocytopenia), loss of red blood cells (autoimmune hemolytic anemia), and loss of white blood cells (autoimmune neutropenia). Removal of the causative antigen resolves the symptoms over time.

After the initial antigen exposure, Ig antibodies begin to form in 4-10 days.[10] Type III hypersensitivity occurs when these antibodies combine with circulating antigens to form larger molecular complexes that can either bind to receptors on mast cells and leukocytes or induce pro-inflammatory complement cascades. When an antigen is in excess, these large circulating IgG 1-3 immune complexes eventually deposit into joints or tissues and result in local inflammation and tissue damage. Type III reactions may also occur if there is a failure by the immune system to remove the antibody-antigen complexes. Medical conditions associated with Type III reactions include joint inflammation, blood vessel inflammation (vasculitis), kidney inflammation (glomerulonephritis), systemic lupus erythematosus, and rheumatoid arthritis.[5]

IgG 1-3, Chronic Inflammation, and Complement Activation

The complement system is an important part of the innate immune system. Complement is a group of plasma and membrane-associated serum proteins that contribute to the local inflammatory response to antigens such as pathogens, damaged tissue, or foreign environmental proteins.[3] Only IgG 1-3 can activate complement; once activated, the complement pathway produces anaphylotoxins – smaller molecules that promote inflammation, vascular permeability, and inflammatory white blood cell responses. Anaphylotoxins can trigger inflammatory responses from both mast cells and basophils.[11] Sustained activation of the complement system can result in a loss of tolerance and can contribute to chronic inflammation.[12] Over time, sustained activation of complement can increase the risk of autoimmunity.

In contrast, IgG4 does not activate complement or participate in chronic, complement-mediated, inflammatory reactions. Instead, IgG4 can prevent such reactions by blocking white blood cell receptors stimulated by other IgE or IgG subclasses, by binding antigen in circulation, or through the inhibition of immune complex precipitation into joints or tissues.[3]

Allergy, Sensitivity, or Tolerance – What to Measure?

Human studies have demonstrated that IgE and IgG4 trend together in adults, and that IgG4 levels tend to be higher in those with atopic (allergic) IgE-mediated diseases.[13] This makes IgG4 an acceptable stand-in for IgE, as foods or aeroallergens with high IgG4 levels likely indicate the presence of an IgE-mediated type I hypersensitivity (classical "allergy").[14]

This knowledge then creates a dilemma for clinicians trying to interpret total IgG ($_{tot}$IgG) results. There is no way to discern from $_{tot}$IgG which high values are driven by inflammatory IgG1, IgG2, or IgG3 and there is no way to determine which $_{tot}$IgG values are elevated due to the presence of IgG4 blocking antibodies. IgG-mediated food antibodies commonly decrease when foods are eliminated, and many clinicians attempt food reintroductions after eliminating a food and "resting" the immune system from the antigen exposure for a period of time.[15,16] Since all of the IgG subclasses can be tested in either a serum or dried blood spot (fingerstick) format, it is a simple matter to run a separate test for IgG4 and IgG 1-3 when testing a sample.

When food testing is performed, it may not be appropriate to rotate or attempt the re-introduction of a food known to be IgE/IgG4-mediated, since the re-introduction may result in inflammatory symptoms or an anaphylactic reaction.[17] But, if only $_{tot}$IgG is measured, there is no way to know which foods are safe for attempted re-introduction (Figure 1).[18] It may also be imperative to remove or

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Her experiences in private practice evolved into an inclusive model of medicine for use by conventional and CAM providers, designed to allow cross-specialty communication among health care providers ("Forward into the Past: Reclaiming Our Roots Through an Inclusive Model of Medicine." *NDNR eNewsletter*, June 2013). She has presented at a variety of venues, including the American Academy of Environmental Medicine, Integrative Medicine for Mental Health, International College of Integrative Medicine, and the California Naturopathic Doctors Association.

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manage environmental IgE-mediated exposures to minimize the risk of food cross-reactions or type I hypersensitivity reactions to pollens, molds, pets, etc.[16,19,20]

The risk in re-introducing a food with a high IgG4 value lies in the fact that IgG levels can be variable.[21] Depending upon inheritance, nutritional status, infection, comorbid diseases, or medical interventions, IgG levels may not be consistent or reliable and acquired IgG deficiency may occur at any time.[22,23] Acquired IgG deficiency may decrease IgG subclass levels, including protective IgG4 to the point where IgE blocking is no longer possible. The loss of protective IgG4 makes type I IgE-mediated symptoms, including anaphylaxis, much more likely with additional antigen exposures, such as food re-introduction or seasonal exposures.[24]

Conclusion

An improved understanding of the inter-relationship between various IgG immunoglobulin subclasses and IgE highlights the necessity of separate assessments for IgG subclasses 1-3 and IgG4. If IgE-mediated allergens are incorrectly assumed to be IgG-mediated, then the measurement of total IgG can increase the risk of IgE-driven symptoms during food reintroduction, up to and including life-threatening anaphylactic reactions. Clinicians using IgG testing for food or aero-allergen (inhalant) sensitivity must be aware of the clinically relevant difference between IgG 1-3 and IgG4. With this increased awareness the measurement of IgG4 independently from the other IgG subclasses shall become the standard of care to correctly determine the proper treatment path for each antigen and each patient.

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Utilization of Whole, Fractioned, or Ground Teeth for DNA Microbial Testing: Is There a Difference?

by Leslie Douglas, PhD, Blanche D. Grube, DMD, and Anita Vazquez Tibau

Introduction

The impact that oral health has on whole body health is no longer a question; in fact, over 100 systemic diseases have been linked to poor oral health.[1] According to the World Health Organization (WHO) almost half of the global population has an oral disease of some kind.[2] Oral diseases include dental decay, gum disease, and oral cancers. While oral diseases are largely preventable, tooth decay is the most common disease globally.[3] What are now accepted as causative factors of oral cavities include oral microorganisms, oral environment, host, and time.[4]

The Center for Disease Control (CDC) has stated that periodontal disease affects almost 50% of those over 30 years old, and over 70% of those over 65 years old in the US. Statistically, periodontal disease is more common in men, those who are below the poverty level, those with less than a high school education, and current smokers.[5] Observation of oral microbiota is a major indicator for the occurrence, development, and prognosis of disease. Oral bacteria can be used as a biomarker to potentially measure disease risk.[6]

In the early 1980s, Kary Mullis, invented the polymerase chain reaction (PCR) method. This groundbreaking discovery led him to receive the Nobel Prize in chemistry, in 1993.[7] The use of PCR technology has become a mainstay in many disciplines and has been utilized in dentistry since its early stages. For example, in 1993 PCR was used to identify the periodontal pathogen *Porphyromonas gingivalis* in oral plaque samples.[8] *Porphyromonas gingivalis* has been linked to various pathologies such as rheumatoid arthritis, cardiovascular pathologies, and neurodegenerative pathologies.[9] Additionally, in 2005, open-ended PCRs were employed for genome mapping of the complete bacterial spectrum, leading to the development of the Human Oral Microbiome Database and CORE database.[8] In forensics, PCR is able to make identifications utilizing dental DNA, owing to the stability of teeth in either extreme temperature changes or decomposition.[10] PCR uses in dentistry include the following:

- Detection of periodontal pathogens,
- Detection of cariogenic pathogens,
- Detection of microorganisms involved with endodontic infections,
- Detection of viruses present in host cells: To detect human papillomavirus, hepatitis C virus, and other possible virus involvement in the etiology of periodontal disease,
- Detection of useful markers in diagnostic and prognostic of certain types of oral cancer,
- Quantitative estimates of various microorganisms.[11]

According to Levy, the principle source of chronic degenerative disease starts in the oral cavity as follows:

- Root canal-treated teeth (always chronically infected),
- Other chronically infected teeth (often asymptomatic),
- Chronic periodontitis (gum inflammation and infection),
- Cavitational gangrene, at the sites of old extractions,
- Chronically infected tonsils, secondary to the chronic drainage of infected teeth,
- Infected dental implants, and
- Toxic metals, like mercury and nickel (not necessarily associated with infection).[12]

There is an abundance of bacteria found in all oral tissue, the most common being various *Streptococcus species (oralis, mitis*, and *peroris*).[13]

Oral streptococci are deemed an early colonizer representing over 80% of the initial makeup of oral biofilm, which can influence the health or disease of its host. Oral streptococci are divided into five different groups:

- Mutans group (prominent members are *Streptococcus mutans* and *Streptococcus sobrinus*),
- Salivarius group (*Streptococcus salivarius*),
- Anginosus group (*Streptococcus anginosus* and *Streptococcus intermedius*),
- Sanguinis group (*Streptococcus sanguinis* and *Streptococcus gordonii*),
- Mitis group (*Streptococcus mitis* and *Streptococcus oralis*).[14]

Many of these organisms from these five different groups have been discovered in the oral samples sent for PCR testing from patients who were suffering from the symptoms caused by these exact microorganisms.

A 2006 study by Nakano et al, discovered *Streptococcus mutans* was often identified in the heart valve (69%) and atheromatous plaque (74%) specimens, noting that *Streptococcus mutans* may be a causative factor of cardiovascular disease.[15] *Actinomyces* are responsible for the development of dental plaque. These bacteria circulate into the intestinal tract and interact with other microbiota. These are a factor in assorted alimentary tract diseases such as inflammatory bowel disease and celiac disease.[16] Lu et al. found that *Prevotella intermedia* presented in higher levels in gout and hyperuricemia patients. This *Prevotella intermedia* orignates in the oral cavity.[17] The bacteria linked to periodontal health are *Streptococcus, Granulicatella, Neisseria, Haemophilus, Corynebacterium, Rothia, Actinomyces, Prevotella*, and *Capnocytophaga.*[13] As mentioned above, *Porphyromonas gingivalis* was identified in the early use of PCR. *Porphyromonas gingivalis* is found in chronic periodontitis and has also been identified as a significant risk factor for developing Alzheimer's disease.[9,18]

Capnocytophaga species are deemed to be an opportunistic pathogen originating in the oral cavity. *Capnocytophaga* species have been found in many infections of immunocompromised hosts, including lung infections, cancer, bone infections, endocarditis, and sepsis in newborns.[19]

A paper by Yang et al. found that even though *Corynebacterium* sp is considered normal respiratory flora, it has been implicated in pneumonia, and may be more prevalent than previously thought. [20]

Fusobacterium nucleatum is a Gram-negative anaerobe found in the oral cavity; however, in disease states, it becomes dominant and can disseminate throughout the body. *Fusobacterium nucleatum* has been linked to the following:

- Oral infections (aggressive periodontitis, gingivitis, endodontic infections),
- Adverse pregnancy outcomes (chorioamnionitis, preterm birth, stillbirth, preeclampsia),
- GI disorders (colorectal cancer, inflammatory bowel disease, appendicitis),
- Other conditions (atherosclerosis, cerebral aneurysm, Lemierre's syndrome, respiratory tract infections, organ abscesses, rheumatoid arthritis, Alzheimer's).[21]

Root Canal Teeth

Root canal failure can be caused by many factors such as:

- Persistence of bacteria (intra-canal and extra-canal),
- Inadequate filling of the canal (canals that are poorly cleaned and obturated),
- Overextensions of root filling materials,
- Improper coronal seal (leakage),
- Untreated canals (both major and accessory),
- Iatrogenic procedural errors such as poor access cavity design, and
- Complications of instrumentation (ledges, perforations, or separated instruments).

However, the most common cause of root canal failure is persistent bacterial infection.[22]

Montalvo et el. investigated how *Treponema denticola* influenced disease progression in endodontically treated teeth. *Treponema denticola* is commonly found in root canals and may cause tissue damage. Due to its pervasiveness, it may be responsible for periapical bone lesions. The genus *Treponema* has been linked to numerous chronic diseases, such as syphilis (*Treponema pallidum*), periodontal diseases (including chronic periodontitis and acute necrotizing ulcerative gingivitis), endodontic infections, and some acute dental abscesses.[23]

The pathogens of acute apical abscesses and asymptomatic root canal teeth were studied to evaluate the occurrence of the most common taxa using a two-step 16S rRNA gene-based PCR protocol. All samples found bacterial DNA. In abscesses, the most prevalent taxa were *Fusobacterium nucleatum ssp.* (60%), *Porphyromonas endodontalis* (53%), *Parvimonas micra* (51%), and *Streptococcus* species (45%).

The most frequently detected taxa in asymptomatic teeth were *P. endodontalis* (63%), *Dialister invisus* (58%), *Olsenella uli* (56%), and *F. nucleatum ssp* (51%).[24]

A systematic review by Muacevic et al. also found that the principal reason for endodontic failure is due to bacteria, with the most common culprit being *Enterococcus faecalis,* noting that it more likely found in asymptomatic cases than symptomatic cases. ➤

Figure 1. Pre-Ground, Fractioned Samples #18, #19

Figure 2. Kometa BioGrinder

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Enterococcus faecalis was also found to be highly resistant to disinfectant treatments.[25] Microorganisms found in root canal treated teeth such as *P. gingivalis*, *T. denticola*, *T. forsythia*, and *Solobacterium moorei* have been connected with osteomyelitis, bacterial endocarditis, brain abscess, obesity, and preterm low birthweight. Root canal infections can develop into systemic infections.[26]

Lačević et al explored the relationship between *Tannerella forsythia*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum,* and *Aggregatibacter actinomycetemcomitans* at dual sites in concurrent endodontic-periodontal diseases. They found in the sixty samples from both the endodontium and periodontium the following:

- *F. nucleatum ssp* (100% of both endodontic and periodontal samples)
- *T. forsythia* (93% of periodontal pocket samples; 90% in primary endodontic infection)
- *P. gingivalis* (53% of periodontal pocket samples; 70% in primary endodontic infection)
- *A. actinomycetemcomitans* (13% of periodontal pocket samples; 3% in primary endodontic infection)

They concluded that the endodontic bacteria most likely originated from periodontal pockets and that endodontic infections maintained periodontal pockets and periodontal infection.[27]

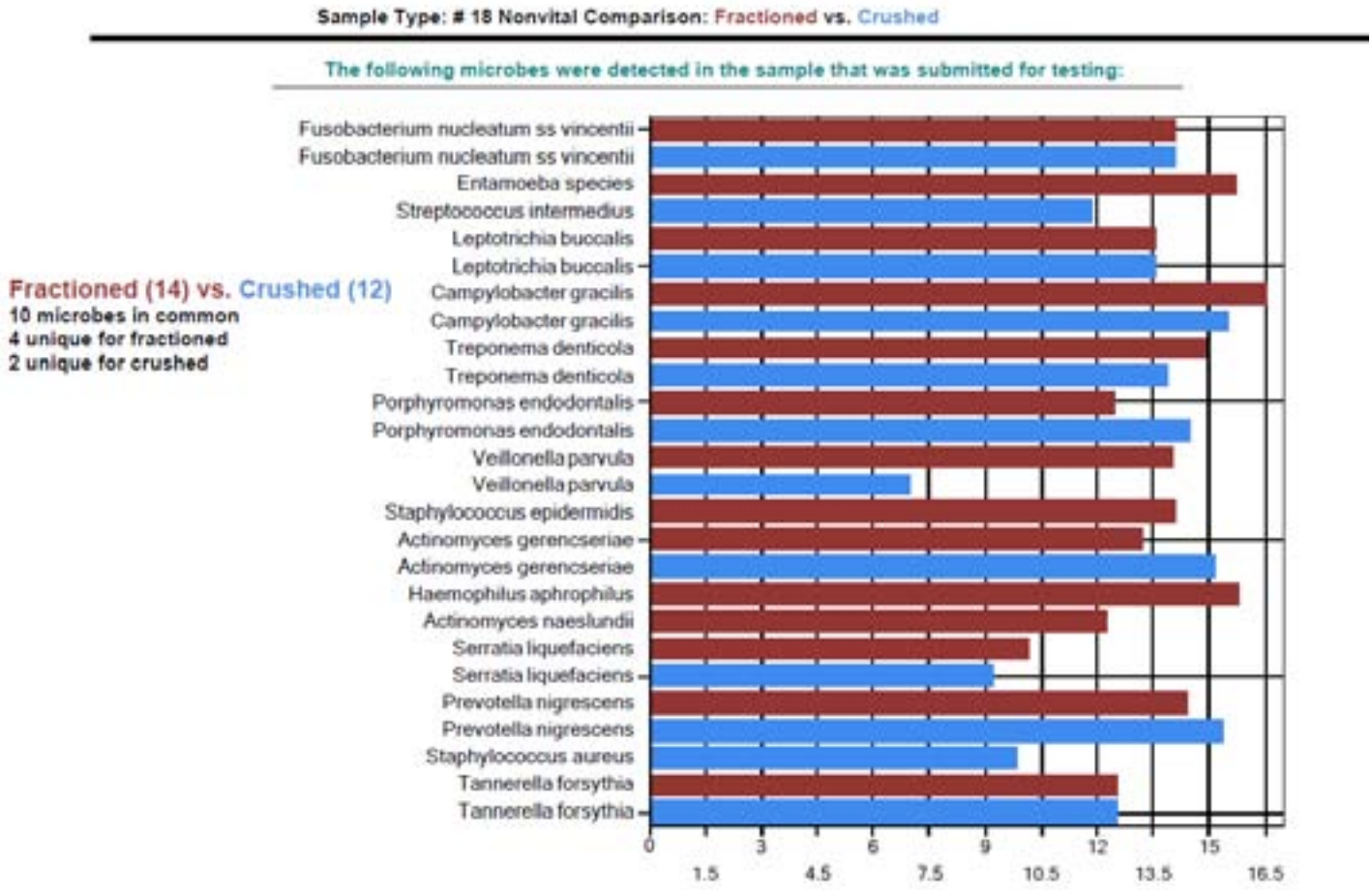
DNA ConneXions Oral Panel

The DNA ConneXions Oral Panel is a DNA PCR-based panel designed to detect the presence or absence of 88 microbes in oral samples. Sampling methods vary, inclusive of teeth, oral blood, bone, dental implants, Super Floss, etc. The question was raised if it is necessary to grind or otherwise fractionate whole tooth samples before employing our DNA extraction techniques. We hypothesized that a more robust and comprehensive microbial DNA extraction could be obtained by fractionating or grinding whole tooth samples. The objective of this study was to elucidate whether or not the porosity of teeth alone allows for the comprehensive release of the microorganisms of such solid samples.

