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The Examiner of Alternative Medicine

Aug/Sept. 2022
Issue #469/470

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Linda L. Isaacs, MD

Pancreatic Enzymes and Cancer

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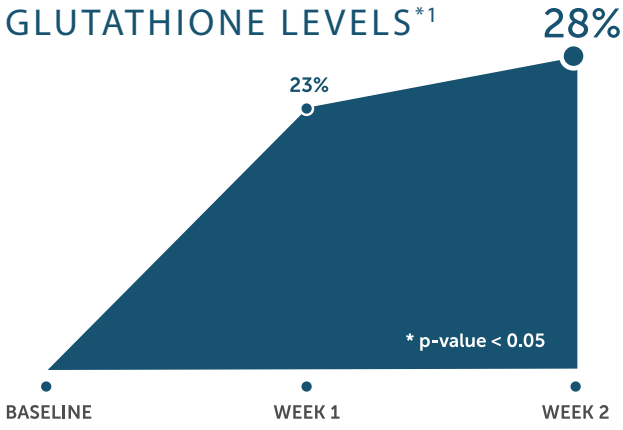

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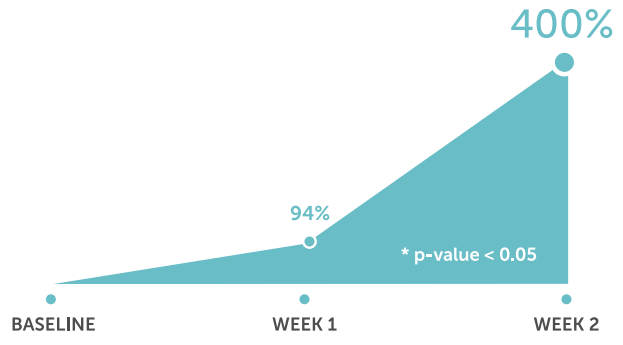

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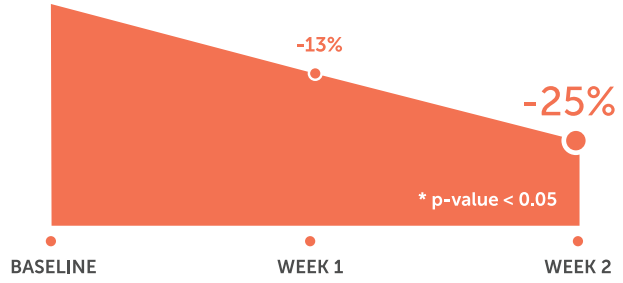

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[1]Sinha R, Sinha I, Calcagnotto A, et al. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. Eur J Clin Nutr. 2018;72(1):105-111. doi:10.1038/ejcn.2017.132

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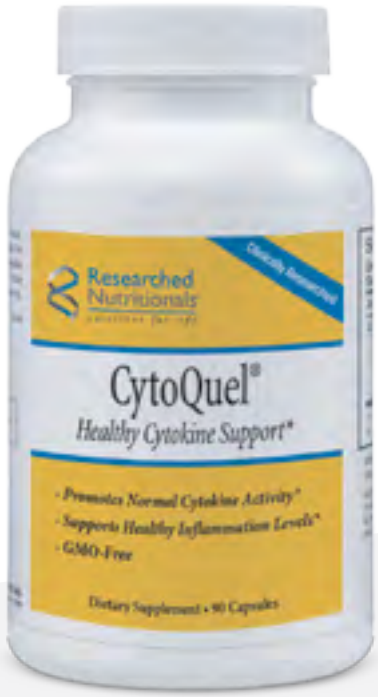

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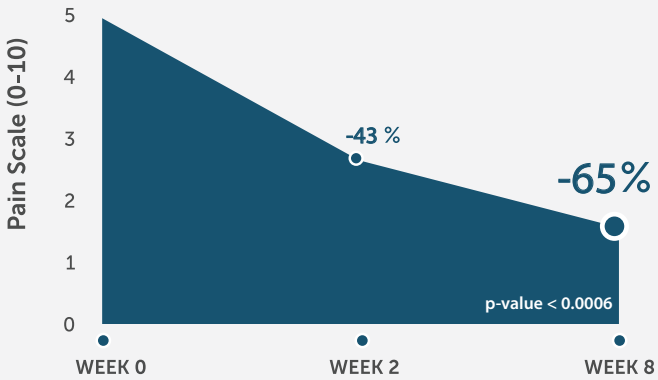

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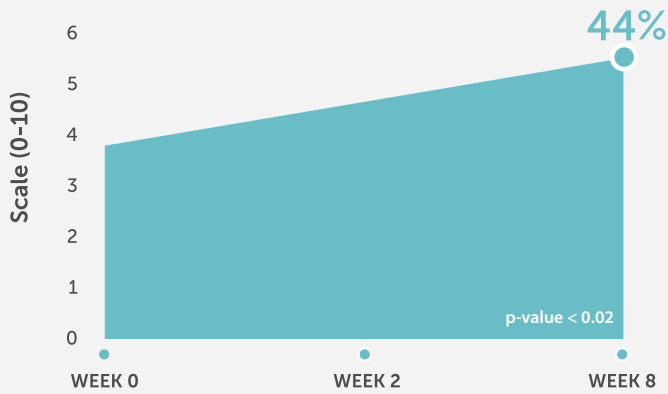

