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From the Publisher

The 2020 Pandemic or How Our World Has Been Turned Upside Down

For some of us fortunate enough to work from home, the past three months have been very strange and filled with inconvenience, but manageable, and a time to heal physically and spiritually. For the health professionals on the "front lines" in the ICUs and ERs or manning the ambulances, life has been an endless routine of donning PPE, assessing and managing patients with minimal breaks, then taking transportation home to remove contaminated clothing and avoiding contact with other family members. For a far larger part of the population who have lost their employment or have had their business shut, shelter-in-place has been an anxiety-ridden process of trying to figure out how the bills will be paid, and for not a few, how to pay for the next meal. And for those individuals who fare poorly when becoming ill, pneumonia requiring a ventilator is the ultimate of horror shows, with a majority of individuals battling for their life, frequently losing the war. The question on everyone's mind is when will the pandemic end, when will life return to normal – but normal in the future will be very different.

Public policy has appropriately focused pandemic control by mandating social distancing, wearing masks while grocery shopping, and emphasizing washing hands and good hygiene. Because there is no vaccine for COVID-19, public health authorities consider there

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Multi-Peptide ELISA is the most comprehensive method for the detection of Lyme disease and other tick-borne diseases.

(US Patent 7,390,626 B2)

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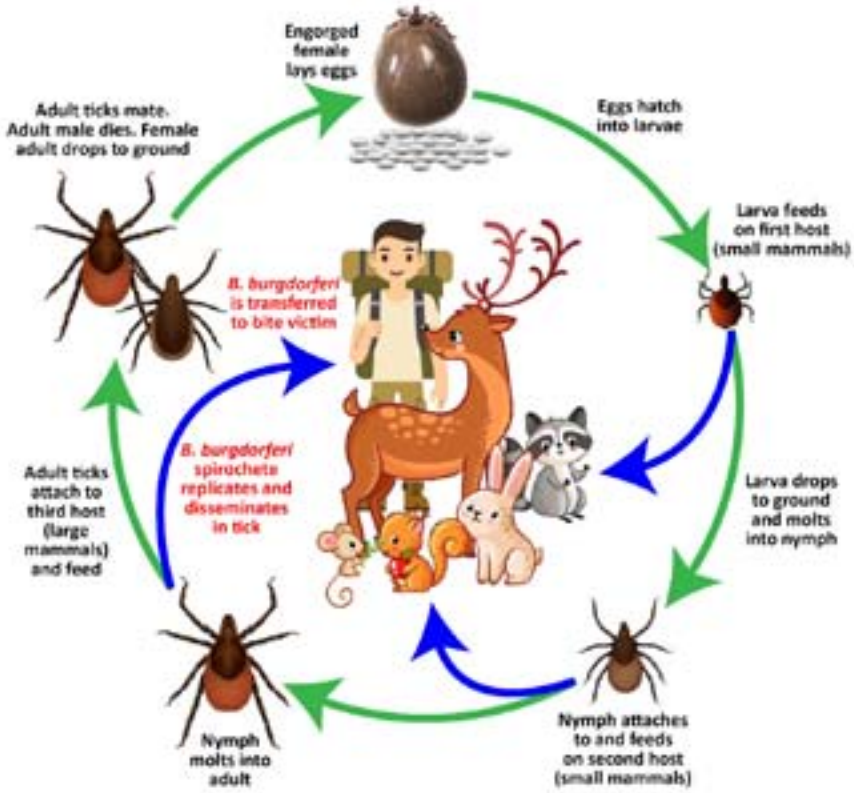

Untreated Lyme disease can turn into chronic Lyme disease, which in turn can lead to Lyme arthritis and neuroborreliosis.

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Letter from the Publisher

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is no effective prevention. However, integrative medicine and naturopathic physicians disagree. Practitioners recommend the use of "higher" dose vitamin, mineral, and herbal supplements as supports to immune functioning. Despite the naysaying of critics, homeopathy is an important preventive support. Hydration, intravenous vitamin C, vitamins A and D, zinc, and elderberry are among the treatments important when first becoming ill. It is disgraceful that conventional medicine has consistently dismissed the value of nutrient supplementation; now such remedies are not even considered during the pandemic. A French medical report advised that the use of NSAIDs increased the risk of dying from COVID-19; a better question would be determining if those dying have lower vitamin C levels.

Early reports from Chinese doctors treating ICU patients in Wuhan indicated the value of intravenous ascorbic acid. For an individual who has not become seriously ill, such an infusion would likely be unavailable. Owen Fonorow, Thomas Hesselink, MD, and Jerry Nowlin were curious to determine how effective oral ascorbic acid would be in comparison to IV vitamin C. In 2012 Fonorow observed that glucose measurements using a glucometer would respond to changing levels of blood vitamin C. It was observed that administration of intravenous ascorbic acid would result in a higher glucose reading – the higher the IV ascorbic acid, the higher the glucose reading. In the experiment that Fonorow et al. did recently, they compared the glucometer readings over time of IV vitamin C to oral vitamin C. The study demonstrated that oral vitamin C resulted in glucose readings as high as those for intravenous vitamin C for the first 14 minutes. In fact, for the first 12 minutes the glucose readings after oral vitamin C were higher than intravenous vitamin C. Their report is published in this issue and was also e-published in March on our website.

Another question that needs answering is what makes the COVID-19 virus so vicious? In this issue Dr. Devaki Lindsey Berkson lays out the mechanisms for how the virus binds to cells in the respiratory tract initiating the process that leads to pneumonia. Apparently, this coronavirus has an affinity for the angiotensin converting enzyme 2 receptor also known as ACE 2 receptor. The lung parenchymal cells are loaded with these receptors making them the ideal binding site for cell entry. In other words, ACE 2 receptors facilitate preferential viral infiltration in lung tissue compared to the digestive tract or central nervous system. Effectively, when the virus binds to the ACE 2 receptor, the receptor is blocked and its role in maintaining parenchymal cell viability is compromised. Meanwhile, the COVID-19 virus is further facilitated by its spike proteins binding with furin enzymes. Berkson lays out other routes of entry for the coronavirus. Are there natural supports that inhibit these binding and entry mechanisms? Berkson cites a very important one that we implement in integrative medicine but goes largely unnoticed in conventional medicine – and is certainly ignored in the current pandemic.

We do well understanding the role integrative medicine plays in supporting one's ability to prevent and treat COVID-19. We don't do so well in distinguishing what works in conventional medicine and

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Letter from the Publisher

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what doesn't. By "we," I mean those members of the alternative medical community who subscribe strongly to anti-establishment theories and who condemn establishment reports. There is a point to having a healthy amount of skepticism when examining the news and media reports. However, such skepticism has taken on a strong taint of stink when everything reported by the mainstream media is dismissed outright and labelled "fake news." Even more worrisome is the championing and echoing of reports based on dubious sources and statistical manipulation. Recent reporting of the overwhelming chaos taking place in and outside New York City emergency rooms as well as in their intensive care units has been disbelieved by "citizen reporters" on YouTube who claim that "hospitals are empty": www.youtube.com/watch?v=k9zJjzoYhwQ. Seriously?!? Could it possibly be that these NY ERs and ICUs are empty, and the news media are staging medical war zones for our entertainment? Throughout history there have always been those who deny murder, rape, and destruction, particularly if such denial suits the advantage of the denier. It is disgusting and outrageous that we do have individuals in the alternative medical community who would take on such a stance. We don't need discord now – we need unity in fighting a common enemy.

Inflammation and Kidney Disease

Months before life changed with COVID-19, we planned to focus the June issue on inflammation. Of course, the severe acute respiratory syndrome of the virus develops following a massive cytokine storm of inflammation. Unfortunately, simply bringing out anti-inflammatory medication does not necessarily quiet such inflammation and some reports suggest that it might very well worsen. Yet, most of the strategies for managing COVID-19 in the ICU largely focus on treatment that attempts to increase oxygenation and reverse inflammation. If we turn our attention elsewhere, inflammation is central to understanding the pathophysiology of much of medicine. It is the underlying factor that fuels the disease process, be it atherosclerosis, cancer, neurologic disorder, infection, autoimmune disease, arthritis, etc. It would be very unusual to find any medical condition that is unaffected by inflammation. On that note I would like to introduce Dr. Jenna Henderson's article in this issue, "Uremia and Inflammation."

Long-time readers of the *Townsend Letter* are aware that Henderson has written a number of articles on the naturopathic approach to diagnosis and managing kidney disease. (Please look for her June 2019 article on our website.) We generally focus on blood urea nitrogen and creatinine when we think of uremia. However, Henderson reports that the urine "contains at least 3,079 different waste products," some of which are the product of either our metabolism or our microbiome's; but the vast majority are created from the drugs, cosmetics, and chemicals we use, imbibe, or otherwise absorb. The killer from Henderson's viewpoint is not that these uremic waste products are elevated – it is that they inflame the endothelium of the vasculature leading to cardiovascular disease. Furthermore, these toxins provoke the immune system into generating a wide range of inflammatory factors that work synergistically with the toxins to cause not only cardiovascular damage but multi-tissue pathology.

One of the stumbling blocks in conventional medicine and naturopathy has been what sort of treatment and supplementation can be administered to a patient with advanced renal disease?

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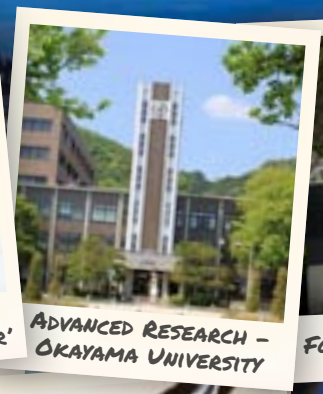
Dr. Iichiroh Ohhira: A Pioneering Genius in Probiotic Science


Malaysian Mystery – 'Drinking Fermented Elixir'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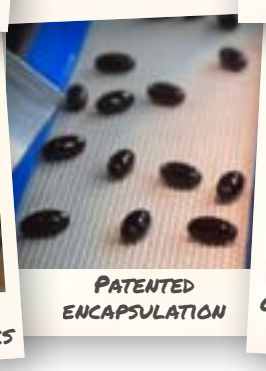
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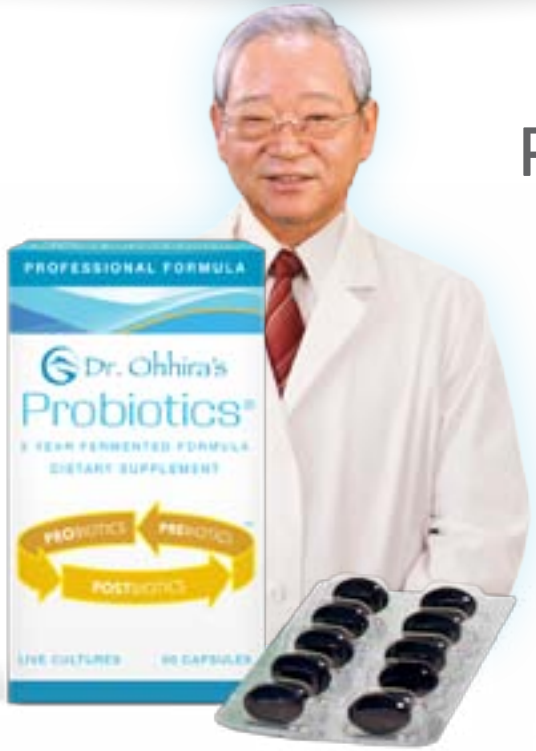

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Letter from the Publisher

➤ *continued from page 6*

Chelation therapy, for example, is contraindicated in such patients. Henderson offers some surprising strategies that support kidney functioning, potentially partially reversing the uremia.

The Link Between Oral and Systemic Inflammation

When I first embraced integrative and alternative medicine not too long after my medical school training, one of the first books I read was Weston Price, DDS's *Nutrition and Physical Degeneration.* Published in 1939 it transformed my thinking on the role of diet on degenerative disease. It also challenged my thinking that contemporary dentistry and conventional medicine offered the best prospects for health and longevity. Of course, the early part of the 20th century was a very different world than the 21st – Price was able to examine people living in non-industrialized society who were self-sufficient, eating the same food their ancestors had eaten. Weston was impressed that across all cultures those people abiding by their traditional diets demonstrated remarkably healthy dentition; in contrast, individuals in developed nations consuming processed food and sugar not only revealed poor dental health but also suffered from a myriad of medical conditions. Moreover, Price deducted that poor oral health played an important role in causing systemic pathology. His experimentation revealed that when root canal teeth were implanted in healthy rabbits the animals would often manifest the same diseases found in humans. Regrettably, his work has been largely ignored both by the dental and medical professions; endodontists continue to do root canal work routinely. Can we continue to ignore the relationship between oral health and systemic inflammation?

Blanche Grube, DMD, Leslie Douglas, PhD, and Anita Tibau tackle this question in this issue. A pioneer in biological dentistry, Hal Huggins, DDS, spent much of his career examining the role mercury amalgams had in causing neuropathology. He was very concerned with the adverse effect of root canals, detailing their role in causing illness in his book, *It's All in Your Head*. Grube worked with Huggins, studying the bio-compatibility of dental materials used in restorations; not surprisingly, many compounds are toxic but continue to be used. Grube and Huggins also studied the oral microbiome finding a wide range of organisms not found elsewhere in the body. The "normal" diversity of microorganisms in the mouth is greatly altered when there are root canals and periodontal disease. Understanding the pathogenicity of the oral microorganisms has become a primary focus for Grube and her co-authors. Moreover, they offer dentists the opportunity to submit tissue from the teeth, gums, and removed restorations for PCR examination, yielding a report of a patient's abnormal oral microbiology.

Perhaps the validation of disease-causing microorganisms may induce the dental profession to reconsider the use of root canals as well as other restoration procedures. Perhaps it will repair the schism between the dental and medical profession, recognizing that inflammation in the body may be the result of oral inflammation.

Jonathan Collin, MD

New Book from Ralph Moss Exposes Greed of Cancer, Incorporated

The cancer drug industry in the US is producing unproven drugs that do little or nothing to benefit real world cancer patients. It makes false claims, while downplaying serious or severe side effects. It needs to be replaced with a public agency that is motivated by a concern for patients' welfare, rather than a greedy company's bottom line. This is the conclusion of a hard-hitting new book from famed medical journalist, Ralph W. Moss, PhD.

Moss has been a long-time critic of the cancer establishment. His first book, *The Cancer Industry* (1980), detailed the manner in which the industry promoted toxic drugs while actively suppressing almost all non-toxic and unpatented alternatives. Fifteen years later, he wrote Q*uestioning Chemotherapy,* which exposed the failure of most toxic drugs to actually extend lives. Now, in 2020, he has exposed the tricks and deceit of Big Pharma in putting across scores of drugs that do little or nothing for real world cancer patients. Although packed with details, the book is written in a way to wake up the public about what is really going on in the cancer field.

Moss knows this world both inside and out. He was the science writer and assistant director of public affairs at Memorial Sloan-Kettering Cancer Center in the 1970s. While there he witnessed at first hand the cover-up of positive laboratory results in mice with a low-cost, plant-based substance known as amygdalin, vitamin B17, or Laetrile. In 1977, he blew the whistle on that cover-up and was fired the next day for "failing to carry out his most basic job responsibility," which, in their view, was to repeat lies to the American people.

Since that time, in articles, newspaper editorials, and 14 books, he has spoken out continuously and forcefully about the lies and deceit in the cancer field. He has been featured on *60 Minutes*, and scores of other TV, radio, and webcasts since then.

Many people are rightfully enraged by the sky-high prices of new cancer drugs. What few understand, however, is that most of these drugs have never been proven to make patients live longer or have a better quality of life. It is a fraud and an illusion.

Drug companies use many tricks to make the public think that these drugs are safe and effective when they are not. In cancer, one of these is to redefine "survival' so it has nothing to do with actually living longer. Companies and bought-and-paid for doctors underplay the side effects of these drugs, which can be serious, severe or even fatal. Dr. Moss provides abundant evidence to show how this crime is taking place.

As government websites document, many key opinion leaders are in the pay of Big Pharma. They receive large amounts of money, as much as $3 million per doctor per year for their own personal use. And these are the same people who lead clinical trials and recommend the approval of drugs to the Food and Drug Administration. As Moss says: "We would not tolerate a judge or a juror receiving payments from one of the parties in a legal case. Why then do we tolerate egregious examples of corruption on the part of those who carry out *clinical* trials of drugs?"

If you would like more information about *Cancer, Incorporated*, and/or to schedule Ralph Moss for on your podcast, YouTube channel or a radio/TV appearance, please contact Ben Moss, ben@mossreports.com

Moss Reports, based in Blue Hill, Maine, is an information service for cancer patients and caregivers. We produce 38 reports of 500+ pages apiece to fully inform laypeople and interested professionals about the latest developments in the cancer field. Our approach is rigorously scientific, while also being readable. ◆

ARTICLES PUBLISHED ONLINE ONLY

Integration of Traditional Chinese Medicine in the Treatment and Support Against the Coronavirus (COVID 19) by Geoff D'Arcy, Lic. Ac, DOM
Co-founder of two integrative medical centers in Massachusetts, Geoff D'Arcy, DOM, has studied herbal medicine and acupuncture in Japan, England, China, and the US. In this article, he shares the traditional herbal treatments that have been used in China to treat COVID-19 and related coronavirus infections.

Corona Infection – A Shift in the Way We Think of Modern Medicine
by Michelle McKeon, MS
Certified clinical nutritionist and author Michelle McKeon, MS, brings to light the under-reported effective use of three therapies for people with COVID-19 that can be integrated with other treatments: high-dose intravenous immunoglobulin therapy, ozone therapy, and high-dose intravenous vitamin C.

Access at www.townsendletter.com

COVID-19 and SARS-CoV-2 Testing Overview

by David M. Brady, ND, DC, CCN, DACBN, IFMCP, FACN*

There is a lot of conversation and controversy surrounding the issue of laboratory testing as it pertains to COVID-19 and SARS-CoV-2, generating an unfortunate amount of media misreporting and confusion on the part of both the lay public and health care providers alike. In this brief article I will attempt to provide some clarification regarding this topic. By intention, this is not a highly technical article written to be submitted to a laboratory science or immunology journal, but simply a high-level overview of the testing options, including their strengths and limitations, and most importantly, their clinical utility.

While "positives" can be relied upon with confidence, rapid tests and saliva tests are prone to false negatives.

What is the COVID-19 diagnostic test?

The diagnostic test for COVID-19 is a RT-PCR molecular test that detects the SARS-CoV-2 virus that causes COVID-19. The assay is for use on samples collected via nasopharyngeal swabs, throat swabs, bronchoalveolar lavages, and bronchial washings.[1-2] The COVID-19 assay test is available now from various high-complexity laboratories, mainly academic and large hospital pathology labs, large national commercial labs, and a handful of smaller independent commercial labs who are technologically capable and have submitted proper validations of their testing to the FDA under Emergency Use Authorization (EUA). See list of lab here: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2#offeringtests

It is important, however, to realize that not all of these tests are the same. Laboratories were allowed under the EUA to develop their own testing methodologies, based on minimum acceptable guidelines issued by FDA, and to submit their own validations to the agency. For example, labs have specific sequencing equipment and will use different reagents and methods to perform the test based on the particular equipment that they have. Some of the tests are based on pre-configured test kits manufactured to only work on certain laboratory analysis platforms, sort of analogous to needing to have the correct ink jet printer cartridge to have it work in a specific brand and model of printer. Another varying factor is the number and type of molecular targets used to accurately identify the virus in a sample. FDA issued guidance that it believes an appropriately validated single viral target SARS-CoV-2 assay could provide acceptable performance. However, the initial CDC-supplied test used two molecular targets, but it did not perform well at properly identifying those targets, as has been reported widely in the media. Under the EUA labs were able to develop their own targets and methods, but had to submit validation data to FDA showing that the test performed adequately before being allowed to commercialize the test. For example, at DSL, our team of molecular laboratory scientists chose to target four specific molecular targets novel to SARS-CoV-2 to identify the pathogen with greater sensitivity and specificity. These include the N1 and N3 nucleocapsid protein targets, that were also used in the in the original CDC assay, plus a novel spike (S) protein and envelope (E) protein. In this way, it is almost impossible to miss the virus as long as the sample is collected properly and there is adequate viral load on the swab or in the sample. Sample collection is the weakest link in the chain in regard to this type of testing, and false negatives have been primarily attributable to faulty sample collection by the health care practitioner, and/or low viral load in the specific areas the sample was derived from, not the molecular laboratory method.[3] However, there is a distinction between COVID-19 molecular tests that use a PCR step to amplify DNA in the sample, and those that do not. There are a several so-called "rapid" testing platforms out there offered by very large biotech companies that get a lot of media attention, but these systems are "rapid" because they lack this PCR step and are, therefore, much more dependent on having a substantially higher viral load on the swab to be "positive." For example, these non-PCR systems generally require a viral load of "e5" or higher, whereas the PCR molecular test methods are often capable of detecting the virus at

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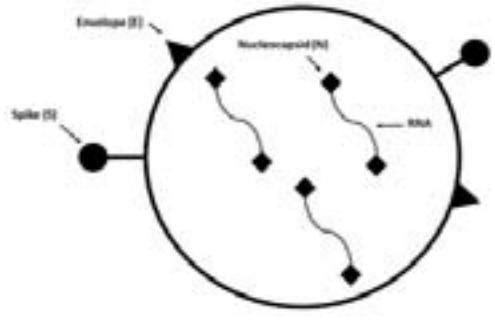
Coronavirus Molecular Targets



Adopted and Modified From: Leung D, Hang T, Hung M, Chan P, et al. "Antibody Response of Patients with Severe Acute Respiratory Syndrome (SARS) Targets the Viral Nucleocapsid." *J. Infectious Disease*. July 15, 2004; 190 (2): 379–386.

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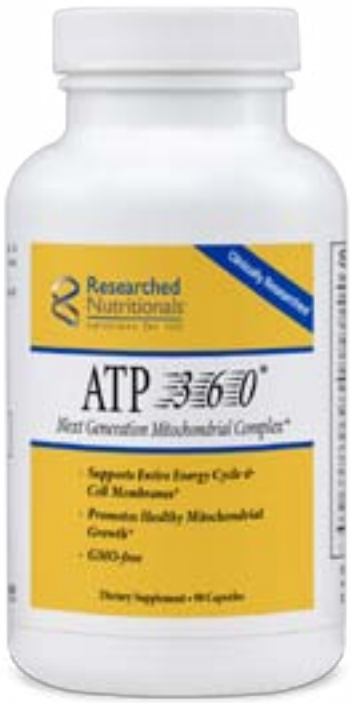

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"e3," or even "e2," levels of viral load, which is exponentially better sensitivity. These non PCR test methods have been criticized by critical care clinicians for what appear to be "false negatives," as patients often have convincing clinical symptoms of COVID-19 and are located in a hot-zone of disease activity, yet these rapid tests come back "negative".

Just prior to completion of this article a new saliva sample test was also approved by FDA through the EUA for COVID-19. While this is also being met with lots of media attention, and there is certainly an appeal to a saliva sample over a NP swab as it is much more comfortable for the patient and safer for the healthcare provider, there are significant drawbacks not reported in these stories. Like rapid tests, the saliva test is more applicable for use in testing subjects who are significantly ill, such as patients in a hospital setting, and/or healthcare workers in acute care facilities who may be exposed continuously to the SARS-CoV-2 virus, as there is a significant viral load threshold that must be met to have enough viable viral particles to detect SARS-CoV-2 in saliva. It is extremely challenging to get the required volume of saliva and concentrate it enough to yield good low-end sensitivity on this type of sample. In summary, both the rapid tests and saliva tests are better suited for point of care situations dealing with significantly clinically ill subjects, and while "positives" can be relied upon with confidence, due to low-end viral load sensitivity they are prone to false negatives, which are being reported commonly by front-line healthcare professionals. Through laboratory experience to date, the preferred samples for which to perform COVID-19 RT-PCR testing for the best sensitivity and specificity in descending order are; bronchoalveolar lavage and bronchial washings, NP swab, OP swab, nasal swab, saliva.

Below see an example of a report showing "detected" SARS-CoV-2 on RT-PCR analysis of a nasopharyngeal (N.P.) swab sample, which is consistent with a COVID-19 diagnosis.

SARS-CoV-2		
COVID-19	Result	Normal
SARS CoV-2	Positive	Negative

What is the SARS-CoV-2 antibody test and why is it important?

This is a blood test for antibodies to the virus that causes COVID-19. To be clear, the virus is named SARS-CoV-2, not COVID-19. The clinical disease is named COVID-19. Antibodies are produced by the immune system as part of its response to fighting foreign invaders like viruses. This test will give information about whether the subject's immune system has responded in some way to an exposure to SARS-CoV-2. The results will help to understand whether the subject has been exposed to the virus, and if so, whether they may have some level of immunity. This test can be used for screening of both subjects with symptoms and subjects without symptoms, which is extremely important as recent studies suggest a high percentage of people who carry the virus show no clinical symptoms.

It is important to understand though that this is NOT a test to independently tell you whether a subject has COVID-19. According to FDA, since COVID-19 is primarily a respiratory disease, the formal diagnostic test is performed by swabbing the nose or mouth, and not by a blood test. For subjects who feel sick with any symptoms of COVID-19, such as fever, body aches, chills, fatigue, new or worsening cough, or shortness of breath, the treating doctor should collect a NP swab and have a RT-PCR test performed to confirm diagnosis.

What do the results mean on antibody testing?

This test is designed to screen the subject's blood for two types of antibodies to the SARS-CoV-2 virus. These antibodies are known as IgM and IgG. You will generally see a "positive/detected" or "negative/not detected" result for IgM and IgG antibodies to the virus on the test report. Note that results may come back in a way that is hard to interpret, and these are generally reported as "equivocal" in this case. This means that the sample showed high enough titers to not be definitively negative, yet not quite high enough to be definitively positive.[4]

Here is a general description of what Positive results mean.

Positive or Detected IgM Results – A positive IgM result suggests that the subject has been recently exposed to this virus and may be fighting an active infection. They may be contagious even if they do not have any symptoms. Public health authorities have stated that people without symptoms can still pass this virus to others. IgM antibodies typically begin to increase in blood 5 days after exposure to the virus, while the rate at which they return to normal is not fully understood in SARS-CoV-2 and may also vary from subject to subject.

Positive Ior Detected IgG Results – A positive IgG result suggests that the subject has had previous exposure to the virus and may have immunity against future exposure. The level of immunity and the length of time it lasts are not yet fully known, but researchers are actively working to understand this. Infection and recovery should allow for at least 18 months of immunity, possibly much longer, and possibly decades. While SARS-CoV-2 is a novel virus we have to assume it will behave similar to other corona viruses, and most other viruses for that matter. However, time and retrospective study will confirm or disprove this, but there simply has not been enough time for this to be fully determined as of yet. In the meantime, subjects with positive, or detected, IgG should continue to follow guidance from the CDC and other public health officials, and all government orders, to help protect themselves and their family from the virus and should continue to follow all social distancing, hand hygiene, sanitation, etc.

The basic way that IgG antibodies work is that they increase after IgM antibodies are present. IgM antibodies are essentially the initial special-forces fighters that set-up the initial beach head, while IgG antibodies are the long term ground troops that serve as the occupying force. The immune system makes IgG from IgM via seroconversion over time after initial pathogen exposure, so subjects may show both positive IgM and IgG at earlier stages, or negative IgM and positive IgG as time goes by.

Here is a general description of what Negative results mean.

Negative or Not Detected IgM Results – A negative IgM result suggests that the subject has not been exposed to this virus recently and that their immune system is not showing evidence of fighting an active infection. If IgM is negative and IgG is positive,

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that probably means they had an infection in the past and likely have at least some level of immunity.

Negative or Not Detected IgG Results – A negative IgG result suggests that the subject has not been exposed to this virus and does not have any level of immunity to the virus. The exception to this is if they have a positive IgM, but not yet a positive IgG. In this case, it may be too early in the subject's exposure to the virus for their body to have made any IgG through seroconversion of IgM.

Below see an example of a report showing "detected" IgG antibodies above the threshold that supports acquired immunity to SARS-CoV-2, and "not detected" IgM antibodies, which is not indicative of very recent exposure and active infection.

COVID Serology		
	Result	Normal
COVID IgG	Detected	Not Detected
COVID IgM	Not Detected	Not Detected

Another big problem very few in the media seem able to understand is that the "rapid blood-spot" collection antibody tests now being commonly referenced in news stories, and now being marketed as at home tests, are not quantitative. They are only qualitative, and you need a very large amount of antibodies to show a "positive" on these tests. This type of testing should be reserved for those with significant clinical symptoms for at least 12-24 hours, as they will show a "positive," generally for IgM, or for both IgG and IgM antibodies, consistent with a significant active infection. Therefore, this type of antibody test method is really more suited to actual "diagnosis confirmation" of active COVID-19 in a clinical setting, such as a hospital ICU, and can be used in parallel with NP swab RT-PCR testing to confirm a clinical diagnosis of COVID-19. For learned or acquired immunity assessment these blood-spot tests do not work well because they can't quantitate the titers specifically enough to determine the slightly, to moderately, elevated antibodies required to see patterns of post-infection acquired immunity (i.e., low-elevations of IgG being maintained, and a return to no IgM). In other words, the rapid blood spot tests need high viral load and subsequent significant antibody production to generate a "positive" result, but they can't discern well the lower levels necessary for assessing long-term immunity. This, unfortunately, requires a blood draw in an SST tube, and a spin down, to acquire a serum sample in order for more specific quantitative antibody testing to be performed.

A final comment on antibody testing involves quality of the assay itself. There have been many smaller niche' labs that have seen their standard testing volume drop precipitously during this crisis, and who lack the molecular talent to have even attempted to develop and validate a RT-PCR diagnostic COVID-19 test. However, possibly to help in the crisis, and possibly to start sample volume and revenue coming in the door again, many have jumped into the antibody testing arena with little to no experience in this type of testing, as it does not require the individual lab to develop the test from scratch, but requires them to simply obtain pre-made ELISA test kits for this purpose. However, lacking the strong supply chain and vendor relationships required to access and obtain the high-quality prepared test kits manufactured in the US and Germany, which are in limited supply, many have had to resort to much lower quality Chinese-made test kits with a somewhat less than stellar track record. I would encourage the clinician to ask these questions of the labs you are considering ordering antibody testing from to try and assure the validity and quality of the results data you ultimately receive in return. The SARS-CoV-2 ELISA IgG and IgM kit assay being used in the DSL lab is US-made and has been approved by FDA under the EUA.

What is the SARS-CoV-2 stool test and why is it important?

The SARS-CoV-2 stool test also uses RT-PCR technology to detect the presence of SARS-CoV-2 in stool. Coronavirus stool tests can help practitioners screen for SARS-CoV-2 and monitor and surveil patients who have tested positive for the disease. Research from around the world indicates that as many as 50 percent of patients who are positive for SARS-CoV-2 experience gastrointestinal complaints, and that those who do have poorer outcomes.[5] Furthermore, evidence suggests SARS-CoV-2 is detectable in stool and its presence in stool may last for up to five weeks after clearance from the respiratory tract and resolution of symptoms.

A recent article published in *Lancet* states: "*Our data suggest the possibility of extended duration of viral shedding in faeces for nearly 5 weeks after the patients' respiratory samples tested negative for SARS-CoV-2 RNA. Although knowledge about the viability of SARS-CoV-2 is limited, the virus could remain viable in the environment for days, which could lead to faecal-oral transmission, as seen with severe acute respiratory virus CoV and Middle East respiratory syndrome CoV. Therefore, routine stool sample testing with real-time RT-PCR is highly recommended after the clearance of viral RNA in a patient's respiratory samples. Strict precautions to prevent transmission should be taken for patients who are in hospital or self-quarantined if their faecal samples test positive*."[6]

For practitioners who are surveilling positively identified SARS-CoV-2 patients, coronavirus stool testing offers an important adjunct test to the NP swab. The stool test does not confirm clinical COVID-19, but it does confirm exposure to and infection with SARS-CoV-2. To be clear, the SARS-CoV-2 stool analysis is not diagnostic of COVID-19. Again, according to FDA, COVID-19 disease can only be diagnosed with positive SARS-CoV-2 results on a respiratory sample. Some individuals with fecal SARS-CoV-2 go on to develop clinical COVID-19, and many do not; and post-exposure sequela varies from asymptomatic to rapid progression to acute respiratory distress syndrome (ARDS) and death. If stool is positive, it means the subject has been exposed and infected with the virus and, even if asymptomatic, is shedding virus in stool and should be compulsive about washing hands and other sanitary measures, especially post-defecation. It also means they likely have post-exposure immunity. This kind of finding, combined with quantitative IgG/IgM antibody testing, may allow clinicians to strategically determine who may be able to safely return to work. We are still learning as this develops and many, including DSL, are working with FDA and CDC on suggested clinical guidelines based on what lessons emerge from the larger population testing experience.

Below see an example of a report showing "detected" SARS-CoV-2 in stool, which is consistent with exposure to the virus and potential fecal viral shedding.

SARS-CoV-2 (Stool)		
Coronavirus	Result	Normal
SARS-CoV-2	Detected	Not Detected

Clinical Integration

It is important for the clinician to understand the clinical application and integration of testing results for the various types of testing options related to SARS-CoV-2 and COVID-19. Again allow me to stress that COVID-19 is a diagnosis that can only be arrived at when the patient is exhibiting the respiratory symptoms correlated with SARS-CoV-2 infection (i.e., cough, sneezing, rhinitis, shortness of breath, elevated temperature) and they are positive on molecular testing of a respiratory sample, preferably with RT-PCR on an NP swab or lung sample (bronchoalveolar lavage or bronchial washing). Additional information supporting this diagnosis can be obtained with "positive" or "detected" IgM antibodies for SARS-CoV-2, preferably with serum sampling. Studies indicate that positive detection rate increased to 98.6% with combined IgM and qPCR testing compared to just qPCR (51.9%).[7-8]

A positive COVID-19 diagnostic test result and/or a "positive" or "detected" IgM antibody to SARS-CoV-2 should constitute reasonable grounds to implement immediate home isolation and, in this author's opinion, should be reported to local public health authorities and all recommended protocols for that jurisdiction should be followed. While definitive reporting policy has been established for positive PCR testing on respiratory samples, the landscape is much murkier when it involves positive IgM results, and one would expect the regulatory policy to start to catch-up over time in this regard. "Positive" or "detected" IgG antibodies, in the absence of IgM, indicates previous exposure and no active infection and there is no reason to quarantine the subject unless symptoms occur. A positive SARS-CoV-2 stool test may occur in a person with, or without, active COVID-19. If the subject exhibits signs and symptoms of COVID-19 they should be managed as such. If no symptoms are present, and in the absence of a positive diagnostic test, they should be considered as having been exposed to SARS-CoV-2 and are harboring it in the gastrointestinal tract and they can potentially spread the virus through oral-fecal contamination. While these subjects are likely not transmitting the virus through the traditional respiratory routes, they must be compulsive about hand washing, especially after using the bathroom to avoid this type of spread.

**Please note that public health policy and recommendations to healthcare providers varies from State to State, and even county to county, so please remain informed about these guidelines and responsibilities for licensed health care providers in your area.*

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Closing Thoughts

I hope this summary of available testing related to COVID-19 and SARS-CoV-2 has been helpful, and please excuse me if some of it was a review of what you likely already know. It was intentionally kept simple and to the point, as the nature of some of the questions that I have been getting on many of the online practitioner forums suggested that this may be useful and necessary. It is my hope that with this review practitioners will have a better understanding of the various testing options, and their clinical utility, as we all learn our way through this new landscape.

Rapid blood-spot antibody tests are best used to confirm diagnosis in people with significant symptoms.

In closing, I wanted to just acknowledge that these have certainly been really surreal times for all of us. For instance, I could not have imagined just a month ago that I would soon be getting calls from critical care physicians from New York City hospital ICUs asking about proper protocols to provide patients with high dose IV vitamin C, or that I would be seeing very conventional hospitals in the US starting trials on administering medical ozone treatments, or that I would be witnessing the rapid discovery of supportive scientific literature that has previously gone totally unnoticed on natural substances (i.e., botanicals, plant polyphenols, melatonin, etc.), and their ability to favorably modulate immune responses and disrupt viral replication and cell penetration, by those who were previously entirely uninterested, and even hostile, to natural medicine. I also never thought I would see the level to which the general public has sought to obtain nutritional supplements and nutraceutical products during this pandemic, effectively turning back to natural medicine when there was no magic pharmaceutical bullet to save them in their time of need. In my almost 30 years in the fields of integrative, functional and naturopathic medicine, I have never been prouder of our collective professions and what we have to offer to the healthcare system, if only we were utilized more fully. I have seen colleagues of mine step-up and uncover amazing data and information on potential therapeutic approaches to help patients have a better chance of successfully surviving this infectious outbreak should they be exposed, and I firmly believe that all of the increased utilization of what have been known as complementary and natural therapies has kept countless people out of acute medical care facilities and has saved lives.