Materials and Methods

The DNA extraction protocol employed at DNA ConneXions requires a 200 ul starting volume of sample. Blood, cavitations, and otherwise liquid samples submitted in volumes in excess of 200 ul are thoroughly homogenized

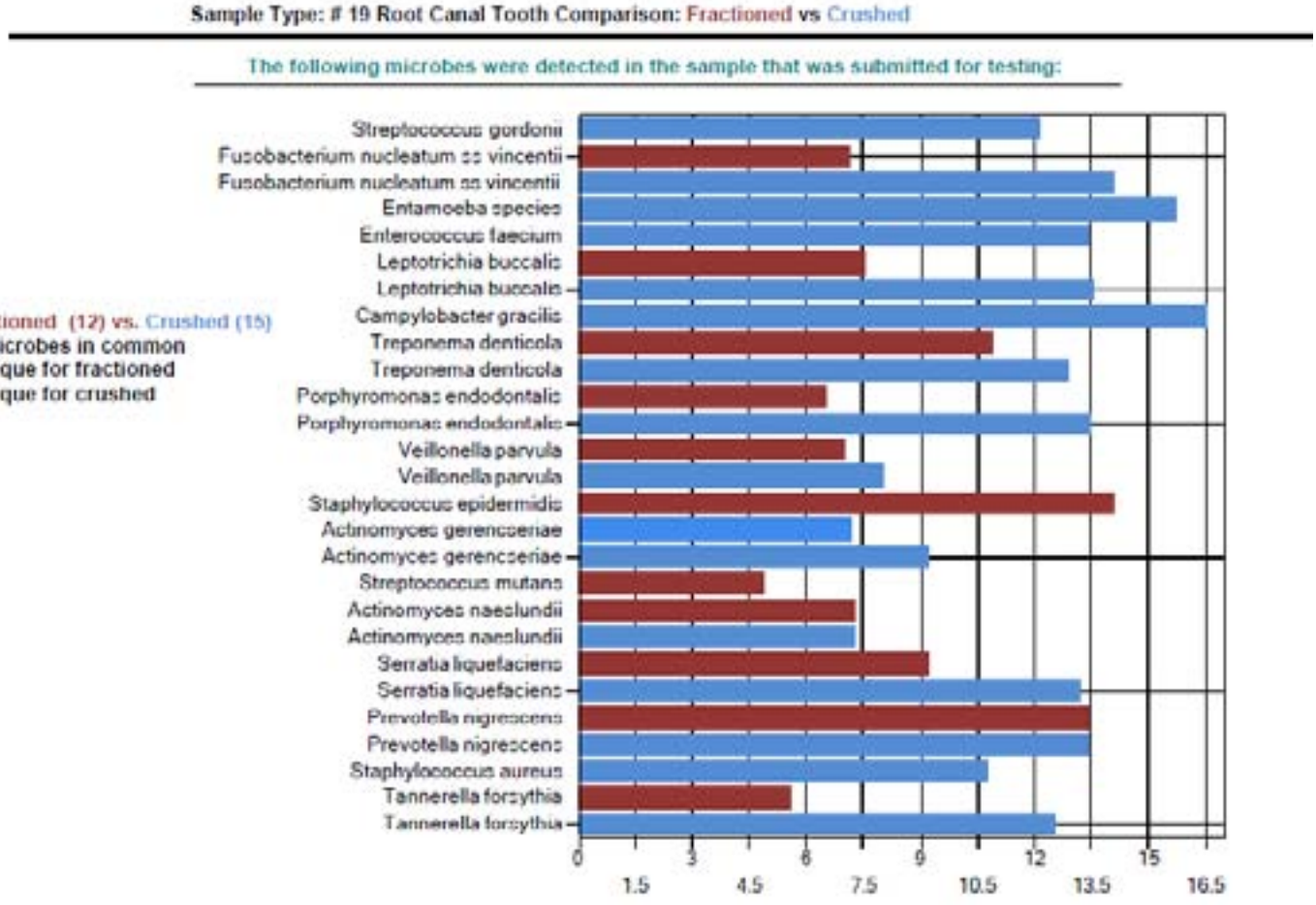
Figure 3. DNA ConneXions Oral Panel Results for # 18 Nonvital Tooth (Fractioned and Ground Comparison)



and 200 ul is aliquoted and purified to obtain a prepared DNA sample. The volume of liquid samples received that are less than 200 ul are supplemented with Molecular Grade Water and are thoroughly homogenized; and 200 ul is aliquoted and utilized. Considering other sampling types (Super Floss, Paper Points, etc.), predetermined volumes of Molecular Grade Water are added, is thoroughly homogenized and 200 ul is obtained for testing/purification. Teeth, implants, either dry or accompanied by tissue, bone, blood, etc. are sampled in the same manner. The amount of Molecular Grade Water added to each sample is designed to supplement low volume/dry samples without compromising sample integrity.

Theoretically the addition of volume, followed by excessive agitation via vortex is thought to 'dislodge' the microbes present from the sample type ➤

Figure 4. DNA ConneXions Oral Panel Results for # 19 Root Canal Tooth (Fractioned and Ground Comparison)



While there are some differences seen between the amounts and identity of the organisms detected for each sampling type, the fractioned vs. ground results are well within the expected range we typically see for the DNA ConneXions Oral Panel, which is between 12-17 microbes detected. The slight differences could be due to the manipulation of the sample (ex. fractioning and/or grinding) and may have had an impact on the PCR results. Based on the number and concentration of microbes detected for the above sampling types, we determined that these variances are not statistically significant; and in general there was an overall consistency seen within the fractioned and ground sampling types, and the typically received whole tooth sampling type.

Site 18
Fractioned (14) vs. ground (12)
10 microbes in common
4 unique for fractioned
2 unique for ground

Site 19
Fractioned (12) vs. ground (15)
10 microbes in common
2 unique for fractioned
5 unique for ground

Site 18 and 19 Comparison
1 unique microbe for site 18
2 unique microbes for site 19

Repeated and various samples from additional participants yielded consistent results with respect to total number of microbes detected, microbes in common between whole and crushed samples, and number of amplification products typically seen on the DNA Connexions Oral Panel (Table 1).

provided, facilitating their transfer into the Molecular Grade Water, which is then drawn off and subjected to the DNA extraction protocol.

For DNA ConneXions, two juxtaposed samples were extracted from the same patient at the same time: #18 Non-vital tooth, #19 Root canal tooth. Each tooth was fractioned into two samples (Figure 1). One half of each sample was placed in sterile, single use plasticware that had been flushed with nitrogen gas to preserve genetic material during return shipping (provided by DNA ConneXions). The remaining half of each sample was ground into a fine powder using the KometaBio Dentin grinder (Fig. 2). Each grinding blade is a single use, sterile blade/collection cup, ensuring no cross contamination between samples occurs. The ground sample was also placed into a single use plasticware that has been flushed with Nitrogen gas. All samples were returned to DNA ConneXions for analysis, where two extractions for each sample was performed with the intent of comparing current and hypothesized methodologies.

Each sample was subjected to the standard DNA ConneXions customary protocol for Oral Panel samples. Quantification via NanoDrop spectrophotometry was performed to ensure both nucleic acid purity and concentration. Samples were inoculated into prepared PCR plates encompassing the 88 microorganisms, included on the DNA ConneXions Oral Panel.

DNA extraction is performed utilizing a non-organic, spin column extraction protocol. DNA is precipitated with ethanol, and a series of ethanol-based washes are utilized, and purified DNA is collected and suspended in an elution buffer.

Purified samples are quantified for nucleic acid purity and concentration utilizing NanoDrop instrumentation. Acceptable concentration range is between 3-24 ng/ul, and acceptable 260/280 ratio is between 1.5-187. All four purified samples passed quantification.

Batches of 40 Oral Panel reaction plates are prepared at a time and stored at -20°C. Each 96 well plate contains 88 unique sets of species-specific PCR primers, five positive controls and one negative control. A multichannel pipette is employed to dispense 3 ul of purified DNA per reaction well containing typical PCR reaction components. The plates are sealed with thermal films and amplified in Bioer Thermocyclers on a 23-step annealing gradient profile.

Amplification products are run on 1.2% agarose gels, with products ranging in size from 198bp – 1020bp, visualized with ultraviolet light and ethidium bromide stain.

Results

The DNA ConneXions Oral Panel report provides a general description, symptoms of infection, and CDC recommended treatment options for each organism detected. A Total Risk Factor is calculated for each organism which considers the concentration of the organism present (Measured Risk Factor) and the characteristics of that organism (Pathogen Risk Factor). Pathogen Risk Factors are determined based on the overall characteristics of the organism: its overall pathogenicity and ability to cause disease, resistance to treatment, illness causing properties, links to systemic diseases, etc. The Measured Risk Factor is based on the visualized intensity of the amplification product, which has a direct linear correlation to the amount of the organismal starting material present in the sample.

Utilizing the proprietary DNA ConneXions Alpha-5 software, the combination of both the Measured Risk Factor and the Pathogen Risk Factor yields the Total Risk Factor of each organism detected. Figure 3 and Figure 4 graphically display both the whole and ground microbial flora detected with the DNA ConneXions Oral Panel, of #18 Nonvital Tooth and #19 Root Canal Tooth, respectively. Whole sample results are shown in red and ground sample results are shown in blue. The horizontal scale represents the Total Risk Factor for each microbe, which is based on the quantity of the organisms detected combined with the biological attributes of the organism.

Conclusions

We have included research on some of the most common oral microbes that we commonly detect in utilizing the DNA ConneXions Oral Panel. The reports produced for both site 18 (nonvital tooth), 16 amplification products, and site 19 (root canal tooth), 17 amplification products, are typical Oral Panel reports. Our average number of amplification products spanning several thousand reports is between 12-17, with the highest ever at 52. As the crushed and fractioned samples yielded the same average number of results as previous whole tooth samples, it leads us to conclude that these sampling methods are equivalent and equally effective in the DNA extraction techniques utilized at DNA ConneXions.

We do not instruct dental practitioners to fraction or otherwise

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Table 1. Comparison of Number of Microbes Detected Between Fractioned and Ground Oral Samples

	Fractioned	Ground	
Root Canal Tooth 3	16	17	16 common microbes; 1 unique for ground
Root Canal Tooth 18	12	11	10 common microbes; 2 unique for fractioned, 1 unique for ground
Root Canal Tooth 19	16	16	15 common microbes; 1 unique for both fractioned, ground
Non-Vital Tooth 7	13	14	11 common microbes; 2 unique for fractioned and 3 unique for ground
Non-Vital Tooth 19	7	6	6 common microbes; 1 unique for fractioned

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➤ *continued from page 48*

prepare their submitted tooth samples. Typically, we do not receive fractioned samples, unless it naturally occurs during surgical removal. It was possible that the fractionation and/or grinding of the tooth would yield more prolific results. However, based on the average number of amplification products achieved with whole, fractioned and ground samples, this hypothesis was negated. Had the fractioned and/or ground sample yielded far more amplification products it would have led us to remodel our theory on the aliquot protocol in place at DNA ConneXions. Rather, the 'unremarkable' and 'average' results suggest that the porosity of teeth allows for the transfer of the microbial flora present during the aliquot protocol, therefore, we were able to definitively show that it is not necessary to fraction or otherwise grind the sample in order to achieve an accurate representation of the microbial flora present. The importance of this type of DNA testing is evident, enabling us to assist both doctors and dentists by identifying potential pathogens that are linked to common diseases, using either sampling method. This insight can provide valuable information to aid in the implementation of appropriate interventions for the patient.

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Blanche D. Grube graduated from Queens College, CUNY and received her doctorate from UMDNJ, now Rutgers School of Dental Medicine. She holds a second doctorate from Capital University of Integrative Medicine, Washington DC, and is a board-certified biological dentist and a past president of International Academy of Biological Dentistry and Medicine. She has lectured internationally on the Huggins-Grube Protocol. Besides holding several fellowships, she is the owner and CEO of DNA ConneXions, Biocomp Laboratories, Huggins Applied Healing, and Centers for Healing.

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Regulating the Regulators

by Dr. Michaël Friedman

The following excerpt is from Dr. Michaël Friedman's book *There's No Pill for This: A Naturopathic Doctor's Personal Prescription for Managing Multiple Sclerosis* (Chelsea Green Publishing, November 2020) and is reprinted with permission from the publisher.

Research has established that multiple sclerosis involves inflammation in the brain and damage to the myelin sheath that protects nerve cells. And it's long been known that hormones play a key role in maintenance of brain and central nervous system (CNS) health. Putting this information together, it becomes clear that in order to effectively treat MS symptoms, it's important to understand the role of hormones in the body and how to achieve and maintain hormonal balance.

Most hormones are produced in the endocrine system, a system of glands distributed throughout the body. Once produced, hormones enter the bloodstream and travel to their target sites, where they bind to specific receptors and exert some form of influence.

Hormone Production in the Brain, CNS, and Gut

The brain is part of the central nervous system, and it also acts as an endocrine organ. For example, the brain converts one type of hormone secreted by the thyroid gland into a more active form for the body's use. The brain has receptors for targeted endocrine hormones, and is part of an important feedback loop involving the pituitary gland (which regulates hormone production) and a variety of organs whose function depends upon those hormones. Consequently, the brain has the ability to direct and adjust bodily functions. It does so via production of neurotransmitters such as serotonin and dopamine. The brain and CNS also produce hormones known as neurosteroids. Synthesized from cholesterol, neurosteroids play a role in the myelination of neurons, as well as the growth, differentiation, and maintenance of neurons. (Because of cholesterol's importance in hormone production, I advise MS patients to think twice about using statins to lower their cholesterol levels. And because the human body manufactures cholesterol from fat, this is also why I advise including a variety of healthy fats in the diet – especially omega-3s.)

Bacteria in the human microbiome also impact hormone production. In fact, gut bacteria produce almost 50 percent of the dopamine used by the body. The microbiome also impacts thyroid hormone conversion and the production of melatonin. This is why I adamantly recommend avoiding processed foods. Many of these may contain chemicals and preservatives that can disrupt hormone balance.

Hormones serve two functions: messaging and the regulation of body systems. In some cases a pair of hormones work in a kind of feedback loop. When this happens, Hormone X acts as a messenger to stimulate or depress an endocrine gland in response to the body's needs. That gland then releases either more or less of a second hormone, Hormone Y.

When thyroid hormone levels in the body reach normal levels, the brain receives another message through the feedback loop. The brain calls upon the pituitary gland to slow its release of thyroid-stimulating hormone (TSH). The reduction of TSH in the bloodstream signals the thyroid gland to slow the release of thyroid hormone.

When working properly, feedback loops help ensure that cells have the proper amount of necessary hormones at all times, keeping the body in balance. But sometimes those loops can lose their balance, causing too little or too much of a hormone to be released, which can result in damage to cells and tissues. Even worse, a domino effect can occur, triggering imbalances in other hormones. which can lead to other interrelated health problems.

The Impact of Aging on Hormones

As we age, hormone production naturally declines, causing physical and psychological changes in both men and women. The pace at which hormones decline, and thus the rate at which we age, are determined by our genetic makeup, lifestyle, diet choices, exercise levels, weight/BMI, stress level, relationship status, community involvement, and other factors. For example, common life situations such as smoking or gaining excessive weight can cause testosterone production to decline faster.[1] The stress related to job loss or divorce can increase cortisol levels and cause weight gain and damage to neurons. In women, the precipitous drop in estrogen due to age combined with the fact that females tend to have longer life expectancy than males means that women generally experience more cognitive changes with age and have higher rates of Alzheimer's disease than men.

Many other factors influence the complex aging process, and aging is the result of the accumulation of factors, not a single hormonal change.[2]

The Role of Thyroid Hormones in MS and Other Neurodegenerative Diseases

Over the short and the long term, hormones can have both positive and negative effects on the health of the brain and the central nervous system. One example is the effect of hormones on neurons in multiple sclerosis. ➤

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Although their actions are not well understood, neurosteroid hormones can help to mitigate the severity and the progression of MS. They do so by influencing oligodendrocytes to provide neuroprotection and remyelination that reduces and repairs damage to the myelin sheath.

To date, many of the studies examining the connections between hormones and neurodegenerative disease have focused on Alzheimer's – which is why I reference studies on Alzheimer's quite often in my book. Although research into hormones and MS is relatively young, the implications are similar. The following is a brief explanation of thyroid hormones and their therapeutic use for MS.

The thyroid produces two hormones, T3 and T4, that regulate the body's metabolic rate and other elements of health, including breathing, heart rate, central and peripheral nervous systems, body weight, muscle strength, menstrual cycles, body temperature, and cholesterol levels.

Thyroid hormones also support proper central nervous system function and interact with many facets of the nervous system to help prevent dementia. Maturation of oligodendrocytes and myelination is influenced by thyroid hormone (TH) signaling. Thyroid hormone interacts with acetylcholine, which, as mentioned previously, improves memory and prevents cognitive decline. Low thyroid hormone status can cause insufficient production of acetylcholine. Research has shown that patients with Alzheimer's disease have diminishing levels of acetylcholine relative to the progression of the disease.[3]

Triiodothyronine (also called T3) and thyroxine (also called T4) are two hormones that are critical for normal metabolic functioning. Most (about 80 percent) of T3, known as the active thyroid hormone, results from *deiodination* – the process by which organs such as the liver and kidneys remove one of the four iodine molecules that are part of T4. Some inactive thyroid hormone results from this process as well; that hormone is called reverse T3, or rT3. The thyroid gland produces the other 20 percent of T3 (by combining dietary iodine with the amino acid tyrosine) as well as all of T4.

T3, the active thyroid hormone, promotes nerve growth factor (NGF). (NGF supports nerve growth, proliferation, function, and nerve myelination.) T3 also enhances remyelination by supporting oligodendrocyte precursor cells (OPCs). Without adequate thyroid hormone, there is a deficiency of mature, active OPCs and limited ability for myelin repair.[4]

The brain is extremely dependent on thyroid hormone. Low thyroid levels are believed to cause shrinking of the hippocampus, the part of the brain that shifts short-term memories to long-term, enables spatial memory related to navigation, and supports memory and learning. The hippocampus is particularly significant because it is the part of the brain that shows the earliest signs of damage in Alzheimer's disease (AD) patients. When present in adequate amounts, thyroid hormones may help ward off dementia by hindering a protein that promotes amyloid production and indirectly prevents plaque deposits. On the other hand, deficient thyroid levels may open the floodgates for more amyloid production and consequent damage to the brain.[5]

Adults who develop hypothyroidism can suffer from poor memory, confusion, and difficulty learning new tasks. Fortunately, these symptoms are reversible in adult hypothyroidism, simply by restoring thyroid hormone levels and body temperature.

Thyroid hormone may indirectly contribute to dementia through its influence on the cardiovascular system. Hypothyroidism is a significant risk factor for developing cardiovascular disease. In this condition, blood flow to the brain may become impaired due to a compromised vascular system. Diminished blood flow and the resulting poor delivery of oxygen and nutrients to the brain can contribute to damage in the brain and an increased risk of developing AD.[6]

Thyroid hormone is so crucial to the brain that if there is inadequate thyroid hormone available to a fetus developing in the womb, its brain and neurons will not mature properly, causing irreversible mental deficiencies in the form of cretinism.

A very large clinical trial conducted by Boston University in collaboration with the National Heart, Lung, and Blood Institute known as the Framingham Study collected health data on almost 2,000 people over the course of nearly 13 years to better learn about risk factors for various diseases. It found that for women with non-normal TSH levels (which is an indicator of either elevated or deficient thyroid hormone), there was more than *double* the risk of developing AD as for women with healthy normal levels.[7]

Therapeutic Use for MS

MS patients are shown to have higher rates of thyroid disorders as compared with healthy peers. One study showed that patients with MS had a significantly higher risk of also having *autoimmune* thyroid disease, specifically Graves' disease (hyperthyroidism) and Hashimoto's disease (hypothyroidism).[8] I mention this here because individuals with one autoimmune condition are more susceptible to developing others – which could explain the correlation between MS and these types of thyroid disease.

Animal research has shown that daily injections of T3, the active form of thyroid hormone, contributes to remyelination. These studies also show that thyroid hormone supplementation can improve neurological symptoms in animals and improve proliferation and activation of OPC.[9] At Oregon Health and Science University, thyroid hormone is being studied as a potential MS therapy due to its critical role in protecting myelin and promoting remyelination.

T3 supplementation is not standard of care for MS, but I have found it one of the top three significant therapies in treating my own fatigue and brain fog. When demyelination occurs during an MS attack, the body does produce more rT3, which blocks the active T3 hormone from working. Reverse T3 slows the activity of metabolism in the body and the CNS. It is a normal function to slow metabolic processes during

times of fasting, to conserve energy, and also during times of grief. However when the rT3 stays high for the long term, this otherwise healthy slowing process can persist to the point that it leads to chronic disease. It is analogous in this way to inflammation – an appropriate amount of inflammation helps tissues heal, but excess can be damaging. In the case of rT3, overly high levels can contribute to significant, debilitating fatigue. Adding T3 to the body can help take the edge off the fatigue that MS patients experience, especially after an attack, and help the mind become clearer. Interestingly, thyroid hormones stimulate myelination.

Every couple of years, I take 5 mcg of T3 twice a day for a three-month period. This dosage has a beneficial effect for me. I also take a product that I formulated myself called Thyroid Px. This supplement combines iodine, selenium, and thyroid-activating herbs. Over time, my MRI scans have shown some lesions to decrease in size and some to disappear. Although I cannot know for sure, because some types of MS lesions do heal on their own over time, I attribute the size reduction and disappearance of some of my lesions in part to the body's natural ability to heal itself and in part to the restorative treatments I take.

Michaël Friedman, ND is a naturopathic physician and founder of the Association for the Advancement of Restorative Medicine. He is cofounder and president of the Restorative Formulations supplement company, and lives in Montpelier, Vermont.

Regulating the Regulators

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More Lifestyle Modifications to Lessen the Impacts of Chronic Stress

Meditation. ***Mindfulness meditation*** should be offered to patients as a durable treatment that assists with stress management by improving emotional regulation. This particular type of meditation, "is premised on stabilizing attention, acknowledging discursive sensory events as 'momentary' and 'releasing' them without affective reaction" (p.751).[97] The benefits of mindfulness meditation can be experienced rather quickly even when it is practiced for short periods of time. Some examples from the published literature will be cited as proof of the quick benefits that can be ascribed to mindfulness meditation.