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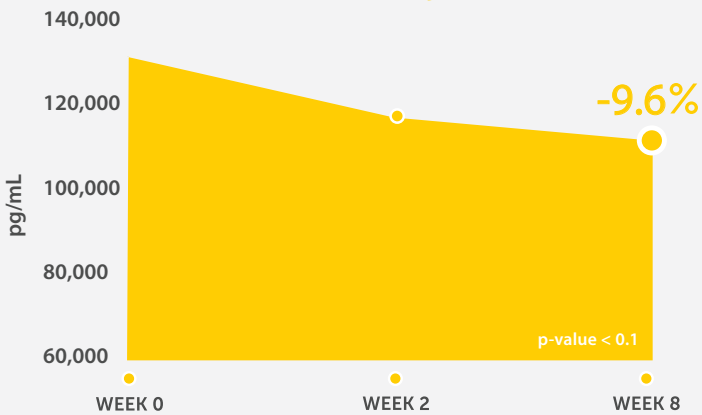

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From the Publisher

The State of Alternative Cancer Care

Over the past two-year stretch of lockdowns and Covid-19 illness, many cancer patients avoided seeking medical care much to their detriment. Surgeries were postponed, chemotherapy and radiation treatment were delayed, and immunotherapy was often not even being offered. Cancer treatment remains nearly the same as it has been for several decades, and the outcome for too many patients with advanced cancers is abysmal. Of course, "precision" cancer care has occasionally brought great success given the plethora of new oncological pharmaceuticals. Still cancer care remains brutal and often does not yield remarkable quality-of-life survival despite being standard of care (SOC). Given the limited response available for some cancers, it is understandable that people look for alternatives. Unfortunately, approaching alternative cancer treatment is fraught with resistance from family and health professionals and uncertainty about its effectiveness, safety, and cost. Adding insult to injury alternative care is not covered by insurance and sometimes is outlawed. Yet does it really make sense to stay the course of a failed conventional cancer protocol?

This is essentially the same question we ask now that we were asking in 1987 when the Office of Technology Assessment (OTA) of the US Congress authorized a committee to study alternative cancer treatment. At that time patients and health professionals convinced House representatives that alternative medicine does have a place in cancer care and should not be outlawed. The OTA eventually published a lengthy monograph that touted the benefit of meditation and stress reduction, eating well, exercise, and good sleep. "Alternative therapies" such as mind-body medicine through visualization were accepted. Traditional medicine such as acupuncture was also recognized to be merit worthy. However, unusual diets were generally not given approval. Similarly, herbal therapies were thought to be lacking evidence. Of course, all unproven cancer cures were disdained. By and large, vitamin supplementation was thought to be useless and not infrequently detrimental to SOC. Nevertheless, as a result of the committee's report Congress appropriated funding for the Office of Alternative Medicine in 1991. Ultimately this division of the NIH received ongoing funding as the Center for Complementary and Integrative Medicine, as it is known today. Despite the backlash from critics, alternative and integrative and naturopathic cancer care is now being recognized at the research level as well as in practice. In this issue we take a look at the state of alternative cancer care in 2022.

Cover Article: Linda Isaacs, MD, on Pancreatic Proenzymes and Cancer

When I first was introduced to alternative medicine in the late 1970s, I mentored under Leo Bolles, MD, in Washington State. Quite a few patients under his care were seeking an alternative to their cancer treatment. The two interventions Bolles always implemented was a change in diet and the prescribing of numerous vitamin supplements. For the diet the patient was asked to abstain from processed carbohydrates, reduce sugar and fat, move away from animal proteins except for fish, consume much more vegetables, and avoid alcohol and nicotine. Vitamin supplementation always included a strong dose of vitamin C, potassium/magnesium and other minerals, B vitamins, fish oil,and digestive enzymes. However, the digestive enzymes were not for digesting food; for food digestion Bolles recommended the use of betaine HCl. Instead the digestive enzymes, so-called "proteolytic enzymes," were to be taken in between meals. The idea was that the enzymes would be absorbed from the digestive tract and make their way into the circulation. Somehow the enzymes would circulate and disrupt the cancer cell's external and interior environment enabling the body's immune system to better kill the cancer cell. Using high concentrations of trypsin, chymotrypsin, lipase, and pancreatin, supplemental enzymes could be routinely administered, raising enzymatic activity within the bloodstream. Who originated this application of enzyme therapy?

As Dr. Isaacs explains in this issue of the *Townsend Letter* as well as in the April 2022 issue of *Integrative Cancer Therapies,* enzyme treatment was devised by an embryologist over 100

years ago by the name of John Beard. Beard observed the similarity between the embryonic trophoblast and cancer. Both undergo rapid growth of relatively undifferentiated cells. Beard noted that at a certain time the trophoblast differentiates into the placenta and that transformation is signaled by the fetal pancreas's first production of enzymes. Beard reasoned that a cancer grows unchecked because of the absence of this enzyme signaling in the body. His theory was briefly acclaimed in the early 1900s but was later criticized and largely ignored. However, others pursued his work making enzyme therapy a cornerstone of their cancer treatment.

The orthodontist William Donald Kelley self-diagnosed with pancreatic cancer treated himself solely with dietary changes and digestive enzymes. Based on his own case Kelley designed an entire healing system to manage cancer and other chronic illness. Kelley's work eventually fell into the hands of a budding immunologist, Nicholas Gonzalez, who closely examined Kelley's protocol and patient cases. Gonzalez modified Kelley's protocol, ultimately treating thousands of patients with diet and pancreatic enzymes. He mentored Isaacs who collaborated on his research and treatment. What Gonzalez and Isaacs discovered is that for enzyme therapy to be most effective, the enzyme needed to be a "pro-enzyme" rather than the enzyme itself. For example, trypsin needed to be trypsinogen, while chymotrypsin was better as chymotrypsinogen. Pro-enzymes did not need to be manufactured; instead the pro-enzyme is readily available in raw pancreas tissue. It is the administration of high concentrations of pro-enzymes that Gonzalez and Isaacs theorized as the key to the cancer cell transforming back into a non-cancerous cell and/or engaging in apoptosis.

After reading Isaac's article in this issue do take the time to read her 2022 *Integrative Cancer Therapies* article for the evidence supporting proteolytic enzymes' role in treatment of cancer.[1]

Yes, Tree Bathing is Healing, but How About Visiting a Swamp?