I also wanted to acknowledge the scientific team at Diagnostic Solutions Lab (DSL) for basically pivoting on a dime from their usual work and diving head-first into the rapid development of various types of COVID-19 and SARS-CoV-2 testing platforms when their nation, and the world, called. To think that a comparatively small high-complexity independent laboratory that predominantly serves the integrative and functional medicine market could be one of the very first laboratories in the US to submit FDA validation data and begin the desperately needed COVID-19 testing for some of the largest and most prestigious hospital systems in the country, when even their own institutional-based pathology labs could not, is just mind boggling. To be one of the first thirty labs in the US on the FDA list of laboratories for COVID-19 testing, when the others were the two massive national reference labs and a short list of very large prestigious academic medical institution-affiliated laboratories, is impressive to say the least. And to offer much faster turn-around time to critical care clinicians in desperate need of answers for their patients is also laudable and likely saved lives. So, to all of DSL's molecular and laboratory diagnostic scientists (PhD's), clinical doctors (MD's and ND's), the front line clinical laboratory, and the back-end support staff who have not slept much in well over a month, I salute you. You are real heroes and you have done integrative, functional, and naturopathic medicine proud, and many people, inclusing healthcare and government regulators have noticed.

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Rebecca Harder is the author of "Gastra Girl: Saving America One Colon at a Time," and owner of an immaculate and highly esteemed clinic in Portland, OR. She offers this well-researched comprehensive resource guide of holistic health information on topics such as environmental toxicity, vaccines, EMF, autism, hyperbaric oxygen, ozone therapy, colon hydrotherapy, far infrared saunas and much more.

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The Link Between Oral Health and Whole-Body Health: Is It Really, "All in Your Head"?

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

Introduction

Oral health has been separated from whole body health since the mid-1800s, when dental schools became formalized as their own institutions, disconnected from medical schools.[1] About the same time, dental and oral sepsis as a cause of disease and its relationship to general medicine became a subject of interest. Several luminaries of the day, like Dr. William Hunter, remarked that oral conditions not only included pyorrhea alveolaris, but stomatitis, and gingivitis of every degree. These conditions were septic in nature and produced pus organisms that were invariably associated with every case of dental caries, even if they seemed insignificant. Dr. Hunter stated, "What the effect had on the person was determined by the individual's resistance."[2] Then came Dr. Frank Billings who coined the term "focal infection" as "a circumscribed area of tissue infected with pathogenic organisms."[3] Dr. Edwin Rosenow followed Billings and spoke of infections of the teeth, especially multirooted teeth. He found evidence of infection of the pulp, even with asymptomatic teeth. Rosenow concluded that they may be the source of systemic effects and may need to be removed. He stated that root canals should cease.[4]

No one, however, before or since, has ever done the extensive work on the relationship between root canal teeth and degenerative diseases other than Dr. Weston Price. He founded the research institute originally called the National Dental Association, which became the research section of the American Dental Association. In 1915, he became their first director. During his career, he published over one hundred fifty papers in scientific journals. Throughout his time as director, he led a team of sixty scientists, including leading experts such as Victor Vaughn, president of the American Medical Association; Charles Mayo, the founder of the Mayo Clinic; Milton Rosenau, Professor of Preventive Medicine, Harvard University; Ludwig Hektoen, Professor of Pathology, University of Chicago; Thomas Forsyth, head of the Children's Dental Infirmary in Boston; and Truman Brophy, Dean of the Chicago College of Dental Surgery. All branches of medicine and dentistry were represented on his research team, including bacteriology, pathology, rheumatology, immunology, chemistry, cardiology, and surgery.[5]

Weston Price, DDS, found that root canal teeth were *always* infected.

Dr. Price spent 25 years of his dental career studying and performing research on endodontically treated and pulpless teeth as a continuation of the Focal Infection Theory. Price's impeccable research on root canal teeth and its causation of many diseases was done by removing the infected tooth from a patient and placing it into a rabbit. Whatever disease the patient had, the rabbit would inevitably develop the same disease symptoms. As a true scientist, Price replicated this protocol thousands of time.[5]

He found that root canal teeth were *always* infected, regardless if they were symptomatic or asymptomatic. Dr. Price expanded on this concept and studied root canals, infections, and systemic disease and wrote the two revolutionary books titled, *Dental Infections Oral & Systemic* and *Dental Infections and the Degenerative Diseases*.[5] By the 1930s, the Focal Infection Theory, which resulted in removal of teeth and tonsils, fell out of favor with some who observed: "'If this craze of violent removal goes on, it will come to pass that we will have a gutless, glandless, toothless – and I am not so sure that we may have, thanks to false psychology and surgery, a witless race.'"[6] As stated in the *American Journal of Ophthalmology*: "'Stripped of tonsils and teeth, often the victim of colonic irrigation, abdominal, and genitourinary operations, the patient may finally be reduced to only those organs necessary for existence, while all the time his ocular disease progresses remorsely to blindness.'"[7] Even in the 1930s, some medical doctors were blindsided.

In 1952, the *Journal of the American Medical Association* published an editorial written by the American Dental Association which stated, "After exerting a tremendous influence on the practice of medicine for a generation, the Theory of Focal Infection in the past 10 to 15 years has fallen in part into disfavor… none of them actually disproves the theory that some foci of infection can in the presence of predisposing or accessory factors produce some systemic diseases."[8]

Decades later, Dr. Hal Huggins, author of the ground-breaking book *It's All in Your Head* and one of the most outspoken, internationally renowned pioneers of mercury-free dentistry, started

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what is considered the third amalgam war. Huggins was already a trailblazer in training and educating dentists and health care professionals in biological dentistry, when he started to research oral pathogens. Huggins was a stanch follower of Dr. Weston Price and was keenly aware of the link between the state of the oral cavity, good or bad, and the state of the patient's overall health. His desire to really get to the root cause of disease prompted him to start his own laboratory, where he developed what was called the "Full View Test," now known as the Oral Panel offered by DNA Connexions. Based on previous works of Anne Haffajee, Huggins focused on the microbial DNA present in extracted root canal teeth and identified 83 different microbial species of interest. He stated, "Dentists claim they can "sterilize" the tooth before forcing the gutta percha wax down into the canal. Perhaps they can sterilize a column of air in the center of the tooth, but is that really where the problem is? Bacteria wandering out of the dentinal tubules is what Price was finding, and what we were finding in the crushed tooth samples. We tested blood samples adjacent to the removed teeth and analyzed them for the presence of anaerobic bacteria. Approximately 400% more bacteria were found in the blood surrounding the root canal tooth, than were in the tooth itself. It seems that the tooth is the incubator. The periodontal ligament supplies more food, therefore, we saw a higher concentration of bacteria, just outside the root canal tooth."[9]

As an educator, Dr. Huggins mentored Dr. Blanche Grube, and together they developed the Huggins-Grube Protocol. The protocol involves restoring the mouth by removing infection and toxic dental materials and replacing them with biocompatible materials. This is referred to as a "Full Dental Revision." Before his death, Dr. Huggins passed his torch to Dr. Grube. His archives and his laboratory were also taken over by Dr. Grube. She has since changed the name of the lab to DNA Connexions and is expanding various test panels from the original test panels that Dr. Huggins developed. Dr. Grube is also carrying on his legacy by training dentists around the world on the Huggins-Grube Protocol.

Oral Health and Disease

Only recently has the Focal Infection Theory been revisited, and from this, a new area of periodontology has been created, called "periodontal medicine." This resurgence is due to a plethora of new research in the literature that shows both the direct and indirect impact of periodontal pathogens on overall health. Recent epidemiological, clinical, and experimental studies support the relationship between bacteremia or inflammation due to periodontal disease (PD) and systemic disease.[10] Somma et al. described a focal infection as "A localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection in various organic districts, including the oral district" and stated "Oral inflammatory lesions have been shown unequivocally to contribute to elevated systemic inflammatory responses."[11]

The Global Burden of Disease Study (2016) estimated that oral diseases affected half of the world's population (3.58 billion people) with tooth decay in permanent teeth as the most widespread condition measured. Severe periodontal (gum) disease may result in tooth loss and was estimated to be the 11th most common disease globally.[12] A commentary in the *Journal of the American Dental Association* by Weyant et al. discussed *The Lancet* (2019) journal's coverage on oral health. This was *The Lancet's* first time in their 196-year history that they ever reported on oral health. The authors posed the question, "If this is in fact the 'tipping point?'" on raising awareness on the long-neglected subject of oral health around the world. They observed that the inequality of the social economics, of dentistry's availability to all populations, has failed to recognize and improve oral health care globally. This has created a burden on all of society – due to health-related costs, loss of work, etc. – with the most vulnerable populations being the most at risk. *The Lancet* series is shining a light on oral health and is demanding policy makers to make changes that can only be achieved by uncompromising system transformations of the oral health care systems.[13] For example, poor oral health in geriatric patients was investigated in a retrospective observational study to verify if it was a predictor of a mortality risk factor. Their findings showed that there are many diseases of the elderly that are linked to poor oral health and that it increases the risk of hospitalization due to infectious and non-infectious diseases, including in-hospital mortality.[14] *Oral Manifestations of Systemic Diseases* by Rosengard et al. developed an extensive list of general illnesses that are linked to oral health (see sidebar).

What Science Says About Dental Materials, Root Canal Treatment, Risk Factors, and Periodontal Disease

According to the American Association of Endodontists (AAE), bacteria are the major cause of pulpal and periapical diseases. Due to the complexity of the root canal system even with saline

General Illnesses Linked to Oral Health[15]

- Ulcerative colitis
- Crohn disease
- Pyostomatitis vegetans
- Gastroesophageal reflux
- Chronic liver disease
- White blood cell disorders
- Leukemias
- Lymphoma
- Cyclic neutropenia
- Langerhans cell histiocytosis
- Multiple myeloma
- Mastocytosis
- Platelet disorders
- Thrombocytopenia
- Red blood cell disorders
- Anemias
- Hemochromatosis
- Congenital erythropoietic porphyria
- Pulmonary Conditions
- Granulomatosis with polyangiitis
- Sarcoidosis
- Multisystem Conditions
- Amyloidosis
- HIV Disease
- Candidiasis
- Herpes simplex
- Hairy leukoplakia
- Kaposi sarcoma
- Cytomegalovirus
- Human papillomavirus
- Aphthous like ulcerations
- Cutaneous Diseases
- Psoriasis
- Acanthosis nigricans
- Neurologic Diseases
- Neurofibromatosis types 1 and 2
- Endocrine Diseases
- Diabetes
- Multiple endocrine neoplasia
- Thyroid disorders
- Parathyroid disorders
- Adrenal disorders
- *Hypocorticalism*
- *Hypercortisolism*
- Drug-Induced Conditions
- Aphthous stomatitis
- Dry mouth
- Lichen planus
- Gingival overgrowth (hyperplasia)
- Candidiasis (secondary to inhaled steroids)

irrigants or antibacterial irrigants, none are perfect. Researchers continue to look for a technique or ideal material that can completely clean an infected root canal.[16] The Endodontic Treatment Statistics survey (2005-2006) estimated that 22.3 million endodontic procedures were performed in the United States.[17] Carlson stated, "In our dental research we demonstrate the hundreds of infected but asymptomatic 'root canals' and 'dental implants' were in fact obstacles to the innate 'cleansing process' inherent in Nature. Overwhelming evidence is presented confirming that 'modern endodontics' leaves gangrenous tissues in the human jaw."[18]

Gutta-percha has been used as a root canal filling material since its discovery by Edwin Truman in 1847. In 1990, Pascon et al. looked at the cytotoxicity of fourteen commercially available and three experimental brands of gutta-percha. They found that all gutta-percha points tested were toxic and that toxicity was attributed to leakage of zinc ions into the fluids.[19] Additionally, there are many other types of root canal sealers, some are resin-based, silicone-based, bioceramic-based, and even mercury amalgam has been used as a root-end filling material. Root canal sealer materials have been studied and have been found to cause DNA damage and also have been shown to be toxic.[20] For example, a prospective clinical study on blood mercury levels following endodontic root-end surgery with amalgam was conducted on fourteen patients using a zinc-free amalgam. The sample collection of blood was done three times: immediately before, immediately after, and one week after treatment. After one-week, mercury levels increased in the blood. The research found that while the level of mercury increased significantly after one week, the amalgam retroseal may continue to release mercury causing a threat to the patient. Even though the blood levels were under the toxic mercury threshold, they cautioned to use non-mercury biocompatible root-end filling materials.[21]

Alkahtani et al. investigated the cytotoxicity of QMix™ endodontic irrigating solution on human bone marrow mesenchymal stem cells to compare it with sodium hypochlorite. They stated that "an ideal root canal irrigant solution should be non-toxic, with a broad antimicrobial spectrum and the ability to dissolve necrotic pulp tissue, inactivating endotoxins, and either prevent the formation of a smear layer or dissolve it. Currently, no single solution is able to achieve these goals, and the combined, concomitant or sequential use of two or more irrigating solutions is thus required." They found both solutions tested to be toxic to human bone marrow, but QMix™ was more biocompatible.[22]

Prada et al. noted that the main cause of endodontic failure is the persistence of microorganisms that cause an intraradicular or extratradicular infection and that become resistant to disinfection measures. These microorganisms have the following similarities, which make them able to evade sterilization: the ability to form a biofilm, to locate in areas unreachable to root canal instrumentation techniques, synergism, and the ability to express survival genes and activate alternative metabolic pathways.[23] A study by Yan et al. revealed that the difficulty with root canal treatments is that dentin from root canal teeth presented considerably lower strength than unrestored teeth. Even though the durability of dentin decreases with age, the dentin of root canal teeth showed more damage.[24] It has been reported that vertical root fractures, are the third most common cause of tooth loss, after dental caries and periodontal disease (PD). Additionally, it is these fractures, whether detected or undetected, that give the microorganisms more surface area to colonize. Vertical fractures, are complete or incomplete, starting at the root of a tooth. According to Garcia-Guerrero et al. endodontic treatment had the highest risk factor for vertical root fractures after a one-to-eight-year follow up, noting that 94% of the root fractures, had been endodontically treated.[25]

Another pervasive problem is apical periodontitis (AP), which is an inflammatory process around the apex of a tooth's root. This worsens with age, and one in two people over 50 years old, will develop AP.[26] Risk factors for developing AP includes root fillings, coronal restorations, primary carious lesions, and reduced marginal bone level and molar teeth.[27]

A national study on AP in root-filled teeth was conducted on the 30 year and older population in Finland. The results showed that AP occurred more often in root-filled teeth and more often in men than women. If there was insufficient root filling material during the endodontic treatment in either men or women, the risk for AP doubled.[28] The incidence of AP in root canal teeth was also explored in an urban Saudi female population. Of the 1,108 root-canal treated teeth, 813 (73.4%) also presented with AP, noting that the quality of root canal treatment, coronal restoration, and of cast restoration is significantly associated with periapical status in root-filled teeth.[29]

One hundred fifty dentists in Abidjan, Cote d'Ivoire, West Africa, were sent a survey that included public and private clinics, to determine the incidence of complications arising from endodontic procedures. Of the original questionnaires sent, 135 dentists responded, and almost all of them (94.8%) had faced problems during the treatment. Some problems that were common were fracturing of instruments during exploring of the root canal (72.58%) also during shaping (55.47%), canal wall damage (54.68%), overfill of the obturation (55.47%), and flare-up without swelling often after the procedure (81.49).[30] A study on 1,085 root canal-treated teeth were randomly selected in a Taiwanese population and were assessed as to the quality of treatment by eight endodontic experts. Some of the results included overfilling, underfilling, adequate filling, and no filling. They found that about 70% of the teeth that were treated had either insufficient filling length or sealing density.[31] Lechner et al. investigated the impact of AP in root-filled and endodontically treated teeth and its relationship among healthy controls and patients with systemic diseases. They found the frequency of AP was almost twice as high in the patients with systemic diseases, stating that local pathologies caused by endodontically treated teeth may increase immunological and systemic dysfunction.[32]

Lin et al. investigated the risk association between unfinished root canal treatments and hospitalization for pneumonia using a nationwide population-based database. The study included 116,490 subjects who received and started a root canal treatment with no history of pneumonia before 2005, and were observed until the end of 2011.

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During 2005 to 2011, a total of 1,285 subjects were hospitalized for pneumonia. They reported that an unfinished root canal treatment can leave a space for bacterial accumulation, that can leak into the oral cavity, and disseminate into the lower respiratory tract and the lungs, which can then cause infection. They concluded that individuals with incomplete root canal treatments have a higher risk of pneumonia hospitalization.[33] Another study by Lin et al. looked at unfinished root canal treatments and its relationship to cardiovascular disease, again using a nationwide population-based database. In this study there were a total of 283,590 participants who had at least one root canal, with no cardiovascular history prior to 2005. They tracked the participants until the end of 2011 and found that 3,626 patients had been hospitalized for cardiovascular disease, concluding unfinished root canals were also linked to cardiovascular disease.[34]

There is a connection between specific microorganisms from the oral cavity and various cancers and systemic diseases.

As mentioned above, microorganisms in the mouth have been linked to various diseases, including cancer, which is the second leading cause of death globally. According to the World Health Organization (WHO) lung, breast, colorectal, prostate, skin, and stomach cancer are amongst the most prevalent around the world.[35] It was only in the 1990s when the first bacterial species, *Helicobacter pylori*, was declared as a definitive cause of cancer by the WHO. These three common microorganisms, *Porphyromonas gingivalis, Tannerella forsythia (*formerly *Bacteroides forsythus)*, and *Actinobacillus actinomycetemcomitans* have been implicated in periodontitis.[36] Research is definitively showing that there is a connection between specific micro-organisms from the oral cavity and various cancers and systemic diseases; in fact, oral squamous cell carcinoma has been identified as one of the most pervasive cancers globally.[37] The link between oral bacteria and its role in development of various cancers, in addition to oral cancer, are colorectal and pancreatic cancer. The most commonly identified oral bacteria related to cancer are *Fusobacterium nucleatum* and *Porphyromonas gingivalis. Streptococcus sp., Peptostreptococcus sp., Prevotella sp.,* and *Capnocytophaga gingivalis* have also been linked in the pathology of cancer.[38]

Porphyromonas gingivalis and *Actinobacillus actinomycetemcomitans* were associated with a higher risk of pancreatic cancer in a population-based nested case-control study from two prospective cohort studies, the American Cancer Society Cancer Prevention Study II and the National Cancer Institute Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. The significance of this study showed the specific bacteria, which can be helpful to identify high risk individuals, as well as prospective treatments to lessen the risk of pancreatic cancer.[39] Other large cohort studies have been published on different types of cancer and its relationship to oral health. The connection between non-Hodgkin lymphoma and PD was explored in the Health Professionals Follow-Up Study. The original findings reported a 31% higher risk of non-Hodgkin lymphoma when individuals had severe PD at baseline. By extending the study by another eight years of follow-up, the outcome suggests that PD is a risk factor for non-Hodgkin lymphoma.[40] In the Atherosclerosis Risk in Communities Study, that included 7,466 participants, six sites were measured on all teeth to identify the severity of PD. The statistical analyses were two-sided with a median of a 14.7-year follow-up. The findings showed an increased risk of total cancer for severe PD, notably for lung and colorectal cancer.[41]

A prospective cohort study of postmenopausal women and the relationship between PD and breast cancer was conducted by the Women's Health Initiative Observational Study. The study followed 73,737 postmenopausal women who did not have breast cancer. The mean follow-up was 6.7 years, where 2,124 invasive breast cancer cases were found. PD was reported by 26.1% of the women, particularly among former smokers who quit within 20 years. PD was concluded to be a risk factor of postmenopausal breast cancer, especially among former smokers who quit within 20 years.[42]

The relationship of PD and its link to prostate cancer was investigated in a 12-year longitudinal cohort study in South Korea. The investigators used the National Health Insurance Service-Health Examinee Cohort database sample of 187,934 South Koreans, from 2002-2013. While prostate cancer is widespread in the United States and Europe, it is only the seventh leading cause of cancer death in South Korean men. However, due to the aging population in Korea, along with obesity, the rise in prostate cancer has increased dramatically. They found that this cohort study had shown that patients with PD have a significant, but slightly positive link with prostate cancer.[43] The Center for Disease Control and Prevention (2012) estimate that one out of two adults over 30 in the US has PD; for adults that are over 65, the estimate is over 70 percent.[44]

According to Gulati et al. perio-pathogens can enter the bloodstream causing bacteremia. When bacteremia occurs, there are three routes where a focal infection can appear in the bloodstream and organs. They are metastatic infection from oral cavity due to bacteremia, metastatic injury due to microbial toxins, or metastatic inflammation due to immunologic injury caused by oral microorganisms.[45] Both the gastrointestinal tract and the oral cavity have the most highly diversified assorted bacteria found in the human body. Due to the temperate and damp ecosystem of the oral cavity, it is an ideal habitat for microbial communities. Teeth are the only non-shedding surfaces in the human body and dental restorations such as crowns, bridgework, removable protheses and implants, also do not shed and can therefore sustain oral biofilm. The use of these biomaterials may not only have a negative effect on the oral cavity, but may also have a negative impact on a patient's overall health and wellness.[46] Biofilms develop from bacteria attaching to surfaces in the oral cavity such as the teeth, gums, or tongue. These microorganisms can be pathogenic, can cause oral infections, and may lead to dissemination and systemic disease. Dental prosthesis is prone to harbor the most invasive biofilms, more than any other medical devices. It has been found that over 65%

of denture wearers suffer from stomatitis, which impacts poor oral health, dental hygiene, and systemic disease, including diabetes. Infections and inflammation can also be caused from dental implants, when bacteria accumulates in the implant area and forms a biofilm.[47] The American Dental Association (2014) stated more than 5 million titanium dental implants are placed yearly in the United States and placement is expected to grow.[48] It was generally thought that titanium dental implants were not only inert but also fairly biocompatible; however, research is showing that titanium dental implants can break down due to corrosion. Allergic reactions may occur from the disintegration of these implants, producing particles that migrate to other areas far from the original implant site. Traces of metal from dental implants have been found in blood, liver, lungs, and lymph nodes. Although titanium is used in dental implants, other dental uses include membranes, grids, reduction plates, and screws; and titanium is also used in root canal sealers. The International Agency for Research on Cancer has classified titanium as a possible carcinogen.[49]

While the majority of studies have been focusing on the gut microbiota, the actual source point is the oral cavity, which is now being investigated for its potential relationship to many diseases. According to Mitu et al., the oral microbiome is believed to be a significant cause of not only oral diseases but also many systemic diseases such as diabetes, cardiovascular diseases and various syndromes like autism spectrum disorders.[50] The trillions of microorganisms, their diversity in the human body, and how they interact, require a new way of looking at the entire system, according to Le Bars et al. Changes in the oral microbiota can possibly assist in predicting the risk of cancer. This can be accomplished by using next-generation sequencing such as pyrosequencing (Roche 454) and sequencing by synthesis (Illumina), or the sequencing of the 16S rRNA gene, which has shown alterations in oral microbiota and the range and makeup between healthy patients and those with squamous cell carcinoma from the oral cavity.[51]

Bacteria found in root canal teeth associated with acute apical abscesses were examined using molecular methods. It was noted that this method can deliver a more accurate and consistent identification of bacteria that are difficult to identify or can't be precisely identified by other phenotypic tests. Twenty root-canal teeth were cultured, and two hundred and twenty strains of bacteria were identified using 16S rRNA gene sequencing along with clonal analysis, demonstrating a more diverse bacterial flora than previous studies. Fifty-nine different cultivable bacteria were identified by 16S rRNA gene sequencing, belonging to six phyla, with an average number of six species *per* root canal. Their findings demonstrated that the microbiota of infected root canal teeth is composed mainly of anaerobic Gram-negative bacteria, with the greatest majority belonging to the phyla *Firmicutes* and *Bacteroidetes.*[52]

The DNA Connexions Oral Panel

The DNA Connexions Oral Panel was designed to provide patients and practitioners a comprehensive view of patient health based on the oral flora. The panel detects the presence of 88 different microbial pathogens inclusive of bacteria, viruses, fungi, and parasites. Utilizing the molecular tool of polymerase chain reaction (PCR), this direct testing method amplifies the DNA of the targeted organisms, if present.

While the 88 microbes of the Oral Panel may seem comprehensive, there are hundreds of species and millions of microbes present in the oral flora. The oral panel constituents were chosen based on the organisms present in what is considered 'normal' oral flora, those more commonly associated in oral disease processes, and those which are thought to potentially be involved in varying systemic diseases.

As evidenced by 1000s of DNA Connexions Oral Panels, varying microflora constituents make up the species found in the oral cavity, even with wide variation in juxtaposed locations. The oral cavity and its proximity to the bloodstream allows the facilitation of bacteremia, sepsis, and the spreading of individual species throughout the body.

Sample Collection: Oral samples are predominately collected by dental practitioners in a controlled setting. Sampling types are teeth (root canaled, nonvital), oral blood, cavitational blood, dental implants, paperpoints, tissue, bone, and Superfloss (site specific or full mouth survey). Samples are placed in sterile, single use plasticware that has been flushed with nitrogen gas to preserve the DNA during return shipping. Practitioners are instructed to freeze samples until shipping.

DNA Extraction is performed utilizing a spin column extraction protocol. Purified samples are quantified for nucleic acid purity and concentration utilizing nanodrop instrumentation.

Amplification by PCR. The Oral Panel uses ninety-six well plates containing 85 unique species-specific PCR primer sets, 5 positive controls and 1 negative control. Purified, DNA is aliquoted, and a multichannel pipette is utilized to dispense 3 ul per reaction well containing typical PCR reaction components. Plates are sealed with thermal films and amplified using Bioer Thermocyclers on a 23-step annealing gradient profile.

Gel Electrophoresis. Amplification products are run on 1.2% agarose gels, ➤

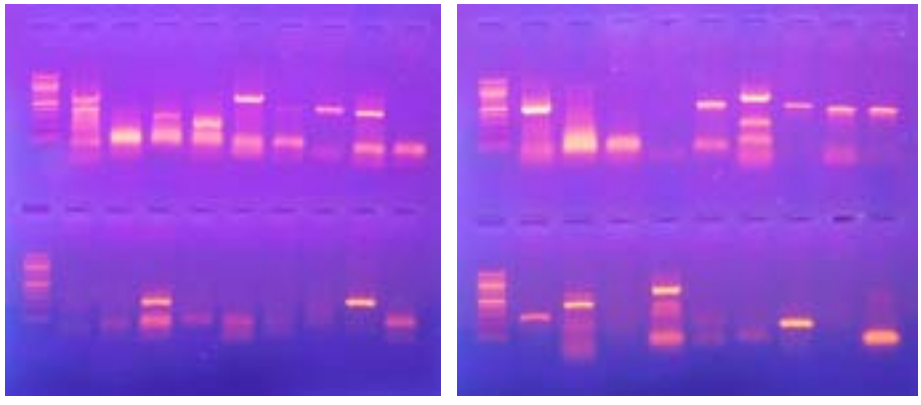

Figure 1. Two examples of PCR amplification products run on 1.2% agarose gels to discern both size and fluorescence intensity which is directly correlated to initial microbial concentration present in the sample. Standards of known sizes (molecular weight ladders) are run in the far left columns on all rows.

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with products ranging in size from 198bp – 1020bp, visualized with ultraviolet light and ethidium bromide stain.

Results. The 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 amount 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: pathogenicity, 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.

Conclusion

Poor oral health is a global pandemic, a fact that can no longer be ignored. It also cannot be overstated that there are many often-overlooked health problems that develop as a consequence of common dental procedures. Some of these universal treatments include root canal treatments, dental implants, nickel braces, or even extraction of wisdom teeth. Oral galvanism is a serious problem, especially when dissimilar metals such as mercury dental amalgam, along with titanium implants are placed in the oral cavity. Patients with existing/chronic health challenges should start by having a complete dental exam to rule out any of these treatments as the root cause of their problem. While treated teeth may appear "stable" on an x-ray and the patient may not be experiencing problems at the site, it is critical to examine these teeth utilizing the best technology that is currently available to see if infections, are in fact, present.

Many studies on the materials used in dentistry are not looking at the long-term exposure risks to the patient or the potential toxicity when these materials breakdown over time. Moreover, functionality of the restorations is often the only consideration of the dentist. As a consequence of this oversight, it is important for the doctor/dentist to study and examine the biocompatibility of each material used in all dental procedures. While there are materials that show less reactivity to many patients, there are "no one size fits all" restorative materials. The toxicity of materials is a major problem, not only in dentistry, but also in medicine. Although the toxicity of materials is being studied, few papers address the synergistic effects of exposure to different materials and more importantly, how these materials will react with the individual patient.

DNA Connexions provides testing to identify oral pathogens to assist qualified practitioners in diagnosis and treatments for their patients, including a recently added test called, the Propensity Panel, which identifies the presence of bacterial species that have been implicated in the progression of a variety of chronic and systemic conditions, as well as various cancers such as colorectal, pancreatic, prostate, and breast cancer. BIOCOMP Labs, provides biocompatibility testing so that a patient has the optimum restorative materials, specifically, to allow the least reactive restorations to be used when doing full dental revisions.

As reported in this paper, the list of diseases related to poor oral health continues to grow, particularly in the aging population. Oral pathogens are proving to be the source of many diseases, including cancer, but are rarely considered by medical professionals. This is because a colossal chasm exists between medical and dental professionals. Therefore, it is prudent not only for dentists to be alerted to the potential health risks that may be caused by common dental procedures, but also for medical doctors to look at the patient's mouth as a potential source of infection and disease.

A simple visual examination of a patient's mouth can often provide insight as to what may be causing health issues or can possibly prevent a potential disease risk. It is only recently that integrative medical doctors are starting to discuss the relationship of how oral health impacts whole-body health. Thus, it is also important to ensure that the dental profession is transformed from being "tooth mechanics," to actually understanding that the foundation of whole-body health starts in the mouth, and the critical role that the dentist plays in patients' overall health.

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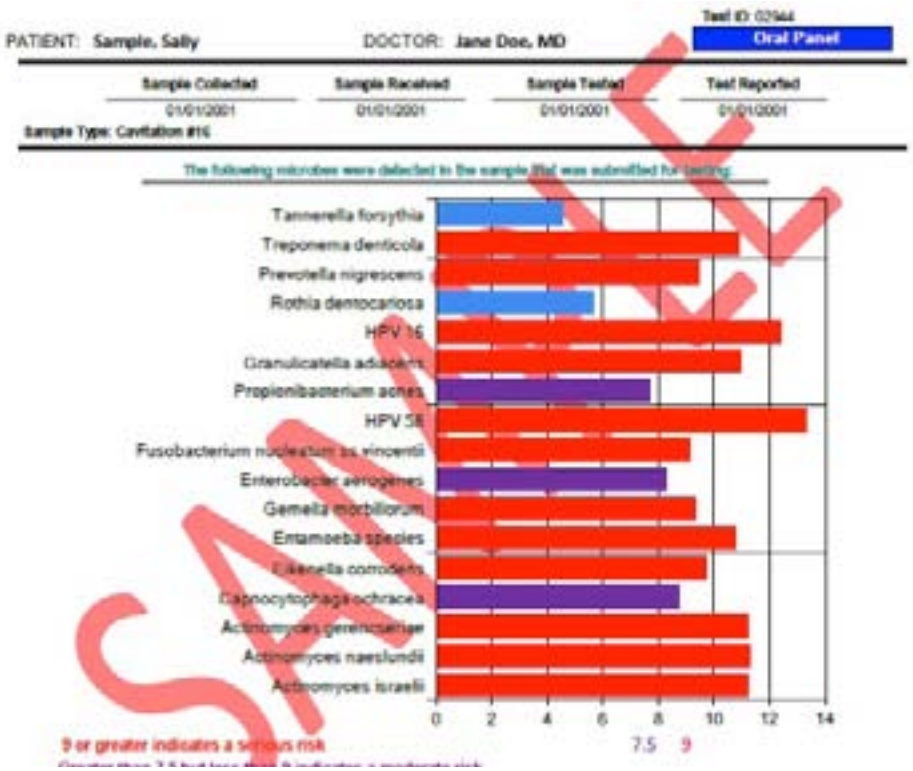

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What we have witnessed through clinical observations over several decades is that doing a complete dental revision, utilizing the most biocompatible restorations, along with a comprehensive detox and supplementation protocol has, in fact, improved the lives of many of our patients. This is because we teach the patients to actively participate in their own health and wellness.

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This paper is dedicated to Dr. Hal Huggins, a man who was persecuted during his lifetime for his revolutionary and visionary work in research and in biological dentistry. Science is finally proving what he wrote so long ago, was right, "It's All in Your Head"!

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Dr. Leslie J. Douglas completed her undergraduate studies in biology at the University of Hawaii at Hilo (UHH) before attending the University of Hawaii at Manoa (UHM), Department of Genetics and Molecular Biology. Currently, she is the principal investigator and laboratory manager of DNA Connexions, a Colorado-based company focusing on bacterial, viral, fungal, and parasitic molecular-based detection assays. Her main focus is the research and development of a PCR-based Lyme test inclusive of *Borrelia burgdorferi* and a number of prevalent tick-borne disease co-infections, as well as the ongoing development of various molecular-based assays. Dr. Douglas's research and patient demographics is yielding invaluable data to better understand the relationships between Lyme and other chronic conditions.

Anita Vazquez Tibau is a researcher at the Center for Environmental and Toxicological Research at the University of Puerto Rico. She has been working on a global ban on dental mercury for two decades, working with various non-governmental organizations. Since 2002, she has been an active participant in what is now called the Minamata Convention on Mercury treaty, where she wrote and delivered the closing statement on behalf of the International Academy of Oral Medicine and Toxicology. She has published articles in international journals, and several of her articles have been translated into multiple languages. She has lectured in the US and abroad. Most recently she was the recipient of the Humanitarian Award at the Doctors Who Rock Gala, 2019, Orlando, Florida.

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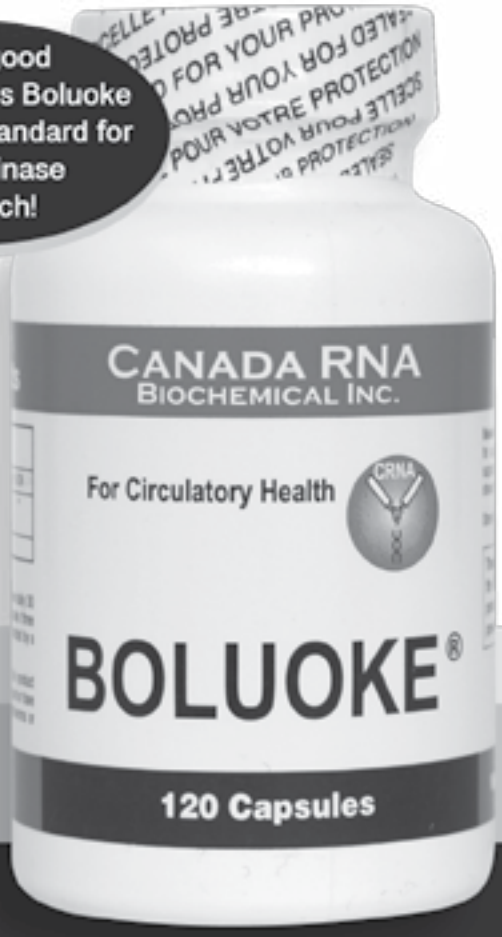

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Shorts

briefed by Jule Klotter
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Preventing Epidemics with Homeopathy

In late January, as the COVID-19 epidemic in China was making headlines, India's Ministry of AYUSH (Ayurveda, Yoga and naturopathy, Unani, Siddha, and Homeopathy) suggested some preventive measures that included the usual hygiene recommendations (handwashing, avoiding those who are sick, etc), Ayurvedic medicines, Unani (traditional Arabic medicine) herbals, and homeopathy. Specifically, AYUSH recommended *Arsenicum alba* 30C, one dose taken for three days on an empty stomach as a *preventive* measure that was to be repeated in a month. *Arsenicum* is a common remedy for flu and pneumonia characterized by fever and chills, profuse discharge from the eyes and nose, great prostration, irritability, and anxiety. It was the primary homeopathic remedy used to treat H1N1 (swine flu) patients in India's 2009 epidemic. Although, at this point, it is still unknown if *Arsenicum* is the remedy that best matches the symptoms of COVID-19 (i.e., the *genus epidemicus*), taking it would do no harm – and might help. Critics of homeopathy assailed AYUSH for its recommendation.

Using homeopathy as a preventive measure during epidemics (aka homeoprophylaxis) has a long history. During a scarlet fever epidemic in 1799, Dr. Samuel Hahnemann, who developed homeopathy, began giving *Belladonna*, the homeopathic treatment for the disease, to people who were exposed but had not yet developed symptoms. Other doctors followed his lead and found that disease incidence greatly decreased in those who received *Belladonna* prophylactically – a finding that led to the Prussian government's order in 1838 to use it as a preventive in all scarlet fever outbreaks. More recently, health agencies in Brazil, Cuba, and India have published research that shows homeopathic remedies or homeopathic nosodes, used as preventives, can decrease morbidity in a range of epidemic diseases, including leptospirosis, dengue, malaria, and influenza. Nosodes are homeopathic (i.e. highly diluted) preparations made from cultures or clinical samples that contain pathogens, parasites, or diseased tissue.