For example, a study demonstrated that just four sessions of mindfulness meditation (i.e., 20 minutes/session) over four consecutive days modulated areas of the brain responsible for state anxiety (i.e., the anterior cingulate cortex, anterior insula, and the PFC area known as the ventromedial PFC). The changes in this PFC area presumably reflected changes in cognitive reappraisal processes, and in down-regulating negative emotions, such as amygdala activity.[97]

In another study, 13 novice university students were given eight weeks of mindfulness meditation with daily practice at home in sessions lasting around 45 minutes.[98] Before and after, ratings of depression and anxiety demonstrated a significant reduction in depression scores after meditation training, and a significant reduction in trait anxiety but not in state anxiety scores following meditation training. Moreover, the significant reductions in depression scores were shown to reflect changes in the resting state functional connectivity of particular brain regions implicated in depression. In other words, meditation training uncoupled certain brain areas that tend to be coupled (i.e., hyperconnected) in major depression, and this was presumed to be the antidepressant effect attributed to mindfulness meditation.

With respect to amygdala activity, another study showed that short-term mindfulness meditation (i.e., 8 weeks) resulted in increased functional connectivity between the amygdala and the ventromedial PFC.[99] The results demonstrated that mindfulness meditation assisted with emotional regulation by reducing amygdala reactivity, and increasing the coupling or functional connectivity between the amygdala and PFC when challenged with affective stimuli. This positive benefit attributed to mindfulness meditation in this study was shown to happen over the short-term, as evidenced by modulating the connectivity between these brain structures. Overall, it appears that short-term mindfulness meditation can produce symptomatic reductions in anxiety and depressive symptoms by altering the way the brain operates and responds to emotional stimuli.

With respect to markers of physiological stress, mindfulness meditation, including other types of meditation, were shown in a systematic review and meta-analysis to decrease biomarkers of stress (i.e., cortisol, blood pressure, heart-rate, lipids and peripheral cytokine expression) in a range of populations.[100] When evaluated in aggregate, all meditation types reduced cortisol, C-reactive protein, blood pressure, heart rate, triglycerides, and tumor necrosis factor-alpha.

Mindfulness meditation was highlighted here because it is among the most popular types of meditation available. It has a rapidly evolving literature base supporting its efficacy as a durable treatment with therapeutic effects happening rather quickly with consistent daily practice (i.e., for as little as 20 minutes/day).

Sleep. Numerous research publications have repeatedly shown deleterious impacts on health when people suffer from chronic insomnia. Among the many factors implicated in chronic insomnia, stressful life events, personality patterns, and psychiatric diagnoses are more etiological in both the development and persistence of chronic insomnia.[101] In terms of stressful life events, insomniacs report less satisfying interpersonal relationships and poor self-concepts, which result in poor coping ability and problems with stress management. Insomniacs also have high levels of psychopathology as evidenced by high scores in depression, hysteria, and psychasthenia as measured by the Minnesota Multiphasic Personality Inventory. As a result, the personality traits of individuals with chronic insomnia

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include problems with the expression of anger, depressed mood, chronic anxiety, rumination, and with the inhibition of emotions. Having chronic insomnia and a psychiatric illness is also really common, and sometimes the presenting symptom of an undiagnosed psychiatric illness are sleep problems. In chronic insomnia, mood disorders dominate (i.e., dysthymic disorder, major depression disorder, bipolar disorder, and cyclothymic disorder), followed by anxiety disorders, and substance abuse disorders.

A possible mediator of chronic insomnia is that of ***high sleep reactivity***, which "is the degree to which a stressor (broadly defined) disrupts sleep," and "behaviourally, sleep reactivity is the degree to which individuals exhibit acute sleep-disruptive responses to stress" (p,3-4).[102] Among individuals with chronic insomnia, usually a major stressor happens at some point, and then an insomnia disorder mediated by high sleep reactivity develops shortly thereafter. It is probable then that many chronic insomniacs have the high sleep reactivity phenotype. Precisely what influences high sleep reactivity is evolving, but female gender, familial history of insomnia, genetics, and environmental stress all impact upon how an individual's sleep system reacts to stress. Moreover, the etiological links to high sleep reactivity include "disrupted cortical networks and dysregulation in the autonomic nervous system and hypothalamic-pituitary adrenal axis" (p.1).[102]

In terms of the brain, in a small pilot study hippocampal volumes were shown to be decreased among patients with chronic insomnia.[103] This was a significant finding since this area of the brain is involved in learning and memory processes. A larger study found hippocampal atrophy among chronic insomniacs, which was also associated with impaired cognitive function.[104] These findings were significant as more current research identified that even one night of sleep deprivation makes it difficult for the brain to clear beta-amyloid (i.e., known as the ***brain beta-amyloid burden***), which is a metabolic waste product that has clear correlations to the development of Alzheimer's disease.[105] The study hypothesized that the increased brain beta-amyloid burden in the hippocampus due to sleep disruptions might result in local neurotoxicity but without "necessarily resulting in marked plaque accumulation" (p.4486).[105]

Ensuring that sleep becomes restful and rejuvenating must therefore be a priority when working with chronically stressed patients. It is imperative then that good sleep is achieved. ***Good sleep*** "is characterized by subjective satisfaction, appropriate timing, adequate duration, high efficiency, and sustained alertness during waking hours" (p.12).[106] Achieving good sleep, therefore, depends on achieving with consistency the following targets: regularly waking up and falling asleep at around the same times (i.e., within an hour) each day; feeling satisfied from sleep; being alert/awake during the day after a night's sleep without any napping; being asleep during the night and not struggling to remain asleep especially between 2AM and 4AM; having less than 30-minutes of total awake time during sleep (i.e., which includes falling asleep and awakenings during the night); and having a sleep duration of around 7-9 hours each day.[106,107]

Helping patients to achieve good sleep depends on their adherence to proper sleep hygiene practices and ensuring that stimulus control is being followed. To learn more about sleep hygiene, see the following reference,[108] or the Sleep Foundation link: https://www.sleepfoundation.org/. For stimulus control, please refer to this article on the Somnology website: https://www.somnologymd.com/2015/05/stimulus-control-therapy/.

Patients with chronic insomnia are often prescribed sleep medications, which are needed in many cases when they cannot fall asleep and remain asleep with consistency. Inadequate sleep will add to the burden of allostatic load (AL) and allostatic overload (AO) and result in durable and adverse brain changes that are unlikely to be reversible with treatment. The most commonly prescribed sleep medications include specific benzodiazepines (i.e., estazolam, flurazepam, quazepam, temazepam and triazolam), which typically have half-lives of over eight hours (except for triazolam).[109] The problems with this class of medication are numerous and include "next-day (residual) fatigue, psychomotor and neuropsychological dysfunction" (p.2).[109] Additional problems involve dependence, withdrawal and rebound symptoms when they are abruptly

Table 5. NHPs that possess calming, sedating and hypnotic effects, and/or that facilitate improved sleep

Treatment	*Primary therapeutic effects*	*Suggested Dose (30-60 minutes prior to bedtime)*	*References*
Broad-Spectrum Micronutrients	Non-sedating anxiolytic that lowers central nervous system hyperarousal and improves an individual's ability to process emotional stress	3 pills twice daily	114
Lavender extract	Non-sedating anxiolytic that produces a calming effect, and improves various sleep parameters	80 mg	115-117
Magnesium bisglycinate	Improves various sleep parameters, and assists with periodic limb movements of sleep and restless leg syndrome	400-600 mg	118,119
Melatonin (timed- or sustained-release formulation)	Sedating, and improves various sleep parameters	2-5 mg	120,121
Passion Flower extract (low-dose extracts often standardized to 4% isovitexin)	Sedating and hypnotic effects, and improves various sleep parameters	425-900 mg or low doses between 60-80 mg (i.e., when standardized)	122-124
Valerian root extract (0.8% valerenic acids)	Sedating and hypnotic effects, and improves various sleep parameters	300-600 mg	112,113,123

discontinued, and the potential for abuse especially among vulnerable patients with prior alcoholism and drug abuse.[109]

There is another class of sleep medication known as the non-benzodiazepines ("but also benzodiazepine receptor agonists") that "selectively attach to the benzodiazepine recognition site on the GABA-A receptor" at the level of the alpha-1, or alpha-2, and/or alpha-3 subtypes (pp.2-3).[109] Sleep medications in this class, known as Z-drugs, include Zaleplon, Zolpidem, and Eszoplicone. Even though they have shorter half-lives compared to benzodiazepines (i.e., 8 hours or less) they still have a spectrum of adverse effects that are similar to benzodiazepines and include "sedation, anterograde amnesia, complex sleep-related behaviors, and impaired balance with subsequent falls" (p.3).[109]

Given how serious these adverse effects are, it is preferable to recommend specific natural health products (NHPs) (Table 5) as first-line treatments since they do not possess similar dependence, withdrawal, and rebound symptoms, and do not appear to be associated with abuse. Among all the NHPs noted, there is data demonstrating that melatonin may assist with benzodiazepine withdrawal[110] though this is by no means conclusive.[111] There is also data demonstrating that valerian extract may help with benzodiazepine withdrawal,[112] but there are equivocal studies that raise concerns about the overall efficacy of valerian extract as an effective sleep treatment.[113]

Substance abuse (e.g., alcohol, cannabis, and cocaine). Chronic stress is a well-recognized risk factor in the use of substances and addiction vulnerability.[125] The etiology is very complex, but early life stress, adverse childhood experiences, and accumulated adversities alter allostasis and associated mechanisms, and are believed to play a significant role in the genesis of addiction. The effects of excessive and repeated substance use result in changes mediated by central catecholamines, particularly norepinephrine and dopamine, both being key players in modulating motivational pathways within the brain. Chronic stress and abuse of substances operate in a feedforward manner to activate the mesolimbic system and beget feelings of reward. This also impairs prefrontal brain circuits, disinhibits executive functioning, activates the amygdala and other brain regions, and causes problems with impulse control, compulsive behaviors, and delaying gratification.

Given this reality, I do not believe it is possible for patients to manage chronic stress and be emotionally regulated if they choose to continue abusing substances. Though harm reduction is a viable approach to managing substance abuse,[126] I have not had many patients improve their ability to manage chronic stress (and all the accompanying problems) with continued but reduced substance use. The goal should be to eliminate substance use so patients can learn to live and manage their complex lives without feeling the need to consistently alter their mental state through the compulsive use of substances.

Psychotherapy and/or Social Support to Lessen the Impacts of Chronic Stress

Promoting or recommending psychotherapy is another important treatment that reduces the impact of chronic stress and has therapeutic effects that promote positive brain changes. As Nobel laureate, Dr. Eric R. Kandel, MD, noted in his seminal paper "Psychotherapy and the Single Synapse":

> When [*capitalization added*] I speak with someone and he or she listens to me, we not only make eye contact and voice contact but the action of the neural machinery in his or her brain, and vice versa. Indeed, I would argue that it is only insofar as our words produce changes in each other's brains that psychotherapeutic interventions produce changes in patients' minds. From this perspective, the biologic and psychologic approaches are joined (p.1037).[127.]

Psychotherapy has been articulated as an ***epigenetic drug*** by inducing "changes in brain circuits that can enhance the efficiency of information processing in malfunctioning neurons to improve symptoms in psychiatric disorders, just like drugs" (p.249).[9] Published studies have shown, for example, that cognitive behavioral therapy for phobias decreases activity in the limbic and paralimbic areas.[128] In depression, psychotherapy was shown to increase and decrease prefrontal metabolism.[129] The effects of psychotherapy implicate more top down effects compared to psychiatric medication that produce more bottom-up effects.

A systematic review showed an increase in BDNF levels among depressed patients given treatment with psychotherapy and psychiatric medication.[130] The same systematic review also demonstrated a rise in BDNF levels among patients with post-traumatic stress disorder (PTSD) that were given both psychotherapy and physical activity, and a rise in BDNF levels among psychotherapy responders diagnosed with bulimia, borderline, and insomnia.[130] A study evaluated the effects on the brain after 15 months of long-term psychodynamic psychotherapy.[131] Compared to the control patients, the patients that received long-term psychotherapy showed marked reductions in depressive symptoms, and more activity in the medial prefrontal cortex (PFC). The latter therapeutic effect is important to note since this particular area of the PFC is associated with voluntary emotional regulation.[131] Based on the data presented

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above, psychotherapy has established therapeutic effects that alter brain areas implicated in emotional regulation.

In terms of social support, it would seem reasonable to conclude that similar therapeutic changes would result when people are more socially engaged in meaningful ways. One such example is that of the Experience Corps©--a high-intensity program that combines education, physical activity, and social engagement (as well as other factors not easily quantifiable like meaning and purpose in life) – that trains elderly volunteers to be teachers' assistants for younger children in neighborhood schools focusing on reading achievement, library support, and classroom behavior.[132,133] Participation in the program resulted in improvements in both physical and mental health, but also improved executive functioning in the PFC among the elderly volunteers having an elevated risk for cognitive impairment.

The brain also expects social relationships to happen, as described in an extensive review paper by Holt-Lunstad on why social relationships are important.[134] A brief section of the review discussed ***social baseline theory***, which posits that the brain needs to have social relationships that include common goals, interdependence, and attention. In fact, when this expectation is not met, the brain will respond as though there are scarce resources, resulting in increased cognitive and physiological effort, often accompanied by acute and chronic distress. All of this presupposes that the brain has been designed for social relationships as its normal state of being. So when socialization has been limited for a variety of reasons, such as social withdrawal from being depressed or alienation due to neighborhood bullying, the individual suffers both emotionally and neurologically from wounds emanating from the outside in, and from the inside out. It is imperative then that the practicing clinician encourage social integration – for example, weekly recreational sports, book clubs, communal organic gardening – as a central goal when helping all patients to assuage the AL and/or AO from being chronically stressed.

An interesting and more widespread example of fostering social integration (as noted by Holt-Lunstad[134]) includes the Blue Zones Project (https://www.bluezonesproject.com/), which supports communities by promoting the same principles as described in the book (i.e., *The Blue Zones Solution* by Dan Buettner). Essentially, the Blue Zones Project advocates for nine factors described in the Blue Zones Solution with the aim to "transform environments to drive physical, mental, social, and professional well-being." Three of the nine factors are social ones (i.e., family first, right tribe, and belong). Multiple cities across the United States are currently engaged in this project.

Additional Strategies to Lessen the Impacts of Chronic Stress

Having practiced naturopathic medicine for over 20 years, and more recently as a psychotherapist, additional strategies need to be embraced by chronically stressed patients if they want durable improvements over time. I am certain that none of the strategies described below are my own original ideas, for I have learned them from clinical experience, training, and regular supervision. When many of these strategies are adhered to (including those mentioned previously), patients find themselves feeling better while gaining increased capacities to manage their chronic stress and complex lives.

Accept and learn to endure emotional discomforts. All chronically stressed patients need to learn that fighting their difficult emotions seldom works. It is actually better for patients to feel emotions without resistance. Tension is about resistance; relaxation is about acceptance and letting go. Working on acceptance is therefore essential, so when patients feel emotionally overwhelmed, they become more adept at coping with their difficult emotions. The more they resist, the more tension develops. Acceptance assists with living in the present, and not in the future or the past.

Additionally, for patients to improve means that they will have to accept what is happening (as described above) and allow the uncomfortable feelings to exist within. Emotions, though intense and sometimes powerful (and sometimes even destructive), are usually impermanent and will lessen. Patients must accept that they will not be able to go through life without experiencing regular discomforts, including periodic massive spikes in the levels of anxiety and depression, as well as other emotions. Setbacks are part of the process, and patients need to know that this will happen even when treatments have been consistently effective. As patients improve and become more emotionally tolerant, setbacks usually become less intense and less frequent. Patients can gain wisdom by understanding that their emotional maturity depends on their capacity to endure difficult experiences. The obvious caveat being, that if things do become too intolerable and/or extreme, they will likely need to go to the nearest emergency department for an evaluation and treatment.

Seek out inspiration through the success stories of other people. A wonderful way for patients to become more hopeful is by listening to podcasts or watching videos about people that have overcome enormous obstacles only to find life worth living again. Hope is something that all patients can access by listening or watching incredible stories. Just by doing some searching on the internet, patients should be able to find great stories of human triumph amidst incredible struggles.

Read (or listen) and learn. This is called bibliotherapy whether through reading or audio books. Patients must commit to self-help or other types of books that facilitate personal growth and/or increased psychological flexibility. They need to have sustainable methods of help in between office visits. Bibliotherapy is a tremendous way in which to develop additional skills of emotional regulation and chronic stress management.

Make decisions. It is unbelievable how often chronically stressed patients willingly refrain from rendering important decisions that, in most situations, would lessen their stress levels and heightened emotionality. I have personally seen patients stew in their own decisional paralysis for months and even years before taking concrete action on something that would invariably improve their emotional and physical well-being. Indecision keeps the brain locked in uncertainty and yields too much bottom-up control by the amygdala and other limbic structures. All decisions exclude other options, or as psychiatrist Dr. Irvin D. Yalom, MD, noted, "alternatives exclude."[135] Patients need to commit to making actual decisions

to move their difficult lives forward; otherwise, they will not find the type of relief, contentment, and emotional freedom that is possible.

Accept responsibility. With almost predictable consistency, a large percentage of chronically stressed patients tell me that their misery is being caused because of someone else, or because of something else. And only if that someone else (or something else) would change, so too would their misery. Of course, I am well aware that there are malicious and horrible people in the world that do awful things to other people, such as stalking, abuse, extortion, oppression, etc. This is not what I am referring to when describing the importance of accepting responsibility. I sincerely believe that all patients must take deliberate personal action to change their circumstances for the better. Not accepting personal responsibility is just a version of learned helplessness, which denotes a self-imposed state of inertia even when viable options exist to significantly improve things. Patients need to mobilize themselves, sometimes matter over mind, to literally shift from their state of immobility, and overcome the stasis that has been ruining their lives.

No chemical treatment for mental health – whether naturopathic or otherwise – will result in a cure. Effective treatment will lessen the intensity of emotional overwhelm but cannot eliminate it. To additionally cope, all patients need to develop their own strategies of living that includes lots of self-care and purposeful work that confronts the very situations that cause anxiety and/or depression. Chemical treatment will not alter behavior though it may assist in facilitating important behavioral change. Some patients, for example, may experience anxiety when in social situations. Other patients, for instance, may feel guilty and bad about themselves and then socially isolate rather than spending time with their family and friends due to depression. Patients need to literally confront and immerse themselves in emotionally challenging situations (rather than avoid them) and learn that this type of committed approach is an essential part of their recovery and self-development.

Regularly do things that provide fun outlets. Having fun appears to be an underrated treatment or activity. Patients need to be encouraged to have fun so as to give their brains and minds a break. Sitting in front of a computer all day will not help, nor will isolation and the avoidance of real human connection. Patients will feel better by intentionally including fun activities into their daily routines.

End toxic relationships. Far too often therapists and other health professionals tell their patients to work harder and remain in their toxic relationships that have been horrible for many years. In fact, most patients have worked pretty hard at trying to make these brutal relationships work long before they have sought help. I take a different perspective. Plus, life is too short! Why try harder if misery has been a constant and omnipresent companion? Calling it quits can be liberating, health promoting, and often necessary for a person's survival. That is why I am a strong believer that most patients in toxic relationships must find a way to emancipate themselves; otherwise, chronic stress will continue to wreak havoc on both their minds and bodies.

Don't compare yourself to other people. I could easily find a person that is far more intelligent than I, far more attractive, has more money, and is way more capable in all the domains of life. Why should I do that to myself? It will only bring me down, resulting in dysphoria, anxiety, stress, and feelings of worthlessness. A much better strategy that I follow is to compare myself to who I was one day before. That way, I attain a realistic baseline and goals can be achieved. Heck, yesterday, I consumed too much processed meat (I happen to like pepperoni sticks), which is a weakness of mine. Today, I can commit to eating better and to not have any pepperoni sticks. This is a completely achievable strategy and works much better than comparing myself to other people. I often recommend that patients jot down 1-2 items to work on when comparing themselves to the day before. They often can reach their daily goals and end up feeling much better about themselves in the process.

Conclusion

There is nothing more difficult than trying to find regulation amidst the constant challenges and chaos of life. The net effect is that chronic stress will insert itself in some manner or another while life continually moves forward in time. One day you are 28 years old and feeling on top of the world, and then decades later you can't believe that you are now 53 years old and suffering from relational loss and estrangement, chronic depression, prostate cancer, and metabolic syndrome. No one is spared. That is why numerous integrative treatments were discussed as viable options that target, regulate, and potentially optimize allostatic mechanisms. In promoting treatments that impact brain and body health, clinicians have a powerful role in materializing this information when working with their patients. Integrative approaches, such as those mentioned in this article, should serve as models of the kinds of interventions that can realistically and dramatically affect the course of chronic stress and prevalent medical diseases via allostatic brain mechanisms.