Have you heard of the Great Black Swamp? It's not exactly a tourist destination. And if you are not a resident of Ohio, you very likely have not known about it much less visited it. Originally it was a massive swamp covering much of Ohio, Indiana, and Michigan. Those traveling west to find new lands to settle were forced to traverse this overwhelming watery bog filled with insects, amphibians, snakes, wild cats, and copious bird species. Attempting to avoid malaria-carrying mosquitoes and quicksand, wagon trains took long detours but still were forced to ford streams. Folks were already frustrated encountering indigenous tribes but becoming lost in swampland led many to call for draining the swamp. At first it was a tedious process laying down clay tiles to create a drainage channel, but industrialization led to steam powered machines creating effective drainage of the Great Black, which is now a pittance of what it once was. The early settlers were amazed at the harvest they were to have farming with the swamp soil. Its peat composition made for the richest and highest quality produce and grain. Of course, once that peat swamp soil was exhausted, it was gone forever; and

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farms no longer were able to produce such bountiful vegetables and fruits without using chemical fertilizers and pesticides.

Why am I writing about swamps? In the July 4th issue of *The New Yorker*, the very talented novelist, Annie Proux, author of *Postcards, The Shipping News,* and *Brokeback Mountain*, writes about why our wetlands matter so much in her article titled, "Swamped."[2] Like her books her writing is beguiling, sweeping one into the swamp and experiencing its beauty, its dank, its darkness and light. When we talk about detoxification, the swamp is nature's great detoxifier. It is the home to pitcher plant and beaver and warbler and heron and butterflies and muskrat and diverse trees and insects. When we worry about climate change, the swamp is a heavy-weight in sequestering carbon dioxide. Proux describes what it is like to step on mossy ground, sphagnum moss – "its billowy heave seemed to me more like a wave of dizziness before you pass out – a very slow falling sensation although you remain upright."

We are fortunate that we do not need to cross the swamp on our daily commute nor do we need to live fretting about a snake bite or getting lost in a bog. But there is something so primordial to the swamp, we can experience life in its rawest form. Adventure takes many forms but we rarely consider the swamp. We need to appreciate its beauty as well as its vitality; the odors of the swamp awaken our senses. Looking for something to do this weekend, why not go visit a swamp near you?

Mistletoe by Steven Johnson, DO, and Nasha Winters, ND

Last year Drs. Johnson and Winters published a book on *Mistletoe* subtitled *the Emerging Future of Integrative Oncology.* If you are like me you have heard about using mistletoe in cancer care but are not familiar with its use. Mistletoe, an extract derived from the vine *Viscum album*, is administered in different formulations subcutaneously, intravenously, even directly into the tumor mass. The complexity of mistletoe administration requires a considerable level of knowledge and experience derived by taking coursework in anthroposophic medicine (AM) and being mentored by physicians dedicated to such work. Johnson and Winters together with Adam Blanning, MD, Marion Debus, MD, Paul Faust, ND, Mark Hancock, MD, and Peter Hinderberger, MD have distilled the essence of anthroposophic medicine as well as the application of mistletoe use into a highly readable 300-page book, suitable as a primer for the beginning AM physician and patient.

Perhaps the most unique aspect of mistletoe is the variability of the extract based on what tree the vine is growing on. The mistletoe growing on an apple tree is entirely different from the mistletoe growing on a fir or a pine or an oak or an ash. The difference lies in the lectin as well as the "viscotoxin" content of mistletoe extracts from different trees as well as manufacturers. Ash mistletoe has very high lectin content, apple extract more moderate content, and pine extract much lower content; however, based on whether Abnoba Viscum or Helixor or Iscador or Iscucin manufactures the mistletoe, lectin content varies greatly. Depending on an individual's cancer status, the type of

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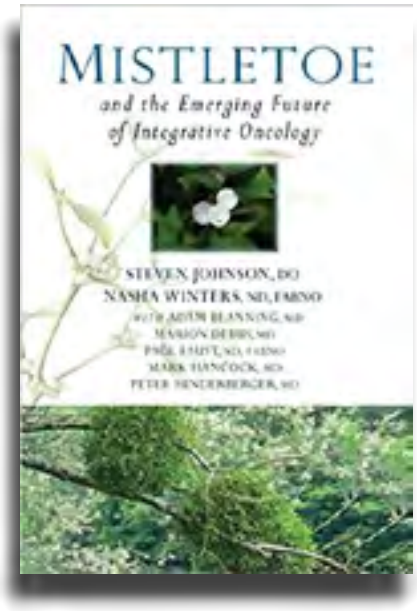
cancer, the staging, a particular mistletoe extract is selected to match what would be most appropriate for how the patient is doing. A strong fraxini (ash) extract may not be used on a patient who is cachectic and very enfeebled while such an extract may very well be used on a pediatric cancer or adult lymphoma patient. However, the authors are quick to point out that there is no exact protocol to spell out which mistletoe is used for each type of cancer. Instead there needs to be a holistic overview of the patient at every level, physical, mental, emotional, and spiritual to diagnose and determine the best treatment approach. Such diagnostics are very nuanced – three women with intraductal breast cancer would likely each be given a different extract and administration route. The thinking that goes on in homeopathic diagnosis very much takes place in anthroposophic diagnostics as well. In fact, it is not unusual to complement the mistletoe treatment with homeopathic formulations.