A Cuban study looked at the effect of giving a nosode made from four inactivated bacterial strains of *Leptospira* on 2.3 million people at risk for contracting leptospirosis in 2007-8. The bacteria, found in the urine of domestic and wild mammals, are transmitted via contact with mucus membranes and open sores. It is a serious problem in largely agricultural, developing nations during rainy/flooding seasons when the bacteria is more likely to enter the water supply. Cuban health personnel distributed two oral doses of the nosode (200C, then 10M given 7 to 9 days after the first) to residents who were at especially high risk. The rest of the population (8.8 million) did not receive the nosode. Despite increased rainfall (and risk of disease) in the intervention area, "the annual number of cases decreased by 84%" over the next year; leptospirosis increased by 21.7% in the population that did not received the nosode. Golden and Bracho explain that a leptospirosis vaccine for people over 15 years has been part of Cuba's vaccine program since 1998, and chemoprophylaxis was also available to all inhabitants. Neither of these measures could account for the difference in outcome. They write, "The Cuban experience with homeoprophylaxis against leptospirosis has been and remains a very positive one. It has given rise to further government-directed immunization against hepatitis A, swine flu, pneumococcal disease, and dengue fever using homoeoprophylaxis."

The Brazilian Public Health System in Petropolis conducted a randomized, triple-blind, placebo-controlled study from April 2009 to March 2010 on the use of homeopathic medicines to prevent flu and acute respiratory infections (ARIs) in 600 children, age 1-5 years. (Changes in residence and health insurance produced a dropout rate of 26%; 445 completed the study.) One group received InfluBio, a nosode made from an infectious strain of H3N2 influenza A virus; in vitro research showed that this nosode stimulated macrophage cells and increased the release of tumor necrosis factor. The second group received a homeopathic complex, composed of inactivated influenza virus and Streptococcus and Staphylococcus bacterial strains; this complex has been "traditionally used" to prevent acute respiratory infections. The third group received the vehicle for the homeopathic medicines (30% ethanol), so all three preparations appeared and tasted the same. The patients, their guardians, physicians, health agents, and researchers who performed the data analysis were all blinded to treatment allocation. The researchers compared the number of flu infections and ARIs for each group that occurred during

the one-year study. Children receiving either homeopathic nosode displayed symptoms of flu or ARI within the first month after treatment but were otherwise free of ARIs; there was no statistically significant difference between the two homeopathic nosodes. In contrast, those receiving the placebo developed ARIs in the second and third month after treatment. The authors say, "In the first year post-intervention 46/151 (30.5%) of children in the placebo group developed 3 or more flu and acute respiratory infection episodes, while there was no episode in the group of 149 children who used Homeopathic Complex, and only 1 episode in the group of 145 (1%) children who received InfluBio." The authors added that the homeopathic medicines were less expensive than conventional medications and caused no adverse effects.

The US-based National Center for Homeopathy reports (as of April 13, 2020) that homeopathic treatment data from homeopaths worldwide is being compiled and analyzed in order to identify a *genus epidemicus* for COVID-19. Data from Europe indicates that Bryonia 200C or Gelsemium 200C, taken every five days, may be preventive for those at risk or on the front lines. A COVID-19 nosode has reportedly been produced (https://immunizationalternatives.com), but I found no information on its effectiveness or safety.

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Regenerating Damaged Kidneys

An Israeli nephrologist, Prof. Benjamin Dekel, and colleagues have developed a technique that has the potential to restore lost kidney function. They have found a way to culture the kidney cells responsible for replacing dead or damaged cells into three-dimensional "kidney spheres." In a 2020 *Cell Reports* article, the researchers explain that the 3-D nephrospheres (nSPHs), unlike previous 2-D cultures of human kidney cells, remain viable and have the ability to form renal tubular structures *in vivo* – at least in mice.

In one experiment, they injected seven-to-eight-day-old, cultured human nSPH cells into mice who had had 5/6 of their kidneys removed two weeks before. HLA staining at 48 hours and two weeks after implantation showed that the human cells had grafted onto the remaining kidney tissue: "Moreover, the cells were seen to generate engrafted renal structures." As part of this study, the researchers evaluated kidney function by measuring creatine (Cr) levels in blood and creatine clearance (CrCL) levels in 24-hour urine samples before implantation and two weeks after each of the three nSPH injections; these levels were also measured at five weeks and at eight weeks after the third (final) injection. Measures after the second injection and all measures after the third injection "showed a significant decrease in blood Cr and an increase in CrCl" (Cr, $p<0.0001$ and CrCl, $p=0.0002$ at the final measurement).

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A similar experiment was conducted with mice whose kidneys were damaged by cisplatin (injected on days 0 and 14), followed by removal of one kidney to simulate chronic renal injury. Like the earlier study, HLA staining showed "robust engraftment of nSPHs in the remnant kidney" and Cr remained "significantly blunted."

The nSPHs in these studies came from healthy human kidneys. Dekel and colleagues wanted to know if they could culture these regenerative cells from the kidneys of people with chronic kidney disease (CKD) and end stage renal disease (ESRD). They found that they could. Being able to form nSPHs from a person's own kidney cells eliminated concern about immune rejection in upcoming human studies.

"A mere 5% change in renal function can differentiate between medical treatment in CKD stage 4 (20% remaining renal function) and dialysis in stage 5 CKD or ESRD (<15% remaining renal function)," the authors write. They do not expect this technique to make a kidney whole again, but they do have reason to believe that their nSPH cells can slow or prevent kidney deterioration and reduce the need for dialysis or kidney transplants.

Gan R. Will Dialysis Become a Thing of the Past? (press release) January 21, 2020.
Harari-Steinberg O, et al. *Ex Vivo* Expanded 3D Human Kidney Spheres Engraft Long Term and Repair Chronic Renal Injury in Mice. *Cell Reports.* January 21, 2020;30:852-869.

Gut Microbiota and Nonalcoholic Fatty Liver Disease

Do gut bacteria and the compounds they produce have a role in nonalcoholic fatty liver disease (NAFLD)? In a 2018 review article, Stefano Bibbò et al reviewed the literature that links intestinal dysbiosis with NAFLD and inflammation. NAFLD is characterized by abnormal triglyceride accumulation. In chronic NAFLD, inflammation and cell damage occur; and the result is nonalcoholic steatohepatitis (NASH). The authors point out that portal circulation takes everything absorbed from the intestinal tract directly to the liver. They found several links between dysbiosis and NAFLD in the literature. Studies have linked small intestinal bacterial overgrowth (SIBO) and increased intestinal permeability to abnormal fat deposits in the liver – although intestinal permeability and blood alcohol and endotoxin levels appear to be a greater factor than SIBO. Some gut bacteria, such as *E. coli*, produce ethanol.

Lipopolysaccharide (LPS), a component of Gram-negative bacteria, is known to activate Toll-like receptors (TLRs), which activate cytokines. Some TLRs (e.g., TLR4 and TLR9) "promote inflammation and liver fibrogenesis through the activation of Kuppfer cells and hepatic stellate cells." Other TLRs (like TLR5 and TLR7) appear to modulate inflammation pathways and protect against damage.

In a comment on this review, Chinese researchers Xia Li and Feng-Lai Yuan point out that microbiota may contribute to NAFLD in ways other than TLRs and inflammation. They say, "…gut microbiota dysbiosis decreases choline metabolism and increases toxic methylamines, which causes the abnormal accumulation of lipids and inflammation in the liver…." Gut microbiota also affect bile acid metabolism. The Chinese researchers state that measures – such as probiotic use, antibiotic treatment, fecal microbiota transplants, and diet changes – may stem the inflammation process in NAFLD that leads to liver injury. Bibbò et al responded that probiotic treatment improved clinical outcomes and reduced inflammation markers in overweight and lean people with NAFLD. Both sets of authors agree that more and larger studies are needed to investigate modulation of gut microbiota as a possible therapy for NAFLD.

Bibbò S, et al. Gut Microbiota as a Driver of Inflammation in Nonalcoholic Fatty Liver Disease. *Mediators of Inflammation.* 2018.
Bibbò S, et al. Response to: Comment on "Gut Microbiota as a Driver of Inflammation in Nonalcoholic Fatty Liver Disease." *Mediators of Inflammation.* 2018.
Li X, Y F-L. Comment on "Gut Microbiota as a Driver of Inflammation in Nonalcoholic Fatty Liver Disease." *Mediators of Inflammation.* 2018.

Social Distancing Option

Physical distancing – even lockdowns that quarantine healthy, at-risk, and exposed alike – have become a normal part of life in many countries that are dealing with the COVID-19 epidemic. As researchers at Harvard's T. H. Chan School of Public Health explained in late March, the main purpose of physical/social distancing is to prevent illness and infection in too many people at the same time, which would make it difficult (if not impossible) for critical-care units and hospital personnel to care for them.

As I write this in mid-April, some governors are voicing the intention that social distancing be kept in place until a vaccine is available so that herd immunity can be attained. The Harvard researchers say, "The problem…is that while strict social distancing may appear to be the most effective strategy, little population-level immunity is developed to a virus that is very likely to come around again." They suggest that social distancing measures be relaxed when cases fall to a certain level and then be reinstated if disease incidence rises to a level that compromises the health care system.

"Depending on seasonality, the models show that social distancing occurring between 25 percent and 75 percent of the time would both build immunity and keep the health care system from overloading," writes Harvard staff writer Alvin Powell. "As time passes and more of the population gains immunity, [the researchers] said, the restrictive episodes could be shorter, with longer intervals between them." With increased population immunity, the virus will eventually have an impact similar to colds, flu, and other contagious illnesses that regularly circulate through populations.

Several factors affect how long such "intermittent" social distancing would remain in place, including whether COVID-19 is a seasonal or year-round ailment, the discovery and use of effective treatments to lessen severity and mortality, increased hospital capacity, effective case identification and ability to trace patients' contacts, and access to a safe and effective vaccine. According to the Harvard model and with what is known at this point, the Harvard researchers say the epidemic would be over sometime in Fall 2020 if we stopped all social distancing now; ***but*** if we did stop, health care systems would be overwhelmed, and patients would have less access to live-saving care. Their model aims to maintain adequate health care and promote population-wide immunity.

Powell A. On-again, off-again looks to be best social-distancing option. *The Harvard Gazette.* March 27, 2020.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Green Tea Catechins Help Prevent Upper Respiratory Infections

Two hundred seventy-three Japanese healthcare workers (mean age, 43 years) were randomly assigned to receive, in single-blind fashion, high-dose catechins (a drink containing 57 mg of catechins 3 times per day), low-dose catechins (a drink containing 57 mg of catechins once a day) or a placebo drink for 12 weeks, from December 2017 through February 2018. The amount of catechins consumed in the high-dose group (171 mg per day) was equivalent to approximately one cup of green tea per day, and included daily 60 mg of epigallocatechin gallate (EGCG), 54 mg of epigallocatechin, and lesser amounts of five other catechins. The incidence of acute upper respiratory tract infections was 26.7% in the placebo group, 28.2% in the low-catechins group, and 13.1% in the high-catechins group ($p = 0.03$ for high-dose catechins vs. placebo).

Comment: Catechins are a group of flavonoids found mainly in green tea. These compounds have demonstrated antiviral activity *in vitro*. The results of the present study suggest that consumption of about one cup of green tea per day or an equivalent amount of green tea catechins can decrease the incidence of upper respiratory tract infections. These findings are consistent with those from previous studies. In a study of elderly nursing home residents, gargling with an aqueous solution of green tea catechins three times per day significantly reduced the incidence of influenza.[1] In a double-blind study of healthy volunteers, administration of a proprietary green tea extract (1 capsule twice a day for 3 months) reduced the number of days with cold or flu symptoms by 36% compared with placebo ($p < 0.002$).[2]

Furushima D, et al. Prevention of acute upper respiratory infections by consumption of catechins in healthcare workers: a randomized, placebo-controlled trial. *Nutrients*. 2019;12:E4.

Tocotrienol-Rich Vitamin E for Diabetic Nephropathy

Fifty-four Malaysian patients (mean age, 61 years) with type 2 diabetes and diabetic nephropathy were randomly assigned to receive, in double-blind fashion, tocotrienol-rich vitamin E (Tocovid SupraBio; 1 capsule twice a day) or placebo for 12 weeks. Each capsule contained 200 mg of tocotrienols (62 mg of d-alpha tocotrienol, 112 mg of d-gamma-tocotrienol, and 26 mg of d-delta-tocotrienol) and 92 IU of d-alpha-tocopherol. The mean serum creatinine concentration decreased in the active-treatment group from 1.36 mg/dl at baseline to 1.32 mg/dl at 12 weeks, and increased in the placebo group from 1.39 mg/dl at baseline to 1.45 mg/dl at 12 weeks ($p < 0.03$ for the difference in the change between groups). The mean estimated glomerular filtration rate (ml/minute/1.73m^2) increased in the active-treatment group from 61.0 at baseline to 62.7 at 12 weeks, and decreased in the placebo group from 59.5 at baseline to 56.7 at 12 weeks ($p < 0.05$ for the difference in the change between groups). Compared with placebo, active treatment had no significant effect on hemoglobin A1c levels.

Comment: Hyperglycemia increases oxidative stress and inflammation, which may contribute to the pathogenesis of diabetic nephropathy. Tocotrienols are considered part of the vitamin E complex (which includes tocopherols and tocotrienols). Tocotrienol-rich vitamin E has been shown to reduce oxidative stress and inflammation and to decrease the severity of diabetic nephropathy in rats. In the present study, supplementation with tocotrienol-rich vitamin E improved renal function in patients with type 2 diabetes and diabetic nephropathy. In previous studies, supplementing with alpha-tocopherol resulted in little or no improvement in diabetic nephropathy, so the positive results seen in the present study may have been due mostly to the tocotrienols.

Tan GC, et al. Tocotrienol-rich vitamin E improves diabetic nephropathy and persists 6-9 months after washout: a phase IIa randomized controlled trial. *Ther Adv Endocrinol Metab*. 2019;10:2042018819895462.

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Gaby's Literature Review

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Vitamin B3 and Glaucoma

The mean plasma concentration of niacinamide was significantly lower by 30% in 34 patients with primary open-angle glaucoma than in age- and sex-matched controls.

Comment: Niacinamide (a form of vitamin B3) is a component of nicotinamide adenine dinucleotide (NAD), which plays a key role in mitochondrial energy production. The concentration of NAD in retinal cells declines with age, potentially rendering ocular neurons more vulnerable to increased intraocular pressure. Degeneration of retinal ganglion cells is one of the key events in the pathogenesis of glaucoma. In a genetic strain of mice that spontaneously develops glaucoma, mitochondrial abnormalities were found in retinal ganglion cells before cellular degeneration was detectable. In those genetically glaucoma-prone mice, oral administration of a large amount of niacinamide (500 mg per kg of body weight per day) prevented the development of glaucoma without decreasing the elevated intraocular pressure.[3]

Such a large dose of niacinamide would be hepatotoxic in humans. The results of the present study raise the possibility that suboptimal vitamin B3 status plays a role in the development of glaucoma, and that supplementation with modest doses of niacinamide (such as 20 to 100 mg per day) might be protective.

Kouassi Nzoughet J, et al. Nicotinamide deficiency in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2019;60:2509-2514.

Folate Status Still Low Despite Fortification

According to data from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2016, the prevalence of folate insufficiency (defined as a red blood cell folate concentration below <748 nmol/L) was 18.6% among women in the United States.

Comment: Folic acid fortification of enriched grain products has been mandatory in the United States since 1998. The main purpose of requiring folic acid fortification was to improve folate status in women of reproductive age and thereby reduce the risk of neural tube defects in their offspring. After folic acid fortification was instituted, the incidence of neural tube defects declined by about 28%. However, the present study demonstrates that low or suboptimal folate status is still common. Folic acid fortification of grains has not invalidated the recommendation from the United States Public Health Service that "All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other [neural tube defects]."

Pfeiffer CM, et al. Folate status in the US population 20 y after the introduction of folic acid fortification. *Am J Clin Nutr*. 2019;110:1088-1097.

Magnesium for Constipation

Thirty-four Japanese women (mean age, 41 years) with chronic constipation were randomly assigned to receive, in double-blind fashion, 500 mg of magnesium oxide or placebo three times per day for 28 days (900 mg per day of elemental magnesium). A positive response was defined as improvement in constipation during at least two of the four weeks. The proportion of participants who had a positive response was significantly higher in the magnesium group than in the placebo group (71% vs. 25%; $p < 0.02$).

Comment: Magnesium, when administered in large doses, acts as an osmotic laxative. The present study demonstrates that supplementing with 900 mg per day of magnesium is beneficial for constipation. In my clinical experience, lower doses (such as 300-600 mg per day) can also improve constipation in some patients. Despite its effectiveness, a case can be made that doses greater than 600 mg per day should not be used indefinitely. According to one practitioner, supplementing with high doses of magnesium may result in excessively rapid intestinal transit time (even in the absence of diarrhea), potentially leading to deficiencies of various nutrients.[4]

Mori S, et al. A randomized double-blind placebo-controlled trial on the effect of magnesium oxide in patients with chronic constipation. *J Neurogastroenterol Motil*. 2019;25:563-575.

Alpha-Lipoic Acid for Tinnitus

Seventy patients (aged 25-75 years) with chronic tinnitus (6 months or longer) who had normal hearing or mild-to-moderate sensorineural hearing loss were randomly assigned to receive, in double-blind fashion, placebo or the combination of 300 mg of alpha-lipoic acid twice a day and a daily moderate-potency multivitamin for three months. Mean tinnitus loudness (decibels) decreased from 45 to 30.8 in the active-treatment group and from 47.1 to 40.4 in the placebo group. The mean improvement was significantly greater in the active-treatment group than in the placebo group (-14.2 db vs. -6.7 db; $p < 0.001$).

Comment: Chronic tinnitus is a difficult-to-treat condition. There is some evidence that melatonin and zinc can decrease the severity of tinnitus. The results of the present study suggest that alpha-lipoic acid in combination with a multivitamin is also beneficial. The mechanism of action of alpha-lipoic acid is not known.

Petridou AI, et al. The effect of antioxidant supplementation in patients with tinnitus and normal hearing or hearing loss: a randomized, double-blind, placebo controlled trial. *Nutrients*. 2019;11:E3037.

Can Vitamin D Prevent Urinary Tract Infections in Men with Benign Prostatic Hyperplasia?

Four hundred Egyptian men (mean age, 64.3 years) with moderate-to-severe symptoms of benign prostatic hyperplasia (BPH), who had not received any prior treatment for BPH, and who had a PSA level below 0.4 ng/ml were recruited over a 14-month period. All patients were treated with tamsulosin (0.4 mg per day) and were randomly assigned to receive or not to receive (control group) 600 IU per day of vitamin D for two years. During the two-year study, monthly clinical and laboratory evaluations were carried out, including urinalysis and urine culture at each visit. Three hundred eighty-nine men completed the trial. The incidence of recurrent (2 or more) urinary tract infections (UTIs) was significantly lower in the

vitamin D group than in the control group (4.6% vs. 13.5%; p = 0.003). The authors noted that they received no funding for this study.

Comment: During the past year, I have pointed out several times in the *Townsend Letter* that a large and growing number of published nutrition studies have left me wondering whether the research is fraudulent. While most of these eyebrow-raising papers are coming from Iran, many are coming from Egypt. The present study from Egypt raises a number of concerns.

1. A randomized controlled trial was conducted before there was any preliminary evidence of efficacy in humans (such as case reports or uncontrolled trials). Because randomized controlled trials are expensive to conduct, such trials are generally reserved for treatments for which there is some evidence of efficacy. This is especially true when there is no funding source. Although there is conflicting evidence suggesting that vitamin D is useful for preventing certain types of infections, there is no prior evidence that vitamin D is effective either for BPH or for preventing urinary tract infections.
2. Issues related to funding: Each of the 389 patients who completed the trial had a total of 24 monthly clinical evaluations, each of which included a urinalysis and urine culture. The median salary of doctors in Egypt is $69-$361 per month (Wikipedia). It is difficult to imagine that the doctors conducting this study would have been willing and able to pay for 9,336 urinalyses and 9,336 urine cultures, not to mention donating their time for 9,336 office visits. One also wonders why the authors of this self-funded study chose an expensive protocol of monthly visits, as opposed to recommending return visits only when new urinary tract symptoms developed. Monthly screening of this patient population for asymptomatic bacteriuria would seem to be of questionable clinical and academic value.
3. Issues related to recruitment: In order to participate in the trial, men with BPH had to have a PSA level below 0.4 ng/ml. In previous studies of men with BPH, means and standard deviations for baseline PSA levels suggest that only about 20% of men with BPH have a PSA level below 0.4 ng/ml. The researchers would therefore have needed to evaluate 2,000 men with BPH over a 14-month period to find 400 with a PSA level below 0.4 ng/ml. Of those 400 men, many would have been excluded because they had previously been treated for BPH (one of the exclusion criteria), or because they were not willing to participate in a clinical trial that required monthly visits for two years, or because they wished to try watchful waiting or an herbal treatment before starting medication. It would be reasonable to expect that these obstacles would exclude at least three of every four eligible patients. However, using a more conservative estimate that one of every two eligible patients would not participate, the researchers would have had to evaluate 4,000 BPH patients over a 14-month period. That equates to 13 to 14 BPH patients every day, five days a week for 14 months. That level of activity would seem to be beyond the capability of most institutions, particularly when there is no funding for the study.

Gaby's Literature Review

4. Issues related to dropouts: Of the 400 men who entered the trial, 11 were excluded for medical reasons, but otherwise there was a 100% completion rate. No one was excluded for reasons such as nonadherence, switching to a different medication due to lack of efficacy of tamsulosin, or failure to attend the monthly visits. Such a low dropout rate is extremely unusual, particularly in a study that requires 24 monthly visits, most of which would be of little value for patients whose symptoms had not changed.

Safwat AS, et al. Cholecalciferol for the prophylaxis against recurrent urinary tract infection among patients with benign prostatic hyperplasia: a randomized, comparative study. *World J Uro*l. 2019;37:1347-1352.

Eating Almonds Improves Skin Wrinkles

Thirty-one healthy postmenopausal US women (mean age, 61 years) with Fitzpatrick skin types 1 and 2 (light skin) were randomly assigned to consume 20% of their daily energy in the form of raw almonds or a calorie-matched snack (a cereal bar, granola bar, and pretzels) for 16 weeks. The mean daily intake of almonds was 2.1 oz. (340 kcal). Participants in both groups were advised to avoid all other nut-containing foods. A facial photograph and image analysis system was used to obtain standardized photographs and information on wrinkle width and severity. The investigators were blinded to the treatment assignments. At 16 weeks, compared with the control group, the almond group had 9% lower wrinkle severity ($p < 0.02$) and 10% less wrinkle width ($p < 0.02$).

Comment: This study showed daily consumption of almonds can decrease the severity of wrinkles in postmenopausal women. While the mechanism of action is not known, the benefits might be due to the fatty acids and antioxidants in almonds.

Foolad N, et al. Prospective randomized controlled pilot study on the effects of almond consumption on skin lipids and wrinkles. *Phytother Res.* 2019;33:3212-3217.

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OncANP 2020

by Jacob Schor, ND, FABNO

In studies on the health benefits of forest walking, you may have you noticed that the participants always seem to walk through lush deciduous or conifer forests rather than through deserts populated by towering prickly cactuses, snakes, or lurking scorpions. In my mind everything in the desert is patiently waiting to hurt me. I remember this each year when we arrive in Arizona for the annual conference of the Oncology Association of Naturopathic Physicians (OncANP). I've spent time in the desert over the years, and there are moments when I'm struck numb by the beauty; but there's always a bit of uneasiness and anxiety about where I'm going to step next. It wouldn't surprise me to read that cortisol levels spike up after what might be called cactus strolling (or dodging?).

Many people apparently like coming to Arizona in the middle of winter; and because of this, the OncANP has held their annual conferences in the Phoenix area almost every year. The ninth annual conference was held this year at We-Ko-Pa Resort, an Indian-owned facility and part of the Fort McDowell Yavapai Nation in Scottsdale, that in addition to a conference center has a golf course and casino to entertain guests.

As mentioned, this was the ninth annual OncANP conference. One gets better at doing some things with practice. These conferences seem to get better with each passing year. Corey Murphy, the executive director of the organization, has been in charge of all the prior conferences and ran this one as well. She clearly has gotten better at her job and has learned to let the conference content committee have a long leash. Professor Lise Alschuler has chaired this content committee for a number of years. That's my new nickname for Dr. Lise Alschuler ever since she took on her current job title, "Professor of Clinical Medicine at the University of Arizona." I don't believe it is possible for her to get any better at doing this. She started out good and quickly reached a superlative ability level a few years back. I credit Professor Alschuler and the work of this committee with much of what makes these conferences so special.

Heather Wright, ND, holding the 2020 President's Award given to her by Dugald Seely, ND, current OncANP President
(photo: Griffin McMath)

Years back the conference committee began instituting practices that have raised the bar. Speakers are required to submit their PowerPoints well in advance, and the committee assigns teams to review and critique the presentations. This started out as simple proofreading with the hope of eliminating the product promotions that prevent attendees from being awarded CE hours. The review process has evolved into full-fledged content critiques with suggestions for how to improve the lectures. If it feels like the OncANP conference is more polished than other conferences, that's because it is. Pretty much all presentations have been refined and improved before the speaker gets to stand up on the stage.

This was brought home by a Harvard researcher, whose work we have followed closely, who thanked us over dinner for our critiques. This may be why it feels like the conference, which started out good almost a decade ago, feels like it's getting better year after year. I know it's customary in these conference reports to write mini-summaries speaker by speaker, but I can't believe anyone actually reads stuff like that. Let me just tell you about the information that sticks in my mind.

According to Drs. Tina Kaczor and Gurdev Parmer, who recently completed their *Textbook of Naturopathic Oncology*, 30% of cancer patients will suffer from hypercalcemia at one time or another. This detail came out during their review of things that we don't want to miss noticing in our patients. (a lecture which I've nicknamed 101 ways not to screw up). Other things we don't want to miss, of course, include a neutropenic fever and distinguishing it from the desired reaction to a fever-inducing therapy, say mistletoe or hyperthermia; this is not always easy to do. Some things need continual repeating: we no longer use acetyl-l-carnitine (ALC) to prevent neuropathy nor combine green tea with bortezomib and so on, things we've certainly heard before but might have forgotten.

It continues to surprise me that not everyone knows about this ALC caution, but that is perhaps because those of us involved with OncANP have a single-minded focus on oncology. ALC may still be indicated for other types of neuropathy, in particular diabetic neuropathy (though the evidence is building that testing for and treating B-12 deficiency should top that malady's differential rather than merely treating with ALC[1]).

Our reliance on ALC for prevention of chemotherapy-induced neuropathy evaporated seven years ago with the publication of Hershman et al's "Randomized double-blind placebo-

controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy" in the *Journal of Clinical Oncology*. The authors had conducted a 24-week trial giving either 3 grams of ALC/per day or placebo to see what effect it had on taxane-induced neurotoxicity, expecting to confirm the benefit of this treatment (n=409). Their results came as a surprise: "There was no evidence that ALC affected CIPN [Chemotherapy-induced peripheral]. at 12 weeks; however, ALC significantly increased CIPN by 24 weeks."[2] In other words, ALC didn't help; instead, it actually made things worse. In 2018 the same authors reported that they had followed the patients from the initial trial; and in those who received ALC their neuropathy persisted and was still significantly worse when evaluated two years later.[3]

"Wheelhouse" seems to be the word of the year. After losing count of how many times Jen Green and others used the term in their lectures, I found myself Googling its definition because I really didn't know what it meant. Apparently, my best guess – that it refers to the shelter surrounding the steering apparatus of boats, and by implication that the term was used to reference one's ability to affect the direction of travel or alter one's course, basically steer the boat or take control – is totally wrong. "According to the Dickson Baseball Dictionary, the term wheelhouse refers to swinging a bat when the ball is right in your crush zone." So really, it's about what one is best at doing. So much for my imagining Dr. Green piloting a paddleboat down the Mississippi while standing in her wheelhouse. This makes me wonder about how lengthy the list of other things that I am wrong about is.

I was delighted to finally meet Dr. Michelle Holmes from Harvard, famous for her work on aspirin and breast cancer recurrence risk. Her original study suggests aspirin might cut risk by nearly half. After reviewing the possible mechanisms of action underlying this phenomenon, she openly admitted that most of these explanations are not adequate. Effective aspirin doses are often too low to decrease inflammation (one early idea); and although NSAIDs inhibit aromatase, the fact that aspirin inhibits both ER positive and ER negative breast cancers argues against the protective action being hormonal, and so on. Given that it took about a hundred years from when Bayer introduced aspirin until we had a decent explanation why it decreased pain and fever, I figure we can be patient a little longer.

Nice photo of Tina Kaczor, editor of the *Textbook of Naturopathic Oncology*, with Professor Lise Alschuler

Dr. Sharon Gurm gave an excellent and fascinating lecture on the utilization of lasers and photo-potentiating agents. This subject seems like it's about to take off. She presented several phenomenal cases that stuck in my mind, the kind of cases one feels envious of, the "I wish my patients did so well" kind of cases.

To return to baseball metaphors, Dr. Gurm, hit it out of the park. My lasting memory from her lecture was the list of instructions about public speaking that she received from her nine-year-old daughter, who had been taught them at school:

1. Stand up straight.
2. Look each individual audience member in the eye.
3. Speak clearly with a loud voice.
4. While on stage, do not pick your nose.

Ian Biers, ND, MPH, LAc and fast talker wowed us all with how much he could say in his brief allotted time. While the lecture was supposed to be about the quality of life benefits from instituting early palliative and hospice care, Dr Biers couldn't resist hammering home again his recurrent message that progression-free survival does not predict overall survival (PFS is not OS) as he has in prior years. His reiterations seem to be working; people now seem to believe him and don't raise their hands in objection. Where once these were radical ideas, solid data now support all of his messages, and repetition does seem to work. Along with the solid science he quotes of course.

OncANP tried something new this year, a concept introduced initially at the Lamson at the NOC conferences. These are small, invitation-only conferences that Davis Lamson has held at random intervals at the Tahoma Clinic in Washington. Because seating is so limited, they have been invitation only. Any attendees who wants is invited to present; the catch is that they only get ten minutes to do so. OncANP tried copying this idea calling the short presentations "lightening talks." After a day and a half of sitting through full length PowerPoint lectures, even ten minutes seemed like too much time. But at least I stayed to listen.

Michael Traub went first and in his lightening talk broke the news about high-dose biotin being a problem. The FDA announced recently that biotin may throw off the results of many common laboratory tests. If your patients were taking biotin to get their hair to grow back or make their fingernails stronger, when their blood was drawn, you should not believe their lab test results. Make them take a couple of days break from the biotin and then retest.[4]

Dugald Seely reported on the results of his clinical trial on melatonin in lung cancer patients that his team in Ottawa conducted over recent years. The paper hasn't been accepted for publication yet so I can't reveal the results here. I can tell you that years back I assumed that melatonin would have no great effect on lung cancer based on Itai Kloog's 2008 light at night paper. Remember that Kloog used nighttime satellite photos to estimate the light at night (LAN) exposures different communities in Israel. Kloog found a strong positive association between LAN

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intensity and breast cancer rates, a 73% higher breast cancer incidence in the brightest lit communities compared to the lowest. Yet in their data, "…no association was found between LAN intensity and lung cancer rate."[5] If light at night doesn't impact lung cancer, it seemed logical that melatonin wouldn't either.

Paul Saunders, PhD, ND, and Davis Lamson, ND

I amended my initial belief that melatonin was useless for lung cancer back when Dugald first initiated this clinical trial. He is way smarter than me and if he thought melatonin worth trying, then he had a good reason.[6] You'll just have to wait until the study is published to find out what the current best evidence suggests we do. Maybe I'll get to gloat and say I told you so or maybe not.

Speaking of Dugald Seely (he's current president of OncANP by the way), his older sister Jean Seely, MD, a radiologist and specialist in mammography, spoke at the conference presenting her arguments that using these imaging techniques improves outcomes. Getting to watch the older sister harass the younger brother was quite fun. It was something of a highlight for me. I've said it before, the best reason to attend conferences is not to sit in lecture halls all day long, it's to see and interact with people in person. This whole online world is a poor substitute for the real thing.

Sticking with Dugald for a moment longer, he wisely chose Heather Wright as the recipient of this year's President Award. I can't think of anyone else who has worked harder for the association in recent years. Dr. Seely has a challenge ahead of him as he takes over leadership from Dr. Wright as president of the association; she may have small feet, but she certainly has left large footprints to fill. (As I read this over, I realize that my metaphor must be wrong. Perhaps it is supposed to be about shoes. It can't be right to suggest someone has big feet? Yet suggesting someone has big shoes can't be much better.)

Well, perhaps I wrote too hastily; we should not forget the Professor, that is Lise Alschuler. Longest serving member of the OncANP board of directors, she continues to chair the OncANP speaker committee, not the easiest group of people to lead, and she does so with charm, tact, and never a trace of annoyance. If my original miscomprehending understanding of what 'wheelhouse' were to be actually true, I could write, "It is the Professor in the Wheelhouse, who should receive most of the credit for steering this conference and the association forward toward another successful year and safe harbor." But of course, wheelhouse is all about baseball and has nothing to do with ships at sea.

As is custom, the best was saved for last and Professor Alschuler and Dr. Kaczor once again finished the conference off for us with their annual lecture summarizing the year's relevant research pertaining to naturopathic oncology. The last study they mentioned, perhaps because of its proximity in time to my mad dash to the airport to catch a flight home, is the one that stuck in my mind the most. It was about tamoxifen dosing and whether lower doses might be as effective as the standard dose that oncologists always prescribe. Perhaps it wasn't just the anticipatory surge in cortisol that thinking about my past experience getting through TSA lines had engendered, but the fact that I have searched unsuccessfully for an answer to this particular question in the past for specific patients that made my memory so retentive.

The last topic was the DeCensi et al paper published in July 2019 in the *Journal of Clinical Oncology*. It is well accepted by the powers that be that 20 mg/day of tamoxifen taken for five years is effective at "decreasing breast cancer proliferation." These authors suspected "… that a lower dose given for a shorter period could be as effective…." And that's what they tried; just 5 mg per day for only three years. This was a decent sized study; five hundred women with a median follow up of over five years. Low dose tamoxifen cut progression risk by more than half (hazard ratio, 0.48; 95% CI, 0.26 to 0.92; P = .02), and risk of contralateral occurrence by 75% (hazard ratio, 0.25; 95% CI, 0.07 to 0.88; P = .02). We should note that this isn't much different than the benefit we expect from full 20 mg dosing, for example, in Allred et al in 2012, the HR was 0.58 (95% CI, 0.42 to 0.81).[7] In fact, these numbers suggest that low-dose tamoxifen was more effective, doesn't it, reducing risk by 52% instead of only 42%; but of course, these numbers are not significantly different, are they? So please don't pretend that low is better than standard dosing. By the way, the women who took the low-dose tamoxifen did not complain significantly more of side effects than those taking placebo. This gives us something to think about next time a patient is reluctant to take tamoxifen; a quarter of the regular 20 mg dose still works, without causing pronounced side effects.[8]

Learning this one thing made the entire conference worth my cost and effort of attending. The 2021 OncANP conference will be June 11-13th in Toronto, Canada.

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High-Dose Intravenous Vitamin C Treatment for COVID-19

by Adnan Erol, MD

Orthomolecular Medicine News Service

The evidence about COVID-19 pneumonia and well-established knowledge about related conditions suggests it is caused by the hyperactivation of immune effector cells. High-dose vitamin C may suppress these immune system effectors. As intravenous high-dose vitamin C treatment is known to be safe, this suggests that intravenous high-dose vitamin C may be the treatment of choice in the early stages of COVID-19.