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At the Canadian College of Naturopathic Medicine, Dr. Prousky's primary responsibility is the delivery of safe and effective naturopathic medical care in his role as the chief naturopathic medical officer. He was the first naturopathic doctor to receive the "Orthomolecular Doctor of the Year" award in 2010. In 2017 he was also the first naturopathic doctor to be recognized for his longstanding commitment to mental health by being inducted into the "Orthomolecular Hall of Fame." Dr. Prousky is the author of several texts, such as *Textbook of Integrative Clinical Nutrition*, and *Anxiety: Orthomolecular Diagnosis and Treatment.*

Staying in the Game – How to Keep Fit and Healthy at Any Age

by Erik Boudreau, ND, FABNO

I'm probably dating myself here, but as I ponder the age-old scenario of a middle-aged man plopped down on the couch with beer-in-hand, belly spilling over his waistband, and a plethora of anecdotes about "the big game," I can't help but think of Al Bundy, the slovenly dad from *Married with Children*. Strangely, the more I think about it, the more it seems as though this image seems to reflect almost every TV sitcom dad. Of course, this is hardly a revelation, as most TV shows gain an audience by either showing us a life that we wish we had or by mirroring back to us the one we ended up with.

That said, it's all too easy to simply reduce the issue to a stereotype and call it a day – no matter how amusing and/or lovable the image may appear. In other words, it can be a dangerous mistake to make the assumption that these men simply *let themselves go*, regardless of the health consequences. To venture beyond TV entertainment and into the world of evidence-based medicine, we know quite assuredly that as we get older, our caloric requirements gradually decline. However, we also know that as many people age, they do not decrease their caloric consumption to the same degree, too accustomed to what they could previously "get away with." The result is a net gain of body fat (along with the corresponding increased risk of Type 2 diabetes, heart disease, etc).[1] And while this more-or-less willful ambivalence toward a healthy lifestyle may certainly apply to many men, it is nonetheless an ignorant view that ignores the struggles many men are having to maintain or re-establish optimal health. Ultimately, it's a slippery slope that can result from a wide range of interweaving factors.

For example, let's consider the case of Rick, a 58-year-old executive who spent pretty much every waking moment of his childhood and adolescence either shooting a puck, hitting a ball, or riding his bike to or from the park/rink/diamond. His diet? Whatever he found in front of him at mealtime. Eventually, Rick makes his way through university, eating horribly for a few years but feeling largely immune to its detrimental effects, but for the grace of his early 20s metabolism (augmented somewhat by semi-regular trips to the gym). Before he knows it, Rick finds himself a few years older, and sitting in front of a computer screen for 10-12 hours a day at his job. He has a gym membership that he never uses, eats what he can, when he can, and downs a few beers a night to shake off the stresses of the day. Time rolls along, and Rick finds himself working more and resting less as he climbs the corporate ladder, with his stress levels escalating right beside him.

While his body (and mind) are able to sustain this less-than-ideal scenario for quite some time, it's only a matter of time before the first cracks begin to show. First, his sleep quality takes a dip. He's diagnosed with sleep apnea and has a CPAP machine that he never wears. His blood sugar and LDL ("bad") cholesterol levels start to climb, and since his dad died from a heart attack at 52, he adds a few prescriptions to his morning routine. His body weight goes up, affecting his mood (and sleep and blood pressure), also prompting him to renew his enthusiasm for "getting back into shape," though his aching back/knees/ankles/you-name-it keep him from sticking with a program. Finally, one day, Rick looks at himself in the mirror and can hardly recognize the sedentary, under-slept, over-stressed, unhealthy person looking back at him. With no energy, no motivation, no self-confidence, aching joints, and the burden of half a dozen heart disease risk factors always on his mind, he winds up on the couch, sighing as he tries to escape from the world with the help of a beer, some chips, and the TV. He may look like a character from a sitcom, but there's something seriously wrong with this picture.

As we've already covered, it's all too easy to wind up caught in a negative cycle of high stress/poor diet/inactivity. Throw a healthy dose of denial into the mix, and it's only a matter of time before the dam (or coronary artery, as it were) finally breaks. Of course, it's always the right time to start a new cycle, where regular exercise offers an outlet for pent-up stress, which not only promotes digestion but can also improve sleep quality. This improved sleep can, in turn, strengthen immune function and decrease inflammation, while providing the rest required to

wake up more refreshed and ready to face the day. As for diet? Many people find that the increased energy, weight loss and improved mood stemming from exercise provides all the incentive they need to start making healthier dietary choices (so as not to undo/negate all the progress that's already been made). Further complementing this is clinical evidence showing a correlation between increased abdominal fat deposition in men and increased rates of depression, as well as greater fatigue and lower self-confidence.[2] This again underscores the synergistic effects that these dietary and lifestyle changes can have on physical, mental and emotional health, with each factor seeming to support a number of others, and vice-versa.

In fact, while all of these elements are also certainly applicable to women, a study exploring the global trend of increased rates of coronary heart disease among men suggested that this was due largely to a particularly impaired ability to manage/cope with stress.[3] Interestingly, an additional study explored the potential difference between men and women at providing support to a loved one when they, themselves, were stressed. The study found that while men and women could provide a similar degree of support to others when they were not stressed, the level of support offered from men tended to decline steeply when they became stressed.[4] Once again, this may serve as evidence that men in general (and always with exceptions) may be less well-equipped to deal with stress when compared to female counterparts. Thus, while adopting healthy stress management techniques (exercise, counseling, deep breathing, etc) can help anyone at any age, this appears to be a particularly important (and, often, neglected) aspect for men.

Of course, this isn't even touching on the countless additional health benefits provided through regular exercise, a healthy diet and proper stress management, such as improved blood sugar and lipid levels, a decreased risk of heart attack and stroke,[5] and a reduced incidence of several cancer types, including prostate cancer[6] (the second-most common cancer diagnosis in men). In addition, even men with a pre-existing cancer diagnosis can see benefit with exercise, as studies show that it may improve energy and overall quality of life in men with prostate cancer.[7]

As for the joint pain and inflammation experienced by Rick as well as many other older men, the decrease in body weight along with corresponding anti-inflammatory benefits from a healthy diet may make it easier to stick to the program. In fact, a study involving over 3000 men over the age of 40 showed that regular exercise produced a marked decrease in functional limitations when compared with sedentary controls.[8] Not surprisingly, when the Honolulu Heart Program sought to quantify the impact that regular physical activity could have on lower risk of coronary heart disease, it found a 30% risk reduction for active men aged 45-64 vs. sedentary controls, and a reduction of over 50% in active men over 64.[9]

Hopefully at this point, the value of 1) stress management, 2) a healthy, balanced diet, and 3) regular physical exercise is self-evident. That each of these measures plays an integral role in supporting overall health is no longer up for debate. And regardless of why or how a given individual ended up straying from a once fit and active lifestyle, it's always a good idea to start taking those first steps back on the path toward better health.

While adopting healthy stress management techniques can help anyone at any age, this appears to be particularly important for men.

Of course, while it's always advantageous to have established healthy habits early on, simply having a history of high-level physical activity does not guarantee that one is immune to these pitfalls. In fact, in some cases, the opposite may be true. A recent US study examining former Division 1 college athletes now in their 40s and 50s showed significantly elevated body weight along with worse strength and stamina assessments when compared to nonathletes.[10] A possible reason for this

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finding speculated by the authors is the increased likelihood of chronic, sports-related musculoskeletal conditions. However, it may also be considered that the aforementioned discrepancy in caloric intake vs. demands in older adults may be accentuated in those who previously needed to consume vastly elevated amounts of calories to perform in their given sport (and continue doing so long after the retiring from the sport). Similarly, a study examining former power sports athletes showed a significantly higher average body weight, BMI, blood pressure, LDL cholesterol level and insulin level compared to controls,[11] for possibly similar reasons as the previous study.

So, has the moral of the story now changed to *exercise is bad, chips+TV is good*? Of course not. It merely underscores the importance of moderation and consistency, as well as ensuring that your dietary intake is appropriate for your level of physical activity (ie. To maintain body weight, calories in = calories out). It's also important to be mindful of balance – not too much or too little of anything, whether talking about two-bite brownies, or sets of barbell squats. To put it another way, every time you go to the gym and perform a biceps curl, you aren't building the muscle – you're breaking it down. With every repetition, you are causing tiny micro-tears in the muscle fiber. The corresponding increase in strength, muscle size, etc. can only occur afterwards, once the muscle has had a chance to recover and grow stronger to meet the increased demand. If we don't allow our bodies adequate time to recover (along with adequate nutrition and hydration), then all we're really doing is compromising the foundation, little-by-little, until eventually, the building collapses (or the rotator cuff tears, etc).

So how much is enough? Well, it's worth noting that in order to improve your health and reduce risk of chronic disease, not everyone needs to diligently attend a cardio boot camp for ninety minutes, six days a week. In fact, research has shown a significant reduction in GI tract cancers in men exercising ten hours each week at the equivalent of an average walking pace.[12] However, most conservative guidelines, including one from the American Heart Association, aim a little lower, recommending roughly 150 minutes (2.5 hours) of moderate-intensity exercise each week.[13] As for diet, there are merits to a number of dietary strategies, from the Paleo diet to the Mediterranean diet, to simply shooting for three moderate (there's that word again!)-sized meals, with a couple of snacks mixed in, focusing on complex carbohydrates rich in fiber, along with healthy fats and lean protein. As with most things in life, optimal health solutions are not one-size-fits-all, with dietary restrictions, pre-existing health conditions, food sensitivities or allergies, and personal preferences all factoring in.

The bottom line? Regaining, maintaining or establishing optimal health should be a goal for anyone at any age. Helping us in this quest is the fact that so many of the health issues that often arise as we get older either have a common origin or can help to drive each other. What makes that helpful is that to stop a harmful, negative cycle, we're not left to chase a million random symptoms with a million random band-aid solutions. Ultimately, our stress levels, sleep quality, digestion, mood, immunity, joint health and energy are all intimately connected. By supporting one process, we're automatically supporting the others. Then, gradually, we can get a new, supportive cycle going. It's true that our bodies (and minds) at 50 may not be operating exactly as they did thirty years ago, with increased risk of injury, decreased metabolism, and a number of other factors beginning to creep in. But ultimately, we're not competing with our younger selves, or anyone else, for that matter. The game may have changed, but it's never to late to play.

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Repurposed Drugs for SARS-CoV-2 Versus Natural Medicine or Orthomolecular Supplementation

by Sue Visser

www.naturefresh.co.za

Finding new applications for some of the well-established drugs we have in the marketplace gives us the advantage of knowing about their side effects. Cheaper generic versions of these silver bullets are available in some cases. As soon as we mention the pandemic, people get excited about Planquenil, the drug we call hydroxychloroquine. Another popular and very expensive antibiotic called Zithromax is often used in combination with this anti-malarial drug. Is treating the viral pandemic with antibiotics and a vintage drug that is currently useless against drug-resistant malaria the best we can do?

Q: What is the most common cause of a respiratory crisis?

Certainly not any deficiency of hydroxychloroquine or Zithromax! A lack of glutathione is now what the latest scientific studies are pointing to as a primary cause of pneumonia COVID-19 complications.[1] There are a number of key micronutrients as well as amino acids we need to maintain our glutathione status to prevent such diseases. When we are full of toxins, pathogens, and chronic conditions caused by poor eating habits, our immune system is already down and out. Dr. Horowitz a renowned researcher of Lyme disease noticed the dramatic, almost immediate relief that patients who could hardly breathe experienced after a dose of glutathione within one hour of administration.[2] "Although anecdotal," he said, "I have heard from patients who were on NAC and glutathione when they were exposed to COVID-19, that they did not get sick or test positive for the virus, when others around them did." Cytokines are made by the body to fight invaders; but when there are too many, when the immune system is on overdrive, the cytokines turn on the host itself. Glutathione and related supplements may well stop COVID's "cytokine storm syndrome."

Glutathione and related supplements may well stop COVID's "cytokine storm syndrome."

Q: What exactly is glutathione – can we buy it over the counter, without a prescription?

Glutathione (GSH) is one of the body's master antioxidants and plays an important role in our defenses, regulating cytokine responses and immunity. GSH is a small protein molecule composed of three amino acids: cysteine, glutamate, and glycine called GSH precursors or building blocks.[3] (I often talk about glutamate and the supplement L-glutamine converts to glutamate, as does MSG.) Vitamin C, another very effective antioxidant also inhibits airway inflammation and increases glutathione. Zinc is known to play a central role in the immune system and is one of the most effective ways to deactivate the replication of the coronavirus's RNA. The most effective way, as we mentioned in the first of our talks on COVID-19 is to tune up the immune system. Selenium is a cofactor for the production of glutathione. Supporting our natural ability to ward off and treat both viral and bacterial diseases is all we need to do. However, this approach is the one we are constantly reminded to forget about!

Oral glutathione supplements that include the bioavailable precursors such as N-acetylcysteine can effectively increase glutathione production and hence improve the outcome of patients. For the emergency treatment of coronavirus-infected patients, some forms of glutathione can be inhaled into the lungs or used transdermally or intravenously.

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Repurposed Drugs

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Q: What is this newly re-discovered wonder drug they call Ebselen and are there any harmful side effects?

How about Ebselen? In the past, doctors have used Ebselen to help treat bipolar disorder, cataracts, and hearing loss. Recent studies show that it inhibits the virus's main protease, which is known as Mpro.[4] As a consequence, scientists have already shown that Ebselen is safe. It also exerts a powerful antibacterial effect on drug-resistant strains like *Staphylococcus aureus* and significantly reduces their elusive biofilms. It doubles up as an anti-inflammatory and can reduce cytokine levels. Ebselen is a selenium-based organic complex, which can mimic the activity of glutathione peroxidase. It is a strong antioxidant, which increases the efficiency of glutathione and has a strong neutralizing effect against free radicals, especially when it comes to inflamed airways – not only for coronavirus patients, but also for lungs that have been damaged by cigarette smoke.

The use of colloidal silver and Ebselen in synergistic formulations has been shown to be effective against five, clinically difficult-to-treat MDR Gram negative bacteria.[5,6] Ebselen has low cytotoxicity (LD50 tests in rats) and its safety in humans has been evaluated in several clinical trials. The clinical potential for the combination of Ebselen plus colloidal silver for SARS-CoV-2 treatment is very promising. It would bypass the necessity for separate antiviral drugs – plus antibiotics and anti-inflammatory drugs as well as antioxidants. Novel antimicrobials are becoming increasingly difficult to develop and are currently unable to keep pace with the emergence of resistant bacteria as it is. Because Ebselen mimics the natural substance we call glutathione peroxidase, it behaves like a micronutrient in its own right with an excellent safety record.

Q: What is colloidal silver and why are we being told it is ineffective – if not dangerous?

According to WEBMED, "There are currently no FDA-approved over-the-counter or prescription drugs containing silver that are taken by mouth. However, there are still colloidal silver products being sold as homeopathic remedies and dietary supplements. Colloidal silver is used for infections, hay fever, skin conditions, and many other conditions, but there is no good scientific evidence to support any of its uses. Colloidal silver can be unsafe when taken by mouth, applied to the skin, inhaled, or given by IV. Despite some claims, there is no good evidence to support using colloidal silver for COVID-19. In fact, it can be unsafe. We are advised to follow healthy lifestyle choices and proven prevention methods instead."[7]

Is this really the case? Absolutely not! Only silver nanoparticles (colloids) can survive inside the body. Metallic silver particles are unaffected by hydrochloric stomach acid and chloride ions and will circulate in the bloodstream. The particles will slowly be eliminated from the body and do not build up. It is the particles of metallic silver that provide the real benefit, especially against viruses as well as bacteria. According to an excellent study in Feb/March and April 2006 editions of the highly respected *Townsend Letter*, licensed practitioners have had access to medically tested/certified forms of silver hydrosol for the past 14 years.[8]

Silver-based remedies have been used for treating virus-related respiratory disorders for many decades and have a safe and reliable track record.[9] There is sufficient evidence (in vitro and in vivo) of its efficacy against over 24 of the dominating strains, plus those responsible for HIV/AIDS and the *Herpesvirus hominis* (HSM) virus. According to Eric Gordon, MD, and Ken Holtorf, MD, the authors of the much-quoted *Townsend* article, oligodynamic silver is all one needs to eliminate deadly viruses – plus their mutations.

Q: How does silver do this?

The atoms of silver that encircle each silver nanoparticle are released into water in order to purify it and this is why in ancient times, water was stored in silver containers to kill the germs.[9] Regardless of understanding the mind-boggling science behind nanosilver and the way that bio-active silver ions react within the bloodstream, the immune system or your drinking water, they zap the infections before they can spread to others. The silver nanoparticles that are measured in nanometres (usually 1-10 nm) are said by some researchers and manufacturers of colloidal silver to be: "the single-most effective all-natural anti-viral substances on the face of the earth."[10] In the 2005 HIV study they found that they could inhibit the virus from binding to host cells, as demonstrated in vitro. In a 1992 study published in the Pharmaceutical Chemistry showed a 700 times reduction in the concentration of smallpox viral particles when Protargol (a commercial brand of colloidal silver) was applied.

Q: If colloidal silver kills bacteria, what happens to our friendly gut flora?

Beneficial microbes and bacteria that reside in the gut are no different in structure to infectious strains that cause pneumonia or tuberculosis. Colloidal silver will kill any bacteria and may continue to destroy its further attempts at trying to emerge.[11] However, we have a few kilograms of beneficial microorganisms within our intestinal tract at any point in time, so a small daily dose will not cause a major disruption. We are usually advised to supplement with probiotics for this reason, when taking regular antibiotics and that would include Zithromax. By adding a small dose of colloidal silver, we discourage, pathogenic bacteria and encourage the fast-growing gut flora. It is important to take a wide variety of different strains,

Contact Information for October Article

To contact the authors of "CRP Screening Protocol to Help Control the Spread of COVID-19… and the Next Pandemic," published in the October 2020 issue, please email John Morgenthaler at jmorgen4@gmail.com.

as the dominance of lactobacillus does not support a healthy biome.[12]

Q: Does silver really make you turn blue and should it be banned?

The adult daily dosage of supplemental colloidal silver is about 5 ml-10 ml daily, and this amount could hardly be deemed as dangerous or the cause of argyria (turning the skin blue) or anything untoward. Unlike the queue of pills that are prescribed for treating both chronic and acute conditions, there has been no evidence of side effects at the recommended dosage.[13] Exceeding the recommended dose by 48 times every day for a year may cause some of the silver to accumulate under the skin, giving a silvery blue complexion.

Colloidal silver/nanosilver are sold as supplements and manufacturers are not authorized to make any claim that they can treat, cure, mitigate or prevent any disease (despite the overwhelming scientific evidence). Buying your own Micro-Particle Colloidal Silver Generator is an alternative to using your favourite commercial brands – should they be banished from the shelves.

We can either choose to take advantage of the decades of scientific studies that support sliver-based drugs against this and future respiratory pandemics or succumb to yet another strain of yet another deadly virus.[14]

Q: What about other drugs that can support glutathione?

Antabuse, a drug that is commonly used for treating alcohol abuse offers a number of benefits as a treatment for SARS-CoV-2. The generic is called disulfiram and as previously demonstrated in vitro with SARS and MERS coronaviruses,[15] it inhibits the main coronavirus protease (M pro) and stops it from replicating.[16] It also helps the body to compensate for a loss of glutathione. As we now know, a glutathione deficiency (antioxidant, anti-inflammatory, anti-viral) is the leading cause of respiratory distress and cytokine storms. The drug is not expensive and has the advantage of doubling up as a treatment for alcoholics. For South Africa this has additional benefits, as many of the vacant coronavirus/pandemic beds are occupied by the victims of alcohol abuse.

Q: Are there any drugs that can help with the cytokine storm?