Mistletoe treatment is meant to complement conventional medicine and integrative/naturopathic oncology care. The side effects of chemotherapy and radiation treatment are definitely within the purview of mistletoe therapy; those patients concurrently receiving mistletoe extract experience far less severe adverse effects. Conventional chemotherapy and immunotherapy are frequently inadequate in achieving remissions and high quality of life; mistletoe extract enables patients to have better outcomes and experience joy of living. Of course, this is not a quick treatment approach. Mistletoe treatment goes on intensively for weeks, months, and maintenance for years. Fortunately, the patient is trained to administer the extract with subcutaneous injections at home; IV treatments still need to be done at the clinic. The treatment is not inexpensive, but it also is not outrageously expensive either; there are financial resources for patients to access because it is not covered by medical insurance.

For those readers who may not be interested in mistletoe, the chapters by Dr. Nasha Winters are particularly worthwhile for general oncology care. Her chapter on lab evaluation is particularly intriguing. Winters depends a great deal on what she labels the "trifecta" lab – quantitative CRP, LDH, and Sed Rate. CRP must be 1.0 or less, LDH must be 175 or less, and Sed Rate must be 10 or less. If these scores are higher and other reasons cannot be ruled out, it must be assumed that the cancer process is worsening or at least not improving. She would argue that a change in treatment would be necessary with the caveat that a lab test alone should never justify treatment change. Winters insists that the patient's diet must be metabolically sound while doing mistletoe therapy. This means that carbs are greatly reduced and pristine fats are consumed to bring on fat burning and ketosis. She would argue that no cancer patient can improve without "metabolic flexibility" and insulin control.

Unfortunately, we do not have an article by Johnson and Winters in this issue. Instead I would strongly recommend purchasing a copy of *Mistletoe* available from www.steinerbooks.org.

Jonathan Collin, MD

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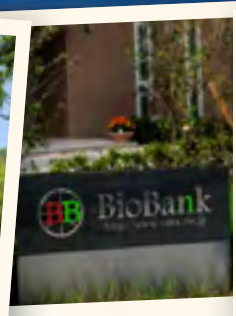

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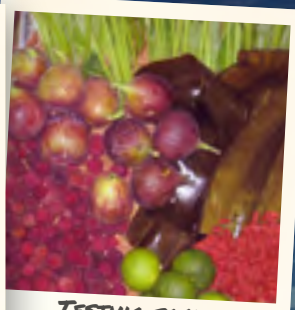

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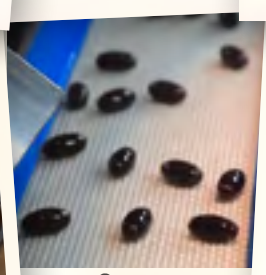

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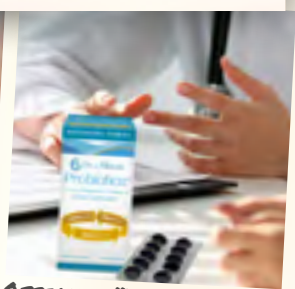

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Shorts

briefed by Jule Klotter
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Cardiotoxic Effects of Radiation Therapy

Heart damage is a potential consequence of radiation therapy (RT) for breast cancer and lung cancer. As Katie Livingston et al in their 2020 review article state, radiation therapy to the chest can adversely affect heart function in a dose-dependent manner. Even though imaging and radiotherapy techniques have improved, exposure to the heart is often unavoidable. The review authors say that underlying mechanisms that lead to cardiac damage are still not fully understood but radiation is known to cause changes in mitochondrial structures and produce dysfunction. It also causes endothelial cell damage and increases inflammation. By understanding the mechanisms underlying radiation-induced cardiac injury, the authors hope that new therapies can be developed that decrease the known cardiovascular risks.

A 2021 study, led by Lauren E. Carlson, MPH, used data from the Women's Environmental Cancer and Radiation Epidemiology Study (WECARE Study) to assess coronary artery disease (CAD) risk in women diagnosed before age 55. The participants were diagnosed with stage I or II invasive breast cancer between 1985 and 2008. Epidemiological risk factors, treatment details, tumor characteristics, and which breast was treated with radiation therapy were collected via structured questionnaires used in phone interviews or sent by mail and by medical records. This 2021 follow-up study looked at the incidence of nonfatal CAD events (cardiomyopathy, myocardial infarction, coronary heart disease, angina requiring medication, arrhythmia, stiff or leaking heart valves or heart surgery) among 972 women who lived in the US, Canada, or Denmark. Median follow-up time was 14 years (range 1-29 years). Women who did not receive radiation therapy (RT) or who had a history of CAD before their breast cancer diagnosis were not included. The researchers compared women treated with left-sided radiation (exposing the heart to more radiation) to those treated on the right, using multivariable Cox proportional hazards models.

The incidence of CAD was nearly twice as great in the group receiving RT to the left breast compared to the right: 10.5% vs. 5.8% (p=0.010). In actual numbers, 14 of 466 women with cancer in the right breast and 32 women of 506 women with cancer in the left breast reported a cardiac event. The researchers say that 91% of the CAD events occurred more than five years after radiation treatment.

CAD incidents in women who received right-sided RT between ages 25-39 was 0%, compared to 5.9% for those treated on the left side. For comparison, coronary heart disease among US women in that age group, according to 2015-2018 data, is 0.9%. For women diagnosed between ages 40-54 years, CAD events occurred in 6.8% of those treated on the right side and 18.7% of those treated on the left. The risk is 6.6% for that age in the general population of US women, according to 2015-2018 data. In the WECARE follow-up, chemotherapy treatment seemed to exacerbate the difference between right- and left-sided RT treatment.

The authors point out that ≥250 mg/m^2 of anthracyclines (chemotherapy) was not used as adjuvant cancer treatment during 1985-2008, when WECARE participants were treated. In a 2020 study, Allison Padegimas, MD, and colleagues report that anthracyclines, particularly when given in bolus dosing, are known to be cardiotoxic. The WECARE authors say, "Further research is needed to identify the types and doses of breast cancer chemotherapy that may increase the risk of RT-associated CAD." Although new techniques to reduce cardiac damage during radiation therapy are now in use, the WECARE authors recommend monitoring younger women treated with RT on the left-side for cardiovascular disease. As Padegimas et al note, "Overall survival outcomes are significantly worse in patients who develop [cardiovascular disease], and in certain breast cancer populations, cardiovascular death exceeds the risk of cancer death in the long-term." Finding ways to mitigate RT cardiac damage is ongoing.