Coronaviruses (CoVs) are large, enveloped, and positive sense RNA viruses that infect a broad range of vertebrates and cause disease of medical and veterinary significance. Human respiratory coronaviruses have been known since the 1960s to circulate worldwide and to cause respiratory infection with rather mild symptoms, suggesting that they are well-adapted to the human host. However, zoonotic coronaviruses, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), can cause severe respiratory tract infection with high mortality.[1]

Pulmonary Pathology During Severe Coronavirus Infection

The primary cell types found in the lower respiratory tract are alveolar epithelial cells and alveolar macrophages (AMs). AMs are susceptible to infections but can also release a significant quantity of infectious virus particles. Pathological examinations of samples obtained from patients who died of SARS revealed diffuse alveolar damage, accompanied by prominent hyperplasia of pulmonary epithelial cells and presentation of activated alveolar and interstitial macrophages. Strikingly, these pulmonary manifestations were usually found after clearance of viremia (viruses in the blood) and in the absence of other opportunistic infections. Therefore, alveolar damage from local inflammatory responses may be due to an excessive host immune response.[2]

In a murine model of SARS infection, fast and robust virus replication was accompanied by a delayed type I IFN (interferon) response. Accordingly, type I IFN expression was barely detectable in most cell types. Plasmacytoid dendritic cells are a notable exception. They utilize TLR7 (toll-like receptor-7) to sense viral nucleic acids and can induce robust expression of type I IFN following coronavirus infection. The extremely rapid replication of SARS-CoV together with the delayed onset of a type I IFN response caused extensive lung inflammation. This was accompanied by influx of inflammatory monocyte-macrophages, which are attracted by inflammatory signals. Furthermore, macrophages additionally produced high levels of inflammatory signals through stimulation of a type I IFN response, resulting in further macrophage influx in a pathological feedback loop. Altogether, massive accumulation of pathogenic inflammatory macrophages increased the severity of SARS. Moreover, type I IFN-induced immune dysregulation enforced apoptosis of T cells, which would normally promote virus clearance, resulting in reduced numbers of virus-specific CD8 and CD4 T cells.[1,3]

Activation of Effector Immune Cells

The rapid kinetics of SARS-CoV replication and the relative delay in type I IFN signaling may promote inflammatory M1 macrophage accumulation, suggesting that targeted antagonism of this pathway would improve outcomes in patients with severe coronavirus infections.[2] Notably, the 2019 novel coronavirus infection (COVID-19) behaves much like SARS-CoV; the virus responsible for COVID-19 has been named SARS-CoV-2. Typically, pneumonia from COVID-19 progresses rapidly with acute respiratory distress syndrome (ARDS) and septic shock, which are eventually followed by multiple organ failure due to a virus-induced cytokine storm in the body.[4]

In response to infection, macrophages must react rapidly with a substantial pro-inflammatory burst to kill microorganisms and to recruit additional immune cells to the infection site. The inflammatory phenotype in macrophages is normally closely associated with a sharp increase in the rate of glycolysis. This causes activated macrophages and effector T lymphocytes to shift to a high glucose uptake, even under oxygen-rich conditions, which is known as the "Warburg effect," similar to cancer cells. The Warburg effect is associated

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with diverse cellular processes, such as angiogenesis, hypoxia, polarization of macrophages, and activation of T cells. This phenomenon is intimately linked to several disorders, including sepsis, autoimmune diseases and cancer.[5]

High-dose vitamin C treatment acts as a prooxidant for immune cells, but as an antioxidant for lung epithelial cells.

Another interesting aspect of glycolysis induction in activated immune cells is the role of the glycolytic enzyme, glyceraldehyde-3-phosphate dehydrogenase (GAPDH). It has been shown that GAPDH binds to the mRNA coding for IFNγ, repressing its translation into protein. However, upon glycolysis activation, GAPDH dissociates from IFNγ mRNA, allowing to its translation into protein.[6] In addition, due to the glycolytic pathway stimulation in activated immune cells, their TCA (citric acid cycle) becomes disrupted. Therefore, an accumulation occurs for several metabolites, including succinate, which, in turn, may increase hypoxia-inducible factor-dependent activation of target genes, such as IL-1ß and the glucose transporter GLUT1.[7] GLUT1 is required for the metabolic reprogramming, activation, and expansion of effector lymphocytes and M1 macrophages.[7,8]

Interaction Between Macrophages and Alveolar Epithelial Type II (ATII) Cells

Type I IFNs (type I interferons) produced by almost all cell types play a vital role in host defense against viral infection and cancer immunosurveillance. In response to viral products, pattern recognition receptors, such as retinoic-acid-inducible gene I (RIG-I)-like receptors (RLRs), send a signal to trigger type I IFN production in alveolar epithelial cells. Upon sensing cytosolic viral RNAs, these RLRs undergo conformational changes and oligomerization to recruit a signaling adaptor called mitochondrial antiviral-signaling (MAVS) protein. Once activated, MAVS causes phosphorylation of IRF3, and subsequent transcription and expression of type I IFNs.[9]

Activated macrophages produce large amounts of lactate, which they readily export with carboxylate transporters.[5] Alveolar epithelial cells import the lactate, and use it as a substrate for mitochondrial oxidative energy (ATP) production.[10] In ATII cells, lactate inhibits the localization of MAVS into mitochondria, the RLR-MAVS association, and MAVS aggregation and downstream signaling activation. Lactate does this by binding to the TM domain of MAVS. Thus, macrophage-released lactate may attenuate host innate immune response by decreasing type I IFN production for viral clearance.[9]

Proposed Mechanism of Action of High-Dose Vitamin C in Immune Effector Cells

Vitamin C is an essential antioxidant and enzymatic co-factor for physiological reactions, such as hormone production, collagen synthesis, and immune potentiation. Humans are unable to synthesize vitamin C; therefore, they must acquire vitamin C from dietary sources.[11] Vitamin C is transported across cellular membranes by the sodium vitamin C co-transporter (SVCT). In addition, vitamin C spontaneously oxidizes both intracellularly and extracellularly to its biologically inactive form, dehydroascorbate (DHA).[11,12] DHA is unstable at physiological pH; and, unless it is reduced back to vitamin C by glutathione (GSH), it may irreversibly be hydrolyzed. Therefore, DHA is reduced to vitamin C after import at the expense of GSH, thioredoxin, and NADPH (reduced nicotinamide adenine dinucleotide phosphate). Consequently, production of reactive oxygen species (ROS) increases inside some activated immune cells (similar to cancer cells) due to the exhaustion of ROS scavenging systems involving redox couples, such as NADPH/NADP+ and GSH/GSSG (glutathione disulfide). Therefore, high-dose vitamin C may function as a pro-oxidant in a cell type-dependent manner.[12]

Sepsis is characterized by systemic inflammation, increased oxidative stress, insulin resistance, and peripheral hypoxia. Remarkably, severe sepsis resulted in about a 43-fold increase in GAPDH expression.[13] GAPDH is a redox-sensitive enzyme that can become rate-limiting when glycolysis is upregulated due to the Warburg effect, as it is in both cancer cells[12] and activated immune cells. In addition to oxidizing and inhibiting GAPDH, the elevated ROS may also lead to the DNA damage and the activation of poly(ADP-ribose) polymerase (PARP). PARP activation leads to the consumption of NAD+ (nicotinamide adenine dinucleotide) following vitamin C treatment. Significantly, NAD+ is required for the enzymatic activity of GAPDH as a co-factor; therefore, the decrease in NAD+ further diminishes GAPDH enzymatic activity.

Altogether, high-dose vitamin C-induced inhibition of GAPDH decreases the generation of ATP and pyruvate that would otherwise induce an energetic crisis, ultimately leading to cell death.[11,12] In other words, inhibition of GAPDH by vitamin C may in turn inhibit immune effector cells and their related immunosuppression. These results provide a mechanistic rationale for exploring the therapeutic use of vitamin C to prevent inflammatory hyperactivation in myeloid and lymphoid cells.

Intravenous High-Dose Vitamin C Treatment for 2019-nCoV Disease

The results of meta-analyses have been demonstrated that intravenous (IV) high-dose vitamin C treatment has significant benefits in the treatment of sepsis and septic shock.[14,15] Sepsis

is a life-threatening organ dysfunction syndrome triggered by a systemic inflammatory reaction to pathogenetic microorganisms and their products. ARDS, devastating and often lethal condition, is also common among patients with systemic inflammatory response, such as sepsis.[16]

Rolipram, a typical phospho-diesterase-4 inhibitor, can inhibit TNFα production in activated macrophages and restrain acute inflammatory response. Rolipram was suggested as a novel drug treatment for sepsis and septic shock due to its potent immunosuppressive effects.[17] By analogy, the beneficial effects of intravenous high-dose vitamin C in sepsis and septic shock may also be due to its immunosuppressive effects.

While immune effector cells are dependent on glycolysis for their bioenergetic functions, lung epithelial cells use mitochondrial oxidative phosphorylation to produce ATP. Therefore, high-dose vitamin C treatment acts as a prooxidant for immune cells, but as an antioxidant for lung epithelial cells. Furthermore, vitamin C treatment may protect innate immunity of ATII through the inhibition of the lactate secretion, produced by the activated immune cells.

In connection with the prooxidant role of vitamin C, which requires pharmacological (millimolar) rather than physiological (micromolar) concentrations, reevaluating the high-dose infusion of vitamin C would be a timely choice for the COVID-19-related ARDS. Altogether, patients diagnosed with COVID-19 and hospitalized with the breathing difficulty and abnormal biomarkers would seem to be excellent candidates for a short period of high-dose intravenous vitamin C treatment in the early period of the disease. However, a concern that may arise with high-dose vitamin C treatment is osmotic cell death of immune cells, (but not apoptosis) which might generate a local inflammation in alveolar medium. Therefore, IV glucocorticoid treatment should be added to attenuate the possible inflammatory complications of high-dose vitamin C treatment. A previously experienced and comparably well-tolerated treatment regimen for high-dose intravenous vitamin C could be the administration of 50 mg/ per kilogram body weight every six hours for four days[16] with a glucose restriction. In addition, hydrocortisone 50 mg IV every six hours for seven days should be added to fight against therapy-induced inflammation. Vitamin C when used as a parenteral agent in high doses may act pleiotropically as a prooxidant to attenuate pro-inflammatory mediator expression, improving alveolar fluid clearance, and to act as an antioxidant to improve epithelial cell functions.

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Unexpected Early Response in Oral Bioavailability of Ascorbic Acid

by Owen Fonorow©

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Introduction

Repeatable and inexpensive experiments have cast doubt on the hypothesis that only 200 mg of vitamin C taken orally can be absorbed. We measured vitamin C blood plasma levels every minute for the first 40 minutes using a novel approach. By contrast to the prevailing paradigm, our results suggest that up to 4,000 mg of ascorbic acid taken by mouth can produce the same rapid increase in plasma concentration as an intravenous infusion. Previous studies did not sample blood levels during this early stage of oral intake. We confirmed that specific glucose meters do provide a reproducible measure of ascorbate (vitamin C) concentration. Researchers had previously demonstrated the ability of specific glucose meters to measure high levels of ascorbate during and after intravenous vitamin C infusions (IV/C).[1] Our initial aim was to confirm the adequacy of the method. However, we observed that the meters are responsive to lower oral intakes and discovered an initial high rate of oral absorption, which may add to understanding of the pharmacokinetics of ascorbate and have clinical and nutritional implications.

Up to 4,000 mg of ascorbic acid taken by mouth can produce the same rapid increase in plasma concentration as an intravenous infusion.

Methods

In 2012, we observed that the Abbott Laboratories FreeStyle® Lite glucose meter was responding quantitatively to vitamin C in blood plasma. This is consistent with the similarity of glucose and ascorbate molecules. Biologically, this similarity leads to the cellular uptake of dehydroascorbate by glucose transporters (GLUT).[2-4] Hence, the sensitivity to ascorbate in glucose meters is expected. The potential "error" due to high vitamin C is mentioned in the glucose meter product's user manuals. Initially, the quantitative response was based on direct observations and reports from members of the Vitamin C Foundation.[5] The observations suggested that there is a practical and inexpensive way of estimating *in vivo* vitamin C levels

Data was obtained using three Abbott FreeStyle® Lite glucose meters that were purchased locally between 2013 and 2015. Each Abbott device was checked to confirm that it responded linearly and proportionately to ascorbate concentrations in test solutions comparable with the concentrations expected while the subject was undergoing intravenous infusions of vitamin C. The data estimation was the result of three different meter readings alternated so that glucose meter A measured minute 1, and minute 4, etc. The mg/dl are the units that USA glucose meters report. These numbers are not correct ascorbate concentrations but are used to show relative changes in blood ascorbate.

Plasma glucose levels were expected to be approximately constant over the period of data collection. The subject in these experiments was a 61-year-old male, insulin-dependent diabetic. These experiments were run on the same individual at the same time, early in the morning after fasting during sleep for at least 8 hours. The lack of endogenous insulin production in this individual minimized any physiological insulin-related response in the control of glucose or ascorbate levels.

In our first experiment, we measured relative ascorbate levels during an intravenous vitamin C infusion directly into the bloodstream. As is required for vitamin C intravenous infusions, the vitamin was administered as sodium ascorbate. Because the vitamin C is the ascorbate ion, we accounted for the sodium by adjusting the sodium ascorbate dosage to 11.3 grams. This adjustment ensured that 10 grams of vitamin C was endogenously introduced to the subject, allowing comparison between all experiments. Figure 1 plots the baseline data from all three meters during the sodium ascorbate IV/C infusion.

Experiment 2 measured the relative ascorbate levels while oral vitamin C (as ascorbic acid) was introduced at the same rate (250 mg/minute) as the sodium ascorbate intravenous infusion. Plasma levels were again measured minute-by-

minute, alternating the meters over the same duration as the short IV/C. Figure 2 compares the plasma response of the slow introduction of oral vitamin C as ascorbic acid with the data from the first experiment, sodium ascorbate IV infusion. The data from all three meters are averaged in the second plot. The baseline IV/C sodium ascorbate data are averaged.

Experiment 3 measured the relative ascorbate concentrations after a single, large 10-gram oral dose of ascorbic acid. The 10 grams is the equivalent vitamin C to the amount given by intravenous infusion in the first experiment. Measurements were minute-by-minute over the same 40-minute period as the baseline IV/C. Figure 3 compares the plasma response of the single oral dosage of vitamin C as ascorbic acid with the data from the first experiment, sodium ascorbate IV/C infusion. The data from all three meters is plotted to show the rapid changes in blood levels from the ascorbic acid gulp. The IV/C baseline data are averaged.

Experiment 4 measured the relative ascorbate concentrations after a single, large, 11.3-gram oral dose of sodium ascorbate. This dosage provided the equivalent 10 grams of vitamin C. Measurements were minute-by-minute, alternating meters, over the same 40-minute period as the baseline IV/C. Figure 4 compares the plasma response of a large dose of oral sodium ascorbate with the equivalent large oral dose of ascorbic acid. The data from all three meters are averaged.

The amount of vitamin C administered in all the experiments was the same (10 grams of ascorbate.)

Experiment 5 measured a 10-gram single oral dose of glucose for comparison against the oral ascorbic acid gulp.

Results

Experiment 1: 10 gram IV/C Infusion (11.3 gram sodium ascorbate)

The first experiment measured "glucose" levels during an intravenous vitamin C infusion, where no glucose was present.

The chart in Figure 1 shows the steady rising blood levels, until the IV/C bag emptied and the relative blood levels then began to decline. Three Abbott meters were used to minimize a random measurement error in one meter.

We performed a regression analysis using Microsoft Excel 2007 Data Analysis package on the meters, which provided significant support for the good agreement on visual inspection of the measurements. The multiple R value for meters A-IV and B-IV was 0.82 (F=30.69; P=5.66x10-5). With A-IV and C-IV the R was 0.72 (F=14.89; p=1.74x10-3). For B-IV and C-IV the R was 0.91 (F=66.58; p=1.09x10-6).

The consistency among these measurements suggest that these meters measured vitamin C blood levels. However, these measurements are mg/dl in terms of glucose and are not accurate vitamin C concentrations.

The IV bag emptied at minute 34, and the line drained and the needle was removed at minute 40. The increase in concentration from the IV is also consistent with our *in vitro* measurements. The decline at the end of the IV illustrates the short 30-minute half-life of the vitamin. To a first approximation, we take the fasting subject's glucose levels to be constant over this period.

Experiment 2: Oral Ascorbic Acid at the Same Rate as IV

The second experiment introduced vitamin C orally at the same rate (250 mg/minute) as the intravenous infusion in Experiment 1. There was little difference in vitamin C blood levels between oral ascorbic acid and intravenous sodium ascorbate for the first 15-16 minutes (4,000 mg). After this period, concentrations from oral intake dropped off. This experiment shows that 4 grams of oral vitamin C as ascorbic acid enters the blood stream as well as vitamin C introduced directly by vein. Indeed, the initial oral measurements appear slightly greater than were obtained with the IV/C suggesting an efficient absorption through the stomach wall.

The subject was administered vitamin C at the same rate as the infusion, i.e., 250 mg of ascorbic acid by mouth every minute for 40 minutes. ➤

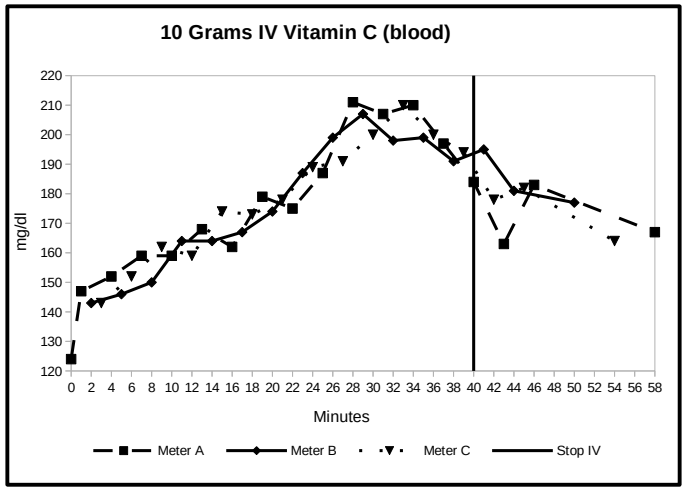

Figure 1. Measurements at one-minute intervals during a 10-gram intravenous infusion of vitamin C.

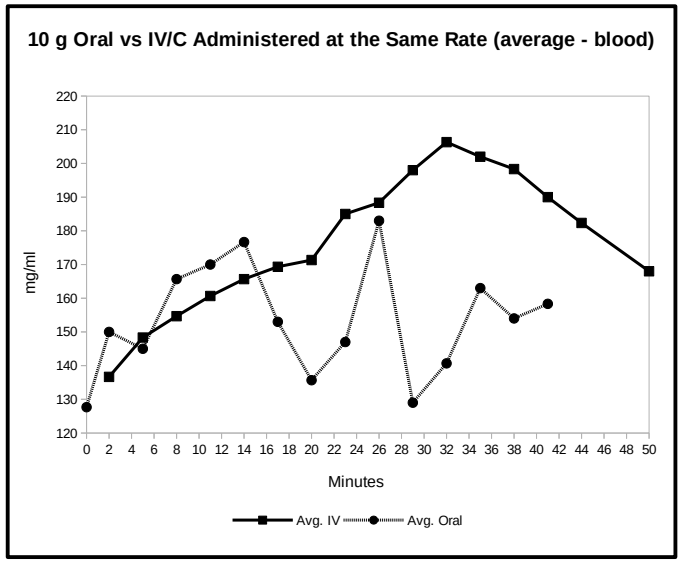

Figure 2 compares the response from oral ascorbic acid when given to match the rate of the intravenous infusion.

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The results of the experiment show comparable blood levels between oral IV/C for the first fifteen minutes. After this period, the oral blood levels declined, relative to the IV/C. The decline in the rate of absorption may reflect the increase in stomach pH as ascorbic acid buffered the stomach contents (HCl).

Experiment 3: Single 10-gram Oral Dose of Ascorbic Acid Compared to IV

The third experiment measured vitamin C after a single large (10 gram) dose of ascorbic acid taken by mouth. The data showed that the blood levels spiked as early as minute 3 to levels higher than the intravenous infusion achieved over 40 minutes. The spiking blood level event was over by minute 12. Anecdotally these totally unexpected results suggest that oral ascorbic acid can produce transient high blood levels of vitamin C. These transient high levels would be missed by any experiment with a longer measurement period. Rapid minute-by-minute measurements are required to observe these high values.

In Figure 3, we measured the blood concentrations after a single oral dose of 10 grams of ascorbic acid.

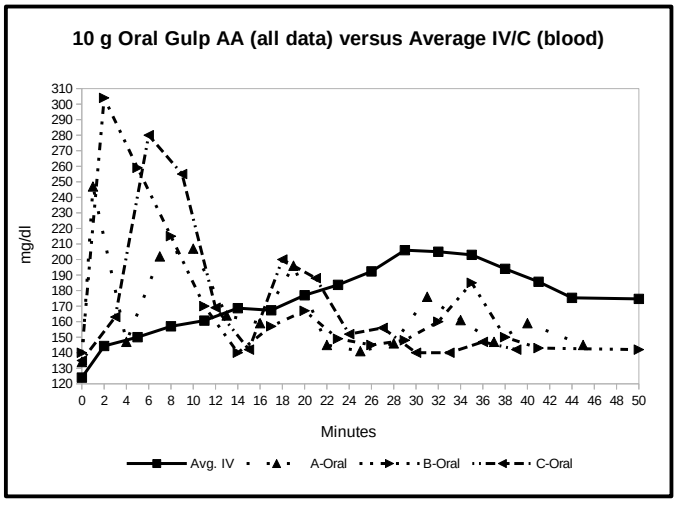

Figure 3. Time series following a single oral dose versus IV – mg/dl versus time in minutes. All three meters are plotted.

Unexpectedly, blood levels of ascorbic acid spiked early and profoundly. The maximum levels appeared as early as minute 3 and varied slightly from minute 3 to minute 7. The initial peak had declined back towards baseline IV/C by the 15th minute. This initial high level was consistent with the results in Experiment 2 in suggesting a rapid initial absorption of oral ascorbic acid.

We investigated whether the quick entry into the blood stream was via the mucous membranes in the mouth or the stomach. We did not find any significant blood "glucose" elevation holding the 10-gram vitamin C solution in the mouth for a long period.

Our original finding is that during the first 12 minutes after a single large dose of ascorbic acid, blood concentrations of vitamin C were substantially higher than the levels produced by the intravenous infusion. The entry into the blood during the first few minutes is most likely from the vitamin's passage through the stomach lining.

Experiment 4: Single 11.3-gram Oral Dose of Sodium Ascorbate

The fourth experiment measured vitamin C after a single large (11.3 gram) dose of sodium ascorbate taken by mouth. In Figure 4, we compare the blood concentrations after a single oral dose of 10 grams of vitamin C as sodium ascorbate with the single 10 gram dose of ascorbic acid data from experiment 3.

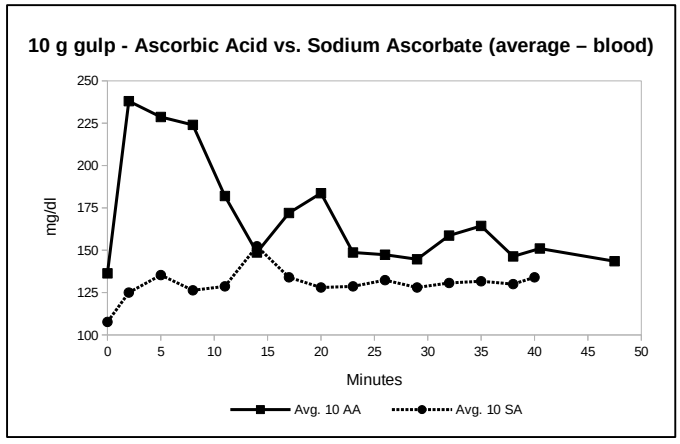

Figure 4. Time series following a single oral dose of 11.3 grams sodium ascorbate compared with 10 grams ascorbic acid. Date from all three meters are averaged.

Figure 4 illustrates the difference in relative vitamin C blood levels depending on whether the vitamin is taken as ascorbic acid, or sodium ascorbate. The data showed a sodium ascorbate produces a slower rise in vitamin C blood levels. No high-level transient spikes were measured.

This experiment with oral sodium ascorbate suggests that the form of the vitamin C may determine the rate at which vitamin C enters the blood stream. The blood concentration pattern after oral sodium ascorbate is markedly different from the oral ascorbic acid. Sodium ascorbate concentrations were lower, perhaps because sodium ascorbate requires more time for absorption into the bloodstream as the vitamin travels past the stomach to the intestines.

Our calibration measurements hinted that the glucose meters may report the same sodium ascorbate and ascorbic acid concentrations differently. (These calibrations were in water, not blood, making the glucose meter readings difficult and prone to error.) Even if the blood levels are not directly comparable, the pattern of entry into the blood is markedly different between the two forms of vitamin C. The mildly acidic ascorbic acid has a rapid entry effect in the blood, while

the rate of entry of the alkaline sodium ascorbate is slower and more like timed release.

Experiment 5: Single 10-gram Oral Dose of Glucose

There was concern that somehow we were measuring glucose. As a control, in Figure 5, we measured the blood concentrations after a single oral dose of 10 grams of glucose. The fifth experiment repeated the method after a single large (10 gram) dose of glucose taken by mouth.

Figure 5 compares the oral ascorbic acid data from experiment 3 with the glucose experiment.

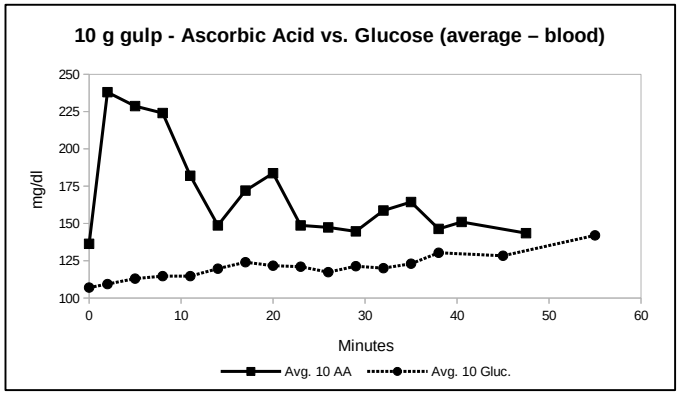

Figure 5. Time series following a single oral dose of 10.0 grams glucose compared with 10.0 grams of ascorbic acid – mg/dl versus time in minutes. The average of all three meters are plotted.

In Figure 5, the blood levels of glucose were compared with vitamin C as ascorbic acid. The measurement values are presumably accurate for glucose. While the actual vitamin C concentration is unknown, the pattern entering the blood stream is different.

Discussion

The vitamin C absorption into the bloodstream findings reported here are generally practical because some glucose meters are sensitive to and can be used to report ascorbate levels in the blood.[1] This sensitivity appears to give a linear quantitative response and reproducible measurements. While plasma glucose is greater than ascorbate levels, in a fasting individual glucose levels are expected to be approximately constant over the periods considered. Insulin may affect the experiments as the vitamin C (or glucose) is made available to enter cells. In this diabetic subject, we had the opportunity to monitor blood levels without this confounding factor. We had previously determined that the meter's response to ascorbate was greater than to glucose, presumably related to a redox aspect of the measurement. These minute-by-minute measurements are new to the literature, partially because of the practical difficulty in collecting and then storing blood for so many measurements, but perhaps reflecting the unexpected nature of the rapid oral response.

Not every brand or model of glucose meter is as sensitive to ascorbate, and the details of the mechanisms are commercially sensitive. We tested several meters that did not provide a robust measure of ascorbate concentration. It is possible that the FDA may consider a glucose meter that reacts to vitamin C flawed. For this reason, manufacturers may be forced to upgrade their meters, rendering future versions of the Abbott and other meters unusable for vitamin C measurements. Ideally, a low-cost finger-prick ascorbate (vitamin C) meter will be made available that makes accurate measurements. A new company in New Zealand recently announced that they are developing such a meter.

We calibrated the Abbott FreeStyle® Lite glucose meters against accurately measured solutions of ascorbic acid equivalent to concentrations in the blood over the range .5 to 1.5 mg/dl.[2] The meter provided a linearly proportional response to the ascorbate concentrations measured. Here we are concerned with rapid changes in blood plasma relative to baseline. These experiments compared relative blood concentrations between oral and intravenous, and different forms of vitamin C.

In this preliminary report, we show that during a slow intravenous infusion of 10 grams of vitamin C, three separate meters report a steady increase in measured ascorbate, consistent with the increased concentration of vitamin C in the blood. At the end of the infusion all three meters showed the decrease in blood levels consistent with ascorbate's 30-minute half-life and the *Dynamic Flow* theory of ascorbate.[6,7]

Our IV/C infusion data from vitamin C introduced directly by vein into the bloodstream (experiment 1) provided an approximation to a 100% bioavailability. Experiment 2 compared oral and intravenous vitamin C introduced at the same rate. We expected that less vitamin C would enter the bloodstream from oral absorption.

The minute-by-minute readings comparing the IV infusion for the first 15 minutes (4000 mg) is unprecedented and leads to the reasonable conclusion that a similar amount of vitamin C entered the bloodstream. Some prior research had reported that only about 250 mg can be absorbed before tissue saturation.[8,9] However, measuring vitamin C in the urine or waiting too long to begin blood measurements would have missed the rapid absorption.

In the third experiment, a single dose of 10 grams of vitamin C as ascorbic acid was consumed all at once. Minute-by-minute measurements were compared to the slow intravenous infusion. The surprising finding is that in the first few minutes, the rapid oral absorption of 10 grams of ascorbic acid created higher blood levels than the low dose IV/C.

The measurements for ascorbic acid were unexpected. The blood concentrations between the baseline and oral ascorbic acid at the same rate were comparable and showed equivalent bioavailability to 4000 mg. The bioavailability of a large one-time dosage produced blood levels higher than the intravenous infusion of the same amount. ➤

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In the fourth experiment, a single dose of 11.3 grams of vitamin C as sodium ascorbate was consumed all at one time. These measurements were compared to oral ascorbic acid. Another (unanticipated) finding was the unexpected difference between the rates of absorption of the different forms of vitamin C.

While the ascorbic acid response was unexpected, it is consistent with known pharmacokinetics of weak acids. A weak acid like ascorbic acid is in the associated relatively non-polar state in the low pH of the stomach becoming more lipid soluble. Weak acids often absorb rapidly from the stomach. However, if the stomach acid is decreased the weak acid disassociates and the polarity inhibits transfer across cell membranes. The ascorbic acid would buffer the stomach pH (from pH ~1 to pH ~4) and inhibit its own absorption. Sodium ascorbate would be a more effective buffering agent, and this would explain why the initial absorption spike was not observed.

One objection to these case study data is individual variation in this preliminary study. This reservation is accepted and is common to case studies, which nevertheless can convey interesting observational data. The measurement is direct, using a technique established elsewhere.[1] Moreover, it would appear that some individuals' large intakes of vitamin C might be rapidly absorbed initially from the oral route. It remains to be established how frequent this phenomenon is in the population. Moreover, if replicated the observations may provide an alternative to IV administration of ascorbate now being clinically trialed in cancer.[10-21] If the process we observed is one of rapid weak acid absorption from the stomach, it may be possible to maintain stomach acidity and promote rapid oral absorption of large doses of vitamin C, at least in some individuals. Consistent with this interpretation we have observed that while ascorbic acid can be rapidly absorbed into the bloodstream, sodium ascorbate raises blood levels more slowly.

Vitamin C blood levels must be measured repeatedly within 30 to 40 minutes to obtain an accurate reading of how much vitamin C enters the bloodstream. Cathcart described how people who are sick and under stress can tolerate very high oral intakes of vitamin C.[22] The Cathcart bowel tolerance amounts, sometimes as high as 200 grams daily, are difficult to reconcile with the current paradigm if blood plasma saturates at 250 mg. Cathcart also reported that he could only obtain "a clinical ascorbate effect" orally with ascorbic acid, not mineral ascorbates. We might speculate that an increased stomach acidity in the sick can at least in part explain Cathcart's observations.

The rapid early absorption and utilization of ascorbic acid presented here, previously unknown, may help explain what Cathcart reported.

Owen Fonorow graduated from the United States Air Force Academy in 1976. In 1996, after his career as a member of the technical staff at AT&T Bell Laboratories, Owen founded the nonprofit Vitamin C Foundation, along with his brother Michael S. Till, Sr. Owen has since written more than thirty articles, and these papers have been published in assorted alternative medical journals including the *Townsend Letter, Nexus, Life Extension Foundation Magazine, American Naturopathic Medical Association's Monitor, Florida ECO Report*, the *International Council for Health Freedom newsletter*, and *Media By-Pass.* Many of the themes in these articles have been incorporated in his book, *Vitamin C Cures* (Formerly *Practicing Medicine Without A License? The Story of the Linus Pauling Therapy for Heart Disease*).

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Coronavirus Update and Integrative Natural Answers

by Dr. Devaki Lindsey Berkson

This article has been abridged from the original. Full article and references available at townsendletter.com.

We are in a WHO-proclaimed *pandemic*. Pandemic does not mean everyone will get devastatingly ill. Most will recover within about two weeks. But some are getting very ill. Some are dying. The CDC guesstimate is that between 160 million and 214 million people in the US "could," in a worst-case scenario, be infected over the course of the epidemic, which could last many more months to possibly a year. No one is sure. Taking functional medicine action steps for protection makes sense.

Social distancing, which in China and other very pro-active countries means keeping approximately six-feet from others, is not being done here in the States. In fact, many young people are defiantly going out to packed bars and partying it up.

Kids are at less risk. In China, 2.1% of cases were children. Children can be exposed to the virus but not get ill, or they get an extremely mild case. Most recover in two weeks. But Los Angeles had a death of a child under 12 years of age from COVID-19, and two infants, one in China and one in Illinois have died from COVID-19.

In most children, COVID-19 rarely goes into the lungs. But kids and young adults can be carriers. The scientific thought as discussed by Dr. Birx is that part of the rapidity of growth is the ability to have no symptoms but still pass it forward.

If you are ill, stage 3 lung involvement can occur from days 9 to 13. The China study reminds us that SARS-CoV-2, can cause pneumonia in adult patients regardless of age.

Health Care Workers

Front line health care workers like ER doctors, *even younger ones*, are getting sicker from the coronavirus than the rest of the population, other than the elderly. Two doctors with COVID-19 are in critical condition at the time of writing this article. One is a Washington physician in his 40s and another is a 70-year-old in New Jersey.

Dr. Li Wenliang, the Wuhan Central Hospital physician who is hailed as a hero for trying to sound the alarm about this virus after diagnosing and treating seven quarantined patients in December, died within weeks of being exposed.

One theory is that front line medical personnel are exposed to higher doses of virus. Add exhaustion and possibly poor dietary choices, as these folks often work hard and eat fast. We don't know yet. But I hope they or someone that loves them reads this article and shares some of the suggestions. Too bad they don't have IV anti-viral nutrients available to try to help, as you will learn below.

Elderly

The elderly seem to be most at risk. If you are 65 or over, with underlying health issues, you're at increased risk. Over 70 years old, the risk starts increasing, and possibly triples (if not more than that) when people are in their 80s. The highest fatalities occur in the eighth decade.

As we age, so do our immune systems. And more so if there is an underlying illness. Or if the person does not regularly exercise, eat healthy food, get enough sleep, etc.

Science demonstrates that older immune systems have less natural "killer cell" activity, which protects against foreign invaders. Seniors have thinner mucous membranes, so immune cells have less healthy "fight" in them. Elders often are insufficient in basic nutrients that act as natural antivirals, such as vitamin A, vitamin D, and vitamin C. More on these later.

Those with underlying health conditions are also very susceptible. They too often have poor immune systems and inadequate killer cell function. People with chronic health conditions are especially at risk, especially if their illness involves the lungs, kidneys, heart, esophagus, or bladder issues. This is because the virus can rapidly attach to specific cells inside these tissues and then proliferate and render havoc.

I think if you are 60 years or older, stay out of all stores, even grocery stores. Stay home. Get curbside. Many towns have free delivery services for those over 60. Call and ask the grocery stores to give you their phone numbers. Be safe.

Underlying Mechanisms of Viral Attack: ACE2 Receptors

A major theory of how COVID-19 attacks and invades the body explains why certain people are at risk and perhaps gives us some other speculative (not yet tested) ideas of protection besides washing your hands with soap, not touching your face, or practicing social distancing, which in my book are not big enough guns for this battle. In February 2020, an article out of Greece,

published in *Current Medical Chemistry*, which explained how the coronavirus is able to invade the body. COVID-19 goes into the body by "binding" to a receptor called the *angiotensin-converting enzyme II,* or the ACE2 receptor.

ACE2 is expressed (lives) in a variety of tissues in your body. For example, it lives throughout the mucosal lining of your mouth (oral cavity). When someone with the virus sits in a seat and touches the metal arm frame, where you might then sit, you can touch the virus or inhale "viral sheddings" or virus droplets that can then gain entrance into your body by binding to the ACE2 receptors inside your mouth. And then into your respiratory tract.

The tissue with the next highest ACE2 receptors are your lungs. Extremely high levels of ACE2 expression occur throughout all lung cells. This is why one of the severe complications of COVID-19 is acute respiratory distress. In fact, the exact pattern of COVID-19 pneumonia matches the distribution of ACE2 in the lungs.

The COVID-19 gets into the lungs by binding to ACE2 receptors and this damages normal lung function and puts the infected person at risk of pneumonia, one of the most serious complications.

ACE2 receptors are robustly found throughout the entire cardiovascular system. In the heart. In your lungs. Your lungs have air sacs and they are encircled with ACE2 receptors. It's this fact that makes COVID-19 pneumonia different from pneumonia you get after a typical flu.

ACE2 is an enzyme with strong beneficial effects in the organs that produce it. The healthier and the more ACE2 receptors you have, the healthier these organs. Young humans have lots of healthy ACE2 receptors. As we age or get more unhealthy from obesity to type2 diabetes, we have less numbers and less healthy ACE2 receptors. We know that being hypertensive seems to be a risk factor for getting a more aggressive case of COVID-19. Knowing what kind of blood pressure medications they were on would be very helpful.

ACE2 receptors are high in healthy individuals. Kids have lots of ACE2 receptors. People with chronic health conditions such as obesity, cancer, type 1 or 2 diabetes, autoimmune diseases etc. have much fewer ACE2 receptors or more poorly functioning ones.