Yes, a surprising one comes from a popular veterinary drug called Ivermectin.[17] It is used for killing scabies and other parasites that affect farm animals. Now, according to Dr Kylie Wagstaff, who led the latest study: "We found that even a single dose could essentially remove all viral RNA by 48 hours and that even at 24 hours there was a really significant reduction in it." Ivermectin is a treatment for roundworm infections as well as scabies and rosacea, a skin condition that results in redness and causes pus-filled bumps on the face. It kills parasites by super-relaxing them, so they lose their grip on the host. Ivermectin is classified as a GABA-agonist. In other words, it works as an activator of GABA, our chief inhibitory neurotransmitter. Natural equivalents we all use come from herbs ➤

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like valerian, passiflora and hops that are herbal tranquillizers and sedatives!

Q: What about natural remedies or the orthomolecular approach?

Like all viruses, the latest strain we now call SARS-CoV-2 spreads by RNA replication, and the race is on to find a novel drug or vaccine to inhibit it. Coronaviruses involve proteases that are situated on their characteristic spikes. In this case, the protease called Mpro is one of the main targets to address with an effective protease inhibitor. The second mode of action is to deactivate the RNA. There are plenty of natural substances we can use, even without promulgating a petro-chemically derived drug such as hydroxychloroquine. It is not even available in South Africa. Fortunately zinc plus natural ionophores like quercetin or green tea are even cheaper and easier to find. As a health researcher and keen observer of COVID-19 treatments for the "2020 global pandemic," it is difficult for me to recommend a tried and tested, reliable natural remedy like Artemisia, olive leaf,[18] or colloidal silver without being viewed with suspicion. As for orthomolecular medicine…can we still argue against our universal toxic overload combined with the paucity of key nutrients that maintain a healthy happy immune system? To some extent, we all lack the basic nutrients like vitamin C, zinc, vitamin D, and selenium, let alone the amino acids glycine, cysteine and glutamine that add up to glutathione. Ventilators cannot save the lives of patients who have one thing in common: a glutathione deficiency.

We are constantly reminded by the WHO that: "While some western, traditional or home remedies may provide comfort and alleviate symptoms of COVID-19, there is no evidence that current medicine can prevent or cure the disease. WHO does not recommend self-medication with any medicines, including antibiotics, as a prevention or cure for COVID-19. However, there are several ongoing clinical trials that include both western and traditional medicines."[19] They say that "Doctors are discouraging the use of drugs recommended by practitioners of alternative medicine because a drug has to be developed keeping in mind its safety and efficacy."

The good news is that when using existing drugs to treat SARS-CoV-2 with those originally intended for other treatments, we can use them as multi-taskers, for alcohol abuse, bipolar disorders, cataracts, rosacea and so on. Olive leaf and artemisia, although ridiculed and scorned by some, as treatments for viral or bacterial treatments certainly do still work against malaria and a lot of other parasites.[20,21] We have many options to choose from, to both prevent as well as treat coronaviruses and mosquito bites!

People are waiting for a new scientifically proven drug to cure or prevent coronavirus infections, but should we ignore alternative strategies in the meantime? Would a new, untested vaccine be safe for everyone to use – especially if there is no guarantee and no liability or comebacks? Some people welcome the idea, others do not.

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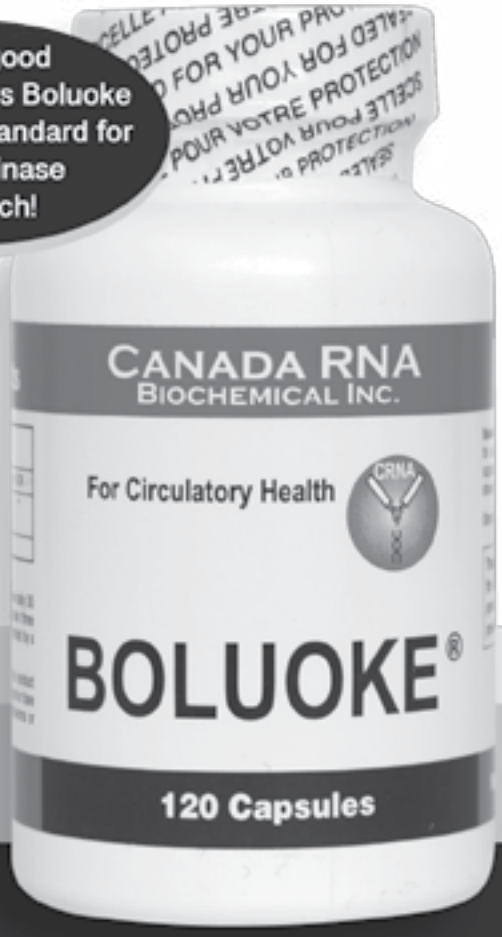

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Checklist: Fatigue and Pain Related to Computer Use

Erik Peper, PhD, Richard Harvey, PhD, and Nancy Faass, MSW, MPH

Fatigue, insomnia, chronic headaches, migraines, back pain, shoulder injury, or wrist disorders can be a sign that computer use is affecting your health.

Tech Stress, a recent release from North Atlantic Books (Peper, Harvey, and Faass, 2020), offers easy, step-by-step instructions on setting up your computer and your work area to minimize fatigue and pain.

Fatigue

These questions are important for anyone who uses a computer more than two hours a day and are useful in identifying possible causes, solutions, and referrals.

Ergonomics (feeling comfortable while you work)

___ How many hours a day do you spend sitting at the computer?
___ Have you had the opportunity to improve the ergonomics of your work area?
___ Is your chair adjustable, and do you know how to adjust it?
___ Are your desktop and keyboard at elbow level?
___ Do you use a laptop stand that places the screen at eye level? If you do, be sure to pair it with an external keyboard.
___ Have you had the opportunity to try a sit-stand desk, to observe the effect on your energy level? Good options include a dedicated sit-stand desk, a sit-stand riser on your desktop, or other types of furniture that provide the same function.

Sit-stand workstyle: If you are working at home, a credenza or dresser can be adapted to sit-stand usage. A large Ikea credenza, for example, makes a marvelous standing desk for a man or woman around 5'6"; the key is having the work surface at elbow height. You can also convert an existing desk or worktable to a sit-stand work area using a portable riser (typically ranging from $100 to $150). This is worth the effort. Many employees who incorporate a sit-stand workstyle find that their energy improves within a day or two.

Stretching, Breaks, and Circulation

Sitting is considered the new smoking. Immobility has been linked to increased risk of some cancers, type 2 diabetes, heart disease, immune dysfunction, back disorders, and shorter lifespan. What matters is the number of hours you spend at the computer *without moving*.

___ How long do you tend to work without taking a break? (Clock yourself!)
___ Can you alternate tasks while you work: for example, typing, then answering the phone (standing), or changing the paper in the printer (across the room).
___ Do you use a break app on your computer or your phone to remind you to take breaks?

- Microbreaks are brief stretches measured in seconds that you can take without ever getting up from your chair.
- Mini-breaks are stretches measured in minutes, and you'll want to take two or three of these an hour. You can begin by standing, taking a big stretch, reaching high over your head, and then rolling your shoulders.
- Large movement breaks mean getting up and walking around once an hour. Make an effort to get outside on your lunch hour if feasible.
- To track the benefit, rate your level of fatigue at the beginning and end of the week.

Your Sleep

A recent survey by the National Safety Council reported that 43% of Americans are not getting enough sleep and experience fatigue to such a degree it compromises their safety at work and on the road, as well as their ability to think clearly and be productive.

___ Do you remember to turn off all visual media an hour before bed?

The goal is to avoid the effects of blue light from the screen, which is interpreted by your brain as blue sky and daylight. This is true of light from not only your phone and your laptop, but also from the TV. The effects of blue light exposure lower your melatonin levels (making it more difficult to get sleepy), and raises cortisol (releasing blood sugar, energizing you just when you want to wind down and get to sleep).

In addition, if your mind is overly active, if your emotions are triggered by an incoming text or email, or if you're watching the nightly news or a thriller right before bed, that can further delay your ability to fall asleep.

Blue light from computers can also disturb your normal day-night rhythm. Consider getting testing which typically requires four saliva samples to track your cortisol curve. That allows you to determine whether your cortisol pattern is disturbing your wake-and-sleep cycle.

Neck Pain

___ How much time do you spend on your phone over the course of a day?

Your smart phone can be a major source of strain on your neck – as you bend forward to see the screen, the weight of your head places about 60 pounds of pressure on your neck vertebrae, in contrast to standing erect (Hansraj, 2014).

___ Do you use your phone during your commute?

To avoid the strain of craning over your phone, consider holding it at eye level using a phone case with a ring or a pop socket.

___ Do you find yourself leaning in to read the screen, suggesting the need for computer glasses?

If vision is an issue, you'll want to avoid bifocals and consider glasses made specifically for the focal length from your eyes to your computer screen.

___ Do you use a tablet and if so, do you experience neck pain or headaches?

Consider using a stand that puts the device at eye level, paired with an external keyboard. Affordable external keyboards weighing less than a pound are now available.

Referrals: If your neck pain persists, consider a biofeedback provider or a massage practitioner skilled in myofascial release or Rolfing.

Back Pain

If you are experiencing frequent stiffness or pain, you'll want to give some thought to:

___ The number of hours at the computer and/or on the phone
___ Your break schedule
___ The set-up of your workstation
___ The level of workplace stress
___ Whether you are getting enough exercise
___ Waistline weight that can cause inflammation and strain on the back

It's important to take back pain seriously because, if ignored, these conditions can gradually worsen and become incapacitating. Short-term, there is the issue of the physical and emotional burden of pain. In the long-term, there are several other major considerations:

- Back injury affects one in every four adults. Direct treatment and lost wages total more than $250 billion annually in the U.S. (boneandjointburden.org, 2020).
- Over-the-counter pain meds, which are often the first defense against pain, have been associated with increased risk of heart attack. An analysis in the *British Medical Journal* (2017) of the medical records of 446,763 individuals in Europe and Canada reported, "Taking any dose of NSAIDs for one week, one month, or more than a month was associated with an increased risk of myocardial infarction." Risk increased by 50% on average for ibuprophen, diclofenac, naproxen, and rofecoxib.
- Stronger medications such as opioids are an even bigger problem. According to the National Institute on Drug Abuse (NIDA) "2018 data shows that every day, 128 people in the United States die after overdosing on opioids." Prescription opioid misuse is also a public health issue in the U.S. with costs to society of more than $78 billion a year, and incalculable human costs.

Referrals: Note that when pain is the result of a sedentary workstyle or ergonomics, the problem could take two or three weeks to resolve. If the pain continues after three weeks, seek treatment. For back pain, consider a chiropractor, an osteopath, an acupuncturist, or specialty massage.

Wrist or Shoulder Pain

A wrist condition such as carpal tunnel syndrome can have a number of causes:

___ Is your keyboard slanted at too great an angle, bending your wrists back and increasing the risk of tendonitis?
___ Have you experienced abdominal weight gain or are you pregnant, which forces you to wing your arms out as you type, increasing the potential for ulnar nerve injury?
___ If you use a wide keyboard that requires a bit of stretch when you're mousing, do you experience shoulder pain?

Resources and referrals: In each case, specialized equipment can resolve these issues with a minimum of effort and expense. In terms of treatment, you can find providers trained in biofeedback, with skills in assessing chronic muscle tension, referred pain, and related issues through the Biofeedback Certification International Alliance (BCIA) and the Association of Applied Psychophysiology and Biofeedback (AAPB) in the US, and the Biofeedback Federation of Europe (BFE) in Europe.

At Home or on the Road

If you work from home, know that home ergonomics are often even worse than those in the office. Yet the solutions are affordable and relatively easy.

Similarly, for those who travel a great deal and find themselves working in coffee shops, on planes, in hotel rooms, or at conferences, there are almost always smart options available to optimize your workspace.

Good Ergonomics. This is not about throwing money at a problem or expensive equipment. Sometimes it is simply a matter of adjusting the equipment you already have. In other cases, you can develop simple solutions, such as adding a pillow to your chair to raise you to the proper height or to provide back support.

*Workarounds***.** For the home office, furniture can be modified (or purchased secondhand) to provide you with excellent ergonomics. For example, a good quality exercise ball can be used as whimsical seating (and greatly benefit your posture and circulation) for less than $25.

Office work doesn't have to hurt. By paying attention to ergonomics and workstyle, taking regular breaks, and building exercise into your day, often pain can be reduced or eliminated.

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A Paradigm Shift in Dentistry

by Dr. Dominik Nischwitz

The following excerpt is from Dr. Dominik Nischwitz's book *It's All in Your Mouth: Biological Dentistry and the Surprising Impact of Oral Health on Whole Body Wellness* (Chelsea Green Publishing, March 2020) and is reprinted with permission from the publisher.

In 1957, a year before the World Cup was held in Sweden, Vicente Feola, coach of the Brazilian national soccer team, took some time to reflect like no other person before him had. Then he began to make detailed preparations for the upcoming contest. Of course, he would need his most talented players and the very best training methods. But Feola wanted to think beyond that. He didn't want to overlook anything that might affect his players' performance, so he decided to take measures that had never before played a role in soccer training. Not only did he send his players to be checked over and looked after by a psychologist, but he also sent the entire team off to the dentist. And there was a lot of work to be done. Of the 470 teeth examined, 32 were diseased or inflamed and had to be taken out. When the Brazilians entered the competition a year later, they probably had the healthiest teeth of all participants.

Despite some particularly energy-sapping preliminaries, given how close the competition was, the Brazilians won the most confident and superior victory ever seen in the tournament. From the outside Feola's methods seemed bizarre. Surely what soccer players need most are strapping calves, ball skills, and a lot of stamina? But today several studies have proven that the coach's intuition was spot-on: Good health and the best possible levels of fitness can only be attained if our mouths and teeth are all in good order.

For decades people thought that tooth decay and gum inflammation were the only types of disease it was possible to get in their mouths. But it's now been proven several times that cardiovascular diseases, diabetes, infertility, strokes, intestinal diseases, and many autoimmune diseases often begin in the mouth, or can be made worse by factors stemming from there. Diseased teeth, inflamed gums, and filling material rejected by the body do not only affect the mouth. Often their effects can be found in completely different places in the body in the form of knee problems, shoulder or back pain, or allergies that we can't quite seem to make sense of. Teeth that are diseased or poorly cared for deplete the body's energy and nutrients, which can initiate processes that trigger depression, affect our hormones and body chemistry, stimulate the immune system, and activate the stress axis twenty-four hours a day.

Today we know that the most chronic illnesses are not down to coincidence, bad luck, or bad genes. Instead they are the result of constant, silent inflammation in the body and the resulting chronic stress. This kind of inflammation often occurs in the mouth. It can be found hiding in the tips of inflamed tooth roots, gingival pockets, around implants, in dead teeth, or in the cavities that are left behind whenever a tooth has to be removed. Although research is constantly revealing new relationships between teeth and the body, this knowledge is far too infrequently used in practice. Doctors and dentists traditionally work in two separate spheres. A general practitioner will seldom look into the mouth, and a dentist's work is primarily technical.

Our medical care system is structured such that we can't see the forest for the trees. What we desperately need is to look at the bigger picture. Up until now the mouth's role as the central organ that connects the two disciplines has been largely neglected, and with it the opportunity to understand the cause of many diseases as early as possible.

It's not only dentists who are taught to judge dental health according to whether the mouth's mechanical functions are in working order and whether the teeth are straight. Our teeth have to do a lot of work to break our food down into digestible pieces. But if we only see them as grinding machines that can be repaired when they break down, then we are doing them a huge injustice. This perspective also disregards what they really are and what role they play in our bodies. The visible part of our teeth is only a third of what is there. Sadly, we never catch sight of the other exciting parts. And yet they ought to have attracted quite a bit of attention: At the core of each tooth lies, in the tiniest space, everything that constitutes an organ – pulsating blood vessels, lymph vessels, a nervous system, and an immune system. Like every other organ, our teeth are connected to the rest of the body via these systems. When the body is run down, our teeth suffer, too. If there is a problem with our teeth, it always has an effect on the rest of the body.

Many of us make great efforts with our oral hygiene but end up feeling disappointed or even ashamed when our teeth become diseased despite regular brushing. For a long time the credo was: A clean tooth is a healthy tooth. Rows of products on supermarket shelves promise to provide the solution. We are offered a selection of interdental brushes, dental floss with added fluoride, antibacterial mouthwash . . . yet 95 percent of people suffer from tooth decay and 65 percent from gum

disease. Many people soon become resigned to the idea that teeth simply aren't built to last. But some people's teeth don't even make it through the first four years of their lives. Our teeth are certainly made to last longer than that. Superficially fixing these patients' teeth in the same way we would give a car a new paint job isn't going to solve this problem. This is why it's so great that there are new ways of looking at the mouth that are changing the way we think about teeth and how they get diseased. Theories that have been considered valid for years are now coming under scrutiny and being corrected. A consensus has existed for a long time, but now a paradigm shift is taking place. We have learned to focus so much on fighting bad bacteria that we have lost sight of those that do us good and help promote good health. We've been concentrating so hard on cavities that we've forgotten about the mechanisms in place that make our teeth resilient and help them to constantly repair themselves. We've learned to see our teeth as inanimate objects, neglecting to ask ourselves whether they can even withstand the repair methods we have invented for them.

Biological dentistry brings together the overlooked factors, making connections and questioning traditions. It takes into account the sensitive biochemistry, physics, and biology of the body. As an organism, we have an enormous capacity to heal ourselves and are remarkably good at rejuvenating ourselves once the cause for any given disease is removed.

A new type of dentistry can help us do exactly that. Only a few of us are given the task of winning a World Cup. But most of us want to be able to stay healthy and active. For a long time people have been desperately seeking answers as to why they have become ill or just not as fit as they used to be. They want to know how they can take care of themselves – how they can get better and stay better. We should no longer overlook or deny the central role that our mouth has to play in answering these questions. Today we have so much more information available to us than the intuition that the coach of the Brazilian soccer team once had to rely on. We have new insights from the world of science that have enabled us to recognize connections in the body more clearly than ever before. We no longer have to content ourselves with snippets. We now have the whole picture.

Let the healing begin!

Dr. Dominik Nischwitz is a dentist and naturopath, a world specialist in biological dentistry and ceramic implants, and the president of the International Society of Metal Free Implantology (ISMI). In 2015, Dr. Nischwitz cofounded DNA Health and Aesthetics, Center for Biological Dentistry, with his father in Tübingen, Germany. A pioneer in the field of holistic odontology, Dr. Nischwitz regularly gives lectures and trainings around the world. He is the author of *It's All in Your Mouth* (Chelsea Green Publishing, March 2020).

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Introduction to the History of PAK Around the World, Part 2

The History of Professional Applied Kinesiology **is available online at www.townsendletter.com.**

Part 2 of this history of Professional Applied Kinesiology's (PAK) growth around the world tells the story of PAK's spread on each of the continents of the world and its penetration into nearly all of the allied natural health care fields. Clinicians from the various disciplines of manual medicine, acupuncture, osteopathy, naturopathy, physiotherapy, dentistry, psychology, nutrition, and massage will tell the story of the growth of PAK manual muscle testing within their professions, and the reasons and dynamics for its appeal to their members. The history of PAK's success in sports medicine is documented here.

Chiropractic, dental, osteopathic, naturopathic, nutrition, and massage colleges have all adopted part of the PAK curriculum and taught it to their students around the world. The reason for this, it will be discovered, is that PAK can be used with most methods of health care practice and can be the unifying factor in finding the best method of treatment among the vast amount of treatment options available today. PAK is a system of examination that evaluates normal and abnormal body function and helps bring together the many forms of complementary therapeutics.

Over time many therapeutic procedures from different disciplines have been found that returned an inhibited muscle to normal status. Because of this success, PAK has become an interdisciplinary examination approach in health care, drawing together the core elements of complementary therapies and creating a more unified approach to the diagnosis and treatment of functional illness.

Dr. George J. Goodheart Jr., the founder of PAK, showed that the muscle system was the most exposed part of the nervous system. Diagnosing neuromuscular problems with muscle testing has proven to offer a great appeal to clinicians across the globe, as evidenced by the fact that there are today an estimated 1 million clinicians who use some or all of Goodheart's PAK method.

Growing from Goodheart's initial published work throughout the chiropractic and biomedical literature of the time, there are now some 40 published textbooks in seven languages about PAK, and a dozen more textbooks that contain chapters specifically covering PAK. The history we've written here covers the intimate hows and whys of a single chiropractic diagnostic technique's spread around the world and answers the questions about why it has been taken up by physicians from a great number of allied disciplines.

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Surviving a Viral Pandemic

review by Dr. Atousa Mahdavi

Surviving a Viral Pandemic: Through the Lens of a Naturopathic Medical Doctor by Heather Herington, NMD
ISBN-13: 978-1735630809; 272 pages; August 2020; Kindle or print.