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FDA and the Doctor-Patient Relationship

On June 2, 2022, three physicians filed a lawsuit against the Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the Secretary of Health and Human Services, and the FDA commissioner in a US federal district court (Southern District of Texas Galveston Division). The physicians – Robert L. Apter, MD, FACEP; Mary Talley Bowden, MD; and Paul E. Marik, MBBCh, M. MED, FCCM, FCCP – are represented by Trent McCotter, a partner with Boyden Gray & Associates. That law firm, based in Washington DC, focuses on constitutional and regulatory issues. McCotter, a former US Deputy Associate Attorney General and Assistant US Attorney, has taken part in many federal appeal cases. This case challenges the legality of FDA's campaign against off-label use of an approved drug – ivermectin – to treat covid-19.

According to the Food, Drug, and Cosmetic Act (FDCA), FDA has the authority to approve drugs for consumer use if they are safe and have an expected effect when used according to the manufacturer label. FDA can also monitor a product's safety after its approval, require changes in labeling, and withdraw approval in some cases. The agency has no authority to interfere with a doctor's off-label use of an approved drug or device:

> …the FDCA further provides in 21 U.S.C § 396 that nothing in the statute "shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device for any condition or disease within a legitimate health care practitioner-patient relationship."

The lawsuit lists several cases in which court decisions have upheld the physician's right to use approved drugs off-label: e.g., "'A physician may prescribe a legal drug to serve any purpose that he or she seems appropriate, regardless of whether the drug has been approved for that use by the FDA'" (*Wash. Legal Found v. Henney,* DC Cir. 2000).

The plaintiffs claim that FDA, which is a branch of DHHS, interfered with the doctor-patient relationship and exceeded its authority when it campaigned against the use of the approved drug ivermectin as a treatment for covid-19. The agency produced a publication on March 5, 2021, called "Why You Should Not Use Ivermectin to Treat or Prevent COVID-19," which failed to highlight its medical uses in humans or acknowledge the legality of off-label use. Beginning in April 2021, FDA publicized the drug's veterinary use while ignoring its long-time (since late 1970s), widespread and safe use in

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See Dr. Leigh Erin Connealy's article on Integrative Cancer Care on page 50

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humans. Several countries permit its sale over the counter. The agency started the Twitter campaign "You are not a horse. You are not a cow. Seriously, y'all. Stop it." – which gained extensive media attention and was repeated by numerous outlets, including *USA Today, The Guardian,* and *NPR.* The agency sent letters warning against its use for covid (but not against its other off-label uses) to the Federation of State Medical Boards and the National Association of Boards of Pharmacy.

"The FDA's actions resulted in their foreseeable and intended effect of stopping doctors from using ivermectin to treat COVID-19," according to the lawsuit. "Following the FDA's lead, the AMA, American Pharmacists Association, and American Society of Health-System Pharmacists all issued a joint statement 'strongly oppos[ing] the ordering, prescribing, or dispensing of ivermectin to prevent or treat COVID-19 outside of a clinical trial,' and pointed to the FDA's 'Why You Should Not Use Ivermectin to Treat or Prevent COVID-19' as part of their justification." Hospitals, courts, and insurers also used the publication as support for prohibiting the drug's use, even when prescribed by a patient's personal physician.

The lawsuit alleges that FDA "did not provide adequate justification for taking official positions on the use of ivermectin to treat COVID-19, failing to address or respond to *any* of the scientific evidence showing that ivermectin is an effective prophylactic or acute treatment for COVID-19." In addition, "[b]y directing against the use of ivermectin to treat COVID-19, the FDA has deliberately interfered with the practice of medicine and the authority of health care practitioners to prescribe approved drugs in bona fide practitioner-patient relationships, in violation of the FDCA."

Each of the plaintiffs say FDA's actions interfered with their ability to take care of their patients. Robert L. Apter, MD, is licensed in Arizona and Washington; he has over 40 years of experience in emergency medicine. He prescribed ivermectin during over 6,000 patient consultations (half for prophylaxis and half for treatment). Pharmacists' refusal to fill the prescriptions delayed treatment – "when early intervention is paramount." Dr. Apter is facing disciplinary proceedings by the Washington Medical Commission and Arizona Medical Board for prescribing ivermectin to treat covid.

Mary Talley Bowden, MD, who is licensed to practice in Texas, completed residency in otolaryngology-head and neck surgery at Stanford University Medical Center in 2003. She has also found that pharmacists have refused to fill ivermectin prescriptions for covid patients, which she began recommending in early 2020. In addition, Houston Methodist Hospital suspended her and forced her to resign her hospital privileges because of her early treatment recommendations. Dr. Bowden is a clinical advisor for Front Line COVID-19 Critical Care Alliance and owner of BreatheMD. Dr. Bowden has treated over 3,900 patients for covid with a success rate over 99.97%. She reports, however, that many patients were reluctant to take ivermectin because of the FDA campaign: "…health professionals, regulatory boards, and patients feel compelled to follow any directives or recommendations from the FDA, which presents itself as the authoritative source on the appropriate use of drugs."

Dr. Paul E. Marik, a critical care specialist who has practiced medicine for over 40 years, is the third plaintiff. Dr. Marik, who "is among the top scientists across all scientific fields according to John P. A. Ioannidis et al," was professor of medicine and chief of pulmonary and critical care medicine at Eastern Virginia Medical School (EVMS) from 2009-2021; he was also a director of the intensive care unit at Sentara Norfolk General Hospital. After the FDA tweet about animals and ivermectin, EVMS ordered Dr. Marik to remove the drug from the hospital's protocol for covid, a protocol that he had developed. Sentara also forbade ivermectin's use. Both EVMS and Sentara forced him to resign.