The healthier and higher number of ACE2 receptors you have, the more likely to be less adversely affected by COVID-19. Hmmmm. There is presently an NIH study looking at the possible use of the blood pressure medicine Losartan's possible protective action on COVID-19.

Once COVID-19 attached to ACE2 receptors, it damages them. COVID-19 virus inactivates or "exhausts" ACE2 receptors. So, part of our nutritional suggestions below aim to enhance the stability or resilience of ACE2 receptors – which, remember, are damaged by COVID-19.

How Do Dangerous Coronaviruses Bind into ACE2?

These viruses have spike (S) proteins. These S proteins are like cars that drive the virus into parking spaces (ACE2). They have high affinity, meaning they love ACE2 parking spaces. It's almost as if the car gets "pulled" in magnetically.

Interestingly, the HIV virus also used similar spike proteins to invade humans. Dangerous viruses have similar dangerous portals of damage!

When virus S proteins bind to ACE2, cells have natural proteolytic enzyme action (proteases-TMPRSS2) which could possibly block the virus's entry. Some people may have better enzymatic action at this level than others, so they don't get ill or get less ill.

The viral ability to park into ACE2 appears to be blocked by some blood pressure medications (such as ACE inhibitors and ARBs), which also improves lung function.

There is the possibility of looking for vaccines that block viral Spike proteins, or drugs that block ACE2 receptors, or delivering more ACE2.

Both mice and pediatric human reports show that giving more ACE2 in patients with severe respiratory distress have improved outcomes. So, more ACE2 might be good.

In 2008, Austrian scientists discussed a *possible* treatment for the severe acute respiratory syndrome caused by SARS-coronavirus (SARS-CoV), which spread rapidly from China throughout the world. It caused more than 800 deaths due to the development of acute respiratory distress syndrome.

What treatment did they recommend in this peer review article? ACE inhibitors. Also, Angiostensin II Receptor Blockers (ARBs). These are both common blood pressure medications. Keep in mind this is speculation but it's being actively looked at.

Select nutrients, foods, and drugs can mitigate the virus' entry into cells and its effects on the body.

These above authors wrote: "Interestingly, a novel homologue of angiotensin converting-enzyme (ACE), termed angiotensin converting enzyme 2 (ACE2) has been identified as a receptor for SARS-CoV."

ACE2 is a negative regulator of the many cells in the body, keeping the "peace" among tissues, so to speak. When the virus binds to ACE2 receptors, that physiologic peace is lost.

Using ACE2 knockout mice (mice genetically raised to have no ACE2 receptors), these mice had severe lung issues. The Austrians demonstrated that ACE2 protects lungs from respiratory distress. Severe viral infections, like SARS-CoV and most likely COVID-19, reduce ACE2 expression. This puts lungs and whatever other tissues are high in ACE2 vulnerable to catastrophic reaction to the viruses and severe illness.

ACE2 Protects Tissues

These Austrian researchers suggest that ACE inhibitor medications will be great new treatments against these nasty viruses. So much so they titled this peer review article: "Lessons From SARS: A New Potential Therapy for Acute Respiratory Distress Syndrome (ARDS) With Angiotensin Converting Enzyme 2 (ACE2)." I love it when scholarly titles tell you what's inside.

They injected the nasty SARS-CoV virus into mice. These mice developed severe lung failure. But if the mice were

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first given ACE inhibitors, lung damage from the virus stopped cold.

However, some experts wonder if ACE along with ARB blood pressure medications elevate the numbers of ACE2 receptors and worsen the disease. I don't agree with this. Some articles suggest that people with hypertension (who are thus on medication) are more at risk of COVID-19.

High blood pressure appears to be a striking underlying health condition in those with the virus who develop severe disease versus those who do not. However, this link has not panned out. Association has only been shown in animals and not in humans.

What we do know is the virus uses the renin-angiotensin system – for you geeks, ACE2 and type II transmembrane serine proteases. Thus, it makes sense to look at this link for protection and/or treatment.

The questions become, do blood pressure medications like ACE and ARBs upregulate more parking spots for viral attack or provide protection? In reading the literature it seems to me that these meds could be protective.

I have spoken at long length with my dear colleague Dr. Mark Houston and we have been madly sending peer review articles back and forth to each other (we teach together for CMEs for MDs and he has designed the world's oldest and best functional cardiology course). Dr. Houston wants me to be clear in this article that the use of these blood pressure medications has not been thoroughly tested in large human studies.

Both animal models and human studies have looked at human patients with viral pneumonia with continued ACE blood pressure medication use. It appears that these patients are not "as sick" as patients in which these meds have been discontinued.

We know that ACE binding sites are critical to coronavirus infection and lung injury. We know ACE2 is route of entry. But studies are a bit all over the place. Decreased ACE2 and normal ACE levels are seen in lungs of mice infected with SARS-CoV. In my opinion the research suggests that meds that address ACE2 appear protective.

I am on a very low dose of ACE inhibitor meds now as I am in a high-risk group even though I do not have hypertension. You need to discuss this with your doctor and especially if you have chronic lung illness and have high blood pressure.

Dr. Houston wrote to me, "This is all still theory. No proof in humans. But I think either (ACE or ARB) will work but, ARB may be better."

In the last two decades, two serious coronavirus infections manifested – severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). They had elevated death rates. They both could bind to the ACE2 receptors in the lungs.

Since part of COVID-19's damage occurs by damaging ACE2 receptors, nutrients, foods or drugs that stabilize and enhance ACE2 receptors make sense. We will share some possibilities below.

ACE2 Receptors and Smoke

ACE2 has also been identified in other areas of the body, including the esophagus, heart, kidney, and bladder. All these organs are at potential risk of COVID-19 infection because they have more ACE2 receptors than other tissues. But there is another confounding lung variable. Quite a bit of research has taken a look at another promoter of acute respiratory distress syndrome: smoke.

Smoke exposure to rats caused an increase in ACE2 lung receptors, lungs, when compared with controls not exposed to smoke. The more ACE2 receptors in any tissue, the more vulnerable it is to COVID-19. Smoke increases that vulnerability. Anyone exposed to excessive smoke, like smokers, or folks exposed to severe air pollution, have increased numbers of ACE2 receptors in their lungs. Thus, they have more terrain for the COVID-19 to "dig in" for invasion and attack.

Smokers will be more prone to having more ACE2 receptors in their lungs. You can be a primary smoker, if you smoke yourself, or a second-hand smoker, if you are environmentally exposed. In China, there is a huge dose of both.

A third of the world's smokers live there. There are over 350 million cigarette smokers there. So many Chinese (mostly men) smoke that their culture has been referred to as suffering from "a pulmonary health crisis." China also has increased levels of smoke pollution. Inhaling smoke in the air literally increases numbers of ACE2 receptors. The Chinese might have had such a huge outbreak because they have more primary smokers and secondarily are exposed to more smoke air pollution, so they are much more vulnerable to DD-19 than non-smokers in the US. In China, 60% of males smoke compared to 4% of females. COVID-19 has been reported to be more deadly in males from the information coming out of China. US smokers are 16% men and 12% of women.

Italy is also a country with lots of smokers. They had a slight decrease for a while, but there have been no changes in smoking rates since 2007. Approximately 21% of their population smoke, while 14% of US citizens smoke. This may partially account for Italy's mass epidemic of COVID-19.

This should be a great inspiration to give up smoking. Get your kids and young adults to stop smoking and/or vaping.

Additional Entry Players: Furins, Inflammasomes, and Viroporins

Once we can see the players that enable COVID-19, we can look to nutrients, foods and/or medications that block each one. So, let's first look at how this virus grows so fast? Another theory that dove tails into the ACE2 theory, are *furins*. Furins are enzymes that control traffic into cells. They are found throughout our bodies. Especially our lungs and other tissues prone to COVID-19 attack.

Viruses, first shown with the SARS coronavirus, contain what you learned above, "spike (S) proteins." What is very unique about the COVID-19 virus is that it also contains "furin-like" cleavage sites that lock the "S" protein into ACE2 receptors. Furins help "push' the virus deeper into cells. By the way, these furin-like sites were not found in the older SARS-like CoVs virus.

Furins are robustly found in lung tissue. Furins help push COVID-19 into lung cells. Furins may also help the virus

enter into cells without ACE2 receptors, but this remains to be seen. Once the COVID-19 virus enters the cell, enabled by furins, "inflammasomes" appear. Inflammasomes are part of our innate immune system. Most inflammasomes are part of what is called the NLR family. Inflammasomes are platforms of protein, referred to as scaffolding, that boost the release of more inflammatory molecules such as pro-inflammatory molecules called *cytokines* such as (IL)1β and IL18. Suddenly inflammatory storms start to erupt at cellular levels.

The SARS-CoV virus gains entry assisted by another player. The virus can boost viroporin production (proteins that allow all this nasty virulence to unfold), which then activates inflammasomes. The University of Michigan (my alma mater) Zhang's lab, has shown that the SARS-CoV-2 virus happens to do a great job of binding to furin enzymes that start the process and also binds to two viroporins that make the process very aggressive.

COVID-19's Potential Routes into Your Body

In summary, viral spike (S) proteins bind to ACE2 and/or furins, allowing the virus inside cells. The cells release *inflammasomes*, which release more inflammatory molecules and/or binds to viroporins. The whole process gets more aggressive and more virus gets inside more cells; tissues get inflamed and fiery; and you get ill. All this takes place in ACE2 receptors. But ACE2 receptors may not be the only way in. Thus, these serious coronaviruses have four players enhancing entry and damage:

1. ACE2 receptors
2. Furins
3. Inflammasomes
4. Viroporins

These nasty viruses have a lot of possible support to enter your cells and create havoc. The good news is that the major inflammasome found to cause extensive lung distress is the NLRP3 inflammasome. And there is a natural hormone that stops it: melatonin!

Let me paint the back-copy.

- There are no COVID-19 fatalities under the age of 9.
- If young kids get COVID-19, they often don't get very ill and the symptoms tend to stay away from the lungs.
- What's a huge difference between youth and adults? The day and night sleep hormone, melatonin. Kids have a lot more melatonin.
- The rise of melatonin starts in the third trimester of pregnancy and continues to be highest at ages one through five. Then melatonin blood levels start to slowly decline and become very low in the elderly. Low melatonin levels in adulthood cause many to suffer with insomnia. The most severe cases are in nursing homes where elders suffer with the "sun-downers" syndrome: they are awake at night and sleep during the day.

Enter the mighty multi-tasking hormone, melatonin.

Most people think of melatonin as a sleep hormone that keeps us in sync with light and dark. It is higher in the blood when it is dark, and we should sleep. And it is lower in the blood when it is light, and we should be awake. But there's more. Of all things, melatonin binds to NLRP3 inflammasomes and blocks their fiery actions.

Melatonin protects against the downstream negative results of NLRP3 inflammasomes. For example, NLRP3 inflammasomes damage the Golgi apparati that make mitochondria and hormone receptors. So, when melatonin stops the inflammatory actions of NLRP3, it protects mitochondria and hormones. Mitochondria are the energy organelles (factories) inside cells that give energy to cells to function optimally.

Melatonin is also one of the most powerful antioxidants in the body. It's a "clean" antioxidant, meaning it doesn't make more damaging molecules as it's metabolized, as most antioxidants do.

So, melatonin lowers production of proinflammatory cytokines. Melatonin inhibits NLRP3 inflammasomes. When it's given to experimental mice with severe heart issues (myocardial septic conditions), it transforms the life-threatening condition into a milder one while enhancing the survival of the mice. Melatonin supplementation counteracts severe inflammatory responses such as pro-inflammatory cytokines and NLRP3 inflammasomes. It seems reasonable that melatonin supplementation in "high sustained-release dosages" will prevent or reduce acute respiratory issues caused by COVID-19 by suppressing NLRP3 inflammasomes.

In an animal model of acute lung injury, melatonin markedly reduced lung damage. How? Melatonin inhibited NLRP3 inflammasomes. In rodent models of acute respiratory distress syndrome similar to what these dangerous coronaviruses can do, melatonin treatment (with added mitochondria) significantly slowed down the lung aspect of the disease.

I have been using high-dose melatonin in breast cancer survivors for years. It tamps down the nasty actions of estrogen and acts like a natural aromatase inhibitor. So much so, a number of drug companies tried to get it added to pharmaceutical aromatase medications. This has become a well-accepted functional oncologic protocol. So, we know one can take high doses of melatonin safely. I wrote about melatonin's amazing job descriptions in *Safe Hormones, Smart Women*. Now melatonin's usefulness shines again.

A study released on March 6, 2020, demonstrated that by increasing melatonin (with the use of a melatonin receptor promoter or agonist) the damaging effects of ventilator-induced lung injury could be prevented in rodent models! It's in mice, but it holds out hope for what melatonin can do in humans in these COVID-19 times.

What else blocks sepsis in mice by inhibiting NLRP3 activation: nitric oxide as well as vitamin C (ascorbic acid). Taking these supplements prophylactically or as adjunctive treatment makes sense. I'm on them myself.

Melatonin is an amazing hormone. Years ago, I was a hormone scholar at an environmental estrogen think tank at Tulane (The Center for Bioenvironmental Research) headed by the world-famous estrogen scientist John McLachan, PhD. I was lucky to attend brown-bag lunch lectures where I learned all about melatonin from Dr. David Blask, an MD,

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PhD. He is one heady scientist with a total focus on melatonin. Dr. Blask's life-long work uncovered melatonin's ability to suppress tumor uptake of glucose. Melatonin has many protective actions in the human body. Now here we add another critical one. Thank you, Mother Nature!

Keep in mind: If you suffer from an autoimmune disease, it may not be advisable to use melatonin, or other immune supporters such as mushrooms, iodine, elderberry and prebiotics or probiotics. These all stimulate innate immune function. If you become sick with symptoms of COVID-19, you should stop the use of immune boosters, some examples being medicinal mushroom extracts, elderberry and immune-enhancing pre- or probiotics.

Two Stages of COVID-19 and Nutrient Use

According to Dr. Leo Galland, an internist and immunologist practicing in NYC, this illness has two stages. Dr. Galland and I are colleagues; a number of decades ago we lectured together and collaborated on digestive formulations. (An interview with Dr. Galland is scheduled to be published early April 2020 on Dr. Berkson's Best Health Radio at www.drlindseyberkson.com, iTunes, Spotify, etc.)

The first stage is approximately the first five days when your "innate immune system" needs to react. Immune boosters such as you will learn below, vitamins A, C, and D, for example, are helpful. They boost your innate immune system's response so *immune boosting* actions makes sense. This is when you may or may not have a fever (only half of COVID-19 patients seem to get a fever), you get fatigue, muscle aches, and possibly GI symptoms.

The second stage is about a pro-inflammatory response, or cytokine storm. Your body is flooded with molecules that in a sense cause "fire" and thus, damage, to many tissues. Many immune boosters would "feed" this fire, so now you want tools that block fire. You want anti-inflammatories. You don't want high-dose immune boosters that can feed the fire.

It's all about "immune balance" – doing what is best at each phase of the illness.

Symptoms

Initially, COVID-19 mimics the flu – higher fever than is typical with the "usual" flu, headache, cough, fatigue, and less muscle aches than a typical flu with onset of lung congestion and/or cough. Some of the unique symptoms of this virus compared to most other viruses are shortness of breath and nausea, as the ACE2 receptors are rich in the lungs and esophagus, where the virus can bind. And reversible loss of taste and smell can occur. GI symptoms like diarrhea can occur. Outcomes for these patients may be worse.

COVID-19 can occur with NO symptoms. Remember, anyone can have this virus and not have the above symptoms because we are all unique, so our symptoms are unique. Also, this virus is alive and has "consciousness," so it is evolving and mutating and the newer forms may have different presenting symptoms.

- First five to seven days of milder symptoms of which 80% of people will get well within two to three weeks.
- Second stage – about 20% of people will go on to develop pneumonia and a quarter of these patients will need intensive care. During this stage there is much greater lung involvement, literally gasping for air, as a storm of fiery molecules rages within the lungs and starts to travel throughout the body.

What to Do

Mask: Wearing masks when you go out to stop touching your face and to block inhalation of contaminated droplets. I am so high risk due to my health issues in the past, especially my lungs, I am hunkered down at home. I have purchased so many glasses from Costco's optometry center that I've become good friends with the staff. One of them brought over a gift of a mask yesterday and left it in my open garage where I will leave it for five days before opening the plastic package.

Washing hands: Wash your hands often with soap and water for at least 20 seconds. If soap and water are unavailable, use an alcohol-based hand sanitizer that contains at least 70% alcohol.

If you are at high risk consider the following (as prevention, immune boosters are science-based sensible to take).

Melatonin: 10 to 20 mg time-release for adults. Kids make their own. If your child gets ill with a documented case of coronavirus, ask your doctor about adding in 1 mg of melatonin to their mix.

*Antiviral nutrients***:** Get your blood flowing with healthy levels of natural antiviral nutrients. No one really knows the extent of this virus, but better safe than sorry and why not use natural answers. The focus here is on vitamins A, C, and D. Many people have insufficient blood levels of vitamin A and C. These nutrients have antiviral abilities and are able to support the immune system when it is under viral attack.

Vitamin C: If you are not ill with the virus but want protection, take 3-5,000 mg/day of vitamin C. At the first sign of an illness, take 1,000 mg/hour until diarrhea develops, then back off for a time period. If and when you get the virus, IV vitamin C has three studies approved for treating COVID-19, mentioned below in the tools for when infected section. Functional doctors have been using high-dose vitamin C IV, along with supportive nutrients, successfully for many years.

Vitamin A: 5,000 Units/day if you are not sick and 100,000 Units/day for four days at the first sign of an illness. Take vitamin A, not beta carotene. If you are a smoker, stay away from high dose beta-carotene, which is linked to increasing the incidence of lung cancer in smokers. *Pregnant women cannot take these doses*.

Vitamin D is also very important for fighting infections. At the onset of an illness, taking 50,000 IU of vitamin D3/day for four days. Then go back down to your normal, much lower levels. Do not stay on high levels of any of the vitamins. It's best to work with a physician that knows how to monitor high-dose nutrient antiviral intake.

Iodine is essential to fight off infections and for proper immune system

functioning. There is no bacteria, virus, parasite or fungus that is known to be resistant to iodine. Dr. David Brownstein is a colleague and dear friend. Dr. Brownstein has written in his amazing book, *Iodine: Why You Need It, Why You Can't Live Without It,* that most of our population is low in iodine.

When I test patient's serum iodine (which we do on every single new patient), 90% are way at the low end if not below it. Iodine levels have fallen nearly 60% over the last 40 years. *The Recommended Dietary Allowance* (RDA) for iodine is inadequate to supply enough iodine for all the bodily tissues.

For protection, taking half of a 12.5 mg iodine caplet twice a week makes sense. At the first sign of illness, increase to 25 mg of iodine for four days and then reduce the dose to one-half of a 12.5 mg caplet three times a week. Please keep in mind that iodine can cause adverse effects; it is best used under the guidance of an iodine-knowledgeable doctor.

Nitric Oxide: Neo-40 was co-formulated by Dr. Nathan Bryan and Dr. Janet Zand, who are old friends and colleagues of mine. Dr. Bryan and I did an NO/dialysis study together and published it in peer review. Neo-40 contains beet powder and a Chinese herb; both boost the production of NO. One lozenge twice a day seems prudent for protection.

Zinc is a powerful antiviral mineral. Zinc is part of the zinc finger proteins that help the body stop growth (replication) of invading viruses. Zinc has been tested and shown to have antiviral activity against a number of viruses, even Ebola, though it's not specifically been tested on COVID-19. Sufficient zinc stores inside cells are needed to help successfully fight viruses.

Zinc has been shown to help shorten the duration of the common cold if taken early in the course of the illness. The common cold virus is a member of the corona family. It's a good idea to test your stores of zinc once a year. This is done by running plasma, white and/or red blood cell levels of zinc. It should be in the upper quartile of the reference range of the lab. Taking about 25 mg/d of zinc for most people, with a small amount of copper like 2 to 3 mg in a backup multi-mineral, is immune supportive. The body works best in optimal ranges, and excessive zinc is immune-suppressive. So, don't go overboard.

Zinc's highest amount in the body is in the brain where zinc "allows" many hormone signals and neuronal actions to protect the brain. Zinc during a viral outbreak helps protect brain tissue from some of the collateral damage.

Mushrooms contain natural polysaccharides in their cell walls called beta-glucans. These substances increase host immune defense by several mechanisms, such as activating a part of the immune system called the complement system, enhancing macrophages (a protective traveling white blood cell that does cellular surveillance), and boosting natural killer cell function. Ill patients, more at risk of the virus, along with the elderly, often have "lower killer cell activity" and thus more viral vulnerability.

Medicinal and dietary mushrooms both contain polysaccharides that can stimulate innate antiviral immunity. The most studied mushrooms are turkey tail (*Coriolus or Trametes versicolor*), maitake (*Grifola frondosa*), shiitake (*Lentinula edodes*) and reishi (*Ganoderma lucidum*). Using mushroom supplements and adding them as whole foods to your diet seems smart.

Nutraceutical Support During Illness

In Stage One, immune boosters listed above are helpful. The lung damage of advanced COVID-19 pneumonia is due to an "overactive" immune response, so immune boosting therapies should be used for prevention or early infection only, and not for severe illness.

During Stage Two, you get much more ill. You need to lower immune boosters and add anti-inflammatories. You can stay on vitamins A, D and C but at lower daily dosages. Stop high dosages of immune boosters. Minerals are still good but in low protective ranges. Mushrooms should be stopped as they are great enhancers of innate immunity. You now want anti-inflammatories that naturally reconstitute ACE2 receptors.

High-dose melatonin still makes sense, taking 10 mg, three-to-four times a day. Adding curcumin, anthocyanins, quercetin, and resveratrol may be helpful. Keep in mind that these nutrients are not easy to absorb or to increase blood levels. Ideally, we consume a diet rich in these healthy compounds, over our life-times, that slowly raises our tissue stores of these nutrients. It's not so easy to get them into cells within short periods of days or in times of duress. This screams out loud why it is critical to live mindfully much of the time.

Curcumin blocks fiery cytokine release. Curcuminoids (flavonoids of turmeric) inhibit the key pro-inflammatory cytokines, interleukin-1, interleukin-6 and tumor necrosis factor-α that attack the lungs, kidney and heart in stage two COVID-19 patients. The suppression of cytokine release by curcumin correlates with clinical improvement in experimental models of disease conditions where a cytokine storm plays a significant role in mortality. The authors of the above study concluded that curcumin should be investigated to help patients with Ebola or suffering from a variety of cytokine storms.

Some curcumins are much more bioavailable than others. Using doctor's brands that address bioavailability issues makes a lot of sense or consider IV (but I don't know anyone doing that at this time). Intravenous formulations may allow achievement of therapeutic blood levels of curcumin. This is something for the functional medicine community to look into. Just recently, the FDA removed the "compoundability" by compounding pharmacists to use curcumin in compounds. Sad.

Ang-1-7 peptide is a booster of ACE2 physiologic activities. It appears it can be compounded. Ask your local compounding pharmacist if they make this available. I have no experience with this peptide. I just wrote Las Colinas Pharmacy in Dallas where I get a lot of my compounded meds, and they just had ordered some to make it available to physicians and patients.

Flavonoids and Anthocyanins

There is an enzyme that allows the virus to proliferate fast and possibly "correct" itself to keep making copies of itself without milder mutations. It's called the *3CL protease enzyme*. It

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breaks down cells and thus "lubes" the pathway for viruses by COVID-19 to flow throughout your body. So, you want to take, especially in this second phase, 3CL protease inhibitors. Many of which are flavonoids and colorful polyphenoloic compounds found in purple, blue and black foods as well as flaxseeds.

Coronaviruses (CoVs) have been rising targets of some flavonoids. The antiviral activity of some flavonoids against CoVs is presumed directly caused by inhibiting 3C-like protease (3CLpro). Korean scientists tested a whole batch of flavonoids for their inhibitory effect against SARS-CoV 3CLpro. Herbacetin, rhoifolin, and pectolinarin were found to efficiently block the enzymatic activity of SARS-CoV 3CLpro.

Herbacetin is found in flaxseed meal. In fact, this is one of the compounds that helps flax fight tumors. It also fights the ability of the virus to move throughout the body creating havoc. So, it makes sense to consume flaxseeds if you are getting really ill from COVID-19.

Anything with lots of purple, blue and black color will be rich in anthocyanins that are able to fight back the virus. Anthocyanins themselves have anti-viral activity. Purple grapes, blue corn, pomegranates, purple carrots, black lentils, black rice, and sprouted black lentils are helpful foods.

Standardized elderberry contains high amounts of 3CL protease blocking protective anthocyanins. You want to purchase brands that state standardized amounts on the label.

Resveratrol is a great second stage antiviral agent. In one cell study resveratrol was found to be a potent inhibitor of the MERS-CoV virus. So much so, the authors stated that we should consider this agent if another dangerous virus shows up. Well, here we are! Resveratrol helps block viral replication and other pathways of viral invasions.But this compound is not easily absorbed by the body. Use brands that have standardized amounts on the label and ideally come from professional lines that physicians utilize.

Quercetin is a flavonoid that blocks the 3CL-protease enzyme, thus inhibiting the pathway of COVID-19 through you. It has been shown to be effective against dangerous viruses such as SARs. A number of studies show it to be an antiviral agent helpful when the fire of cytokines is damaging tissues.

N-acetylcysteine (NAC) is an amino acid that protected lungs from acute injury against the H9N2 swine influenza virus. NAC has been shown to block viral replication, and it also blocks viral carditis. The heart can and often is, in the second stage, adversely effected by COVID-19 so this makes sense with our present pandemic scenario.

ACE and ARB Meds

This class of blood pressure-lowering meds bind to the same receptors as the COVID-19 virus, so they act as inhibitors, meaning they stop the virus from binding with the ACE2 receptors. There is controversy over those who are already taking these types of blood pressure meds; are they more or less protected from the virus? (This would make a good study in those already affected for you epidemiologists out there.)

I have a few elderly patients with chronic lung issues, who are also on blood pressure medicine. I am recommending they and their primary care docs consider substituting their present medication with ACE inhibitors (and/or ARBS), or add a very small amount of ACE inhibitor to their present blood pressure mix, as long as they don't get their blood pressure lowered too much.

ACE inhibitors have long been known to protect renal function by binding to these receptors in the kidneys, which protects renal tissue from damage by a variety of possible assaults to these receptors. It's also why some folks start to cough on these meds as it activates so many lung ACE2 receptors and some folks have more than others.

I don't have high blood pressure but am a high-risk person. I decided to take 2 mg daily of Enalapril (an ACE inhibitor) as a protective measure. I'm tracking my blood pressure to make sure it stays at healthy levels. You cannot make this decision without conferring with your primary healthcare doctor who knows your health history. This is a speculative protocol, not a CDC or medically proven protocol. It's physiologic common sense. This may lower your blood pressure somewhat, which may not be appropriate for you, or it may have little effect other than being a super protective measure for you. But it's trial-and-error, and you must work with a medical practitioner, as it is a prescription.

NSAIDS Controversy

Nonsteroidal inflammatory meds have been shown to be "immunosuppressive," and this is a time when you want your immune system as strong as possible. However, in the US the FDA and other medical authorities have recently examined this issue over the past few weeks. The consensus has been that there is insufficient data to condemn the use of ibuprofen and related drugs in relation to COVID-19.

Stress

Stress, like sugar, depresses the immune system. Make as many decisions as possible by looking at all your options and taking the path of least stress. Mindfulness practices also help you move through stress. Stress, after all, is the perception of lack of control. Mindfulness puts us into a "present" that seems more controllable, no matter the circumstance. That builds resilience even to viruses.

If all the above seem too much or you feel you don't need to cover all your bases, choose what makes most sense for your body. Perhaps do one or two protective measures. I would say put melatonin high on the list. I took 15 mg time-released last evening and had a terrific sleep! Feel like a million bucks this AM to finish this article for you.

The French Marseille Study

A renowned research professor in France has reported successful results from a new treatment for COVID-19, with early tests suggesting it can stop the virus from being contagious in just six days. However, a patient of Dr. Galland's, positive with COVID-19 who found herself in Paris, could not gain access to this treatment. Keep that in mind.

Professor Didier Raoult is an infectious disease specialist in Marseille, France. Professor Raoult was tasked by the French government to research possible treatments of COVID-19. His team

gave chloroquine, which is normally used mainly to prevent and treat malaria as well as rheumatoid arthritis, administered via the named drug, Plaquenil. The treatment has now tested up to 90 patients (4/2/2020), but the first 24 were among the first to become infected in the southeast of France. They had voluntarily admitted themselves for this process.

Patients were given 600 mg per day for 10 days. They were closely monitored, as the drug can interact with other medication and cause severe side effects in some cases. Professor Raoult said: "We were able to ascertain that patients who had not received Plaquenil (the drug containing hydroxychloroquine) were still contagious after six days, but of those that had received Plaquenil, after six days, were only 25% still contagious."

Chloroquine phosphate and hydroxychloroquine have previously been used to treat coronavirus patients in China, in ongoing COVID-19 clinical trials. In another study these researchers found that patients on a combination of Plaquenil along with the antibiotic Zithromax (Z-packs) had a 95% reduction in viral load by day 6. However, some ER doctors in the US have tried this treatment and found it not to be helpful.

Food, Water, and Lifestyle

You want a humming immune system. Avoid things that ding it. Eat lots of colorful veggies and fruits and, during this time, avoid refined sugar completely. For a few hours after consuming refined sugar, white blood cells don't perform optimally. This is proven, replicated science. Dehydration worsens any infectious process. Remember to drink water. I am going to take a short break and go get a glass right now.

Workout regularly, sleep well, and take prescribed meds regularly as directed.

Social Distancing

The countries that have kept this coronavirus under control acted fast and aggressively toward containment. The US has gotten off to a slow start. This is a virus. A protein bag filled with RNA whose only purpose is to replicate. To do this it must have a host. The more it replicates, the more its virulence. The less it can replicate we reduce its virulence.

- Flattening the curve is reducing our exposure and not overwhelming our health care system and our amazing front line providers.
- But social distancing is also about reducing the viral aggressiveness!

Keep this in mind. Social distancing flattens the curve, reducing the rate of the increase in numbers of cases. But it also reduces the aggressiveness of the virus itself. This information does not seem to me to be getting out to our political and medical leaders. If you pass this on, this factoid may help more people comply with isolating.

Data from abroad suggest that 10% to 20% of those who get ill can end up in a more serious condition. This could translate into potentially hundreds of thousands who may need hospital care. To avoid this, we need to take individual and social action. We can't be cavalier Americans thinking we can do whatever we want. South Korea and Taiwan kept people safely at a distance that lowered their fatality rates or at least the ones reported. Volunteers in other countries go around with thermometers checking for fevers. It is good that schools are closed. Don't go to church; pray at home. Don't go to large gatherings and only go out when you must. Instead of restaurants cook at home or order in and let them leave the food at the doorstep. Open up the containers with gloves and don't put the containers on your kitchen counter, throw them away.

People flying into countries now must be in a holding area until they have medical evaluations. America has not been doing this consistently. Folks land and blend and stand in long lines with each other and even share pens to fill out forms. Some countries have closed their air and seaports to foreigners. This makes sense. Act aggressively now and stop this, so we can soon go on with our lives.

If you are young, realize you can still get ill or be a vector of infection. Keeping away from others if you have been exposed for at least 14 days can help "flatten" this potential catapulting curve. We need collective civic responsibility. Be smart. This has not peaked yet, but you can help it slow down. Don't forget to spend some healthy time outside because sunlight and fresh air are part of staying well.

You want a humming immune system. Avoid things that ding it. Eat lots of colorful veggies and fruits and ... avoid refined sugar completely.

If You Get COVID-19

If you become ill with a viral infection, I suggest these viral protocols that have been used for viruses in functional medicine clinics for many years:

IV Vitamin C, if you can get it. Intravenous vitamin C is already being employed (successfully in a number of cases) in China against COVID-19. You can go to a functional medicine doctor or some cities have walk in IV rooms where they have doctors on site. This looks like one of the best options to start right away. If you can't get IV vitamin C, *try vitamin C to bowel tolerance* as described earlier in this article.

Melatonin (30 mg time-release – at this time is my best guesstimate) before bed for one week, you may feel groggy during the day, but you need to sleep anyway and this will give you deep healing sleep; then reduce to 20 mg the next several weeks.

Vitamin D3 (50,000 IU) for four days. After the four days, resume your previous dosing.

Vitamin A Palmitate (100,000 IU) for 4 days, then reduce to 50,000 IUs for 4 days, and then down to 25,000 IU. It is best to work with a holistic doctor who can monitor your levels as both vitamin A and D can become toxic.

Zinc (30 mg 4/day). Go down 30 mg each day till at only one 30 mg. While doing this protocol make sure you ➤

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have a multimineral on board with a bit of copper in it. But do not take too much zinc as, in excess, it is immune-suppressive. Most natural compounds in the body work best at Goldilocks "just right." Never stay at a dose that causes nausea.

Ozone whole blood irradiation is a powerful tool against viruses (and everything else). Hydrogen peroxide IVs are helpful, too. I have not used these, but Dr. Brownstein swears by them. I use ozone regularly at home for prophylaxis as well as treating specific conditions.

Consider clearing nasal passages with a neti pot (with purified water).

Consider Afrin nasal spray (3 sprays in each nostril, 3 days at a time, and then 3 days off). This could potentially keep your sinuses clear and prevent the symptoms from spreading to your lungs.

Thinking of getting the flu shot? This is what Dr. Brownstein says and I agree. "It won't help coronavirus infections. There was a study that found an *increased* risk in non-influenza infections, including coronavirus, in those that received the trivalent flu vaccine."

Most Likely

Death is a tragedy, but the death rate from this new coronavirus strain is most likely not going to be as severe in the US as the recent statistics are suggesting. We don't smoke as much as China or Italy. Our air is less smoky. Plus, we have some heavy-hitting nutritional and drug options. Personally, I'm on all of the suggested items.

Keep in mind the present viral numbers outside of Italy correlate to a 2-3+% death rate, which means 97-98% of those infected survive! Remember that these reports aren't completely accurate as we do not know the total number of cases.

Be mindful that viruses can mutate, so symptoms can morph. That's why during these times it makes sense to take some of the action steps mentioned above, especially if you are over 70 years old or already ill with a chronic underlying condition.

If you must fly, start the following two days ahead of the day of flying:

1. Melatonin, 15 mg time release before bed. (Some people do better with much lower dosages and not in higher dosages (over .5mg) if you have autoimmune illnesses, or work with a savvy physician).
2. 4,000 IU of vitamin C
3. 40,000 IU of vitamin A
4. 5,000 IU of vitamin D
5. Mushroom supplements
6. Colloidal silver is a consideration; but the FDA is blocking clinics and sites that discuss this, so I am leaving this out of this article but am on it myself.

Front Line Angels

People are stepping up. Some grocery store workers are working double-shifts to keep food on the shelves. Some health care workers have sent their families home (transfamilial transference is over 80%) while they go to work exposing themselves seven days a week. As the sane voice in the middle of this epidemic, Andrew Mark Cuomo, governor of the hardest hit state, New York, "This is not a sprint this is a marathon. It's not over quickly." Doctors, nurses, pharmacists (some have lines going out the doors, some are driving all day to deliver medications to folks at home), grocery store workers, police persons, fire fighters, transportation workers and on and on. Even the next-door neighbor that calls or writes on the sidewalk in chalk, "How can I help?" and scratches out their cell number. "Yes" said Governor Cuomo, "We are tired but look what others among us have to do and the challenge they are under and how they are stepping up. Who are we to complain about being tired when so many have done so much monumental efforts?"

We will get through this. We are not in this alone, the world is united as one connected potential set of hosts for this virus. Now we will see what we are all made of. Crisis is the "great make-over." Often making us better after we have lived through it. Our children have not lived through crises such as the Great Depression or World Wars or Vietnam. They are living with world crisis now. They will not be the same.

On the other side of this pandemic, let's hope we are more compassionate and mindful in our own lives and with each other. Perhaps even as the UN chief called for, less war.

The earth is a being. She has become toxic and ill. Yet her ozone layers are healing. Healing can take place on Mother Earth just like it can with you and me. We have seen over the past few decades an increase in virulent viruses. Being a functional practitioner, I look for "root cause." Perhaps our earth has become a more toxic terrain to "allow" more virulent viruses. What if part of our increasing pandemics is a "call to change" like disease can often be for humans to access how their bodies "allowed" themselves to be vulnerable to illness.

May we learn how to caretake the earth and each other with more thoughtfulness toward our children, our future and our health as a world community. ◆

D. Lindsey Berkson, DC, has been a leader in functional medicine, with an emphasis on the gut, hormones, and the environment for several decades. Dr. Berkson has been teaching certification relicensing courses for MDs, pharmacists, NPs, NDs and chiropractors for decades—in the last few years focusing on the gastroenterology module for A4M and hormones and oxytocin for PCCA.

Dr. Berkson formulated Metagenic's first female nutrient line for physicians. Dr. Berkson was a scholar at an estrogen think tank at Tulane University where she worked with the top scientists that discovered "receptor physiology" and growing epidemic of competitive inhibitors found in endocrine disruptors.