In America, where currently even disease is politicized, most rational human beings should be afraid of the flu, a virus that has plagued humanity since the birth of original sin. Viruses play no favorites as they will go after anyone – especially those with underlying medical conditions, that segment of any population most unable to defend against their highly undesirable effects.

We've never worn masks to thwart the spread of flu virus in recent times, that is, with the exception of doctors and medical personnel, until the current onslaught of the flu's toxic, RNA relative, COVID-19. But don't get me wrong, I'm all for wearing a N95 mask to lessen the chances of contracting through droplets and also in hospital and clinical settings. I am also for washing hands.

Still, I have to ask, is that all our outstanding, hand-picked medical establishment can advise coupled with the trendy oxymoron referred to as "social distancing" while so many of our lives and kids' lives are on hold? This particular virus doesn't seem to be going away, with no green light at the end of the tunnel except for the hopeful promise of an antidote in the "near" future in the form of a vaccine. As the reviewer of Dr. Heather Herington's eye-opener, *Surviving A Viral Epidemic: Through The Lens Of a Naturopathic Doctor,* along with its author I repeat: really, is that the best they can do? Why aren't they offering advice on how to boost the immune system and how to take better care of ourselves? For that matter, their silence around obesity, chronic health issues, and poor lifestyle and nutrition is deafening.

As Dr. Heather observes, we're in familiar territory here, folks. The US has never cared for the health of its general population very well. Despite being recognized as a world leader, our system of health care – empowered by the Flexner Report (of 1910) and the ongoing bullying of Big Pharma, private insurance companies, hospital stock holders, and their lobbyists – caters to those who can afford or profit from it, provides reliable access to the less fortunate only in the case of an emergency and, worst of all, places public health care almost exclusively in the hands of allopathic doctors while ignoring natural medical practitioners. In fact, it would be far more apt to label our present health system a "sick care" system with its minimal focus on disease prevention and lack of choice regarding treatment.

Sadly, in Dr. Heather's eyes, it's also fair to conclude that, as a result of this monopoly, too many Americans are in denial about their health care and their own health, since they believe it's basically inaccessible. Add in the fact that any big change in life, like adopting a different lifestyle, is challenging to say the least. We all know "we are what we eat" but continue to ignore it and now you have a perfect viral storm: an extremely contagious and virulent type of virus; a generally unhealthy population with massive amounts of underlying medical conditions; and a health care system that waits until you're sick or extremely ill to extend a welcome greeting but not offering real solutions.

Stepping into this awful void is Dr. Heather Herington. Her startling exposé goes well beyond wearing masks as a last resort and far deeper. To assuage the two-pronged fear of the current pandemic and utilizing the full breadth of natural medicine as a preventive and restorative tool, she cites the past successes of her fellow homeopaths and holistic health care providers, treating victims of the Great Flu, more commonly called the Spanish Flu, of 1918. She reports with documented evidence to show how natural medical practitioners, both past and present, have continued to heal their virally infected patients through clinical nutrition, homeopathy, botanical medicine, traditional Chinese and Ayurvedic medicine, hydrotherapy, and applied psychology.

This book is not only for the clinician and the informed reader but anyone willing to take on the challenge of transforming this prevalent health disaster into an opportunity to broaden one's horizons by ushering natural medicine into their homes. Dr. Herington goes into every detail, both historical and scientific, about the extent of the pathogenic threat posed by viruses like the flu and COVID-19 and describes how the body's natural immune system is set up to respond.

Then, against the current background of increasing environmental and economic stress, she supplies you with a list of affordable vitamins, mineral supplements, and botanicals, along with a set of weekly, nutritional and stress-relieving protocols and recipes to ward off and thwart infection. If or when COVID comes a-callin', you'll have a concrete program on which to rely. Should you contract an aggressive virus, whether the flu or COVID-19, her "sick room" will afford you the best possible care to recover, repair, and rebuild with a program of trusted remedies and treatments.

The most fascinating part of this book is the positive tone from which it speaks. Dr. Heather's lyrical style draws you in and never lets you go. Her aim, from the outset, is to connect on a personal level, no matter your state of health, how old you are, or your income bracket.

Despite being discriminated against throughout her career as a naturopathic physician, misogynistic issues aside, she is a healer. With heart glowing, she writes to serve and inform. Clearly, Dr. Heather has labored long and hard to get this message out to you. Straightforward but detailed, alarming yet comforting, *Surviving A Viral Pandemic* is all that. At long last, here it is. Don't delay. According to one reader, your bedside table is yearning for this gem.

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How to Search Using PubMed and Other Life Science Databases

by Robert G. Smith, PhD
Orthomolecular Medicine News Service

The PubMed database is widely used to find health-related articles about a wide variety of topics. It references articles from hundreds of journals, both domestic USA and international. PubMed contains citations and information from life science journals and online books originally compiled into the MEDLINE database by the US National Library of Medicine, some originally published as far back as the nineteenth century. PubMed and several other life-science databases are run by the National Center for Biotechnology Information (NCBI).

Is Your Search a Complete Search?

Recently a "new" version of the PubMed search page has been designed that is supposed to be easier to use.[1] However some of the features of the previous "legacy" PubMed search page appear on first sight to be missing.[2] For example, a pull-down menu that allows the user to select other databases has been removed. In its place, access to the other databases is available by a simple click at the bottom of the PubMed page. In addition, in both the old and new versions of PubMed, the user can select specific combinations of search terms by clicking on "Advanced" just below the search box. This feature makes PubMed very powerful because it enables searches that can be set with very specific search terms, such as the first or last author, the journal, title, or supplementary concepts. When you click on any paper to view its page, PubMed provides a list of "similar" articles, and also a list of citations (i.e. other papers that refer to the paper you're looking at).

Other widely used databases available at the bottom of the PubMed page include PubMed Central,[3] Europe PMC,[4] PubChem, GENE, Bookshelf, and others. Several of these databases, including PubMed Central, include "Advanced" buttons that allow the user to select which search terms to use.

Many Articles Are Free Access

The PubMed Central (PMC) database is a subset of the PubMed database that contains exclusively full-text articles that are available free for download.[3] A law passed by Congress in 2008 stipulates that articles published through NIH-funded research must be submitted to PMC for free public access: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html. The law allows journals 6-12 months of exclusive publication through a paywall, after which the articles must be available free to the public.

Although many papers published before 2008 are not available in PMC, some are. Articles published before 2008 can be submitted to PMC by the copyright owner (i.e. the author or the journal) for free public access if their free publication is allowed by the journal.

Is There Bias Built into Your Search Engine?

Although PubMed is designed to be easy to use for beginners, to understand how it performs a search given the search words entered by the user can be daunting. The results of a PubMed search can include those from PMC and online journals. But the default search terms are not always obvious and often may seem to ignore some controversial topics and journals. For many early articles, only the authors and title are available to PubMed; for others, the abstract is available but the full text is not.

In contrast, since PMC comprises full-text articles, it has access to the complete full text and References section. Therefore its default search terms normally include the References section. Articles located by PMC often include those that contain the search words only in the References (i.e. not in the main text of the article). Evidently for some articles available only in pdf form, the References section is scanned in as part of the full text of the article. When searching PMC only for author's name, it will not merely return articles as PubMed does that only contain the name in the article's author list -- in some cases it will also return articles that contain the author in the References section. Evidently, if PMC finds papers in its full-text database with the named author in the author list, it searches exclusively using the author list. But if it finds no papers with the named author in the author list, it uses alternate search terms that include the References section. However, since PMC only includes a subset of PubMed papers, when searched with an author's name that is in the author list of some of its papers, it may not return as many hits as PubMed.

If you go to the "new" PubMed and scroll to the bottom, a variety of search paths are available with a click[1]:

Popular

- PubMed
- Bookshelf
- Gene
- Nucleotide
- GEO
- PubMed Central
- PubChem
- BLAST
- Protein

Resources

- Literatureq
- Genomes
- Proteins
- Health
- Genes
- Chemicals

And there are several more general search categories, some of which are "powered by Bing," i.e. they use bing.com to search in their sub-category: NLM | NIH | HHS | USA.gov

The "Health" category includes by default all databases, but there is a pull-down menu that allows the user to select a particular one. They comprise different databases of articles and different default search terms.

From my experience, PMC, though often providing many hits, is by default set up to return a wider search than PubMed because of its default search terms on articles' full text. The default PMC searches can include the References section of its articles – which for some searches can produce more hits. This simply reflects the contents of the PMC database which in many cases originate from a scan of the original pdf file.

The PMC database includes all the full-text articles published by NIH-funded research, so in PMC searches one often gets many articles where the search words are in the Reference section. This is not so obvious when one searches for a general term such as "low carbohydrate" since the hits all show these words somewhere. But when a PMC search is performed on an author's name, very often the hits are papers that don't include the author. The reason is that PMC contains full-text articles so the references are easily available. This is quite obvious when you do a search by author name but not so obvious when you search for a general phrase.

Comparison of Databases

In comparing PubMed and PMC searches, using somewhat general phrases and comparing the total numbers from the different databases, one may get the impression that PMC does a "better" search because it returns more articles. But when doing a search that includes the name of an author, the rationale becomes more obvious. In many cases, the PubMed search will only return articles that include the name entered as an author – in some cases, just a few articles. But the identical search text on PMC returns many more articles. The reason is that PMC has the complete text and Reference section of every article, so it can return articles that contain references to the author name entered in the search. When evaluating the databases using a general phrase in the search, it is difficult to see this pattern, but when using an author name in the search, it is immediately obvious when the author name given is not present in the authors of the search results – because they're listed by author!

Both types of searches are appropriate uses for the different databases, but only when one understands the basic data available for the searches can one get a handle on which database to use. PubMed, though its database includes a wider selection of articles than PMC, can't always access the full text, so the References are evidently not included by default in the search. Europe PMC is similar to PubMed Central, i.e. it contains recently published freely downloadable articles, can include Reference searches, but also includes searches of the PubMed database that do not necessarily have full text content.[4] Google and Duckduckgo can find some of the pdfs but will list articles that only have an abstract or just authors and a title – so they have a mix of search terms.[5,6] Google Scholar searches PubMed, PMC, Europe PMC, and also the entire internet, often producing results from a very wide assortment of articles, books, and online pages.[7]

Let's Try One

It helps to know what each database contains and what the default search terms are. A simple search shows the main point.

PubMed. Let's do a search for vitamin C specialist Frederick Robert Klenner, MD. Search for "klenner vitamin c" on PubMed, and one gets 4 of his original articles. Evidently the name "klenner" is treated as an author:

1. The treatment of poliomyelitis and other virus diseases with vitamin C. KLENNER FR. South Med Surg. 1949 Jul;111(7):209-14. PMID: 18147027 No abstract available.
2. Virus pneumonia and its treatment with vitamin C. KLENNER FR. South Med Surg. 1948 Feb;110(2):36-8. PMID: 18900646 No abstract available.
3. Massive doses of vitamin C and the virus diseases. KLENNER FR. South Med Surg. 1951 Apr;113(4):101-7. PMID: 14855098 No abstract available.
4. The vitamin and massage treatment for acute poliomyelitis. KLENNER FR. South Med Surg. 1952 Aug;114(8):194-7. PMID: 12984224

PubMed Central. Then click on "PubMed Central" at the bottom of the PubMed page, and search for "klenner vitamin c", and one gets 9 fairly recent articles, none of which are Kenner's original reports, but which mention Klenner or have Klenner papers in their reference section:

1. Paul E. Marik. Hydrocortisone, Ascorbic Acid and Thiamine (HAT Therapy) for the Treatment of Sepsis. Focus on Ascorbic Acid. *Nutrients*. 2018 Nov; 10(11): 1762. PMCID: PMC6265973
2. Chang-Hwan Yeom et al. High dose concentration administration of ascorbic acid inhibits tumor growth in BALB/C mice implanted with sarcoma 180 cancer cells via the restriction of angiogenesis. *J Transl Med*. 2009; 7: 70. PMCID: PMC2732919
3. Chang Hwan Yeom, Gyou Chul Jung, Keun Jeong Song. Changes of Terminal Cancer Patients' Health-related Quality of Life after High Dose Vitamin C Administration. *J Korean Med Sci*. 2007 Feb; 22(1): 7?11. PMCID: PMC2693571
4. Edna Ooko et al. Pharmacogenomic Characterization and Isobologram Analysis of the Combination of Ascorbic Acid and Curcumin: Two Main Metabolites of Curcuma longain Cancer Cells. *Front Pharmacol*. 2017; 8: 38. PMCID: PMC5288649
5. M J Bissell, et al. Ascorbic acid inhibits replication and infectivity of avian RNA tumor virus. *Proc Natl Acad Sci U A*. 1980 May; 77(5): 2711?2715. Correction in: *Proc Natl Acad Sci USA*. 1981 Sep; 78(9): 5917. PMCID: PMC349473
6. I. R. Shapiro, et al. Patterns of vitamin C intake from food and supplements: survey of an adult population in Alameda County, California. *Am J Public Health*. 1983 Jul; 73(7): 773?778. PMCID: PMC1650902
7. S Harakeh, R J Jariwalla, L Pauling. Suppression of human immunodeficiency virus replication by ascorbate in chronically and acutely infected cells. *Proc Natl Acad Sci USA*. 1990 Sep; 87(18): 7245?7249. PMCID: PMC54720
8. Steven McRae, et al. Inhibition of AcpA Phosphatase Activity with Ascorbate Attenuates Francisella tularensis Intramacrophage Survival. *J Biol Chem*. 2010 Feb 19; 285(8): 5171?5177. PMCID: PMC2820744
9. A Yazeed, et al. Ascorbate ameliorates Echis coloratus venom-induced oxidative stress in human fibroblasts. *Exp Ther Med*. 2017 Jul; 14(1): 703?713. PMCID: PMC5488744

Then go back to PubMed, and click on "Health" at the bottom (which includes "All Databases" and "Search NCBI"), and search

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for "klenner vitamin c". This shows a list of the four PubMed articles, the nine PMC articles, and three NLM catalog listings (all the same one). The Europe PMC search for "klenner vitamin c" produces 14 articles, many of which are the same as those in the PMC search.

Click instead on "PubChem" and search for "klenner vitamin c", and one gets six hits, four of which are FR Klenner, and two are other Klenners. You can readily do a similar search on google.com (9 results), or on duckduckgo.com (more than 30 results).

Google Scholar

With the same search phrase "klenner vitamin c", Google Scholar gives 923 hits, with a mix of articles, books, and online pages.[7] A more specific search phrase "klenner 1949" gives citations to FR Klenner's two published articles of 1949, taken from Europe PMC. Google Scholar is very powerful but needs specific phrases in order to limit the results to a manageable number. It uses citation counts (i.e. how many other articles refer to an article in their Reference section) to assign a weight to the articles it lists which affects the order in which they are displayed. However, with its tremendous search base, it and other search engines available online have tended to make obsolete many other databases more limited in scope.[8]

Another Author Example

As another example, a search for "Pauling L" gets 229 hits on PubMed, whereas the same search on PMC gets only 123 hits. Note that author initials are important to select a specific author. The initials are included in the search phrase after the author's last name. A search for "Pauling" on PubMed gets 1634 hits, but on PMC it gets 5312 hits! The reason for the extra hits on PMC is evidently that a search for an author's name without initials uses the alternate search terms that include the main text and the References section. There are many perturbations of this effect, so depending on exactly what you are looking for, it may be helpful to experiment with different search word phrases. With "Pauling" Google Scholar gives ~159,000 hits, and with "Linus Pauling," ~27,600 hits.

Exact Phrases

To narrow a search to those articles that include an exact specific phrase, instead of those that include some or all of the words in the phrase, you can enter the phrase inside double quotes. For example, [["klenner vitamin" c]], would search for "klenner vitamin" and also "c". This returns no articles in PMC or Europe PMC, and PubMed finds no articles but then defaults to removing the double quotes to find the same four articles as it did without the quotes.

General or Specific Topics?

It's very easy to use online databases – you only need to enter a search phrase. But how the database server responds can vary widely, depending on the data searched by the database, the search terms it uses for the search, and the "display options." You can set the order of results according to the "best match" or according to the date – and though these give the same results, the results shown on the first several pages will likely vary because the articles that "best match" your search terms may not be the most recent.

An Example

Let's search for "low carbohydrate" in PubMed. That yields some 178,000 articles, and in PMC it gives ~370,000. This is likely for the same reason mentioned above: the search terms for PMC include the entire full text and References section. When the search is limited to a seemingly more specific phrase, e.g. "low carbohydrate diet," PubMed gives a much more restricted ~9,700 articles, and PMC gives ~71,000. In all these cases, the caveat is that the search phrase was not entered inside double quotes. The reason so many articles were given from the above searches is that they include any article that contains the words, "low" and "carbohydrate" anywhere in the article (and in the case of PMC, also including the title of any reference).

When the search phrase is specified exactly, i.e. inside double quotes, ["low carbohydrate"], PubMed returns ~2900 articles, and PMC returns ~8000 articles. Again it appears that PMC returns more articles because its search terms include the full text and references. However, one benefit of the PubMed article listing is that it shows the sentence in which the search phrase occurs, so the user can determine if the match is appropriate. This feature is also provided by Europe PMC and Google Scholar. It is a very powerful feature when a broad search term is specified.

When the search phrase is specified more precisely inside double quotes ["low carbohydrate diet"], PubMed returns ~1200 articles, and PMC returns ~3600. Although PubMed looks for this exact search phrase in the title, abstract, main text, and keywords, apparently PMC finds more articles because it also includes in its search the titles from its References. Google Scholar finds ~27,000 articles, including those listed in PubMed and PMC searches.

Intelligence or Defaults?

The bottom line here is that database search engines do not have what one would call intelligence – they have some default settings, some equivalent phrases (e.g. "vitamin C" = "ascorbic acid"), many options for search terms (in "Advanced"), and several display options. They may also have default exclusions that prevent articles on controversial topics or authors from being listed. If you are searching for a general topic, you may get a huge number of matches that are mostly not appropriate to your intentions. If you want to search for a more specific topic, it helps to include your search terms inside double quotes so the search phrase is specified exactly.

Conclusion

The takeaway point is that each database comprises different categories of articles, and each database uses different default search terms and search methods. Certainly PubMed doesn't contain and can't search through all the articles from all medical fields. It doesn't include certain journals (e.g. JOM).[9] To get the most from an online search, it helps to know what type of articles the databases contain and how the searches are performed.

PubMed and PMC if used wisely are very powerful but should not be used as an "encyclopedia." If you use them informally to search general topics, you may miss important articles, both recent and classic. The searches these services perform are based on matches between the search phrase and a selection of the content of each article, defined by the search terms applied by the database – all of which vary depending on the database. In contrast, Google Scholar uses different search criteria, and searches PubMed, PMC, and scholarly articles and books from entire online internet. While extremely powerful, its greater search space and greater number of listed articles emphasizes the problem of determining relevance.

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Ask Dr. J

by Jim Cross, ND, LAc
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Trippin' Over The Switch

As usual, the great Benjamin Franklin was on the right track with this quote: "Life's tragedy is that we get old too soon and wise too late."[1] Our genetic inheritance excellently prepares us for a paucity of calories, but presently civilization indulges our cravings for salt and sweets without the famine that used to go along with them. We're lasered in on a virus presently, but the greatest pandemic lies in our midst right now and kills over decades: calorie-dense, fiber-less, salt-laden food.

This column will center on some effective choices/ideas for weight loss; but I want to introduce a new term that came to me on one of my morning, forest bathing walks: unopposed insulin. Just like various conditions can cause unopposed estrogen in women's bodies, I think that the Standard American Diet/SAD has caused unopposed insulin in many people's bodies. This unopposed insulin can potentially lead to metabolic syndrome and insulin resistance plus all the downstream maladies that spring from these two conditions. The tide may be turning a tad, as some Mexican states are attempting to ban junk food sales to minors.[2] Hopefully I'll expand on unopposed insulin in a later column.

In terms of weight loss, many people appear to be trippin' over the switch as my title states. This switch could also be termed the insulin switch. In human's past, being able to increase fat stores in times of plenty was crucial for our survival in the lean caloric times. Our fat deposition/burning is tightly scheduled and will switch directions depending upon environmental conditions. A thousand years ago, grocery stores did not give our ancestors access to high sugar, high protein foods 24/7, 12 months/year. Hence, they would enter a calorie-restricted time frame where insulin blood levels would decline. This allowed fat cells to release their stores into the blood and satisfy their body's metabolic demands. Today, the opposite happens with a SAD diet not allowing for calorie restriction and lower insulin levels but stimulating continuously high insulin levels that prevent fat breakdown and encourage increased fat storage, which leads to ineffective weight loss. Basically, many modern Americans have the insulin switch stuck in the on/fat-depositing position.[3] Ah, the conundrum of convenience foods!