The plaintiffs are asking the Court to declare FDA's actions unlawful and to declare "FDA cannot interfere with the practice of medicine, that the FDA cannot issue statements or directives about how or whether health professionals should use ivermectin off-label to treat patients, and that such FDA actions have no legal effect and do not bind health professionals or patients." They also ask for an award of "reasonable attorney fees and allowable costs."

This case has major ramifications for the practice of medicine, the doctor-patient relationship, and – in my opinion – the future of integrative and alternative medicine, which often uses approved devices and drugs off-label. As McCotter states in his brief:

> If the FDA is not limited to its statutory lane, its unlawful actions will no doubt persist and repeat themselves.
>
> Moreover, if the FDA is allowed to interfere with the practice of medicine now under cover of a pandemic, this interference will metastasize to other circumstances, destroying the carefully constructed statutory wall between federal and state regulatory powers, and between the FDA and the professional judgment of health professionals.

R. Trent McCotter. In the United States District Court Sothern District of Texas Galveston Division. Case 3:22-cv-00184. Robert L. Apter, MD, FACEP et al v. Department of Health and Human Services. https://www.courthousenews.com/wp-content/uploads/2022/06/apter-fda-complaint-usdc-texas.pdf

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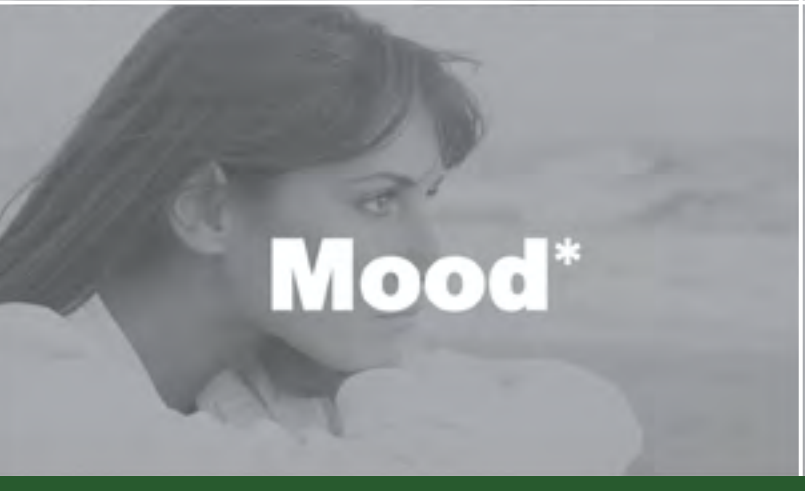

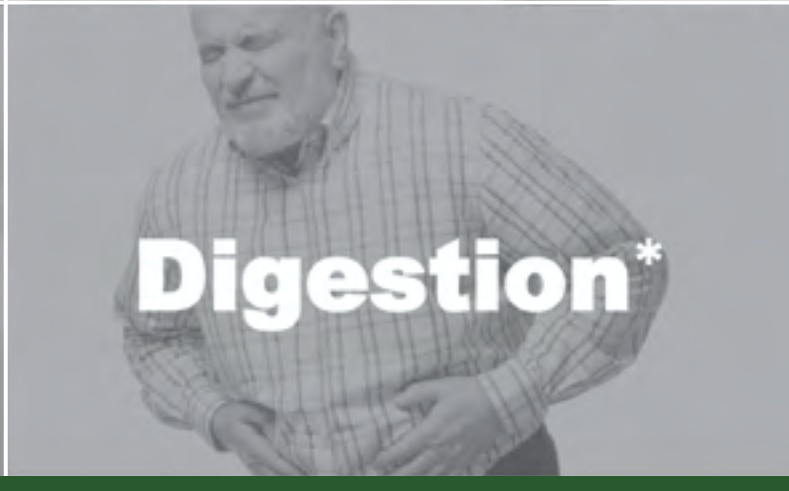

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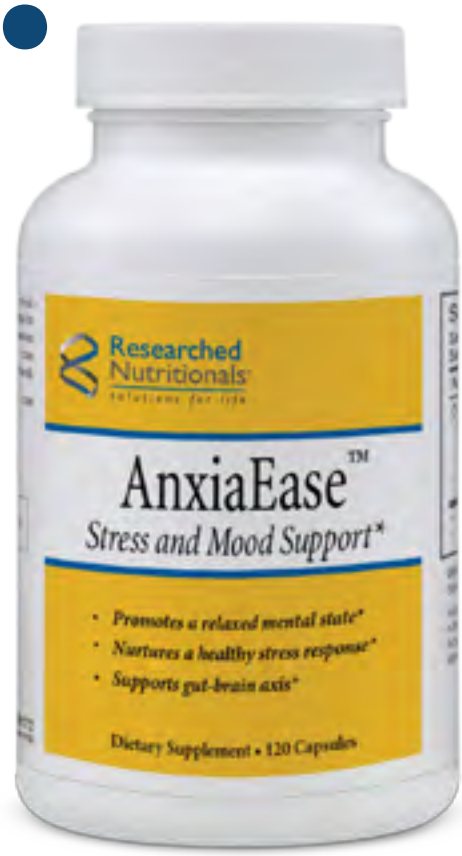

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In this Issue

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ON THE COVER: Linda L. Isaacs, MD – Pancreatic Enzymes and Cancer (pg. 30); Boosting Natural Killer Cell Activity (pgs. 55 & 56); Salicinium's Anti-Cancer Actions (pg. 14); Helping Shift Workers Get Needed Sleep (pg. 82)

Salicinium Clinical Pearls and Caveats

by Virginia Von Schaefer, MD

Many fine articles on salicinium have been published in the *Townsend Letter* in 2013, 2014, 2015, 2016, 2017, and 2021, and are available in the Archives. I would like to present a brief overview of my journey in the world on integrative oncology using salicinium and my current perspective on the task of successful problem solving for cancer patients.