Dr. Berkson has authored 21 books; several have been best sellers. She also hosts the Dr. Berkson's Best Health Radio, writes the Berkson Blog (@ DrLindseyBerkson.com), and is a research fellow with Health Sciences Collegium.

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COVID-19, MERS, SARS, and Other Emerging Coronaviruses: Theoretical Considerations and a Proposal for Critical Care Parenteral Blood Ozonation

by Gérard V. Sunnen, MD©2020

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Ozone: Physical and Physiological Properties

The oxygen atom exists in nature in several forms:

- As a free atomic particle (O), normally produced in the course of metabolism, it is highly reactive and unstable. Exogenous antioxidants are sometimes used to temper its metabolic effects.
- Oxygen (O2), its most common and stable form, is colorless as a gas and pale blue as a liquid. In its ability to give up one of its atoms and accept electrons in return, it drives numerous metabolic reactions.
- Ozone (O3), distinctly blue as a gas and dark blue as a solid, has a molecular weight of 48, a density one and a half times that of oxygen, and contains a large molecular energy excess (O3 → 3/2 O2+ 143 KJ/mole), which can be imparted to many other molecules. Its bond angle of 127 ± 3°, resonates among several forms.
- O4 is a very unstable, rare, nonmagnetic pale blue gas formed at the interface of earth's stratosphere's outer layer where the sun's radiation first encounters earth. O4 readily breaks down to two molecules of oxygen.

Ozone (O3), a naturally occurring configuration of three oxygen atoms, has a half-life of about one hour at room temperature, reverting to oxygen. A powerful oxidant, ozone has unique biological properties. Since some ozone-based therapies are administered by interfacing gaseous oxygen/ozone with blood, basic research on ozone's biological dynamics have often centered upon its effects on blood cellular elements (erythrocytes, leukocytes, and platelets), and on its serum components (proteins, lipids, lipoproteins, glycolipids, carbohydrates and electrolytes).

The effects of ozonation on whole blood are extraordinarily complex and are far from adequately elucidated. Indeed, ozone can react with serum proteins, including enzymes, immunoglobulins, clotting factors, hormones, vitamins, lipoproteins and cholesterol, carbohydrates (including glucose), and electrolytes, among others. Comparing blood to an orchestra, ozone administration can be likened to the introduction of a novel and powerful musical instrument, affecting the interactions of all others.

Even though an in-depth analysis of ozone's multifaceted effects upon the panoply of blood constituents is beyond the intent and scope of this article (The reader is referred to Bocci 2013; Smith 2017), the following points of research are significant.

Erythrocytes have been extensively studied in relation to ozone administration. Many studies that have used erythrocyte suspension in physiologic saline have found hemolysis at relatively low ozone dosages (10 to 30 ug/ml). When ozone is administered in whole blood, however, the dynamics of ozone interaction are such that hemolysis begins to be observed at significantly higher doses, implying a buffering action of blood constituents. Moreover, the functionality of erythrocyte enzymes is maintained, suggesting a protective role of blood's antioxidant systems. There is some evidence that low-dose ozone administration may stimulate erythrocyte formation and release.

Leukocytes, intimately connected to immune function, show good resistance to ozone because, unlike viruses, they possess enzymes that protect them from oxidative confrontation. These enzymes include superoxide dismutase, glutathione, and catalase. A promising area of research centers on cytokine and interferon stimulation in ozone administration and its implication for enhancing immune function. A classical adage of ozone therapy is that lower ozone dosages are stimulating to immune action while higher dosages become inhibitory. Further research will need to clarify the parameters of this phenomenon, as well as the effects of ozone infusion upon different types of leukocytes in relation to the disease under treatment.

Ozone: Antipathogenic Properties

Recently, there has been renewed interest in the potential of ozone for viral inactivation in vivo. It has long been established that ozone effectively works against the viability of bacteria, viruses, fungi, and parasites in aqueous media. This has prompted the creation of water purification processing plants in now hundreds of major municipalities worldwide (e.g., Los Angeles, Paris, Moscow). Ozone's unique physicochemical and biological properties and its environmentally-friendly features have since been applied to a panoply of industrial uses such as the packaging of pharmaceuticals, the ➤

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treatment of homes and buildings (sick building syndrome), the treatment of indoor air in operating theaters and nursing homes, and the disinfection of large-scale air conditioning systems in hospitals.

Lipid-enveloped viruses are easily oxidized and destroyed by ozone.

Ozone's remarkable capacity for pan-antipathogenic action have been applied to the treatment of poorly healing wounds and burns.

A partial list of organisms susceptible to ozone inactivation in these clinical situations includes all those commonly contaminating all manner of wounds, both aerobic and anaerobic bacteria: Bacteroids, Campylobacter, Clostridium, Corynebacteria, Escherichia, Klebsiella, Legionella, Mycobacteria, Propriobacteria, Pseudomonas, Salmonella, Shigella, Staphylococcus, Streptococcus, and Yersinia.

Ozone-susceptible viruses include Adenoviridae, Filiviridae, Hepnaviridae, Herpesviridae, Orthomyxoviridae, Picornaviridae, Reoviridae, Retroviridae, and Coronaviridae.

Ozone-sensitive fungi include Actinomycoses, Aspergillus, Candida, Cryptococcus, Epidermophyton, Histoplasma, Microsporum, and Trichophyton, among others.

Some viruses are more susceptible to ozone's action than others. It has been found that lipid-enveloped viruses are the most sensitive. This makes intuitive sense, since enveloped viruses are designed to blend into the dynamically constant milieu of their mammalian hosts. This group includes hepatitis B and C, herpes 1 and 2, Cytomegalus (Epstein-Barr), HIV 1 and 2, influenza A and B, West Nile virus, Togaviridae, Eastern and Western equine encephalitis, rabies, and Filiviridae (Ebola, Marburg), among others. Prominent are all Coronaviridae family members, including Covid-19, SARS, and MERS.

The envelopes of viruses provide for intricate cell attachment, penetration, and cell exit strategies. Peplomer crowns, finely tuned to adjust to changing receptors on a variety of host cells, constantly elaborate slightly new glycoprotein configurations under the direction of the viral genome, thus adapting to host cell defenses. Lipid-enveloped viruses leave their coats on entering cells, replicate by hijacking host genetic integrity, then exit surreptitiously though host cell membranes donning usurped fashionable new garments. But lipid coats and envelopes are fragile; they are easily oxidized and destroyed by ozone's actions.

Lipid-enveloped viruses in aqueous media are readily inactivated by ozone via the oxidation of their envelope lipoproteins and glycoproteins. In whole blood, however, ozone's viricidal actions are buffered by the spectrum of its components, and ozone becomes less effective. This situation is further complicated in the case of retroviruses, which ensconce themselves within host DNA, and in Herpesviridae, where virions have the capacity to persist indefinitely in their hosts through the formation of episomes in the nuclei of the cells that harbor them.

Several studies have reported the safety and the benefits of ozone administration in vivo. Wells et al. (1991) showed that ozone-treated HIV-spiked Factor VIII maintained its biological capacity, and that, concomitantly, there was an 11-log reduction in virion presence.

The improvement of liver enzymes in hepatitis C patients after several months of ozone therapy was described. An 80% hepatitis C viral load reduction in 82 patients using autohemotherapy was also reported. It is remarkable, however, that to date, no adequate double-blinded study has addressed ozone therapy in viral conditions such as hepatitis B and C, HIV, or herpes – all long-time afflicters of humans.

Ozone: Clinical Methodology

Ozone may be utilized for the therapy of a spectrum of clinical conditions and may involve external and internal applications. Most promising are externally-applied oxygen/ozone gas mixtures for the resolution of diabetic and vascular skin ulcers that are notoriously difficult to heal and all too often result in limb amputations (Sunnen, USPTO patent # 6,073,627, "Apparatus for the application of ozone/oxygen for the treatment of external pathogenic conditions").

In the technique of ozone autohemotherapy (AHT), an aliquot of blood (50 to 500 ml) is withdrawn from a virally afflicted patient, anticoagulated, interfaced with a calibrated ozone/oxygen mixture, then reinfused. This process is repeated serially, in a manner consonant with treatment protocols until viral load reduction and symptom abatement are observed.

Another, more experimental and more intensive technique of oxygen/ozone gas administration, is called extracorporeal blood oxygenation ozonation (EBOO), which treats the entire blood volume using an ozone-resistant hollow-fiber oxygenator-ozonizer, much in the model of dialysis intervention. Bocci describes the caveats in using this method, not the least of which involves problems interfacing complex biomechanical machinery with a lethal agent. Given human ingenuity, however, these problems are solvable.

This and similar methods are likely to be the most efficient in culling the massive virion waves that viremic episodes spawn. For the present time, however, AHT offers simpler – yet totally un-researched in Covid-19 – interventions that involve only one venipuncture per treatment (while EBOO requires two). Research is first needed to gauge EBOO's viral culling action in innocuous Covid-19 surrogates.

Ozone: Possible Mechanisms of Anti-Viral Actions

The average adult has four to six liters of blood, accounting for about 7% of body weight. How can any viral load reduction reported via ozone therapies be explained in the face of a technique that treats relatively small percentages of blood volume, as in AHT, albeit serially? Would not more comprehensive approaches, that recruit the entire blood and lymph volumes, much as in dialysis,

be more efficient in Covid-19 virion harvesting? All is fodder for research, yet several theoretical bases for blood-to-oxygen/ozone interfacing suggest that the viral culling effects of ozone in infected blood may recruit a variety of mechanisms. Research is needed to ascribe relative importance to each of these, and possibly other mechanisms accounting for ozone's anti-viral actions:

- The denaturation of virions through direct contact with ozone. Ozone, via this mechanism, disrupts viral proteins, lipoproteins, lipids, glycolipids, and glycoproteins. The presence of numerous double and triple chemical bonds in these molecules makes them vulnerable to the oxidizing actions of ozone's molecule, which readily donates its oxygen atom and accepts electrons in redox reactions. Unsaturated chemical bonds are thus reconfigured, viral molecular architecture is disrupted, and breakage of the envelope ensues. Deprived of an envelope, virions cannot sustain nor replicate themselves.
- Ozone proper and the peroxide compounds it creates may alter structures of the viral envelope that are necessary for attachment to host cells. Peplomers, the viral glycoproteins protuberances that connect to host cell receptors, are posited to be likely sites of ozone action. Even minimal alterations in peplomer integrity through lipoprotein peroxidation could impair attachment capability to host cellular membranes, thus foiling viral attachment and penetration.
- Introduction of ozone into the serum portion of whole blood induces the formation of lipid and protein peroxides. While these peroxides are not toxic to the host in quantities produced by ozone therapies, they nevertheless possess oxidizing properties of their own that persist in the bloodstream for up to several hours. Peroxides created by ozone administration show long-term antiviral effects that may serve to further reduce viral load.
- The immunological effects of ozone have been documented. Cytokines, proteins manufactured by several types of cells, regulate the functions of other cells. Mostly released by leucocytes, they are important in mobilizing immune reactivity. Ozone-induced release of cytokines may constitute an avenue for the reduction of circulating virions.
- Ozone's actions on viral particles circulating in infected blood yield several possible outcomes. One outcome is the modification of virions so that they remain grossly structurally intact yet sufficiently dysfunctional as to be nonpathogenic. This attenuation of viral particle functionality through slight modifications of the viral envelope, and possibly the viral genome itself, not only modifies pathogenicity but also allows the host to diversify its immune response. The creation of dysfunctional viruses by ozone offers novel therapeutic possibilities. In view of the fact that so many mutational variants exist in any one afflicted individual, the creation of an antigenic spectrum of crippled virions could provide for a unique host-specific stimulation of the immune system, thus designing what may be called a host-specific autovaccine.
- An exciting research thrust suggests that the viricidal properties of antibodies are predicated upon their ability to catalyze highly active forms of oxygen, including ozone. A key element in the microbe-inactivating capacity of antibodies may thus reside in the formation of ozone and other oxygen reactive species (ROS) integral to antigen-antibody reactions.

Indeed, according to these revolutionary findings, the very crux of our human defense against microorganisms may reside in our capacity to produce endogenous ozone and ROS. Exogenously administered ozone may, in this model, add to the efficacy of the body's antigen-antibody dynamics.

COVID-19, MERS, SARS, and Ozone: The Future of Research

Covid-19, MERS, and SARS are produced by novel coronaviruses that have succeeded in breaching the immunological defenses of our contemporary human populations. They appear to have developed an uncomfortable balance between viral propagation and lethality.

A universal strategy in mastering infections, whether bacterial or viral, is the body's culling of pathogenic organisms to the point where they no longer represent an invasive and

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replicative threat. This may be achieved by responsive systems of host immune counter-offense, with molecular memory capable of neutralizing future viral attacks.

Covid-19, SARS, and MERS are acute, rapidly progressing, pan-inflammatory infections that, predicated upon the coronavirus quasi-species involved, may present distressful morbidity and mortality outcomes. A salient clinical configuration in these infections stems from their acute involvement of the respiratory system and their rapid disruption of blood gas balance. When pO2 and pCO2 are sufficiently compromised, chemoreceptors in the medulla begin to fail and respiration stops.

Because of their galloping symptomatology, Covid-19, MERS, and SARS ideally would benefit from proactive emergency viral culling. With estimated 10 billion viral particles disgorged daily in the general circulation, viremic reproductive juggernauts commonly seen in lipid-enveloped viral cycles need modulation.

Can systemically administered oxygen/ozone mixtures assist in this process? In severe Covid-19 cases, the disease progression may be stunningly rapid. Present countermeasures are non-existent. Indeed, Covid-19 may need more intensive intervention and emergency abatement of viral aggressiveness.

COVID-19, MERS, and SARS: Disinfection/Sterilization of the Environment

The recent findings that Covid-19 has the capacity to remain infectious on fomites for up to several days indicates that it is a hardier organism than most of its other lipid-enveloped colleagues.

Predictably, disinfectants such as bleach, phenol, formaldehyde and ozone have been found to be effective in deactivating the coronaviruses. Liquid agents have the disadvantage of faring poorly in decontaminating complex medical equipment and the hospital room milieus of coronavirus patients. Medizone International Inc. has developed a patented ozone/hydrogen peroxide mix that is remarkably effective in decontaminating the surfaces, nooks, and crannies of hospital treatment rooms and patient rooms (and ships' quarters) from all pathogenic organisms.

Ozone, in light of its pan-viricidal profile, offers the advantage of existing as a gas, with its attendant ability to disinfect poorly accessible spaces. Moreover, ozone has the distinct benefit of naturally reverting to natural oxygen molecules, while liquid–based disinfectants are likely to injure the surfaces to which they are applied and to leave toxic residues. Ozone-mediated environmental decontamination, however, needs to respect stringent protocols to ensure that the ambient ozone in the process of disinfecting target environments has time to revert to its stable parent, oxygen, without inflicting toxicity to the personnel.

Summary and Conclusions

Covid-19, SARS, and MERS are acute pan-inflammatory multi-system syndromes caused by hitherto unknown coronavirus species. These virions incorporate novel RNA genomes and lipid bi-layered envelopes. The Covid-19, SARS, and MERS viruses all possess high mutation rates, allowing any one infected individual to harbor numerous quasi-species, all with variable infectivity and lethality.

Ozone is an energy-rich naturally occurring molecule that embodies unique physico-chemical and biological properties suggesting a possible role in the systemic therapy of Covid-19, MERS, and SARS, either as a monotherapy or, more realistically, as an adjunct to standard treatment regimens. Ubiquitously found in the earth's ecosphere, ozone, amazingly, is also intrinsically found in bodily systems, generated by normal immune functions as an inactivator for multitudes of pathogens.

This paper outlines six possible mechanisms by which ozone may exert its antiviral actions. Due to the excess energy inherent in the ozone molecule and supported by the vast scientific literature attesting to its pan-microbial powers, it is quasi-certain that ozone can demonstrate effectiveness across the entire coronavirus spectrum.

The acute infective phase of Covid-19 is marked by massive viral replications with viral flooding of blood and lymph compartments. These viremic invasions present serious clinical challenges because they contribute to the swiftness of downhill clinical courses. This paper proposes a method of viral culling, during these acute phases of coronavirus illnesses, via systemically administered oxygen/ozone gas-to-blood interfacing strategies.

Herewith proposed is consideration for the modification of technologies that already use blood-to-oxygen interfacing for assisting patients in cardiopulmonary distress for maintaining proper blood gas configurations. The technology, developed since the 1950s and known as extracorporeal membrane oxygenation (ECMO), can be upgraded to accept ozone's addition by rendering its systems, such as gas exchange membranes, ozone-resistant. Posited

Gérard V. Sunnen, MD, received his medical degree from the State of New York Medical School, Downstate Medical Center. Following an internship in surgery and medicine at Bellevue Hospital, New York, he was appointed resident, then chief resident at Bellevue Psychiatric Hospital. He has practiced medicine and psychiatry in general hospital, academic, Air Force, forensic and hospice settings. Dr. Sunnen was certified as Diplomate of the American Board of Psychiatry and Neurology in 1977. He was appointed Assistant Clinical Professor of Psychiatry at the New York University-Bellevue Medical Center in 1977, and Associate Clinical Professor in 1987.

Interested in medical research for many years, Dr. Sunnen was president and director of research, from 1997 to 2002, of Medizone International, Inc., a publicly held company engaged in the research and development of ozone-based technologies for diseases caused by lipid-enveloped viruses and for biological fluid decontamination. He is the recipient of two patents relative to the medical use of ozone's unique antimicrobial dynamics for the healing of diabetic skin ulcers and poorly healing surgical skin lesions. In 2005, Dr. Sunnen founded Ozonics International, LLC, a company dedicated to the development of ozone-based and other forward-looking medical technologies.

is that appropriately calibrated added ozone dosages can become adjuncts to the mission of assisting Covid-19 patients maintain not only healthy blood oxygen/carbon dioxide balance, but also provide them with Covid-19 viral harvesting and elimination.

Ozone has unique disinfectant properties. As a gas, it has a penetration capacity that liquids do not possess. In view of the fact that Covid-19, MERS, and SARS persist on fomites for up to several days, it is suggested that ozone technology be applied to the decontamination of medical and other environments.

As our world becomes increasingly challenged by viral adversaries, the need for rapidly developing specific vaccines adapted to each viral species becomes evident. Yet, in parallel, research also needs to center on finding new methods of relieving the biological stress caused by onslaughts of viremic invasions that are common to many families of pathogenic viruses. The coronaviruses are a case in point, as they all possess lipid envelopes susceptible to structural modifications by ozone.

In conclusion, a proposal is herewith made that oxygen/ozone systemic therapies are granted research consideration for Covid-19 treatment. Such therapeutic approaches may then be found useful not only in these specific coronavirus conditions, but also in a number of human lipid-enveloped viral pathogenic infections, and importantly for the future coronavirus epidemics that are certain to emerge. ◆

This article has been abridged from the original. Full article and references are available at www.townsendletter.com.

Uremia and Inflammation

by Jenna Henderson, ND

It has long been known that the most common cause of mortality in kidney patients is not kidney failure directly but secondary heart disease. As more is understood about the mechanisms of secondary heart disease, it becomes clear that inflammation is a major contributor to degeneration in kidney patients, not just in cardiac health but with vascular calcification, premature aging, telomere shortening, mitochondrial dysfunction, muscle wasting, and osteoporosis. Historically, strategies to address chronic kidney disease have focused on preserving filtration and also renal replacement therapy with dialysis and transplants to avoid uremic toxicity. Additionally, addressing inflammation may also go a long way to improving the long-term prognosis of kidney patients.

Urine contains at least 3,079 different waste products, as revealed by the latest cataloguing of uremic compounds. Of these compounds 1,453 come from the human metabolism. Seventy-two are made from bacteria and another 2,282 come from diet, drugs, cosmetics or environmental exposure (some compounds belong to more than one group). The kidneys handle any water-soluble material the body needs to get rid of. Creatinine has been determined to be the most steady, stable indicator of a uremic state. When creatinine is high, other uremic waste products are also present in the blood.[1]

For most kidney patients only creatinine and BUN are tested. Sometimes uric acid is also tested if the patient is experiencing symptoms of gout. High uric acid itself can cause injury to kidneys through inflammation fibroblast expansion and Endothelin-1 expression.[2] Uric acid crystals can even settle in the heart.[3] However, uric acid may not be the biggest culprit as allopurinol therapy, in one study, did not improve cardiovascular outcomes in patients.[4]

Unfortunately, the most worrisome uremic waste products are not tested; and most kidney patients are not followed by a cardiologist. Also, the usual markers of inflammation – CRP and ESR – are generally not tested. With most kidney patients, a shortened life span is usually the outcome; but it doesn't have to be this way. By understanding the link between uremia and inflammation, kidney patients can take steps to reduce their cardiovascular risk.

Inflammatory markers are present with early stage kidney disease but increase as the kidneys lose the ability to filter waste. A study published in 2017 looked at patients undergoing cardiac bypass surgery. Patients were divided into three groups: (1) with creatinine under 1.3 mg/dl (control group), (2) with creatinine between 1.3 and 2.0 (early chronic kidney disease) and (3) patients with creatinine >2.0 (advanced chronic kidney disease). Both the early stage kidney patients and the later stage kidney patients showed high levels of proinflammatory markers, while marked calcification of the blood vessels was seen with advanced kidney disease.[5]

Uremic toxins in the blood are in constant contact with the endothelium of vascular tissue. A 2019 study looked at the effect of uremic serum on cultured human endothelial cells and measured the levels of expression of molecules associated with vascular injury and repair. Monocyte chemoattractant protein 1 (MCP-1) was markedly increased in sera from uremic patients with diabetes as well as sera from uremic patients with hypertension. MCP-1 caused endothelial injury and inflammation. Sera from diabetic patients also included an increase in vascular endothelial growth factor (VEGF) and stromal cell-derived factor 1 (SDF-1), which are initiators of the vascular repair process. VEGF and SDF-1 were not elevated in the sera from patients who reached end stage renal disease due to hypertension, suggesting that the cause of renal failure can be a factor in expression of inflammatory markers.[6]

Advanced kidney disease can blunt the immune response, while at the same time inducing constant low-grade systemic inflammation. The uremic patient has a high level of cytokines trying to invoke an immune response, but a general senescence of the immune system. Unable to mount a proper immune defense, this inflamed state can wreak havoc with patients, resulting in the cardiovascular damage seen with late stage kidney disease.[7]

The immune senescence of chronic kidney disease can bring changes that include a low thymic output, an increase in C-reactive protein, and an increase in terminally differentiated CD8+ T-cells. While low thymic output was most associated with infections, changes in T-cell expansion were associated with cardiovascular events.[8] This premature aging of the immune system is also related to telomere shortening, mitochondrial dysfunction, and altered nutritional status. The combination of inflammation and reduced kidney function can reduce the body's resilience to external and internal stressors, reduce tissue reserves, and impair normal organ crosstalk.[9]

Increased macrophages appear to contribute to atherosclerotic lesions in uremic patients.[10] Surprisingly, adipose tissue may be a source of inflammation in kidney patients, even with non-obese patients. Diabetes is the most common cause of kidney disease, and obesity can be a major contributor to kidney decline. However, even without a high

degree of adipose tissue, uremic patients have increased macrophage infiltration into subcutaneous and visceral adipose tissue.[11] These macrophages appear to be activated by indoxyl sulfate, a uremic waste product that evades clearance by dialysis, although other protein-bound uremic toxins may play a role as well. Indoxyl sulfate is also known to upregulate adhesion molecules and induces proliferation of vascular smooth muscle cells.[10]

In addition to Indoxyl sulfate, p-cresol sulfate and indole-3-acetic acid are uremic toxins associated with cardiovascular disease in chronic kidney disease. Low estimated glomerular filtration rate (eGFR) is associated with higher uremic toxins as well as high markers of inflammation like Il-6, hs-CRP, MCP-1 and soluble vascular adhesion molecule-1 (sVCAM-1). Higher levels of urinary toxins and inflammatory markers were associated with higher mortality in kidney patients tracked over a five-year period. Researchers in this study also looked at arterial segments collected at the time of kidney transplantation and found increased plaque associated with uremic toxicity.[12]

Secondary cardiac issues are so pervasive with chronic kidney disease, a distinct phenotype of uremic cardiomyopathy has been identified. Characterized by left ventricular hypertrophy and fibrosis, inflammation and uremic toxins are important contributors along with volume overload, hypertension and anemia. These changes are seen to reverse following a kidney transplant and resolution of uremic toxicity.[13] Oxidative stress also contributes to prevalent coronary artery disease,[14] uremic pericarditis and in severe cases cardiac tamponade.[15] Inflammation can also be a factor with non-responsiveness to erythropoietin therapy, an independent risk factor for kidney patient mortality.[16]

Although cardiovascular disease is the major cause of mortality for kidney patients, uremic inflammation can cause other problems including central nervous system disorders, muscle wasting, and uremic pruritis. Uremic inflammation may inhibit the cytoprotective system and erode the cerebral capillary junctional complex, the blood brain barrier. The result may be cognitive decline, seizures, and encephalopathy.[17] Skeletal muscle wasting is common with chronic kidney disease, even if patients have adequate protein nutritional intake. New information indicates that uremia inhibits satellite cells, progenitor cells important for maintaining muscle mass.[18] Uremic pruritis, although not life-threatening, is often attributed to high levels of phosphorus, but elevated Il-2 and overactivity of the TH1 immune response appears to be the biggest culprit.[19]

Although dialysis is an imperfect solution, it clearly prevents immediate death from uremia and reduces inflammation. At least 18 identified uremic toxins with a large molecular weight can be difficult to remove with dialysis.[20] Other changes to the immune system in uremic patients include an increase in Th22 cells, a decrease of Treg cells, increased TNF-α, increased CRP, increased Il-6, and decreased Il-10. Although increased dialysis time is the last thing most patients want, prolonged dialysis sessions do appear to alleviate some of the inflammation of uremia.[21]

In addition to cardiovascular disease, inflammation due to uremia can cause central nervous system disorders and muscle wasting diseases.

One category of uremic wastes that causes increased oxidative stress is advanced oxidation protein products (AOPP). This group includes indoxyl sulfate as well as several types of waste products: protein carbonyls, protein-bound di-tyrosines, and S-thiolated proteins. These inflammatory mediators increase along with creatinine and urea, the common indicators of uremic toxicity, but were also seen to increase with age. Higher AOPP levels were also associated with higher CRP and white blood cell counts.[22] Other uremic toxins involved in inflammation include p-cresol,[23] serum amyloid A,[24] endocan,[25] leptin,[26] and aluminum.[27]

Management of inflammation in late stage kidney disease should include efforts to control both inflammation and the underlying toxicity. The patient's own native kidney will always be better than renal replacement therapy – dialysis or a kidney transplant. Efforts should be made to preserve existing kidney filtration and help a marginally functioning kidney continue. (See article from June 2019. https://www.townsendletter.com/article/431-is-this-actually-chronic-kidney-disease-and-what-can-be-done-about-it/)

If these efforts fail, helping patients accept the need for dialysis is more constructive than encouraging them to hold out and rely entirely on natural means. It is interesting how people accept technology in every other area of life except for dialysis, a procedure that has been around more than 60 years. Dialysis is imperfect and doesn't clear all uremic wastes, but mechanically removing uremic waste is better than keeping it in. Many patients are under the impression that dialysis itself would hurt the kidneys or diminish kidney function, but this is not the case.

When it's time to start dialysis may not be entirely clear. In the past it was started with an eGFR < 15. Now many nephrologists begin treatment with an eGFR <5. Looking at creatinine, for many patients, plans to surgically create a dialysis access begin when creatinine approaches 6.0 and dialysis begins with creatinine around 8.0. If the nephrologist calls for dialysis earlier than would seem necessary, there may be a reason such as fluid overload. Nephrologists do not make the decision to start dialysis lightly. How the patient feels is not the determinant. Symptoms of uremia may be easy to ignore or completely absent. Kidney disease is called the silent killer for good reason.

The use of the right probiotics can be an important adjunct therapy for the uremic patient to reduce uremic toxicity and inflammation. Clinical trials have shown a significant reduction in CRP in end stage kidney disease patients who use probiotics.[28] Dysbiosis of the colon can drive overproduction of uremic toxins associated with inflammation. *Streptococcus thermophilus* was especially helpful in reducing mucosal pro-inflammatory activity.[29] Lactobacillus may also reduce the microinflammation of uremia,[30] as well as the specific strain *Bifidobacterium animalis* subsp. Lactis Bi-07.[31] Probiotics can even reduce homocysteine, which is an intestinal-derived uremic toxin.[32]

Another strategy is the use of activated charcoal to bind uremic wastes in the gut.

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Activated charcoal is especially effective at binding indoxyl sulfate. One study showed activated charcoal reduced the damage of indoxyl sulfate through several parameters, including improved vascular tone and preventing endothelial cell loss.[33]

Although supplementation is important, a good diet is also helpful. Many kidney patients with advanced kidney disease avoid high potassium foods due to cardiac stress of hyperkalemia. Yet reducing fruits, vegetables and yogurt will lead to a predominance of indole-producing intestinal flora and increased indoxyl sulfate. Proper food choice that include foods low in potassium yet high in fiber may improve gut health and reduce key uremic toxins.[34] Apples in particular are low in potassium and high in polyphenols, which protect from vascular oxidative stress.[35]

Besides reducing uremic toxins, adding antioxidants can also help inflammation in kidney patients. N-acetyl cysteine, quercetin, and curcumin have been shown to be especially effective with kidney patients. N-acetyl cysteine helped reduce oxidative stress triggered from AOPP and the respiratory burst of activated neutrophils.[36] Quercetin inhibits inflammatory compounds and radical oxygen species (ROS) in endothelial cells exposed to the sera of uremic patients.[37] Use of turmeric by dialysis patients reduced inflammatory markers including hs-CRP, Il-6 and TNF-α.[38]

Case Studies

Patient A is a 54-year-old, Hispanic-American woman who lost her kidneys to lupus. She has been on dialysis for two years. With an extremely high ANA, her doctors wish to control the lupus activity before she is considered a good candidate for a transplant. She has been offered immunosuppressive medication but has refused it. She tolerates hemodialysis well with sessions three times a week and has a good urea reduction as measured on monthly labs. Her potassium is well controlled with diet, and phosphorus is controlled with prescription phosphorus binders. She also takes Synthroid for low thyroid and Sensipar for high parathyroid. Renal anemia is controlled with synthetic erythropoietin injections on a monthly basis.

Her lupus symptoms have become progressively more severe since she lost kidney function. Patient complains of debilitating joint pain, especially in the neck and hips. She is also experiencing lupus alopecia with patches of thinning starting at the hairline on her forehead. She works a full-time job and has four children – two grown and two living at home. Husband is supportive but work stress is high. She has struggled for a long time with insomnia, and her current pain level makes sleep even more difficult. Her joint pain is especially bad upon awakening.

Patient has been on four different blood pressure medications over the past three years. She was especially eager to reduce her need for prescription medications. With guidance from her naturopathic doctor, she was able to reduce and then discontinue her medications. She is currently not on any medication for blood pressure but uses taurine, hibiscus, and beet powder extract.

She has tried a variety of approaches for her joint pain with limited success including glucosamine/ chondroitin, MSM, and curcumin. Epsom salt baths give temporary relief. She has seen a massage therapist, which was also somewhat helpful.

She agreed to try activated charcoal to bind the uremic waste products not cleared in dialysis. She started with two capsules of 560 mg taken two hours after lunch. Within 24 hours she noticed a dramatic improvement in her joint pain. With improved sleep her daytime energy also improved. As the charcoal was well tolerated, she increased the dosage to four capsules.

She was open to incorporating a probiotic into her routine and began using a specific formula for kidney patients. The patient continued curcumin and added NAC 500 mg TID. She noticed her energy level was much improved. Her alopecia so far is unchanged but is not continuing to get worse.

Patient B is a 77-year-old African-American male with long-standing hypertension. He has had bypass surgery and occasionally experiences angina and shortness of breath. Blood pressure is now controlled with a combination of supplements and prescription medications. His creatinine is 7.14 and eGFR is approaching 5. His nephrologist does not believe that dialysis would be well tolerated.

He has been on a number of supplements to support kidney function for several years. Given his history he is especially concerned with a potential cardiac event. There were no blood tests for indoxyl sulfate or other specific uremic toxins. However, adding probiotics and activated charcoal seemed to reduce his angina and shortness of breath. He was also willing to incorporate more low potassium fruits and vegetables like berries, apples, pears, green beans, cauliflower, zucchini, and onions. As he has a low urine output, he has a reduced intake of fluids and did not want to drink green tea. He is able to maintain a reasonable quality of life even without the intervention of dialysis.

In conclusion kidney patients have a high mortality rate due to secondary cardiovascular disease. Specific uremic waste products have a pro-inflammatory effect. This is pronounced with late stage kidney disease but can begin even early on. Efforts to control uremic toxicity and reduce inflammation may improve the prognosis in kidney patients and reduce the danger of a shortened life span.

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

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

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The Canary in the Coal Mine or How to Improve Kidney Function

by Dr. Douglas Lobay, BSc, ND

This article has been abridged from the original. Full article and references available at townsendletter.com.

Improving kidney function can be difficult and exasperating. As a practicing naturopathic physician, I am always interested in improving the health of my patients. True to the tenets of do no harm, treat the whole patient, and stress preventative medicine, I am looking for ways to improve kidney function in my patients. I have become particularly interested in variations of creatinine and glomerular filtration rate and declining levels of function at the stage 2 and stage 3 kidney disease. I have been fortunate to practice chelation therapy, and I have monitored kidney function in hundreds of patients. Over the years I have analyzed many blood chemistry panels and performed countless urinalyses in the office. I have evaluated kidney function based on serum creatinine levels and estimated glomerular filtration rate (eGFR). Through continuity of care I have compared lab values over time for many patients and tried to figure out what improves kidney function and what causes its decline. Like the canary in the coal that is sent down into mine shafts to sniff out toxins before the miners are sent in, finding ways to improve kidney function before irreversible kidney damage occurs can be indemnifying.

Diet and Kidneys

There is a direct association between water intake and kidney function. Water intake is related to chronic kidney disease, polycystic kidney disease, and nepthrolithiasis or kidney stones. Benefits have been noticed when urine output has been measured to be between 3 to 4 liters per day. Increased water intake blocks the renal vasopressin V2 receptor. A comprehensive literature review studied the effects of hydration on kidney function. Increased water intake decreases vasopressin levels. Hydration can improve kidney function in all forms of chronic kidney disease, recurrent renal calculi, and slow renal cyst formation. A beneficial effect on kidney function in patients who are at risk for development of chronic kidney disease was noted. Although increased hydration and reduced vasopressin secretion appear to slow progression in patients with chronic kidney disease, over-hydration can be detrimental in patients with end-stage kidney disease. Beneficial effects have been noted in patients with earlier chronic kidney disease, diabetic nephropathy, and nephrolitiasis.

A randomized controlled trial was conducted for one-year duration to study the effect of increased water intake on kidney function. Increased water intake was associated with a decreased concentration of calcium oxylate, calcium phosphate, and uric acid. Increased urine output between 2 to 2.5 liters per days was a consequence of increased water intake. Increased water intake was associated with a decreased growth rate of polycystic kidneys. Six hundred and thirty-one participants with stage 3 chronic kidney disease and a GFR between 30 to 60 ml/minute were selected for this study. The participants were coached to increase water intake by 1.0 to 1.5 liters per day (4 to 6 cups of water in addition to other beverages usually consumed). Plasma copeptin levels were directly correlated with anti-diuretic hormone or vasopressin levels. Vasopressin was the first hormone released during the early stages of dehydration. The increased level of vasopressin was correlated with early kidney disease. Other surrogate markers, including estimated glomerular filtration rate, copeptin, and microalmunuria, were measured. Increased water intake was associated with improved kidney function markers.

Fluid self-management recommendations were made for prevention of kidney stones based on epidemiological evidence. A urine fluid output of 2.5 liters per day or more was recommended. Potassium-rich foods protected against kidney stone formation. Increasing fluid intake of 500 ml of water per day decreased kidney stone formation. Tea and alcohol consumption also decreased kidney stone formation. Fruit juice, soda and pop did not decrease kidney stone formation and were suggested to increase rates. Coffee and milk showed inconsistent results and could not be recommended as a fluid to decrease kidney stone formation. The combined interaction of environmental exposure, dietary habits, and genetic factors cause kidney stones. Water intake is recommended to be three liters or greater per day to help prevent kidney stones. It is not the quality of water, rather the quantity of water consumed that matters in most cases. The correlation between water hardness, which increased mineral concentration, and the development of kidney stones remains controversial.

Low-protein and plant-based diets are beneficial in chronic kidney disease. Low protein diets can reduce protein intake, phosphorus and sodium. Plant-based diets are low in saturated fats, high in fiber, and high in unsaturated fats and potassium. These diets are low in creatine.

High salt intake can have detrimental effects on kidneys by affecting glomerular function. Increased glomerular hyper-

filtration, increased filtrate formation, and increased glomerular pressure are a consequence of high-salt consumption. Increased sodium intake blunts the anti-proteinuria effects of various drugs, including ACE inhibitors. Increased sodium further causes increased blood pressure, increased renal hypertrophy, renal fibrosis, decreased glomerular basement membrane, and decreased anionic membrane function. Restricting sodium intake is an important preventable measure in patients with chronic kidney disease.