To summarize the above paragraph is an excerpt that I learned from Alan McDaniel, MD: *In briefest terms, the hormone insulin makes us fat and keeps us fat. One more time, for emphasis, our body wants to be fat.* Wow, is there anything more important? People attempting to lose weight must be extremely cognizant of the above statement, or they will always fail in their weight loss regimens. Our ancestors intuitively understood this, as fatter means better survival in a competitive environment. They would then correspondingly lose that fat during their long, hard, calorie-deprived winters.

The excess insulin that is being produced will eventually lead to a metabolic condition termed insulin resistance. This is problematic for a certain segment of our population. Our ancestors developed a genetic mutation that conferred a huge survival benefit, which was resistance to starvation. This mutation is called the thrifty gene.[4] It was what humans needed to survive the fairly, frequent famines of pre-Safeway times by allowing us to store fat more readily. In times of lower food intake, the body becomes more fuel-efficient by having its caloric needs reduced.[5] Metabolic function returns to normal when sufficient caloric intake resumes. In stressful famine times, the vulnerable perished; but those with thrifty genes possessed a much greater chance of surviving. The rub, though, is that these thrifty genes that bestow resistance to reduced calories are the same genes that initiate insulin resistance and lead to obesity in our modern calorie-laden world.

Insulin resistance then was not such a negative quality in our famine pasts. Unfortunately, the thrifty gene is still very much a thriving presence in segments of our population living amidst a caloric boomtown: approximately 40% of the US population and greater than 50% of Blacks and Hispanics are insulin resistant.[6,7] The Pima Indians of New Mexico are almost all essentially insulin resistant and 80% become diabetic by age 40.[8]

Essentially, insulin resistance is just a different type of metabolism and not a curse. This type of metabolism unfortunately does not fit a 21st century calorie-rich, fiber-less diet. A friend of mine mistakenly put diesel fuel into

her VW. Did it still run? Yes, it just ran extremely poorly and very loudly. The same scenario exists for thrifty gene people: their metabolisms still run, but they don't run optimally on a SAD diet; and they tend to gain weight very easily and have difficulty losing weight with a SAD diet. In essence, SAD is ruining people's metabolisms with the thrifty gene.

So, the question to be answered now is how do we turn off this unopposed insulin switch and begin to break down the adipose tissue that insulin is so nicely constructing? Obviously, this is accomplished via much more restrictive dietary choices that would need to follow this mantra: *Eat more local, photon-rich, nutrient dense, fiber-rich food.* This is actually becoming a much easier lifestyle choice with our ever-expanding farmer's markets and semi-natural food stores. I and other *Townsend* writers have expanded on exactly what types of macro nutrients to consume more and less of, so I won't belabor this idea here. The above mantra is a great place to start with your patients, and you can easily expound on each segment in much greater detail with them.

Another excellent choice is through calorie restriction (CR), which is consumption of fewer calories without malnutrition or deprivation of essential nutrients. The CR diet is also defined as a non-starvation diet. In addition, you would recommend that their CR include foods from the above paragraph. A study in 2011, Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy/CALERIE, compared a group who consumed their normal amount of calories versus another group who consumed 25% fewer calories/day for two years. This study differed from other weight loss studies because they emphasized adherence to a prescribed CR goal rather than a specific degree of weight loss. The study authors also wanted to establish if the weight loss established would be stable after two years or if the weight loss was transitory.[9]

After two years, 80% of the CR group, who were overweight at baseline, achieved a normal weight compared with a 27% increase in those who became overweight in the control group. Also, there were significant decreases in visceral adiposity of the control group which was suggestive of mobilization from fat stores that are associated with a much higher metabolic risk. This could also indicate potentially extra cardiometabolic risk reduction with CR.[10]

To summarize, insulin resistance can be adaptive in specific, calorie-deficient circumstances. Our Western lifestyle, which includes the SAD diet plus inadequate exercise and sleep, has turned this evolutionarily positive adaptation into a liability. To minimize weight gain in insulin-resistant individuals, we must educate them as to how they can maximize their positive metabolic physiology and minimize modern society's detrimental disadvantages to that same metabolic physiology.

I wish to also thank Alan McDaniel, MD, for generous access to his data-rich 2018 Power Point: "Insulin Resistance: The Metabolic Syndrome and Type II Diabetes."

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Healing with Homeopathy

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Parents and Kids on the Edge During COVID-19: Homeopathy for ADHD

Ritalin-Free Kids

Bob and I wrote *Ritalin-Free Kids* back in 1996, when the incidence of ADHD in the US was starting to skyrocket. At that time Ritalin was being touted as the solution, and the nationwide CHADD support groups for parents were being funded largely by Novartis, the manufacturer of the drug. Kids were lining up in the school nurses' offices to get their doses of the drug. ADD and ADHD were epidemic enough that our book, public talks to parents, and seminars for homeopathic professionals took us around the world: New Zealand, Switzerland, Australia, Scotland, the UK. Wherever we spoke, parents were desperate for help with their hyperactive kids who were not living up to their potential. I remember how amazed we were, to speaking to a room full of parents in Perth, Australia, which turned out to be an epicenter of ADHD!

Youngsters, wherever we went, just couldn't seem to sit still, concentrate, and keep their hands and thoughts to themselves. We presented countless cases of kids with behavioral and learning problems that responded significantly, sometimes dramatically with homeopathy. Was the epidemic manufactured, or at least the flames fanned, by the pharmaceutical companies? What we found was that many of these children, carrying diagnoses of attention deficit disorder, attention deficit hyperactivity disorder, oppositional defiant disorder, sensory integration disorder, learning disabilities, and many other labels, could be profoundly helped by homeopathic remedies. Now that Bob has retired, all of these cases have come under my care. And I find homeopathy to be as effective for many of these children as ever.

Overamped, Underperforming, Challenged Kids During the Pandemic

Parents and children alike are trying to navigate the waters of education COVID-19-style. I find in my practice that many of these families are homeschooling, often through virtual classes, for the foreseeable future. And these same parents may be making a superhuman attempt, on the part of one or both of them, to work a full-time job from home while supervising their kids, coordinating their children's curricula, getting food on the table, plus trying to create opportunities, online or off, for sports, exercise, and socialization. A recipe for overload at the least and frustration/insanity at best. Frankly, I don't know how they do it!

Add to the mix children who can't sit still, concentrate, focus, or get along with the rest of the family. All of this makes for short fuses leading to explosions, frustration all around, exhausted parents, and children whose moods and self-confidence may plummet. The pressures are even greater when kids can't socialize as they always did before and are limited as far as sports, exercise, and group activities of all kinds. I am not only talking about hyperactive kids, but those who are underperforming or lacking confidence due to learning challenges of various kinds. The cases we shared in *Ritalin-Free Kids* and our enthusiasm about how effective homeopathy could be are just as true now as then. The frazzled, exhausted parents are as much in need of support on all levels as their kids, but it's harder to get them to seek out help and they typically put their kids first.

Here are the cases of two children whose follow-ups I saw just today. In the early days of our treating these kids, many were already taking stimulant medication. That is no longer the case and I am often able to intervene before any pharmaceuticals are used. These are two families who thank their lucky stars to have found homeopathy during this intense and bewildering time. Both of these kids needed very common homeopathic remedies.

Case 1: A Southern Spitfire

Dylan's mom is one of my favorite parents. Her Southern accent is just charming. She first contacted me four months before the start of COVID-19: "He is full of energy. A little comedian. He thinks he's hilarious. He loves to be the center of attention and to entertain. He loves tornadoes. He tells me he'd like to be a tornado chaser! Dylan hates socks and would rather be barefoot. He likes soft things like soft blankets and pants… The only time he'll ever sit still is when he's helping his dad. Otherwise he hugs, hits, and gets into everyone's personal space. He loves potty language and often gets into trouble for using it at school. Dylan is a real spitfire. He loves going fast, play fighting, wrestling, and jumping on the trampoline… Anything that makes a noise grabs his attention. Or things he can tinker with. Like how box cutters open and shut. We had to take the blade out because he was obsessed. Dylan skipped walking entirely. It was crawling then running. He was fascinated with where pee and poop come from and where they come out."

It was Dylan's tantrums that were the final straw prompting his mom to contact me. "He goes spastic, crazy. Putting him down for a nap turns into a thirty- to forty-minute battle." Nighttime fears caused Dylan to wake in the middle of the night and he insisted on a nightlight. He loved to tell folks about this dream of the toilet exploding. He loved dinosaurs and spaceships. Dylan dreamed about being an astronaut, despite his fear of heights.

When I chatted with Dylan, he told me about his fear of drains, the exploding toilet in his dream, and his worries about poopoo coming out. His mom confided that he avoided pooping in the toilet for fear of falling in. When he was goofy, which was often, Dylan displayed his naked butt. The child just loved to laugh and to make friends. "His main M.O. is to get attention by farting or sticking out his tongue…whatever it takes. And he loves to push buttons whenever he gets a chance. He'll do whatever he can to get my attention."

The Remedy. Dylan was a classic presentation of *Hyoscyamus* (henbane), a plant from the nightshade family. Fundamentally, kids needing this remedy feel neglected, jealous, let down, betrayed, and deprived of attention. They compensate by being provocative, silly, and attention-seeking, all to get the love that they seek. If they do have siblings, which Dylan did not, there can be significant sibling rivalry to the point of violence. Mooning, potty talk, and sexualized behavior, in a foolish way, are classic in kids needing this remedy. Underlying the acting out, like the other nightshades, is terror, rage, and panic. I prescribed four doses of *Hyoscyamus* 1M in water twelve hours apart and LM8 daily.

Six weeks after the *Hyoscyamus*: "He's a little calmer… Getting along with his friends at school a lot better, which is awesome. Dylan is back in martial arts and this time he can stay for a whole hour. Now he'll apologize if he says something ugly or acts impulsively. His tantrums are shorter and not as

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intense. He's playing by himself more than he ever would. In the past he would just punch me. He still does sometimes, but now he warns me ahead of time. Dylan is so much more loving and sweeter. His grandparents are amazed at the improvement." He continued the daily LM8.

Three months (the beginning of the pandemic): "Dylan is hitting less. He's sweeter than ever. He still needs reminding and redirecting. He has so much energy. He can still plead, beg, and tune you out. But his tantrums aren't as bad. Dylan is no longer punching me. But he can still become goofy, hyper, and obsessed with saying 'booty' and 'poop.'" I gave another four doses of Hyoscyamus 1M and instructed the mom to also give the remedy up to once a week.

Four and a half months (two months into COVID-19): "His good days are great… Dylan is sweeter than ever. We're starting to thrive, not just survive. I told his dad that I'm really starting to enjoy my son… We're kind of enjoying the quarantine." I increased the frequency of the *Hyoscyamus* 1M plussed to once a day.

Six months: "He's missing his friends. He can still be disrespectful at time and backtalk. I'm giving the remedy once a week. Dylan is no longer afraid to go to the bathroom. He no longer needs his night lights in the hall and bathroom. He stopped pulling down his pants and there are no more pooping accidents." I raised the potency of the remedy to *Hyoscyamus* 10M plussed as needed.

Seven and a half months: Dylan is much better. He's not hyperactive. We're about to begin kindergarten. His mom had been dosing him about once a week.

Nine months (six months into the pandemic): "Dylan is really doing beautifully. Honestly, better than I ever dreamed he could. He's hardly gotten into any trouble. He really likes kindergarten…it is shocking. Dylan's not the same kid he was before the homeopathy. He is so much calmer. Maybe an off day once a month. He's hardly getting into any trouble at all. He's going to school and even read a book to the class. Dylan's not the same kid he was before… he's able to look me in the eye, obey. I'd say he is 90% better than when we started. Our

Dr. Tapas Kumar Bhattacharyya's Fourier Transform Infra-Red (FTIR) Spectroscopic Studies on Homeopathic Medicines

As a homeopathic clinician, my goal, over the past nearly forty years, has been helping patients transform their health and lives, physically, mentally, and emotionally. Homeopathic philosophy rang a chord with me from the first time I read about it in James Tyler Kent's *Lectures on Homeopathic Philosophy.* I have found the principles of homeopathy to prove true in my experience of having seen thousands of patients over the years. That is certainly not to say that I have helped every patient – that is too much, too great a hope for any healer or medical practitioner. But I have found, again and again, that those same principles espoused by Samuel Hahnemann, James Tyler Kent, and homeopaths since then, bear brilliant fruit.

I have seen so many patients helped by these gentle yet powerful, diluted substances that no one could ever convince me that homeopathy does not work. I have hoped fervently over the years that I would finally witness a scientific explanation, corroboration, of the mechanism of homeopathic remedies. There have been many attempts to do so in the four decades that I have been involved with homeopathy: from electron spectroscopy (which claimed to prove that different homeopathic remedies, and even different potencies had different frequencies), to the memory of water, Jacques Benveniste, and others. I have always believed, to the core of my being, that it was not that homeopathy did not work, but rather that the mechanism was not yet revealed, understood, verified. And the research studies, including the one that Dr. Ullman and I participated in regarding the homeopathic effectiveness in treating ADHD, always fell short.

Over my decades of homeopathic study and practice, I have witnessed thousands of cases with videos of patients before and after homeopathic care. This alone, even without scientific corroboration, has been enough to convince me of its effectiveness, in addition to the thousands of my own patients, many of whom have been helped significantly by these microdilutions, based on a philosophy misunderstood and criticized by many and defended vehemently, over more two hundred years, by relatively few.

It has been in India that there has been enough openness and funding to pursue homeopathic research. It has been far more challenging, if not impossible, to get studies published in Europe or North America, due to inadequate funding, bias, opposition by the pharmaceutical industry, and other factors (take a look at the recent film, *Just One Drop Homeopathy* to see for yourself). Even Wikipedia informs that homeopathy is bogus. And now, in the US, homeopathy is threatened by the FDA, which I hope and pray will allow practitioners and the public to enjoy continued access to our remedies.

So now, I have been asked to weigh in on Dr. Bhattacharyya's contemporary research published recently in *The International Journal of Homoeopathic Sciences* (IJHS 2020; 4(2):226-234). There are over 5000 existing homeopathic remedies, more being proven each year, and literally millions more substances that could, in the future, be made into homeopathic preparations. This study analyzes eight different homeopathic remedies, all but one (*Magnetis Polus Australis*) of which I have prescribed at some point in my practice. I see that he intentionally included samples of remedies from different kingdoms (animal, plant, mineral, and imponderable), including a homeopathic nosode (*Carcinosin*), and even *Uranium nitricum.* And he chose potencies ranging from 30C to 1M (all commonly used potencies in classical homeopathic practice).

I do not have the scientific expertise to analyze the methodology, nor is this the first time I have read about a study scientifically corroborating the uniqueness, and even the methodology, of homeopathic remedies. But I am impressed by the research design, variety of remedy preparations selected in the study, and, of course, Dr. Bhattacharyya's careful efforts to prove the uniqueness, through Fourier Transform Infra-Red (FTIR), of the unique remedies.

Whether it be through scientific studies such as this one, or through some other breakthrough, I hope and pray that the mechanism and effectiveness of homeopathy will eventually be proven, before it is taken away from us by the powers that be.

family is thriving rather than just surviving. Life is no longer a battle, a struggle. Dylan is just a normal little boy testing the waters. Nine times out of ten he makes the right choice. I could not have said that about him before. I'm giving him the remedy every week and a half or two weeks, or sometimes less often." We are all thrilled with how Dylan is doing since homeopathy. I will continue to see Dylan every couple of months for the near future.

Case Two: Losing Was Not an Option

Antonio, twelve years old, was driving his parents crazy. It was a good thing that I took his case this past April, near the start of the pandemic! He was difficult from the start: very colicky, inconsolable, and could only be put to sleep while being held or bounced. Now, at twelve, he exhibited night terrors, bedwetting, and walking and talking during his sleep. Empathic by nature, Antonio was unable to control his impulses. Although he was well-liked by other kids, his defiance towards any authority figure exhausted his parents and teachers. The child's vibrant personality and energy vented in the direction of extreme competitiveness and hypersensitivity to reprimands or criticism. Above all, he hated losing, which resulted in his "spiraling out of control." It could be a race, a board game, throwing a baseball – if Antonio didn't do it up to his high standards, he would beat himself up and fall apart. Screaming, throwing things, and cheating were all fair game: combativeness instead of cooperation. The alpha of the family, everyone else gave in rather than face confrontation. Antonio demonstrated little respect for his parents or siblings, who were forced to constantly adapt and adjust to his domination.

Antonio had been given *Nux vomica* (Quaker's button) by his previous homeopath, with partial improvement, but his behavior was still intolerable both at home and at school and his manipulativeness "relentless." To make matters worse, he insisted on sleeping with his mom every night.

When I spoke with Antonio, after hearing his parents' frank assessment, I was able to differentiate between the *Nux* and a second very close, and common, remedy. He admitted, candidly, that his image was extremely important to him, and that he would avoid embarrassment at all costs – in public, outside his home. He hated making a mistake in front of anyone. When one teacher called him out and embarrassed him in front of the class, he refused to go back.

The Remedy. It can be tough to differentiate, in this type of child, between *Nux vomica,* which did help partially for a number of years, and *Lycopodium* (Club moss). In both cases, kids can be argumentative, defiant, smart, highly sensitive, and competitive. But the strong emphasis on maintaining one's cool and image in front of others, outside the family, is much more typical of *Lycopodium*. It was in mid-April that I first saw Antonio, a month into COVID-19. I prescribed four doses of *Lycopodium* 1M to take twelve hours apart, and a daily liquid dose of *Lycopodium* LM8.

Four and a half pandemic-months later: Antonio's parents were overwhelmed with working from home virtually plus having two kids at home sheltering in place. Fortunately, no news (no follow-ups) was good news: "Antonio is taking things in stride. He is much more able to control his anger. He still has the competitive edge, but he is able to recover faster. His greatest nightmare is being embarrassed in front of people. But, since the last remedy, Antonio is not as argumentative. He can take "no" for an answer. He can actually go along with what the younger kids want to play now and is much more able to switch gears. His angry outbursts are much less frequent and far less physical. Antonio is even asking to sleep in his own room."

One month later: Antonio has handled himself really well, even though he really doesn't like online school much. Overall this remedy has done wonders for him!

Many Cases of Pandemic Pandemonium

These are two of many similar cases in which homeopathy has saved families' sanity during these tumultuous, claustrophobic, challenging times. Among families from India to the UK to Australia, and throughout the US, the parents have expressed gratitude for maintaining their sanity and relative harmony amidst a very unpredictable and unsettling time, to say the least. Whether the remedies are common ones, such as these, or more obscure ones, as are sometimes needed, homeopathic care can take a tremendous edge off families during the pandemic!

Dr. Reichenberg-Ullman is the author of *Whole Woman Homeopathy* and co-author with Dr. Robert Ullman of books on homeopathy: *Ritalin-Free Kids, Homeopathic Self Care (with companion kit), The Savvy Traveler's Guide to Homeopathy and Natural Medicine, A Drug-Free Approach to Asperger Syndrome and Autism, The Homeopathic Treatment of Depression, Anxiety, and Bipolar Disorder*, and *Rage-Free Kids* as well as *Mystics, Masters, Saints and Sages – Stories of Enlightenment*. Pioneers in their field, they have been columnists for the *Townsend Letter* since the early 1990s. They taught originally at Bastyr University, then offered seminars internationally. They live on Whidbey Island Washington, and in Pucón, Chile.

Please visit www.healthyhomeopathy.com (where you will find a wealth of articles, blogs, and more) and Facebook at Healthy Homeopathy. Dr. Reichenberg-Ullman can be reached at drreichenberg@gmail.com. Check the website for a number of upcoming interviews and webinars.

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Our next issue, the February/March issue, featuring women's health, will be mailed on February 3.

(There will be no issue mailed in January.)

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Can We Hurry Up the Truth in the COVID-Era?

There's a new trend in medical research publishing that we are seeing more often in the last weeks. Scientific studies are being released as pre-prints before they have undergone formal peer review or revision with the 'understanding' that they will eventually be published the normal way. Basically, what we see is the first draft.