The field of integrative oncology is a new frontier for medical problem solving. Cancer is the epidemic no one is talking about. Even five year "disease free" survival is increasingly difficult to achieve. We are seeing a huge increase in new cases of first-time diagnosis at Stage IV cancer in patients under the age of 35. Worldwide hope for a "cure" remains paramount in patient consciousnesses, yet even disease-free survival is difficult to attain despite our advances in drug development and technology. When we look at the traditional treatment options of chemotherapy, radiation therapy, surgery, hormonal modulation, and immunotherapy, these modalities continue to evolve. Nonetheless, many patients are seeking treatment outside of these options.

There is increasing discontent on the part of patients and families when faced with these choices. With the instances of cancer being so high in the population, it seems everyone knows several people who have cancer; and many have watched their friends and family suffer and die on traditional regimens. A week does not pass when I interview a new patient who tells me of someone they know who died after the first dose of chemotherapy or was told "your only hope is to receive chemotherapy until you die." Thus, many are turning away from the "standard of care" since they feel it will not produce the result they want and hope for, namely life and vitality beyond cancer. Fear of death is one thing, but patients state that fear of death by torture is unacceptable.

As a family member, I walked with my sister through her journey with leukemia that transformed into an aggressive B-cell lymphoma. She chose the traditional route of chemotherapy with Rituximab and all of her tumors would disappear only to reoccur 3-4 months later. Her diet of sugar and carbs never changed. Eventually, her cancer became resistant to Rituximab and she began taking an experimental oral chemo agent and continued with Rituximab. Only three weeks after starting, she developed a complication of the drug called, "Richter's transformation'' where the bone marrow pours all formed white blood cells at once. She developed bilateral pneumonia and died 48 hours later. After this life experience, I decided I could do better. A spinal cord injury subsequently stopped my career as a vascular surgeon and I turned back to my life passion and combined all my experiences to applying my knowledge of cell biology and biochemistry to medical problem solving. My intention was to discover how to treat cancer from multiple aspects of its unique metabolism and to use traditional methods of treatment combined with metabolic based modalities in a synergistic and non-conventional way.

I have been studying and treating patients using this strategy for many years. I noticed cancer is increasingly difficult to eradicate, and environmental challenges such as EMFs (5G), long term side effects of pesticide use, toxicity from synthetic materials, and untreated surreptitious viral and bacterial infections have become prominent confounding factors. If not addressed, patients have no hope of achieving disease-free survival.

The genius of Otto Warburg, a Nobel prize winning biochemist who lived from 1883-1970, brought to our attention the profound observation that normal cells will convert from oxidative metabolism (mitochondria produced energy) to anaerobic fermentation or glycolysis, when exposed to low oxygen tension for an extended period of time. We experience this phenomenon on a temporary basis, when we exercise heavily and work our muscles to "failure" with repeated reps. Anyone who has undergone a strenuous workout has had muscle soreness caused by lactate release that can last for hours, if not a day or two. With rest and hydration our muscles revert back to oxidative phosphorylation and the lactate washes out, relieving pain. This phenomenon is called facultative anaerobic metabolism because the cells can convert back to normal. However, Warburg demonstrated that all sick cells, which include those infected with bacteria, viruses, fungi, candida, parasites, and cancer cells all use glycolysis as a primary mode of energy production forever.

Glycolysis is an energy inefficient process that can only yield 2 ATP vs. 34 ATP, which is produced by mitochondrial oxidative phosphorylation. Furthermore, "perfect storm'' conditions required for glycolysis points towards how cancer can develop. In a situation of low oxygen tension, moist dark environment, low energy frequency, access to excess glucose and iron, these factors all play a part in developing an aerotolerant anaerobe. Concurrent with Otto Warburg's research, Japanese researchers identified another key fact – that these sick cells can secrete nagalase (Alpha-N-acetylgalactosaminidase), which "cloaks" the cells from immune system recognition and repels phagocytes (like a hormonal trophoblastic cell). The combination of these observations led people to conclude that nagalase production allowed cancer cells to thrive. Permanent conversion to anaerobic fermentation metabolism combined with nagalase release made cancer cells cloaked from immune system surveillance and, thus, could not be eliminated.

This information opened the door for changing our thinking about how to treat cancer from many different perspectives besides poisoning, cutting, or burning with radiation. Specifically, if you want to kill a cancer cell just destroy the environment it needs to thrive and create metabolic tricks "that will enter only sick cells and wreak havoc on their metabolism."

Salicinium is the Trojan horse for cancer cells. In 2005, Joe Brown collaborated with Professor Darrell Lemaire, head of the Department of Chemistry at the University of Nevada, Reno, to investigate the potential for phytochemicals. In the early 1970s, Japanese researchers demonstrated the anti-tumor effects of benzaldehyde via several different mechanisms. Joe Brown and his team created a stable glucoside/complex glycome of 4-hydroxy-benzaldehyde extracted from the plant *Helicia nilagirica* (from fig) and conjugated it to a glucose molecule (Salicinium)..

Salicinium is the Trojan horse for cancer cells.

Indirect and Direct Actions of Salicinium

Anaerobic metabolizing cells are "needy" for excess glucose to fuel their energy inefficient anaerobic metabolism. To that end, the GLUT transport "pores" are overly expressed on the surface of cancer cells to take in as much glucose as possible. Thus a benzaldehyde ring, which would not normally penetrate a cell, enters readily because it is conjugated with glucose. Once inside the cell, glucose is removed and used as an energy substrate.