A modest coffee intake of one to two cups per day decreased the risk of developing chronic kidney disease. The odds ratio of developing kidney disease was 0.76 with drinking one cup of coffee per day. The odds ratio of developing kidney disease was 0.80 by drinking two cups of coffee per day. Decreased plasma creatinine levels were observed in mice that consumed decaf coffee for two weeks. High-dose decaf coffee increased nucleotide activation in the kidney cortex, which increased kidney function. A meta-analysis of four observational studies with 14,098 people showed no significant association between coffee intake and development of chronic kidney disease. Interestingly however, the odds ratio was 0.81 in females and 1.10 in males.

Green tea consumption was associated with a decreased risk of developing kidney stones in a large prospective study of elderly Chinese people. The odds ratio was 0.78 in males and 0.80 in females. Green tea polyphenols protected the kidneys against oxidative stress damage in early renal damage.

Apple cider vinegar induces a protective effect on oxidative damage to the kidney in ovariectomized mice fed a high-cholesterol diet.

Dietary treatment of urinary risk factors for renal stone formation was assessed. A general conservative therapy was recommended. Decreased fluid intake was associated with decreased urine output less than 2 liters per day. Dietary calcium supplementation was not recommended. Dietary calcium less than 1 gram per day, low protein diet, and low sodium diet were recommended. Mild dietary salt intake was associated with decreased calcium excretion. Calcium supplementation was recommended between 800-1200 mg per day. A low normal protein diet was associated with decreased calcium loss. Alkaline citrate minerals were recommended. Increased fruit and vegetables excluding high oxalate food were suggested. Increased consumption of citrate foods and melons increased urinary citrate levels.

Recurrent kidney stone formation in patients with normal renal function who have a defect in ascorbic acid to oxylate metabolites should restrict vitamin C supplementation to less than 100 mg per day. However, a large scale prospective study showed that the group with the highest quintile of vitamin C intake, which was greater than 1500 mg/day, had the lowest risk of kidney stone formation.

Several botanicals and supplements are known to maintain and improve kidney function.

Vitamins, Minerals, and Kidneys

Oxidative stress is a disruption of the balance between the production of reactive oxygen species or ROS and antioxidant defense mechanisms. Oxidative stress was identified in early kidney disease. Suggested potential useful antioxidants have been identified in food and supplements. Some proposed antioxidant supplements include vitamin B, C, D and E, coenzyme Q10, L-carnitine, alpha lipoic acid, curcumin, green tea, flavonoids, polyphenols, omega-3 poly-unsaturated fatty acids, statins, trace elements and n-acetyl cysteine.

In a double-blind randomized controlled trial, 60 patients with diabetic nephropathy were supplemented with 1200 IU of vitamin E or placebo for 12 weeks. Vitamin E supplementation was observed to increase serum levels. Decreased protein to creatinine ratio, decreased tumor necrosis factor or TNF, decreased matrix metalloproteins, and decreased malondialdehyde levels were noted. No effects on other biomarkers of kidney disease were observed. Decreased levels of inflammation, kidney injury, and oxidative were also observed. Vitamin E supplementation of 300 milligrams per day for 12 weeks with 20 diabetic and 20 non-diabetic patients with end stage kidney disease undergoing hemodialysis. Vitamin E supplementation improved HDL levels and vascular endothelial function.

High homocysteine has been correlated with kidney disease. Low levels of vitamins B12, B9, and B6 have been associated with high homocysteine levels. One hundred and forty-eight patients with chronic kidney disease from the Ukraine were measured for homocysteine levels; 58.7% of patients had high homocysteine levels. Homocysteine was believed to be a specific indicator of low vitamin status, especially for vitamin B9 or folic acid.

Long-term intake of vitamin D resulted in an increased risk of hypercalcemia and hypercalcuria, which appeared to be not dose related. However, vitamin D supplementation did not increase the risk of kidney stone formation. It was recommended that large randomized controlled trials of vitamin D are needed to confirm these findings.

Magnesium is utilized for over 300 different biochemical reactions in the human body. Magnesium helps to decrease vascular calcium and decrease phosphate absorption.

Supplements and Kidneys

Coenzyme Q10 is a strong antioxidant and mitochondrial nutrient. Decreased Q10 levels have been observed in patients with chronic kidney disease. A meta-analysis of seven randomized controlled trials of patients with chronic kidney disease were selected from 721 potential papers from PubMed, Cochrane, and other medical databases were selected. Coenzyme Q10 supplementation was associated with decreased total cholesterol, decreased LDL cholesterol, decreased malondialdehyde, and decreased creatinine levels. Triglyceride levels as well as HDL cholesterol, glucose, insulin and CRP levels were not affected by Q10 supplementation. The effect of coenzyme Q10 supplementation was studied on 72 rats exposed to radiation-induced nephropathy. Q10 was administered at a dose of 10 mg/kg body weight. Signs of poor kidney function were observed after radiation exposure. Q10 supplementation decreased BUN and creatinine levels. Q10 seemed to attenuate glomerular and tubular function in irradiated

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kidneys. Administration of Q10 seemed to alleviate radiation induced kidney damage. The effect of benfotiamine, a derivative of vitamin B1 or thiamine and co-enzyme Q10 was studied a group of rats that had gentamycin-induced kidney damage. Gentamycin was severely toxic to rats. Benfotiamine supplementation decreased nephrotoxicity, decreased BUN and creatinine levels and decreased malondialdehyde levels. Q10 supplementation decreased necrotic tubular tissue levels and hyaline accumulation.

Resveratrol is a natural polyphenolic compounds found in grapes and other compounds. Resveratrol is a robust antioxidant that scavenges reactive oxygen species or ROS. Resveratrol is also a SIRT-1 activator, which increases enzyme functions, decreases apoptosis, and increases mitochondrial biogenesis. Resveratrol has demonstrated to have some renal protective effects.

N-acetyl cysteine or NAC administration ameliorates renal function by decreasing oxidative damage as observed in Wistar rats with induced kidney damage following bilateral ureteral obstruction.

Acetyl-l-carnitine improved energy metabolism in the kidneys of hypoxic-ischemic brain-injured rats. L-carnitine levels have been observed to be low in patients with advanced kidney disease. A systematic review of the evidence of carnitine and kidney disease was undertaken. Fourteen references were identified for review. A meta-analysis shows some useful pieces of information and the potential benefit of carnitine supplementation in patients with advanced kidney disease. The authors recommend carrying out better designed studies to show the potential benefits of this supplement.

Lipoic acid is a free radical scavenger of reactive oxygen species (ROS) and nitric oxide (NO). It's mechanism of action is not completely understood but is believed to operate with different kinase pathways. Lipoic acid is known to affect multiple signaling pathways and has demonstrated renal protective effects in contrast-induced kidney injury.

Melatonin prevents drug-induced renal injury by decreasing inflammatory cytokine production and decreased aquaporin water channels in male rat's kidneys with bilateral ureteral obstruction.

Herbs and Kidneys

Berberine showed antioxidant, anti-apoptotic, and anti-inflammatory activity in 30 diabetic rats exposed to nephrotoxic streptozotocin. Decreased levels of BUN and creatinine were observed with berberine doses of 100 and 150 milligrams per kilogram. Improved histopathological kidney function was also observed with declining levels of BUN and creatinine. Increased free fatty acids and disturbed mitochondrial function play a role in diabetic kidney disease. Diabetic mice were fed berberine for eight weeks. Berberine reversed glucose and lipid metabolic podocyte damage, basement membrane thickening, mesangial expansion and glomerular sclerosis. Decreased podocyte apoptosis was also observed. Berberine demonstrated a protective effect on kidney and liver function in rats exposed to iron overload for two weeks. Increased iron consumption increased oxidative damage causing histopathological changes to these organs. Elevated levels of oxidative damage also increased malondialdehyde levels, which is a marker of oxidative damage. Berberine protected the liver and kidney against ferrous sulphate-induced toxicity, reduced lipid peroxides, and also chelated iron. Chronic diabetic kidney disease causes microvascular damage to the renal glomerulus and causes interstitial fibrosis to the renal tubules. Berberine showed a significant positive effect by decreasing total blood sugar levels, improving renal hemodynamics, improving lipid profiles, and was shown to attenuate local and systemic inflammation.

Berberine protects renal tubular cells from ischemia and reperfusion injury in rats. Berberine protects renal tubular epithelial cells from hypoxia and reperfusion mitochondrial dysfunction by regulating sirtuin-2 and c53 pathways. Berberine also protects renal tubular epithelial cells from hypoxia and apoptosis through activation of HIF-1alpha in the signaling pathway suggesting that berberine could be a potential drug in diabetic ketoacidosis.

Hydrangea or Hydrangea paniculata extract was given to mice with cisplatin-induced kidney damage. Improved renal function was observed with decreased creatinine and BUN levels. The coumarin glycosides of this plant were believed to attenuate oxidative stress, decrease tubular injury and decrease apoptosis. Decreased inflammatory cytokines and regulation of protease enzymes, including caspase, an enzyme involved in inflammation and programmed cell death, were noted. Hydrangea extracts ameliorated kidney damage by antioxidant activity and suppressing harmful renal infiltrates and tubular apoptosis. Decreased renal infiltrates down regulated signaling pathways, which further decreased macrophage and neutrophil activation.

Hydrangea extracts containing coumarin were given to mice with acute septic kidney injury. Bioactive coumarin compounds isolated from *Hydrangea paniculata* were identified to be umbelliferone and esculetin. Hydrangea demonstrated specific anti-oxidant and anti-inflammatory activity on kidney tissue. Decreased infiltrate of macrophages and neutrophils in renal infiltrate was noted. Decreased BUN levels and decreased tubular interstitial injury were noted. Improved kidney function and increased animal survival were observed. Water extracts of *Hydrangea paniculata* were rich in coumarin glycosides. A water extract of this plant was given to diabetic rats that were exposed to strepozotocin kidney damage. Hydrangea extracts were given once per day for three months. A decrease in BUN and creatinine was observed. The hydrangea extract upregulated some enzyme activity and decreased other signaling pathways.

Silybin from milk thistle (*Silybum marianum)* protected against cisplatin-induced acute kidney injury. Silybin increased sirtuin-3 or Sirt-3 expression in mice, which was shown to protect against cisplatin-induced kidney damage by decreasing tubular apoptosis and increasing mitochondrial function. A standardized mixture of silymarin flavonolignans from milk thistle has demonstrated antioxidant activity for reactive oxidant species (ROS). Contrast-induced nephropathy caused tubular injury in mice kidneys. Silymarin preserved renal function by improving glomerular and tubular function in a dose

dependent manner in mice exposed to contrast injury.

Apigenin is a flavonoid isolated from celery (*Apium graveolens*). Apigenin is an anti-hypertensive flavone that is abundant in celery. Apigenin acts as an agonist of transient receptor-potential vanilloid-4 or TRPV4 in rats. Apigenin has demonstrated promising anti-hypertensive activity in treating hypertensive-induced renal damage in those who consume a high sodium diet. A hydroalcoholic extract of celery was used to treat uncomplicated urinary tract infection in mice caused by uropathogenic *E.coli*. A direct anti-adhesive effect of celery on the urinary epithelium was observed in a dose dependent manner within four to seven days of treatment. The extract significantly reduced the bacterial load in uncomplicated UTIs in this group of mice. In another study, rats were exposed to a chlorinated propanediol chemical that induced kidney damage. Apigenin decreased serum creatinine and reduced kidney damage by modulating mitochondria dependent caspase activity.

An herbal decoction of the Chinese medicine *Huangqi-Danshen* was fed to a group of rats for four weeks. Improved levels of BUN and creatinine were observed after treatment. Decreased tubular atrophy and decreased interstitial fibrosis was also observed. Also improved mitochondrial function was also observed in kidney tissue of these animals. A water extract of *Salvia miltiorrhiza* called Danshen was studied against renal injury in rats exposed to cadmium. The salvia extract displayed antioxidant activity, decreased swelling of renal tubule epithelial cells, and improved overall renal function. Salvia miltiorrhiza extract was given to diabetic rats and was shown to decrease renal injury and damage and improve glycolipid metabolism. Multi-modal effects were observed, including phospholipid, arachidonic acid, wnt/B-catenin and TGY-B signaling inhibition. Salvianolic acid A (SAA) is a phenolic carboxylic acid derivative of *Salvia miltiorrhiza*. SAA helped to decrease inflammation and decrease renal tubular fibrosis in six rats that were exposed to doxorubicin-induced nephrotoxicity. SAA was believed to be a signaling molecule that decreases activation of natural factor beta-kappa (NF-KB) and thereby decreases inflammatory pathways.

An aqueous extract of parsley (*Petroselinum sativum*) was studied on a group of rats. The parsley extract showed diuretic effects including decreased sodium reabsorption, decreased potassium secretion, increased potassium concentration in the intercellular space, and decreased potassium efflux across cellular tight junctions. An inhibition of sodium/potassium pump activity was noted leading to a reduction of sodium reabsorption and potassium loss. The effects of an aqueous extract of parsley on ethylene glycol-induced kidney calculi in rats were studied. A decrease in calcium oxalate stone formation and deposition were noted.

The effect of Diyarbakir watermelon juice on lipid peroxidation was studied in rats after exposure to carbon tetrachloride. The watermelon juice showed antioxidant activity and inhibition of lipid peroxide formation. However, excessive watermelon consumption was associated with high potassium levels or hyperkalemia and increased symptom burden of end stage renal disease. The anti-urolithiatic and diuretic effects of watermelon (*Citrullus lanatus*) was studied in a group of male rats. Kidney protective effects and a suppression of calcium oxylate precipitation were noted. Increased creatinine clearance, decreased urea, decreased sodium and urinary output were also observed. Watermelon pulp displayed significant anti-urolithic and diuretic activity.

Thirty-four neutered cats were put on a nutraceutical diet containing Lespedeza, Vaccinium and Taraxacum herbs for 90 days. There was a significant decrease in BUN, creatinine in lab samples and a decrease in total protein lost from their kidneys. Researchers compared the effects of taraxasterol aqueous extract from dandelion (*Taraxacum officinale*) aerial parts and potassium citrate on oxylate crystallization in vitro. Taraxasterol and potassium citrate extract decreased calcium oxylate crystallization more than taraxasterol alone. It was hypothesized that there was a synergistic effect between Taraxacum extracts and potassium citrate.

The effect of green asparagus (*Asparagus officinalis*) extract was studied in hypertensive rats. A constituent of asparagus, 2'-hydroxynicotianamine, was believed to act as an angiotension converting enzyme or ACE inhibitor. The asparagus extract decreased blood pressure levels and improved renal function. The effect of asparagus extract was studied in bisphenol-causing liver and kidney damage in Wistar rats. Coadministration of asparagus extract and bisphenol exposure increased total antioxidant capability and decreased malondialdehyde levels, which is indicator of oxidative stress. Decreased levels of oxidative damage to liver and kidneys with asparagus consumption were noted.

Black seed (*Nigella sativa*) has been used in the prevention of kidney stones. In a placebo controlled double-blind study 60 patients consumed 500 mg of black seed or placebo twice per day for 12 weeks. Those who consumed black seed were 44.4% more likely to excrete kidney stones compared to 15.3% who took placebo. The black seed treated group showed a decrease in the size of kidney stones in 51.8% of people while stone size was unchanged in 57.6% of those who took a placebo. The effect of black seed oil was studied in cisplatin-induced nephropathy in rats. The group that consumed black seed oil showed a marked decrease in histopathological changes to kidney tissue. Black seed displayed antioxidant activity and was shown to modulate enzyme activity in the kidney.

The long-term survival rate was studied in retrospective analysis of Taiwan patients with chronic kidney disease who took a Chinese herbal medicine containing *Rheum officinale*. The Chinese herbal medicine improved long-term survival in patients with CKD suggesting that this medicine is an effective adjuvant in individuals with chronic kidney disease.

An aqueous extract of hibiscus (*Hibiscus sabdariffa*) was given to rats for 28 days with adenine-induced kidney disease. The hibiscus extract demonstrated a similar effect to the angiotensin converting enzyme or ACE inhibitor drug lisinopril. The hibiscus extract was further demonstrated to decrease the progression of chronic kidney disease.

Goldenrod (*Solidago virgaurea*) has been used for centuries for the treatment

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of urinary tract disease. Goldenrod has displayed anti-inflammatory, anti-urothiac, diuretic, anti-spasmodic, and analgesic effects. Goldenrod has been used for urinary infections and inflammation, to prevent kidney stone formation, and to remove urinary gravel. It appears to be safe and non-toxic and no adverse side effects were noted.

Curcumin was reported to have kidney protective effects. Four hundred and fourteen patients with chronic kidney disease with a glomerular filtration rate between 15 to 60 ml/min were included in this randomized controlled trial. Patients consumed 90 milligrams of micro-particle curcumin once daily or placebo for six months.

Butein from Chinese lacquer tree (*Rhus verniciflua*) has been shown to improve kidney function in cisplatin-induced acute renal failure in rats. Butein upregulates aquaporin 2 channels in the kidney cortex and medulla.

Other herbal medicines have also been suggested to improve kidney function, including beets, chamomile, *Chanca piedra*, cinnamon, ginger, gravel root, horsetail, marshmallow, nettles, and uva ursi to name a few.

Toxins and Kidneys

Certain dietary supplements and herbs have been identified to cause potential kidney toxicity and renal damage. Implicated herbs include Chinese yew (*Taxus celebica*), *Callilepsis laureola*, morning cypress (*Cupressus tunebris*), Saint John's wort (*Hypericum perforatum*), Thunder God vine (*Tripteryglum wildfordi*), tribulus (*Tribulus terrestris*), and wormwood (*Artemnesia alba*). Herbs no longer sold in the US include chocolate vine (mu tong or *Caulis aristolochiae*), Guang fang ji (*Artistolochia fungchi*), and Ma huang (*Ephedra sinensis*). Other dietary supplements include sheep bile, chlorella, chromium, creatine, fish gall bladder, glucosamine, hydrazine, NO-xplode, Spanish fly, and excessive consumption of vitamins A, C, D and germanium. In descending order of toxicity, the top two offenders were aristolochic acid in the herb *Guang fang ji* and chocolate vine. Kidney toxic foods include ajenkol bean, gall bladder from carp fish, puffer fish, star fruit, and uncooked yam powder or juice.

Aristolochic acid from Aristolochia species of herbs causes nephropathy. In the 1990s aritstolochia was used in various weight-loss products. Consumption of products containing aristolochic acid causes kidney injury and renal damage. Increased serum creatinine, significant anemia, and histopathological changes in renal interstitial infiltrates causing severe fibrosis occurred.

Chronic kidney disease is associated with an increased level of uremic toxins. Certain toxins may be modified by the gut microbiota. Potential toxins identified include phosphates, l-carnitine, choline, phosphatidylcholine, tryptophan and tyrosine, tri-methylamine-n-oxide, indoxy sulphate, p-cresyl sulfate, and indole-3 acetic acid.

Recommendations

It is clear that diet and nutrition play an important role in kidney function. Water intake can be measured and increased in individuals with stage 2 and 3 chronic kidney disease. There are exceptions to increased water intake especially with people with lung and peripheral edema. Fluid restrictions are further necessary in individuals with advanced kidney disease, including stage 4 and 5 levels. Salt and sodium should be restricted in usually all levels of kidney disease, especially with high dietary intake. Protein intake can be measured and modulated in individuals with high dietary intake. Electrolyte levels, including potassium and phosphorus, can be monitored and measured along with creatinine and GFR in basic lab tests. Recommendations can be made after reviewing lab values. Eating a diet rich in fresh fruits, vegetables, whole grains and cereals and high-quality protein is strongly suggested. Limiting processed foods, highly refined sugar foods, excessive protein and alcohol is also suggested. Eating better can perhaps help kidney function and improve overall health.

A review of the scientific literature suggests that vitamins and minerals, supplements and herbal medicines may help to maintain and, in some cases, improve kidney health. Many of the studies are done on animal models that include rats and mice. While interesting it is important to note that these are not humans. There are some human studies that are interesting and show benefit, but it clear that most of the conclusions are preliminary at best. Further randomized double blind placebo-controlled trials are suggested with larger patient populations and limiting extraneous factors. This is not to say that certain nutrients and supplements are not beneficial and cannot actually improve kidney function. There are many vitamins, minerals, supplements and herbal medicines as discussed in this article that have been shown to prevent kidney decline and may improve renal function. How they combine with other nutrients is not known but probably not harmful in recommended doses. They are certainly worth a try with individuals with declining kidney function, especially earlier in stage 2 and 3 levels of kidney disease. Discussing a treatment plan with a licensed naturopathic physician or other qualified health professional is recommended. Of course, it is caveat emptor or patient trial and error. Like the canary in the coal mine, I think kidney function decline with early kidney disease can be averted with dietary changes and nutritional supplementation. ◆

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This article has been abridged from the original. Full article and references available at www.townsendletter.com.

Unusually Quick Recovery to an Achilles Tendon Tear By Self-Treatment

by Davis W. Lamson, MS, ND, and John A. Sherman, ND

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A 70-year-old man, in good physical condition from regular engagement in basketball, presented with an Achilles tendon tear acquired playing basketball. Achilles tendon tears come in degrees and variable severity, from complete tendon rupture to minor fibrous tear. Determination of severity usually requires magnetic resonance imaging, but all cases present with common signs and symptoms, including calf pain and swelling. MRI was not ordered in the case described per emergency department protocol, but the resulting pain and debility required an immobilizing walking boot and crutches for mobility.

Achilles tendon repair is a relatively frequent occurrence in athletes, most commonly in ages 20-39, and has been a challenging orthopedic problem in promoting hasty recovery. The Achilles tendon is the largest in the body, and such injuries usually require 12 weeks to four-to-six months for recovery.[1] Injuries to the Achilles tendon are common in "weekend warriors" who play basketball, tennis, or racquetball infrequently. Avoiding weight bearing, a 24-hour walking boot to prevent dorsiflexion, and regular icing and rest are critical to a speedy recovery. In the case described below, recovery was surprisingly expedited to only four weeks. Details are below.

The Event

Patient presented two days after the injury, which he described as if "a spear" penetrated his posterior calf. At the time, he thought that another player had landed directly on his leg, although no others were close by. The injury occurred while jettisoning his entire body weight forward on the injured leg at maximum speed (for a 70-year-old), similar to a 50-yard dash track star, pushing off "the blocks." At presentation the inferior leg was quite edematous, with moderate ecchymosis, and very painful to palpation. Ambulation was difficult, with limping and pain, and only slight weight bearing tolerable on the heel. Thompson sign was negative (Squeezing the calf while patient is prone. A positive sign elicits no movement of the ankle). He also showed ability to point his toes in different directions. He was immediately instructed to avoid weight-bearing, acquire an immobilization boot, and walk only with crutches.

Treatment

In searching the National Library of Medicine (PubMed) for Achilles tendinopathy, an in vivo study was found in which rats with ruptured Achilles tendons were treated by injection of 150 mg of ascorbic acid every two days.[2,3] Increased angiogenesis was evident by the third day and significant increase in collagen synthesis by the tenth day, for which ascorbate is a known requirement. Treatment decision was made for oral administration of vitamin C four times daily because blood level only remains elevated for a few hours per dose. Further, as dimethylsulfoxide (DMSO) carries molecules through the skin efficiently, a DMSO solution of ascorbic acid was used for direct application to the Achilles tendon area three times daily. Treatment details follow:

1. A 90% aqueous DMSO solution was used as it dries the skin less.
2. The patient was instructed how to prepare a saturated solution of vitamin C (about 10 mg per ml), 30 ml at a time. (Use of 1/8 to 1/4 teaspoonful of vitamin C powder per 30 ml of solution leaves a small amount of undissolved material for a saturated solution.)
3. Application was by eyedropper to the cleaned affected area and rubbed in with clean fingers. After a few minutes for absorption, the area was wiped. Application was three times daily.
4. As the solution gradually becomes yellow colored, it was prepared fresh weekly. Refrigeration slows coloration.

Discussion

Because of the initial severity of the injury and the speed of recovery, it is thought that the vitamin C/DMSO treatment was responsible for the unexpectedly rapid rate of healing. While vitamin C is required for collagen protein regeneration, DMSO is well known as an anti-inflammatory and so probably both helped the situation. Thus, it is not possible to say which agent was more contributory, since every injury produces inflammatory chemistry causing further tissue damage, which causes more inflammation in a feed forward manner.

Success in a single case does not allow any generalization, so it is not known whether this simple procedure of patient self-treatment will allow a shorter, less expensive, and less complicated resolution of Achilles tendinopathy than the varieties recorded in the National Library of Medicine. However, the success of this one case was deemed worthwhile to share with other like-minded physicians, dealing with common tendinopathy injuries.

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Innovative Solutions for NAFLD

by Carrie Decker, ND

As we move well into the 21st century, diseases related to a sedentary lifestyle and an overabundance of food are increasingly common. The rate of type 2 diabetes (T2D), a condition that was estimated to affect 120 million people worldwide in 2000,[1] has quadrupled in global incidence over the last three decades.[2] Diabetes and obesity are often accompanied by nonalcoholic fatty liver disease (NAFLD), a condition characterized by fat, in the form of triglycerides (TGs), accumulating in the liver.[3] Nonalcoholic steatohepatitis (NASH), a more severe form of NAFLD that also involves inflammation, was first described medically in 1952 and not identified as a disease until 1980.[4,5] Nowadays, recent surveys have shown that about 30 to 40% of adults have NAFLD and 3 to 12% are affected by NASH.[6,7] The numbers are shockingly high in those who are obese or affected by diabetes: 30 to 90% of individuals who are obese and 60 to 75% of individuals with T2D have NAFLD.[8-10]

Four natural substances can help resolve fatty liver disease.

Botanical substances with clinical evidence for their use in the setting of NAFLD are milk thistle and berberine. Many are well acquainted with milk thistle as a hepatoprotective herb and with berberine's metabolic regulating aspects, but they may not be aware of the clinical data in the setting of NAFLD, which will be reviewed herein. Additionally, two nutritional interventions that we probably don't think of as agents for metabolic and liver disease, melatonin and molecular hydrogen, also have clinical evidence suggesting they may be of benefit and will be discussed in regard to their use for these conditions.

Milk Thistle

Milk thistle (*Silybum marianum*) is well known for its liver-protective effects. Not surprisingly, this botanical has also been investigated for the treatment of NAFLD in several clinical studies. The active compounds found in milk thistle, silybin and silymarin, have been shown to activate a nuclear bile acid receptor known as farnesoid X receptor (FXR) in hepatocytes. FXR regulates bile acid, glucose, and lipid metabolism[11] – each of which plays a role in liver health. Activation of FXR by silymarin has been shown to down-regulate inflammatory pathways and metabolic dysfunction induced by high-fat diet (HFD) feeding.[12] Medications that interact with FXR in a similar manner to these milk thistle-derived compounds are also being investigated for the treatment of NAFLD.[13] Silymarin has additionally been shown to increase both hepatic and intestinal glutathione levels, which tend to be lower in individuals with NAFLD.[14,15]

Clinical studies have shown milk thistle improves various parameters associated with NAFLD. A 2017 meta-analysis found that treatment with milk thistle significantly reduces alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by 5.08 IU/L and 5.44 IU/L, respectively, in patients with NAFLD.[16] Dosages ranged from 140 mg once a day to 200 mg three times a day, for a duration of eight to 24 weeks. After eight weeks at the lowest dosage of 140 mg daily, significant improvements were seen in fasting blood glucose (FBG), lipid profiles, and serum insulin levels; additionally, AST and ALT were reduced from 56 to 37.77 IU/L and 78.73 to 53.05 IU/L, respectively.[17]

Milk thistle has also been investigated for the treatment of NAFLD in children ranging from five to 16 years of age.[18] In this population, silymarin was provided in divided dosages at mealtime with a total dose of 5 mg/kg/day. Children diagnosed with NAFLD (based on history, physical examination, liver sonography, and liver enzymes) were randomized into two groups, with the control and intervention groups both being recommended lifestyle interventions (LI) of 150 to 250 minutes of walking a week and a low-fat and low-carbohydrate diet. After 12 weeks of the interventions, the children receiving silymarin in addition to LI had a significantly lower grade of fatty liver and significantly improved AST and ALT levels, while none of these parameters changed significantly in the control group.

Berberine

Berberine is another botanically derived substance that has numerous mechanisms by which it may help protect against NAFLD and support its resolution.[19]

The antidiabetic and lipid-balancing effects of berberine have been demonstrated in several clinical trials,[20] and may be means via which berberine positively affects liver function. Berberine has been shown to alter metabolism-related gene expression and bile acid metabolism via pathways involving FXR as well.[21] In animals, berberine has been shown to have the effect of preventing HFD-associated obesity and hepatic triglyceride accumulation in wild-type (normal) mice, but not in those that had the genetic elimination of intestinal FXR expression. Berberine has also been shown to suppress obesity-associated inflammation and hepatic steatosis in mice by decreasing phosphorylation of the inflammatory complex known as JNK1,[22] a protein kinase implicated in the development of steatohepatitis.[23] JNK1 is strongly activated by environmental

stressors and pro-inflammatory cytokines. Berberine also has direct anti-inflammatory effects.[24]

Liver enzyme elevation and fatty liver changes are often seen in gastrointestinal conditions including small intestinal bacterial overgrowth (SIBO),[25] celiac disease,[26] and inflammatory bowel disease.[27] Common to each of these conditions is dysbiosis and increased gastrointestinal permeability, which conventional hepatologists and gastroenterologists even point to as an underlying factor contributing to NAFLD.[28,29] The action of berberine in the gut also may be a mechanism via which it improves fatty liver changes, as it has been shown to affect the gut microbial balance and improve tight junction integrity, reducing intestinal permeability.[30-32]

The benefits berberine offers for NAFLD have also been demonstrated in a randomized, parallel controlled, open-label clinical trial.[33] Patients with NAFLD (diagnosed if liver fat content exceeded 13%, as assessed by proton magnetic resonance spectroscopy) were prescribed LI changes (diet and exercise per standard guidelines), while one of the groups was additionally prescribed berberine, at a dose of 500 mg thrice daily for 16 weeks. At the end of the study period, the group additionally receiving berberine had significantly lower hepatic fat content and body weight as well as improved glucose and lipid profiles compared to the population who only implemented LI changes. Interestingly, the parallel animal model showed that berberine preferentially distributes to the liver following oral administration, with levels shown to be more than 50 times higher in the liver than the plasma.

Melatonin

In recent years, there has been considerable research regarding the use of melatonin for metabolic disease and its consequences.[34,35] In addition to its antioxidant and sleep cycle regulating effects,[36] melatonin is involved in metabolism and affects insulin signaling, cellular glucose uptake, the balance of white and brown adipose, and adipokine secretion, among other things.[37-39]

Benefits with melatonin supplementation have been seen in obese patients following a calorie-restricted diet, where, compared to placebo, supplementation of 10 mg of melatonin at bedtime improved markers of oxidative stress, regulated adipokine secretion, and supported weight loss.[40] Other clinical studies have also shown melatonin may help ameliorate metabolic issues associated with antipsychotic medication use and the inflammation and oxidative stress associated with obesity.[41-44]

Liver disease is accompanied by oxidative stress, whether it is one of the initiating factors or a consequence of disease. Hepatic mitochondrial dysfunction, often due to oxidative stress, is a contributor to hepatic fibrosis.[45] Melatonin has been shown in several animal models to improve hepatic mitochondrial dysfunction and associated oxidative stress.[46,47] Because melatonin is found at a high concentration in the mitochondria (possibly even being *produced* by this organelle), this may be one of the key cellular locations where its protective effects have their greatest impact.[48,49] ➤

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In patients with histologically-proven NASH, supplementation with 5 mg of melatonin twice daily (in the morning and before bed) for 28 days significantly improved insulin resistance, AST, ALT, and gamma-glutamyl transferase (GGT) compared to baseline levels.[50] In this study, much like the others investigating melatonin as an intervention for metabolic disease, despite the morning dosing, there were no reports of somnolence or other side effects.

A longer three-month study of individuals with biopsy-diagnosed NASH also used this same dosing regimen.[51] Those taking melatonin experienced significant improvements in AST and GGT compared to placebo and baseline, with reductions of 38 and 47%, respectively, at 12 weeks. ALT levels were also reduced significantly compared to baseline. With the continuation of the intervention for an additional 12 weeks, improvements were maintained, although an addition 12 weeks later (after discontinuing treatment), AST levels returned close to baseline.[52]

An additional study investigated melatonin as a therapy for statin-induced liver enzyme elevation, finding that treatment with 5 mg of melatonin twice daily for six months significantly improved AST, ALT, and GGT compared to placebo.[53] In this study, mild morning fatigue was noted in 20% of the individuals taking melatonin for the first two weeks, but was not reported after this point.

A review of the research pertaining to melatonin and liver disease suggests that melatonin may be useful for an array of additional insults to the liver including environmental toxicants, mycotoxins, medication overdoses, alcohol use, surgery, radiation exposure, viral infection, and cancer.[54]

Molecular Hydrogen

Molecular hydrogen (H2) is a novel tool that also may be useful in the fight against metabolic disease and its consequences, as well as numerous other health concerns. With positive findings from more than 15 clinical studies ranging from treatment-resistant psoriasis to Parkinson's,[55,56] the ability of this small molecule with substantial antioxidant and anti-inflammatory potential to easily traverse cellular membranes and biological barriers makes its use as a therapy potentially applicable to every human disease condition.[57] Not surprisingly, in the last two decades, there have been over 1000 scientific studies on the therapeutic application of H2,[58] reflecting over 170 different human and animal disease conditions or models.[59]

Both metabolic syndrome and NAFLD have clinical evidence they may be improved by treatment with molecular H2. Clinically, consumption of 900 mL of H2-rich water for eight weeks was shown to significantly decrease levels of modified low-density lipoprotein (LDL) cholesterol; small, dense LDL; and urinary 8-isoprostanes (a marker of oxidative stress) in patients with T2D or impaired glucose tolerance (IGT).[60] In four of the six patients with IGT, treatment with the H2-rich water also normalized the oral glucose tolerance test. In an open-label pilot study of subjects with potential metabolic syndrome, consumption of 1.5 to 2 L of H2-rich water daily for eight weeks improved high-density lipoprotein (HDL) cholesterol and the ratio of total cholesterol to HDL cholesterol, also improving markers of antioxidant status and lipid peroxidation.[61]

Animal models show H2 is hepatoprotective in the common challenges of alcohol and acetaminophen-induced injury,[62,63] restoring glutathione and antioxidant enzyme levels, even promoting liver regeneration. Multiple studies have also investigated H2 as a therapy for fatty liver disease and the prevention of its complications. Similar to the other research, in animal models of fatty liver disease, treatment with H2 decreased oxidative stress, inflammation, and tissue damage, as well as reduced hepatic lipid accumulation.[64,65] Investigation into the effect of dose found that treatment with a higher level of H2 was more protective, also resulting in an increase in lean body mass.[65] In the standard model of NASH-induced hepatocarcinogenesis, a reduction in the amount of tumors and their size was seen with H2 treatment.[64]

In a small randomized, double-blind, placebo-controlled study with a two-week washout, the effects of H2 were studied in 12 overweight patients with mild to moderate NAFLD. Participants were instructed to consume 1 L of H2-rich water or placebo daily for 28 days. After treatment with the H2-rich water, individuals were found to have significantly decreased liver fat accumulation (as assessed by dual-echo MRI) compared to treatment with placebo, as well as a reduction in AST levels.[66] No other parameters evaluated were significantly altered by the treatment.

Conclusion

Given the increasing rate of incidence of NAFLD in both adults and children and the lack of an indicated pharmaceutical treatment, natural strategies for the treatment of this condition stand well-poised as the "next-best thing." In addition to these interventions, therapies such as vitamin E (tocopherols and tocotrienols),[67,68] essential fatty acids,[69] choline,[70] and probiotics[71] also have substantial evidence suggesting they may help resolve this increasingly common condition. ◆

Dr. Carrie Decker graduated with honors from the National College of Natural Medicine (now the National University of Natural Medicine) in Portland, Oregon. Prior to becoming a naturopathic physician, Dr. Decker was an engineer and obtained graduate degrees in biomedical and mechanical engineering from the University of Wisconsin-Madison and University of Illinois at Urbana-Champaign respectively. Dr. Decker continues to enjoy academic research and writing and uses these skills to support integrative medicine education as a writer and contributor to various resources. Dr. Decker supports Allergy Research Group as a member of their education and product development team.

References can be accessed at www.townsendletter.com

Letters to the Editor

Re: What Can Really Stop Binge Eating?

The January 2020 *Townsend Letter* included an article on the treatment of binge eating by psychiatrist and author James Greenblatt. Dr. Greenblatt is a dedicated and innovative force in the otherwise desolate field of eating disorders treatment; I highly recommend his book, *Answering Anorexia* and enjoyed much of his January article. However, the article's crucial recommendations for the treatment of *over*eaters with individual amino acids are inadequate and misleading. Particularly at this time, when supporting immunity is so vital and diet generally so poor, health practitioners need to know how best to help clients overcome their food cravings.