The advantage to this is that urgent information is made available to other researchers, medical practitioners and the public sooner rather than later. COVID-19 has brought a layer of urgency to our world, a sense of now or never, and we want the information as soon as possible without the inherent delays built into the reviewing process.

The disadvantage is a kind of 'caveat emptor'. We are left wondering if the findings are actually true or not. One could say that this is always the case, that just because information is published in a peer reviewed journal is no guarantee; but now this is even more the case.

Two separate preprint papers have been sitting on my desktop. The first to arrive was a preprint of William Grant's "Vitamin D Supplementation Could Prevent and Treat Influenza, Coronavirus, and Pneumonia Infections." This was received by the website PrePrint on March 12, posted March 15, and as of April 2 is now published in the journal *Nutrients*.[1]

Most of us are familiar with William Grant or at least his work. He's been one of the driving forces behind the, what do shall we call it? the Vitamin D Revolution? or the Vitamin D Fad? You can review his ideas on the Vitamin D Society's website (https://www.vitamindsociety.org) or on SunArc.org. Most of us are quite familiar with the message. This paper clearly presents their side of the topic. Nothing wrong with having a bias, well, except what gets left out. Reading this paper one could easily believe that all of the published vitamin D research supports Grant's view of reality. They neglect to mention the multiple meta-analyses that sum up past RCTs trials that testing vitamin D to prevent disease as "futile."[2-5]

Grant recaps Cannell's original 2006 paper that suggested vitamin D would protect against seasonal influenza.[6] Cannell's thesis relied heavily on Edgar Hope-Simpson's book, *The Transmission of Epidemic Influenza,*[7] and this inspired me to pull it from my shelf to page through. I recall how influential this book was: much of it is underlined in yellow highlighter, I must have hoped to commit those lines to memory.

The actual clinical trial described in the Grant paper is an analysis of online questionnaires completed by individuals who purchased vitamin D testing kits through GrassRootsHealth.net, another group whose mission is to promote vitamin D.

Test purchasers whose tested vitamin D levels were 60 ng/ml or above had lower risk of reporting that they had the flu in the prior six months compared to those whose test showed vitamin D levels of 20 ng/ml or less; reported infection rates dropped from 12% to 8% (N = 12,605). The authors reported this as a 43% change in risk, which makes it sound like a lot more. This was an open trial. It does not tell us whether low vitamin D status increases risk of disease or whether vitamin D levels are reactive to other factors that influence disease risk. Serum iron levels are an example of a reactive nutrient that drops rapidly with infection, cancer, or other inflammatory conditions.

Grant et al then argue that vitamin D will be protective against COVID-19 because the epidemic in China started in the fall when vitamin D levels drop and that prior epidemics caused by other coronaviruses show seasonal variations. The best argument in support of Grant's theory will be whether COVID-19 infections also exhibit a seasonal variability. Perhaps by the time you read this, the data will tell us if infections rates decrease in the summer or not, the way influenza does.

The second preprint paper on my desktop is Wu et al's "Exposure to air pollution and COVID-19 mortality in the United States" that was released in early April 2020.[8] This team effort comes to us from the research lab of Francesca Dominici of the T.H. Chan School of Public Health at Harvard University.

This group has produced a series of research papers in recent years focused on fine particulate air pollution and have already earned our respect in this specialty.

The Chan researchers collected air pollution data for 3,000 counties in the United States right up to April 04, 2020, the day prior to the paper's release, and then compared county level COVID-19 deaths against county level long-term average PM2.5 exposure. Adjustments were made by population size, hospital beds, number of individuals tested, weather, and socioeconomic and behavioral variables, including but not limited to obesity and smoking. Their compiled data covered 98% of the US population.

Wu's team calculated that an increase of 1 μg/m^3 in PM2.5 is associated with a 15% increase in the COVID-19 death rate, [95% CI:5%, 25%]. Results are statistically significant and robust to secondary and sensitivity analyses.

In our lifetimes there has not been a public health emergency that matches the COVID-19 pandemic. Both the suddenness and global scope of this disease has created great urgency to identify modifiable factors that will affect disease spread and outcomes. Thus, we are in a hurry to find ways to shift disease morbidity and are willing to look outside the normal published literature to find answers or at least clues to what might help.

Many of the risk factors already known to increase risk of mortality from COVID-19 infection are conditions that are known to be worsened by PM2.5 exposure and that are associated with low vitamin D status. These include diabetes, hypertension, heart disease and others.

The Global Burden of Disease Study identified air pollution as a major risk factor for total and cardiovascular disease mortality and, in 2015, suggested it was responsible for 5.5 million deaths worldwide a year.[9,10] These various groups promoting vitamin D have probably produced a similar calculation although recent studies have questioned earlier predictions.

The findings of the air pollution study are relevant for several reasons. The first is that we can reduce the risk of severe disease in high-risk populations by lowering the burden on their health due to air pollution. While ambient pollution levels are beyond an individual's immediate control, indoor air quality can be rapidly improved by using a home air filter. The second reason this information is relevant is that any move that will lower outdoor air pollution may lower mortality rates during the pandemic and should be encouraged. Conversely, any increase in outdoor air pollution may increase mortality rates. This should inform our assessment of the March 26, 2020 announcement from the EPA that they have instituted a "… sweeping relaxation of environmental rules in response to the coronavirus pandemic, allowing power plants, factories and other facilities to determine for themselves if they are able to meet legal requirements on reporting air and water pollution."

The vitamin D study is harder for me to interpret as, at this point, the proposition that vitamin D will impact COVID-19 feels more tenuous. The actual study as described sounds weak and the authors could not be more biased. Still, the risk associated with supplemental vitamin D appears small. The change in infection risk, if it even applies to COVID-19, also seems small. The impact that our nationwide efforts at social distancing will have on vitamin D status is yet to be determined. Will levels increase as people work from home or will they drop as people eschew outdoor activities? At this point we can only guess.

Let's try to unwrap these numbers more carefully. Harvard's air pollution researchers tell us that an increase of only 1 g/m^3 in long-term average PM2.5 is associated with a statistically significant increase of 15% in the COVID-19 death rate. In New York City if an intervention were to lower the long-term average PM2.5 exposure by only 1 g/m^3, there would have been 248 fewer deaths up to April 4, 2020, when the total was 1905 – or 861 fewer as of today, April 11, when the total is up to 5,742. As I wrote this, the PM2.5 level in NYC is 28 g/m^3. It has fluctuated from 10 to 58 g/m^3 over the past 24 hours. In China, pollution levels dropped 25% during the lockdown, so conceivably NYC could see a similar drop of 2 to 14 gm/m^3. We might be talking about rather serious shifts in mortality risk. There is ample room for additional improvement.

In a previous study published in 2017, these same authors examined data from 61 million American Medicare beneficiaries and found that an increase of 1 mg/m3 long-term PM2.5 exposure was associated with a 0.73% increase in the rate of all-cause mortality.[11] Therefore, a small increase in long-term exposure to PM2.5 leads to a large increase in COVID-19 death rate of a magnitude that is 20 times the one estimated for all-cause mortality. ➤

CALENDAR

Please visit www.TownsendLetter.com for the complete calendar

JANUARY 29-30: GREAT PLAINS LABORATORY PRACTITIONER WORKSHOPS on Organic Acids Testing and Environmental Toxins Testing ONLINE. CMEs. **CONTACT:** 913.341.8949; www.GPLWorkshops.com

FEBRUARY 4-6: AMERICAN CHIROPRACTIC ASSOCIATION ANNUAL MEETING AND CONFERENCE. Virtual online. CONTACT: https://www.acatoday.org/Education-Events/ACA-Engage-2021

MARCH 5-7: FLORIDA HOMEOPATHIC SOCIETY ANNUAL CONFERENCE – Homeopathy & Traditional Chinese Medicine: Where the Modalities Meet with Hilery Dorrian, LAc, LCH in Orlando, Florida. CONTACT: www.floridahomeopathicsociety.org; cicamp7@gmail.com

MARCH 5-7: THE FORUM FOR INTEGRATIVE MEDICINE "Navigating Recovery in Complex Chronic Illness" ONLINE. CONTACT: forumforintegrativemedicine.org

MARCH 10-14: 68th CONGRESS OF THE INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE – Endocrine Ecosystem: Balanced Hormones and Reduced Toxicity for Patient Health and Happiness in Memphis, Tennessee. CONTACT: https://www.eventbrite.com/e/endocrine-ecosystem-balanced-hormones-and-reduced-toxicity-tickets-94725166523

APRIL 22-25: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING with Simon Yu, MD, in St. Louis, Missouri. Also, **AUGUST 26-29.** CONTACT: 314-432-7802; http://www.preventionandhealing.com/

APRIL 23-25: 16th ANNUAL JOINT HOMEOPATHIC CONFERENCE in Reston, Virginia. CONTACT: www.homeopathycenter.org

MAY 28-JUNE 1: 12th INTERNATIONAL CONGRESS ON AUTOIMMUNITY in Athens, Greece. Special session on diet and autoimmunity, chaired by Dr. Aristo Vojdani. CONTACT: https://autoimmunity.kenes.com/

JUNE 3-6: SASKATCHEWAN ASSOCATION OF NATUROPATHIC DOCTORS HEALING SKIES CONFERENCE in Saskatoon, Saskatchewan. CONTACT: http://www.sanp.ca/index.html

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Air pollution levels were also associated with increased risk of death during the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003, which was also caused by a type of coronavirus.[12]

If Grant's vitamin D predictions are accurate and we were to distribute massive doses of vitamin D to large segments of the US population, we might see a 4% reduction in risk of flu infection. Trying to infer what this would do to COVID-19 infection rates and, more importantly, mortality rates feels like too big a stretch given the weakness of these data. Still it can't hurt to encourage supplementation and, perhaps more important, getting some sun exposure.

That's all assuming that these draft papers do not contain major errors in their calculations. I can't say that for sure. Wu's calculations are far beyond my mathematical skills to follow. There were obvious typographical errors in the released draft that I read, but the reputation of the authors makes me want to assume that their main findings are unbiased and accurate.

The preliminary status of the air pollution paper hasn't prevented the conclusions from being picked up and broadcast worldwide both on the news and social media. Does that make them fake news? More like premature news. Yet where do we draw the line? Probably the same way we always do when dealing with uncertainty of medical efficacy. We fall back on Auguste Chomel's now universal[13] (not Hippocrates) proscription of *primo non nocere*; we look for potential harm and balance that against possible benefit. Breathing clean air or basking in sunlight seem to pose little danger, while both might offer possible benefit.

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What Is a Preprint? And Why Do We Care?

These two articles mentioned were posted on bioRxiv, pronounced "bio archive." This site was first launched in 2013 and is overseen by Cold Spring Harbor Laboratory, an old and highly respected research institution that was founded in 1890. BioRxiv is modeled after arXiv, (pronounced Archive) a preprint server focused on the physical sciences that was begun in 1991. The hope that inspired creation of these websites was that rapid dissemination of biological research would help other researchers. A third preprint site, medRxiv (as in Medical Archive) was launched in July 2019 to focus on health sciences.

With the COVID-19 pandemic in full force, utilization of these preprint services has grown with the urgency to share new findings on the disease. Downloads from medRxiv increased 100-fold between December 2019 and April 2020. About 70% of papers posted on bioRxiv and arXiv have ended up being eventually being published. MedRxiv is too new to have similar statistics on yet.

There is a low bar to get a paper posted. To have a paper posted on bioRxiv or arXiv, all that is required is for all of the authors to consent and declare that their study had ethical approval and participant consent and state any conflicts of interest and if the study was a clinical trial.

Once uploaded the paper is screened to be sure it wasn't plagiarized. BioRxiv prohibits health claims and medRxiv won't accept case reports or trials with small sample sizes. In theory, both servers refuse papers that may encourage dangerous behavior. That's pretty much it. In the past this was enough.

Problems have started to crop up though. News editors and writers are eager to write about new science and will quote preprint papers as if they were actually published studies. This happened in early April 2020. The *New York Times* mentioned the study on fine particulates being associated with COVID-19 mortality rates in an article describing how the Trump administration halted plans by the EPA to tighten pollution standards, "Harvard University this month also published research showing that the coronavirus causes a higher death toll among patients in parts of the country with increased levels of fine particulate pollution."[14]

Technically this study was not published. It was only posted on bioRxiv. There is an important difference.

We see repeated examples of individuals embracing and promoting the information read in a preprint either from ignorance or malicious intent. Preprint papers have been posted online and used to fuel conspiracy theories.

"Science is a conversation," said Dr. Ivan Oransky, one of the founders of Retraction Watch, a blog that reports on retractions of scientific papers. "Unfortunately, people in times of crisis forget that science is a proposition and a conversation and an argument. I know everybody's desperate for absolute truth, but any scientist will say that's not what we're dealing with."[15]

While we are eager for information related to COVID-19, we need to be extremely cautious if we are reading preprints rather than published studies.

This has become increasingly important as published science for many of us has become a defensive line against 'fake news', that is the spread of falsified information that is amplified by social networks online. For those of you who still think this isn't a significant concern I would suggest reading Soroush Vosoughi's study on the spread of fake news published in *Science* two years ago.[16] Or at a minimum read the excellent summary of the study by Robinson Meyer published in *The Atlantic*.[17]

➤ *continued from page 88*

lower in the intervention group than in the control group, both before (-2.96 points; p = 0.002) and after (-3.84 points; p = 0.001) adjustment for potential confounding variables.

A second recent study was a randomized controlled trial that examined the effect of calcifediol in patients hospitalized with COVID-19.[2] Calcifediol is more commonly known as 25-hydroxyvitamin D, which is a normal metabolite of vitamin D. It is approved by the US Food and Drug Administration as a prescription drug for the treatment of secondary hyperparathyroidism in patients with stage 3 or 4 chronic kidney disease. The new study enrolled 76 patients (mean age, 53 years) hospitalized in Cordoba, Spain, who had a positive polymerase chain reaction (PCR) test for COVID-19, a clinical picture of acute respiratory infection, and radiographic evidence of viral pneumonia. The patients received best-available therapy (including hydroxychloroquine and azithromycin) and were randomly assigned to receive in a 2:1 ratio, oral calcifediol (n = 50) or no calcifediol (control group; n = 26). The dosage of calcifediol was 0.532 mg on the day of admission, 0.266 mg on days 3 and 7, and then 0.266 mg once a week until discharge or admission to the intensive care unit (ICU). The proportion of patients who required admission to the ICU was significantly lower in the calcifediol group than in the control group (2% vs. 50%; p < 0.001). After adjustment for potential confounding variables (such as hypertension or type 2 diabetes), the risk ratio for ICU admission was 0.03 (95% confidence interval, 0.003-0.25). The death rate was 0% in the calcifediol group and 7.7% in the control group (p value not stated).

Vitamin D is converted *in vivo* to calcifediol, so it would be reasonable to assume that vitamin D would also have some degree of efficacy against COVID-19. That assumption is supported by the quasi-experimental study reviewed above. Widespread use of calcifediol for COVID-19 is not feasible, because it is a prescription drug and because it is very expensive (more than $1,200 for a course of treatment). In contrast, vitamin D is inexpensive and can be obtained without a prescription. Vitamin D therefore seems to be a better candidate than calcifediol for routine use during the COVID-19 pandemic.

It is not clear what dosage of vitamin D would be equivalent to the dosages of calcifediol used in the study described above. A dose of 0.532 mg of vitamin D3 (the amount of calcifediol given on the first day) is equal to 21,200 IU. However, calcifediol is considered to be more potent than vitamin D because it produces greater increases in serum 25-hydroxyvitamin D concentrations.[3]

The available evidence suggests that it is important to maintain adequate vitamin D status during the pandemic, and that short-term vigorous vitamin D supplementation may be beneficial for people who become infected with COVID-19. Vitamin D may be used in combination with other potentially beneficial treatments for COVID-19, such as zinc lozenges, vitamin C, and black elderberry (*Sambucus nigra*). I discussed these treatments in the June 2020 issue of the *Townsend Letter*.

Alan R. Gaby, MD

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Vitamin D for COVID-19

In previous editorials I have expressed doubts about the safety and efficacy of using high-dose vitamin D for the prevention and treatment of various skeletal and non-skeletal diseases. Results from randomized controlled trials suggest that large doses of vitamin D (such as 4,000 IU per day or more) are generally not more effective, and may even be less effective, than moderate doses (such as 800 IU per day). In addition, long-term use of high-dose vitamin D may increase the risk of developing kidney stones and (at least according to animal studies) atherosclerosis.

It has been hypothesized that vitamin D could help prevent or decrease the severity of COVID-19 infection by regulating the renin-angiotensin system and by enhancing innate or adaptive immunity. *In vitro* studies suggest that vitamin D may also decrease the severity of the cytokine storm, which contributes to morbidity and mortality in patients with severe COVID-19 disease. In observational studies, COVID-19 patients with lower serum concentrations of 25-hydroxyvitamin D had worse outcomes, when compared with patients with higher 25-hydroxyvitamin D levels. This latter finding does not necessarily suggest that vitamin D sufficiency confers protection against COVID-19. That is because 25-hydroxyvitamin D levels decline in response to inflammation, so a low 25-hydroxyvitamin D level may be an effect, rather than a cause of more severe disease. Nevertheless, because vitamin D is inexpensive, usually safe for short-term use even in relatively high doses, and widely available throughout the world, its potential as a treatment for COVID-19 deserves serious consideration. At the time of this writing, two clinical trials have been published, and the results are very encouraging.

In one study,[1] which the authors described as a quasi-experimental study, data were collected retrospectively on 66 frail elderly individuals (mean age, 87.7 years) living in a nursing home in France who had been infected with COVID-19 in March or April of 2020. Because of the high prevalence of vitamin D deficiency in the French nursing home population, all residents of this nursing home regularly receive vitamin D3 supplements from the nursing staff. The dosage is 80,000 IU, given as a single oral dose, every two to three months. The COVID-19 patients were divided into two groups. The intervention group (n = 57) included those who received their regular dose of vitamin D either in the week after the onset of COVID-19 or in the previous month. The control group (n = 9) consisted of patients who did not receive vitamin D during those time periods. The patients were followed until May 15, 2020, a mean of 36 days after diagnosis. The primary outcome was death due to COVID-19. The secondary outcome was disease severity, which was measured by the World Health Organization's Ordinal Scale for Clinical Improvement (OSCI) during the most severe acute phase of the disease for each patient. OSCI scores range from 0 to 8, with 0 indicating benign disease and 8 indicating death. An OSCI score of 4 corresponds to the use of oxygen and a score of 6 corresponds to intubation and the use of a ventilator. During the follow-up period, 15 people died and 51 survived. The mortality rate was significantly lower in the intervention group than in the control group (17.5% vs. 55.6%; p = 0.023). In addition, the mean OSCI score was significantly

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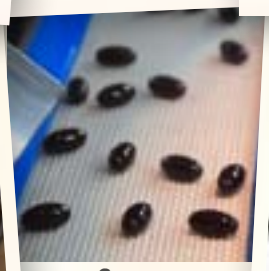
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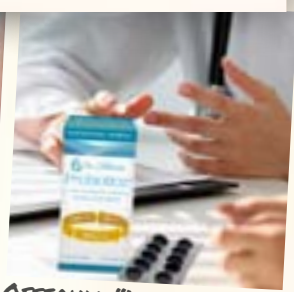
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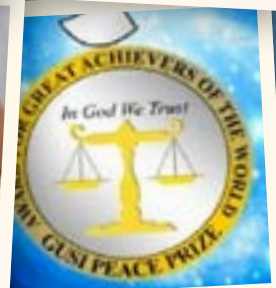

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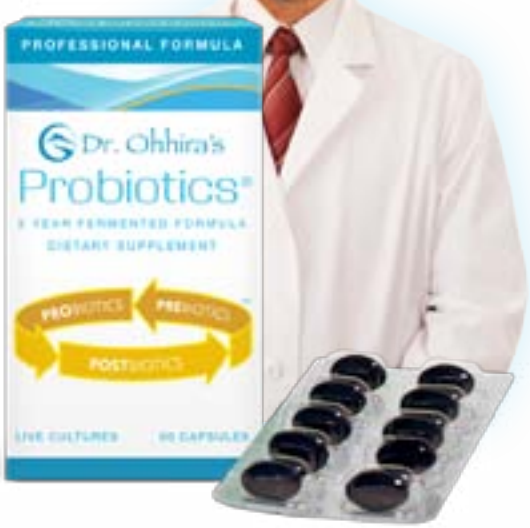

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