Note: When I contacted Dr. Greenblatt about my concerns, he responded that much of his article was excerpted, unchanged, from an older edition of his book on this subject and that he now chooses from the much-expanded list of therapeutic aminos that I have included in this letter.

Amino acid therapy is the only real hope for most of those now over-consuming health-damaging foods. The food industry has systematically created a worldwide dependence on edible, but nutrient-void, drugs that are intended to disable the brain's five-part appetite-regulating system. This system relies on a steady supply of very specific amino acids. Each overeater's appetite-regulating dysfunction can be accurately assessed, and appropriate repair-aminos selected. Most victims of the physically addictive American diet can recover by supplementing with one to five of these aminos. The resulting craving-elimination is almost immediate.

First Aid for the Food Addicted

Dr. Greenblatt's article recommended two aminos: 5-HTP and DLPA. We now know that there are nine amino acids that can be used to stop the five types of compulsive eating. For almost every type there are two choices. If one has negative or weak effects, the alternate typically works well. The lowest and safest starting doses for adults are listed in parentheses behind each amino:

1) *Either* Tryptophan (500 mg) *or* 5-HTP (50 mg) can correct the underlying *serotonin* deficits in those who binge for relief of worry, depression, obsessiveness, insomnia, and other low-serotonin symptoms.
2) *Either* GABA (125 mg) *or* Theanine (100 mg) can stop stress-eating by correcting *GABA* deficits.
3) *Either* DPA (D-phenylalanine, 500 mg) *or* DLPA (500 mg) can correct the *endorphin* deficits that drive comfort-food cravings.
4) Glutamine (500 mg) can instantly stop hypoglycemic cravings for sugar, starch, or alcohol.
   Any of the above aminos can be taken alone or together, as needed, typically two-to-three times a day at first, as the effects of the aminos only last about four hours, initially.
5) *Either* Tyrosine (500 mg) *or* Phenylalanine (500 mg), taken in the early part of the day, can correct *dopamine* and *norepinephrine* deficits for those fatigued, inattentive eaters who crave caffeinated or chocolate treats. *Note: These stimulating aminos can counteract the effects of soothing aminos 1) and 2) (and vice versa) if taken together.*

The types, number, and doses of aminos needed vary with the individual, but the outcome is the same for almost everyone: Complete release from the tyranny of addiction to toxic foods and a return of the 'native appetite' for healthy food. As soon as doses are optimized (within a few days, at most), even frequent bingers, who often need to take *all five* types of aminos are craving-free.

As you might expect, restoring neurotransmitter and blood sugar function not only optimizes appetite, it optimizes mood as well. This is something many of us are badly in need of in the face of coronavirus-related trauma.

For more detailed amino acid therapy guidance:

- See my January 2019 *Townsend Letter* article.
- Find the symptom assessment questionnaire and list of possible contraindications to amino use at CravingCure.com.
- Find the above, along with detailed treatment protocols, in Chapters 11 and 12 of my most recent book, *The Craving Cure.*
- Or start getting certified as a Neuro Nutrient Therapist!

This is not too good to be true. We can vanquish commercial food science with nutritional neuroscience and stop all food cravings in as little as 24 hours! I've been watching this happen in thousands of cases since 1988. Try it and save your patients from obesity, diabetes, and weakened immunity. Their diet is not their fault. Food addiction is an involuntary and increasingly fatal condition.

For survival in health,

Julia Ross, MA, NNTS
Author of *The Craving Cure, The Mood Cure,* and *The Diet Cure*
Director of the Nutritional Therapy Institute's Virtual Clinic and its Neuro Nutrient Therapy Training Programs
https://www.juliarosscures.com

Re: "Progesterone Use as Hormone Replacement Therapy: Myths, Facts and Solutions"

I wish to comment on interpretations of certain "facts" that may not be fully grounded. And there are some points that are great.

Dr. Huber makes a welcome point that transdermal bioidentical progesterone is the right form for safety and uptake. Progesterone can be applied anywhere as there are receptors everywhere.

It is disturbing, though, to have him emphatically make the case for transdermal progesterone, but then claim that women should only dose to a certain small amount.

I quote from J. Bowles, author of *The Unselfish Genome*[1]: "… progesterone is not just for the reproductive system but is also known as the most neuroprotective substance known to man and this is why women recover from brain injuries much better than men…." and "…maintaining high levels of progesterone is important for anti-aging purposes because it suppresses the pro-aging hormones of FSH and LH which skyrocket in men and women after the age of 50."

Progesterone itself acts as an aromatase inhibitor as well as an inhibitor of 5-alpha reductase. It is an immediate precursor to cortisol and serves to replenish those adrenal hormones depleted by stress. It is the hormone that balances the excess action of adrenaline.[2] Generous levels of progesterone can turn off the symptoms produced by mast cell degranulation.[3] It is produced and used independently by the Schwann cells in the nervous system.[4] It is also produced and used in the brain independently as a neurosteroid.[5] Progesterone can stimulate the activity of estrogen by sensitizing receptors. Unless enough progesterone is used, the estrogen-related symptoms dominate leaving the patient even more estrogen dominant than before.

I am a biochemist who has spent years studying mechanisms of bioidentical molecules. I did the original molecular spectra on progesterone with Dwight Smith, the former chair of the department of chemistry/biochemistry at the University of Denver, which clearly distinguishes the nature of progesterone from synthetic, so-called "progestins or progestogens." My particular expertise involves the importance of progesterone and its profound effect on mood.[6]

Ultimately the purpose of our work is to help women get balanced enough to trust their own intuition. I, and my scientific colleagues, reject the premise that many women can get calm with these baby amounts suggested by Dr. Huber.

Bioidentical hormones do not follow an exact path, though there are pathways to specific receptors. Nor can they be quantified exactly as each woman will metabolize them somewhat distinctly.

Dr. Huber appears to think it's recommended to dose exactly what the body makes without any consideration that not every mg is going to make it through the skin. The only route that provides 100% bioavailability is intravenous. Depending upon the delivery system and the nature of the skin of the patient, the absorption can be highly variable.

It is so important to have enough progesterone to fulfill its important functions. The ability to replenish stress hormones is a large demand upon progesterone.[7-9]

Testing hormones with urine, dried urine, blood spot, and saliva are all limited in their application because none identifies the success of the hormone to reach receptors and produce the intended effect. Only the clinical benefits of applied hormones can define the success of replenishment. If a bioidentical hormone replenishment protocol is going well, then constant testing in unnecessary as the woman's symptoms will alert you and her. In the research world, blood levels are used, as most gender hormones are loosely bound to blood proteins and available to dock readily at receptors when called upon.

And it seems plausible to us, that a lifetime of too little progesterone, relative to potentially more aggressive molecules, would set a woman up to being vulnerable to the oxidative stressors of aging neurons.[10]

In my clinical practice, many women have gotten off lifetime addictions to benzodiazepines if they get enough progesterone. Enough has to be used throughout the day – along with GABA, as it takes enough progesterone catabolizing to allopregnanolone to dampen the GABA-AR; they work together. Without enough progesterone, GABA can become neuro-excitatory.

Additionally, allopregnanolone, which is the most neural active hormone, is synthesized from progesterone by the sequential actions of two enzymes, 5α-reductase type I (5α-RI), which transforms progesterone into 5α-dihydroprogesterone, and 3α-hydroxysteroid dehydrogenase (3α-HSD), which converts the 5α-dihydroprogesterone into allopregnanolone.[5]

Phyllis Bronson, PhD
Biochemical Research Foundation
with Carol Petersen, RPh, CNP

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Ask Dr. J

by Jim Cross, ND, LAc
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Lateral Immunological Thinking

My wife is always worried that someone is going to give her a cold or the flu, or so and so gave her a cold. I, of course, gently attempt to reassure her that the situation is more complicated than that. I gently remind her that, when she becomes infected with some sort of microbe, I massage her, sleep next to her every night, and do not become infected with whatever she is potentially carrying. I use the word potentially because many people and practitioners around our globe believe that we become ill because of a dysfunctional internal terrain or milieu and not from an external microbe. So, why did the chicken cross the road or why do some humans become acutely ill with colds and/or flus?

In this article, I want to veer off into a different direction that will hopefully think laterally (I prefer laterally to the more accepted term "critically") about the above scenario. So, was Bill Murray correct, in his much under-watched movie *The Razor's Edge*, when he tells his friend Gray at the end of the movie that "it's just the luck of the draw"(meaning, we're helpless immunologically and a plucky virus infects us and we magically inherit a cold or the flu)? Or is the opposite side of the immune coin real: can we actualize change in our life that either keeps the internal terrain healthy by building an impenetrable wall to the exterior world or supercharges our immune system to prevent any breaches or contain any breaches in the scenario of a successful microbial occupation? Let's call this second choice Michael Jordan immunity. Personally, I want to be more like Mike. Let's look first at a historical "luck of the draw" example of immunity.

Iron content in our body is one of those "good/bad" scenarios. Too little iron leads to anemia, which leads to fatigue and many other symptoms. Too much iron lends itself to a disease called hemochromatosis and a constellation of other problems. As George Block so astutely taught me in naturopathic physiology class, homeostasis, not too much or not too little, is the place to be. It turns out that infectious microbes need iron to survive; and all the places in our bodies that they can possibly invade, including our bloodstream, have been declared no-fly zones by our bodies to iron. In addition, these possible areas of microbial penetrance are patrolled by proteins that can lock up or chelate the iron to prevent usage by these invading microbes. Finally, during a microbial invasion, there is a prison lockdown of sorts as iron is stored away into the liver or spleen to prevent these intruders from using the iron to replicate and overwhelm our immune systems.[1,2]

To illustrate how smart our ancestors were, there is an old wives' tale that you place egg white-soaked straw onto a wound to protect it from infection. As it turns out, egg whites are chock full of chelators so that they are securing the guns (iron) at the door (wound site) to prevent the microbes from using the iron to gain an upper hand against our immune systems and enter our bodies through the wound.[2] Not only were our ancestors smarter than us, so too are our bodies – as the next example illustrates. Mother's milk contains lactoferrin, which helps prevent infections in the newborn gastrointestinal tract by chelating iron there.[2] ➤

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During the Middle Ages in Europe, the bubonic plague or black death swept through Europe decimating between one-third and one-half of the population. The bacteria *Yersinia pestis* is the source of this bacteriological scourge.[3] So, why did some people die, and others survive. Is my son correct that Bill Murray is always right?

It turns out that Bill is partially wrong, and it's not just the luck of the draw. Modern science has shown that the more iron present in individuals in a given population the more susceptible that population is to bacterial infection. It has also been theorized that the Vikings interjected the hemochromatosis gene into the European population during one of their invasions[4] (Interestingly, it also turns out that Ancestry told me I have Viking ancestors even though my mother was 100% German.).

Hemochromatosis is a form of iron-locking going on as a permanent condition. It can kill you in your 40s due to excess storage of iron in the body, which in the long run didn't matter as much in the Middle Ages as nature just needed humans to survive into adulthood to reproduce.[5]

In non-homochromatic individuals, macrophages have a good supply of iron, which is readily available to invading microbes. When these macrophages encounter microbes, they inadvertently give them the iron they need to replicate. That allows the microbes to decisively win their battle with our immune systems. The macs become not the front-line of defense but Trojan horses.[6]

A different scenario occurs in a hemochromatic person. There is a cell surface protein on macrophages, HFE, that senses iron status and regulates the expression of hepcidin by hepatocytes. Hepcidin is the principal regulator of iron homeostasis. With iron loading as in hemochromatosis, the production of hepcidin increases. Ferroportin is the protein that allows iron to be exported out of the macrophage. Hepcidin binds to it and induces ferroportin to degrade. Voila, we have secured the iron inside the macrophage so that it isn't available to blood-borne pathogens.[7,8]

Ultimately then, the ability to access iron within our macrophages determines the conditions in which a microbial infection becomes deadly or benign. Maybe Bill is right. It was just the luck of the draw for some people whose ancestral Viking(s) donated their genetic material. On the other hand, as Paul Harvey used to say on his radiocasts: "Now, for the rest of the story"!!

Yes, it is the luck of the draw whether our macrophages sequester iron or not from the marauding microbes. We are not helpless though. At our functional fingertips are a vast armamentarium of herbs, supplements, and lifestyle choices that can prevent the microbes from gaining access to our bodies or deter them once they have entered, even if our bodies don't sequester the iron from the microbes. These include but are not limited to the following:

- Repletion of vitamins A/C/D and zinc
- Daily intake of elderberry tincture
- Daily intake of proteolytic enzymes between meals
- Adequate sleep
- Keeping our parasympathetic nervous systems active through meditation or yoga so our immune systems are in tip top shape
- Shinrin-yoku or Forest Bathing to access phytoncides from the multiple types of trees and bushes that increase natural killer cell activity
- Staying away from neo-carbs or white flour, whole wheat flour, and sugar that dramatically decrease the efficiency of our immune systems.

Adhering to the above regimen can turn your perhaps vulnerable immune system into one "Like Mike." So, don't just be safe against COVID-19. Be smart dietarily, nutritionally, herbally, and lifestyle-wise and more than likely you'll be snug, as a bug in a rug, from the virus!

Nota Addendum: In these trying viral times, I think we need to look to the inherent wisdom of our bodies for guidance. All the various parts of my body continuously work in harmony (except for my prefrontal cortex sometimes!). So, this might be the message that the virus is really sending to us: the human race. This message is best summarized by lines from Stephen Stills' wonderful song, "We Are Not Helpless": We are not helpless/We are friends/What lies between us/It can be set aside and ended/ All are strangers/All are friends/All are brothers.

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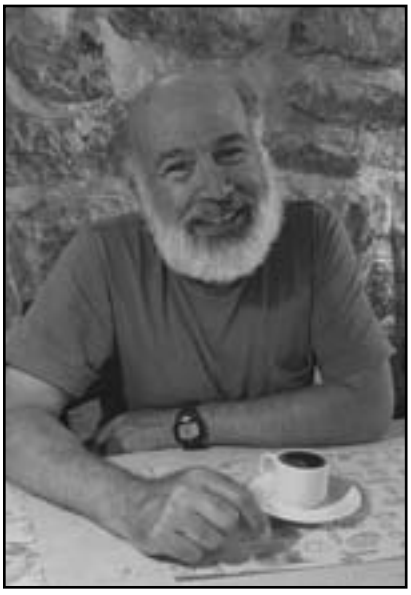

Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Pollen Exposure and COVID-19

We can hope that by the time this is printed that the virus will be under control, and this article will be irrelevant. At the moment it is anything but under control. Thus, let me tell you about a fascinating paper that came out in early March in the journal *Allergy* that may give us a tool to help control this COVID-19 thing we've got going on.[1] After reading this article yesterday, I turned on our air filter and hesitate to ever turn it off again even though local pollution levels have dropped to their lowest level in memory.

This study consisted of multiple experiments that combined data from human cell cultures, mouse models and human cohorts to test the authors' hypothesis that pollen exposure weakens immune defense against viral infection. It wasn't about corona or COVID-19 specifically, but the knowledge gathered may be useful now.

Every springtime, plants dump pollen into the air. There are days here in Denver that we use a broom to sweep pine pollen that has blown down from the mountains off our front porch. During this period many people experience allergy symptoms as this pollen triggers sensitivity reactions; and many people end up at their doctors with respiratory tract infections. This is particularly true of people who are atopic or have asthma.[2] These researchers wanted to figure out why, in particular why people who supposedly don't have allergies still get sick. Prior to this study these researchers had already shown that pollen grains have potent immune-modulatory effects independent of them acting as allergens in some people.[3] Pollen components have been shown to alter the barrier functions in respiratory epithelial cells.[4]

The first part of the study was done on tissue cultures. Primary bronchial epithelial cells were obtained via bronchoscopy from healthy individuals and expanded in appropriate growth media and induced to differentiate. That means they scraped some lung tissue out of people and grew the cells coaxing them into looking like lung tissue. Nasal epithelia were also obtained from healthy volunteers who were undergoing nasal surgeries or from nasal brush biopsies and cultured in appropriate media. Same deal, the scientists grew nasal mucosa tissue. Six-week-old female mice were used for the ex vivo section of the experiments.[5]

There were several sections to the human portion of this study, including both prospective, observational, and interventional controlled experiments along with a large retrospective study. For the observational and interventional portions, healthy non-allergic volunteers were recruited in Augsburg, Germany, and were screened for allergies; and only non-sensitive individuals were enrolled into the cohorts. Eight participants were only monitored for symptom intensity over the 2016 allergy season. Two groups of nine participants each, (again non-allergic subjects) were enrolled as an experimental group to be challenged with either pollen exposure or as a control group treated with placebo.

The retrospective human study was big; researchers examined nasal swabs from 20,062 participants collected at Sahlgrenska University Hospital in Gothenburg, Sweden, from 2010 to 2013. They determined whether these people had viral infections and compared frequency of infection with pollen counts.

The cultured bronchial and epithelial tissues were stimulated with pollen extracts and then exposed to human rhinovirus-16 viral cultures. Six-week-old female mice were infected with RSV and then exposed to ragweed pollen by intranasal instillation on three successive days.

In the small human experimental study, the 18 subjects were subjected to three nasal lavage challenges with either a placebo of saline solution or birch pollen extract (n=9). Unilateral curettage biopsies were taken before and after the study.

All of these experiments told a consistent story. Pollen exposure weakens the immune response against viruses.

In the tissue cultures and mice, pollen exposure significantly diminished interferon-λ and pro-inflammatory chemokine responses of the airway epithelia to rhinovirus and viral mimics and decreased nuclear translocation of interferon regulatory factors. In mice infected with RSV, co-exposure to pollen weakened expression of antiviral genes and increased pulmonary viral titers. In the non-allergic human volunteers, nasal symptoms were positively correlated with airborne birch pollen abundance, and nasal birch pollen challenge led to downregulation of type I and -III interferons in their nasal mucosa. In the large patient cohort, numbers of rhinovirus positive cases were correlated with airborne birch pollen concentrations.

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Curmudgeon's Corner

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Among the 20,062 Swedish participants, over the three-year period, there were 5,782 rhinovirus-positive cases. In these people, nasal symptoms were positively correlated with airborne birch pollen abundance. Time series analysis revealed a significant correlation between rhinovirus-positive cases, airborne birch pollen concentrations and precipitation (P = .005). There was a positive nonlinear relationship between rhinovirus and pollen comparing the RSV cases with pollen counts. Whereas the association was negative between rhinovirus/pollen and precipitation. (It sounds like if it rained and decreased pollen levels, the risk of RSV cases went down rather than up.)

The data from the eight nonallergic volunteers who tracked their symptoms during 2016 were used to establish that their nasal symptoms corelated with pollen concentrations. Time series analysis revealed a significant correlation between nasal symptoms and birch pollen with a lag effect of up to nine days though the strongest correlation of symptoms was to pollen levels the day prior. In those nine volunteers who were challenged directly with birch pollen, the exposure led to downregulation of type I and -III interferons in nasal mucosa compared to those treated with control saline.

This combination of tissue culture, mouse and human data creates a compelling argument that pollen exposure weakens innate immune defense against viral infection. What is of particular note is that the participants in this study were not 'allergy' patients. In other words, these findings apply to everyone and not just those 'sensitive individuals.' Pollen levels, of course, vary seasonally, and we are generally made aware of these concentrations by individuals who do display symptoms. Pollen concentrations are also carefully monitored by health departments and these levels can easily be accessed online either on government or commercial sites (https://www.pollen.com). The knowledge that increasing pollen levels may leave us more susceptible to viral infection is of special concern this year during the COVID-19 pandemic.

It was in light of these basic findings that a news story broadcast by Radio Sweden (March 29, 2020) caught our attention. The news writer interviews and quotes one of the authors of this study, Åslög Dahl who heads the pollen laboratory at Gothenburg University. She had announced preliminary findings from a new study. Using COVID-19 data from the World Health Organization, "…Dahl says that areas with the highest mortality rates from the Corona virus have been shown to have the highest pollen levels too." Although Dahl points out these results have been hastily assembled and require further study, she suggests that everyone, whether they have allergies or not, should currently follow the advice given to those sensitive to pollen and allergies.[6] Or to quote the original study's abstract: "The ability of pollen to suppress innate antiviral immunity, independent of allergy, suggests that high-risk population groups should avoid extensive outdoor activities when pollen and respiratory virus seasons coincide." When pollen levels are high, don't exert yourself and stay indoors day and night.

Well, at this point we are pretty much doing that anyway, you might think. But this is an argument against some outdoor activities when pollen exposure is high, even if there isn't a soul in sight and social distance is not a concern.

Even though Dahl's COVID-19 information is still preliminary, taken together with this current study, it is compelling enough that we should encourage patients to follow it. There is no risk in lowering pollen exposure. Hopefully by the time this is published more clarifying data will have been published. In the meantime, let's pretend we have hay fever this spring.

Mayo Clinic's advice to allergy sufferers[7]:

- Stay indoors on dry, windy days. The best time to go outside is after a good rain, which helps clear pollen from the air.
- Delegate lawn mowing, weed pulling, and other gardening chores that stir up allergens.
- Remove clothes you've worn outside and shower to rinse pollen from your skin and hair.
- Don't hang laundry outside – pollen can stick to sheets and towels.
- Wear a pollen mask if you do outside chores (that mask thing again).

One last point about this virus: In an April 6, 2020 article in the *NY Times* written by cardiologist Harlan Krumholz, he describes being surprised by the lack of the normally expected numbers of cardiac patients at his hospital. He goes on to write, "cardiologists have shared with me that their cardiology consultations have shrunk, except those related to COVID-19. In an informal Twitter poll, almost half of the respondents reported that they are seeing a 40 percent to 60 percent reduction in admissions for heart attacks; about 20 percent reported more than a 60 percent reduction."[8]

Resources

https://www.pollen.com/map

https://www.theguardian.com/world/ng-interactive/2020/mar/31/coronavirus-map-us-latest-cases-state-by-state

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CALENDAR

Please visit www.TownsendLetter.com for the complete calendar

MAY 29-30: MEDICINES FROM THE EARTH HERB VIRTUAL SYMPOSIUM online. CE credits for nurses, acupuncturists and naturopathic physicians. CONTACT: 541-482-3016; https://www.botanicalmedicine.org/.

MAY 30-31: MORPHOGENIC FIELD TECHNIQUE SEMINAR FOR BIOTICS (INTERMEDIATE) in Chicago, Illinois. CONTACT: https://www.morphogenicfieldtechnique.com/

JUNE 5-7: INJECTION THERAPY WORKSHOP with Marc Harris, MD, ND, PhD in Parker, Colorado. CONTACT: 866-338-4883.

JUNE 5-7: BIOLOGIC ALLOGRAFT SEMINAR (ADVANCED) in Parker, Colorado. CONTACT: https://www.brimhall.com/t-biologic%20allograft.aspx

JUNE 11-14: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING For Doctors, Dentists & Health Professionals: Detecting Parasites, Dental & Fungal in St. Louis, Missouri. Simon Yu, MD, CONTACT: www.preventionandhealing.com. 314-432-7802**.**

JUNE 12-13: INSTITUTE FOR FUNCTIONAL MEDICINE 2020 CONFERENCE – Advancements in Clinical Research and Innovative Practices in Functional Medicine online. CONTACT: 800-228-0622; info@ifm.org; www.ifm.org/aic

JUNE 12-14: THE GREAT PLAINS LABORATORY, INC. presents GPL ACADEMY MASTER PRACTITIONER WORKSHOP in Kansas City, Missouri. CONTACT: http://www.gplworkshops.com/kansas-city

JUNE 13-14: PRIMARY CARE UPDATE FOR NATUROPATHIC DOCTORS in Toronto, Ontario, Canada. Online & in person registration options. Earn up to 11 CEs. CONTACT: info@collaborativeeducation.ca ; http://www.collaborativeeducation.ca/toronto-naturopathic-conference/

JUNE 15-19: FREQUENCY SPECIFIC MICROCURRENT SEMINAR (CORE) in Tuscany, Italy. Also, **OCTOBER 22-26** in Taiwan. CONTACT: 360-695-7500; https://frequencyspecific.com/

JUNE 20-21: FREQUENCY SPECIFIC MICROCURRENT ADVANCED SEMINAR in Tuscany, Italy. Also, **SEPTEMBER 9-11 (Master Class)** in London, United Kingdom; **OCTOBER 30-NOVEMBER 1 (Master Class)** in Taiwan. CONTACT: 360-695-7500; https://frequencyspecific.com/

JUNE 20-27: CLINICAL AND COMPARATIVE MATERIA MEDICA @ Allen College of Homeopathy in the United Kingdom. On-site or interactive online course. CONTACT: https://homoeopathy-course.com/courses/england/7-day-summer-school

JULY 10-12: FREQUENCY SPECIFIC MICROCURRENT CORE MODULE 2 – NEURO & VISCERAL in Philadelphia, Pennsylvania. Also, **NOVEMBER 6-8** in Chicago, Illinois; **DECEMBER 3-5** in San Francisco, California. CONTACT: 360-695-7500; https://frequencyspecific.com/

JULY 10-12: THE GREAT PLAINS LABORATORY, INC. presents **ENVIRONMENTAL TOXIN SUMMIT** in Portland, Oregon. CONTACT: http://www.gplworkshops.com/

JULY 17-19: GENETIC METHYLATION SERIES 2 with Marc Harris, MD, ND, PhD, in Orlando, Florida. CONTACT: 800-890-4547

AUGUST 14-16: INTERNATIONAL CONGRESS OF REGENERATIVE MEDICINE ONLINE CONFERENCE. CMEs available. CONTACT: https://www.icrmlearn.org/

AUGUST 20-22: 28th ANNUAL A4M/MMI SPRING CONFERENCE in Orlando, Florida. CONTACT: 561-997-0112; https://www.a4m.com/

AUGUST 20-23: 11th ANNUAL INTEGRATIVE MEDICINE FOR MENTAL HEALTH CONFERENCE in Chicago, Illinois. CONTACT: https://www.immh2020.com/

AUGUST 21-23: ADVANCED APPLICATIONS IN MEDICAL PRACTICES (AAMP) SPRING EVENT – Chronic Digestive Disorders in Scottsdale, Arizona. CMEs available. CONTACT: https://aampscottsdale.com/

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Editorial

➤ *continued from page 84*

Clinical trials indicate that vitamin C in the dosage range of 1.5-4.0 g per day (in divided doses) can shorten the duration of symptoms caused by the common cold.[5] Anecdotal evidence suggests that doses much larger than that may be needed to achieve the best results against viral infections. Dr. Robert Cathcart, who treated more than 11,000 patients with large doses of vitamin C, recommended the use of "bowel tolerance" doses to treat viral illnesses.[6 7] The bowel-tolerance dose is the dose just below that which produces diarrhea. It can be determined by taking vitamin C in progressively larger amounts (usually in 3 to 6 divided doses per day) until diarrhea occurs, and then reducing the dose slightly. Increasing the frequency of administration increases the total daily amount of vitamin C tolerated. Cathcart observed that the benefits of vitamin C become most pronounced as the bowel-tolerance level is approached. Patients are often able to tolerate much larger doses of vitamin C when they are ill than when they are well. As they improve, their bowel-tolerance limit decreases. His patients with viral pneumonia (one of the complications of COVID-19) often tolerated 100-200 g of vitamin C per day in 12 to 25 divided doses per day, although older patients tolerated less than that. High-dose vitamin C is contraindicated in people with end-stage renal disease.

Intravenous Vitamin C

In severe cases of COVID-19, intravenous vitamin C should be considered. Intravenous vitamin C can produce substantially higher serum concentrations of the vitamin than those achievable with oral administration. At high concentrations, vitamin C may have various pharmacological effects, including inactivating viruses[8] and stimulating the production of the antiviral compound, interferon.[9] Vitamin C may also help quench the free radicals that are generated during the massive inflammatory response to severe COVID-19 infection. Those free radicals are thought to contribute to the morbidity and mortality associated with the disease.

Some doctors in New York are prescribing 1.5 g of intravenous vitamin C every six hours for patients hospitalized with COVID-19. These patients are said to be faring better than those not receiving vitamin C, but the evidence so far is only anecdotal. Randomized controlled trials are in progress in China, and are expected to be completed in September. There is one published case report of a critically ill woman with acute respiratory distress syndrome resulting from enterovirus/rhinovirus respiratory infection. The woman had a dramatic and rapid recovery after receiving intravenous vitamin C. The dosage was 50 mg per kg of body weight every six hours for seven days, followed by a lower dose for two more days.[10] That dosage is equivalent to 14 g per day for a 70-kg person.

A number of years ago, I saw a middle-aged woman who had a three-week history of viral pneumonia, manifesting as fatigue, malaise, and a persistent cough. She was given an intravenous infusion of 50 g of vitamin C over a period of three hours. Halfway through the infusion, she became symptom-free, and the symptoms did not recur.

According to the clinical observations of Klenner[11] and others, higher doses of intravenous vitamin C are often more effective than lower doses. Research is urgently needed to determine whether the dosages being used in New York hospitals (1.5 g every 6 hours) are large enough to produce the best results with COVID-19 infections. People with glucose-phosphate dehydrogenase deficiency should not be given very large doses of intravenous vitamin C, but there is no evidence that 1.5 g every 6 hours is unsafe for these individuals.

Zinc Lozenges

Zinc ions have been reported to inhibit the replication of a wide range of viruses *in vitro*. In some, but not all, clinical trials, administration of zinc lozenges significantly decreased the duration of symptoms in people experiencing the common cold. These observations raise the possibility that bathing the nasopharynx region with zinc ions could help prevent an early COVID-19 infection from progressing to pneumonia. It would be reasonable to start using zinc lozenges at the first sign of an illness that could be due to COVID-19. A typical dosage is one lozenge (13.3 mg of elemental zinc) taken every two-to-four hours (up to 6 lozenges per day) for seven to 14 days.

It has been suggested that lozenges containing loosely bound zinc salts such as zinc gluconate and zinc acetate release more zinc ions into the oral cavity, compared with lozenges containing more tightly bound zinc salts such as zinc picolinate, zinc citrate, zinc orotate, and zinc aspartate. In addition, certain flavoring agents or excipients may chelate zinc and prevent it from ionizing in the mouth. Differences in product formulation may explain why zinc lozenges were ineffective as a treatment for the common cold in some studies. Products that have been shown to be effective contain zinc gluconate or zinc acetate, do not contain citric acid, mannitol, sorbitol, or tartrate, and do not contain fatty acids that have been heated to high temperatures.

People who are at high risk of being exposed to COVID-19 (such as healthcare workers, police, and firefighters) might consider using zinc lozenges prophylactically (perhaps 1 lozenge 3 times a day). Long-term use of large amounts of zinc can lead to copper deficiency, which can result in impaired immune function, anemia, or myelopathy. It would be prudent for people to take a copper supplement if they are taking zinc for more than two weeks. A reasonable dose of copper would be 1-2 mg per day for 15-30 mg per day of zinc, 2-3 mg per day for 30-60 mg per day of zinc, and 3-4 mg per day for more than 60 mg per day of zinc. Nausea is a dose-related side effect of both zinc and copper.

***Sambucus nigra* (Black Elderberry)**

Sambucus nigra (black elderberry; *Sambucus*) has been used traditionally to treat respiratory infections. *In vitro* studies found that extracts of *Sambucus* inhibited the replication of influenza virus types A and B and decreased the infectivity of the H1N1 virus, which was responsible for the swine flu pandemic in 2009. A meta-analysis of four randomized controlled trials (including a total of 180 participants) found that *Sambucus* significantly reduced upper respiratory symptoms in people with influenza or colds. The effect size was considered to be large.[12]

In vitro, an extract of *Sambucus* also inhibited the replication of infectious bronchitis virus, which is a coronavirus that infects the respiratory tract of chickens.[13] That finding raises the possibility that *Sambucus* would be beneficial in the treatment of human coronavirus infections. Some people have argued that *Sambucus* is contraindicated

in people infected with COVID-19. Their concern is that *Sambucus* might stimulate the release of inflammatory mediators known as cytokines, such as tumor necrosis factor-alpha and interleukins.

The severe morbidity and mortality that occurs in a small percentage of people with COVID-19 does not appear to come from the infection itself but, rather, from a massive inflammatory response to the infection – the so-called cytokine storm – which can cause major damage to the lungs and other tissues and organs. If *Sambucus* increases cytokine release, then it could in theory lead to worse outcomes in people with COVID-19. However, the concern about cytokine storm is based only on one *in vitro* study, in which *Sambucus* increased cytokine release from the white blood cells of healthy volunteers.[14] It is not known whether this effect would also occur *in vivo*, and in particular in a person suffering from a viral infection. One study in mice with diet-induced obesity[15] found that oral administration of a *Sambucus* extract actually decreased serum concentrations of tumor necrosis factor-alpha, one of the major cytokines involved in the inflammatory response.

There are still a lot of unknowns regarding *Sambucus* and COVID-19. If it turns out that *Sambucus* inhibits the replication of this virus, then using it in the earlier stages of the infection could help people recover, and might decrease the risk of progression to the stage where a cytokine storm may occur. On the other hand, in the absence of additional information, it might not be a good idea to give *Sambucus* to people in the more advanced stages of the disease.

Green Tea

In a randomized controlled trial, gargling with an aqueous solution of a green tea extract three times per day for three months during the winter significantly decreased the incidence of influenza in elderly nursing home residents.[16] The green tea extract may have worked in part by inhibiting the growth of influenza virus, an effect that has been demonstrated *in vitro*.[17] Green tea extracts also enhance the function of (gamma, delta T cells), which is a type T cell that plays a role in initiating and propagating immune responses.[18] It is not known whether compounds in green tea also inhibit COVID-19. However, the effect on T cell activity might be helpful for fighting COVID-19. Since green tea has a number of other health benefits, there is nothing to be lost by adding a cup or two of green tea per day to the diet for potential COVID-19 prophylaxis.

Other Recommendations

Healthy people can fight infections more effectively than unhealthy people. We should do everything we can to try to stay healthy, which includes avoiding refined sugar and junk food, emphasizing whole foods, exercising regularly, getting enough sleep, and trying not to worry. We will get through this.

Alan R. Gaby, MD

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Thoughts on COVID-19, the Coronavirus

At the time this article is being written (April 1, 2020), the number of infections and deaths from COVID-19 are increasing exponentially. We do not yet have enough data to know whether this pandemic will turn out to be like a bad flu season or something much worse. Below are some thoughts on natural remedies that might be useful for preventing or treating COVID-19.

Vitamin C for Prophylaxis

Vitamin C plays a role in immune function and in the maintenance of tissue integrity, both of which are important factors in the body's response to infections. People with low or suboptimal vitamin C status are likely to have a reduced capacity to ward off a viral infection in its earliest stages. In population surveys among US adults, more than half were consuming less than the Recommended Dietary Allowance for vitamin C,[1] and 7.1% had vitamin C deficiency as determined by serum vitamin C levels.[2] For most healthy people, supplementing with 200-500 mg per day of vitamin C would improve low or suboptimal vitamin C status. Cigarette smokers and people with chronic illnesses might need more than that in order to achieve vitamin C "adequacy." Some people take multi-gram doses of vitamin C for infection prophylaxis, but there is no clear evidence that these higher doses are more effective for preventing infections.

Vitamin C for Treatment

At the first sign of an illness that could be due to COVID-19, a reasonable strategy would be to begin high-dose vitamin C. Vitamin C levels (measured in leukocytes) have been reported to fall dramatically within 24 hours of the onset of a cold, to the levels seen in people with scurvy.[3] This decline is presumably due to increased vitamin C utilization for implementation of tissue defense mechanisms.[4] Multi-gram daily doses, beginning at the first sign of illness, appear to be needed to prevent this decline in vitamin C levels from occurring.

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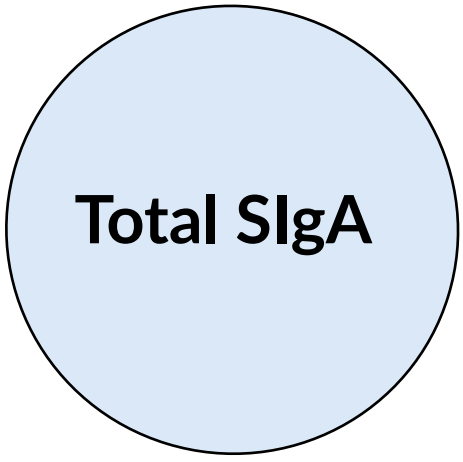

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Article

A Novel Self-Emulsifying Drug Delivery System (SEDDS) Based on VESIsorb® Formulation Technology Improving the Oral Bioavailability of Cannabidiol in Healthy Subjects

MDPI

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tract: Cannabidiol (CBD), a phytocannabinoid compound of *Cannabis sativa*, shows limited oral vailability due to its lipophilicity and extensive first-pass metabolism. CBD is also known for gh intra- and inter-subject absorption variability in humans. To overcome these limitations a self-emulsifying drug delivery system (SEDDS) based on VESIsorb® formulation technology porating CBD, as Hemp-Extract, was developed (SEDDS-CBD). The study objective was to te the pharmacokinetic profile of SEDDS-CBD in a randomized, double-blind, cross-over design the same Hemp-Extract

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