Benzaldehyde is now able to donate its hydrogen and complexes with NADPH to form NADP-benzaldehyde. This reaction blocks forward progression of glycolysis, and changes intracellular pH just enough to cause quantum change in intracellular energy, which blocks acid extrusion and lactate formation. In this manner, these sick cells starve and lack energy to produce nagalase, the fibrin coat that "cloaks" cancer cells from recognition by macrophages.

The intracellular pH changes that occur also destroy mitochondrial function by causing their membranes to become "leaky."

Another factor of great interest is that the benzaldehyde ring causes a reduction of phosphorylation of the "hub signaling protein 14-3-3ζ [14-3-3 zeta]." The 14-3-3 ligand has a number of differential configurational states that regulate all normal cell functions. In cancer cells a mutant form of 14-3-3ζ is present. When benzaldehyde reduces the phosphorylation of 14-3-3ζ, its interaction with many "client proteins" is blocked – e.g., familiar mutations mTOR, c-RAD, STAT3, FOXO, NFKβ, RicToR, and

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TGF-β to name a few.[1] It would appear that as a result of these observations salicinium does more than disrupt glycolysis, starve cancer cells, and block nagalase production. It may well be able to prevent expression and function of many mutational pathways and ultimately cause apoptosis from even more avenues.

The topic of studying 14-3-3ζ is an active area for new ongoing research. Discoveries about the complex show 14-3-3ζ is implicated in causing chemoresistance and, thus, contribute to poor patient outcomes. Specifically, 14-3-3ζ overexpression confers chemoresistance and promotes oncogenic pathways PI3k/AKT, IGF-IR, ERK/MAPK, TGF-Beta, Beta-Catenin (related to WnT) and h-TERT in breast, lung, multiple myeloma, head and neck, glioblastoma. The question that needs to be answered *in vitro* is "does salicinium show specificity for multiple 14-3-3 isoforms and bind to phosphate binding pockets or to the divergent to C-terminal tail of different 14-3-3 isoforms." That results in blocking these mutational functions.

Salicinium can cross the blood-brain barrier.

Administration of IV Salicinium

- 3 grams per dose daily in 5 ccs in DMSO added to 0.9 NS 250 ccs over a span of 45 minutes-1 hour.
- Advise patient they will exude an odd/strong odor during the IV saturation phase, which disappears when patient converts to Orasal.
- IVs must be given five days per week consecutively, with Orasal on weekends, for a minimum of three weeks to ensure maximum tissue saturation before converting to oral only.
- Patient should follow accompanying protocol with pHenomenal, Impact, and React (https://forperfectbalance.com) daily.
- Orasal alone without IV loading may not give a significant result in adults.
- Avoid ozone, H2O2, DCA (dichloroacetate), arteminisin, high-dose vitamin C, SOD (superoxide dismutase), high-dose curcumin on salicinium protocol.
- Keep in mind salicinium is a food additive, a natural phytochemical and not chemotherapy.

Salicinium Application Do's and Don'ts

- Due to saturation of bone, tissue, and lymph nodes, the IV salicinium is an excellent option to combine with IPT for bone metastases and hematologic origin cancers
- Remember, tumor mass may dissolve, soften, and/or puff up as it is dying. Thus, palpable masses may not diminish in size and yet microscopically die on pathology analysis.
- Due to the metabolic effects on other sick cells that predispose a patient to developing or perpetuating cancer, Salicinium is an effective adjuvant for patients with EBV, HPV, HSV, parasites, fungus, and candida.
- If possible, obtain a PET/CT scan prior to treatment to assess intensity of tumor activity. Be aware, subsequent scans may not show full resolution SUV because even dying tumors may show metabolic activity. The key is that the SUV should decrease with treatment.
- Salicinium can be an excellent protocol for preoperative optimization of a cancer patient having surgical removal of the tumor. Salicinium tends to cause the tumor to coalesce and localize to allow resection with clear margins.
- Salicinium can be used alone or in combination with other natural agents.
- If angio-embolization of a tumor mass is planned, do not use salicinium before the procedure because feeding vessels may become tortuous and cannot be catheterized.

Clinical Cases

Stage I & II: Utilize the opportunity to treat pre-op and post-op, when desired, to "shrink" a large lesion prior to surgery. Treating the whole abnormal metabolic environment includes viral infections.

Fifty-eight-year-old female, with triple negative breast cancer, 5 cm lesion with two satellite lesions (1cm+2cm) plus positive axillary adenopathy on pre-op. Treated with six weeks of IV salicinium and IV mistletoe, interspersed with four sessions of AIPT. At operation (total mastectomy, no immediate reconstruction, limited axillary dissection). Pathology revealed 0.7 cm residual lesion in the breast plus all nodes negative in the axilla. Patient to complete post-op IV salicinium and IV mistletoe plus two more AIPT sessions before transitioning to Orasal/SubQ Mistletoe/herbal treatments.

Stage III: 45-year-old GoPo, ER-, PR-, HER2 Neu+ breast cancer with positive axillary nodes. Palpable 4 cm tumor disappeared completely with salicinium, mistletoe, IPT, and herceptin. Pathology at the operation showed no carcinoma, residual DCIS with negative sentinel lymph nodes after 12 months of herceptin. The patient is still disease free at three years.

Stage IV: Stage IV breast cancer diagnosed in 2015. No surgery. No chemotherapy. No ERT. Large bilateral axillary tumors (8x7 cm) and 8 liters ascites weekly (due to 2 small (2 cm) peritoneal implants). Patient had received >20 high-dose infusions of IV vitamin C, which had no positive effect on the tumors, and only increased ascites production. After five weeks of IV salicinium and IV mistletoe, bilateral axillary tumors were 100% reabsorbed, breast tumor volume shrank >50%, and ascites was gone. F/U PET Scan showed no SUV in right breast and low residual SUV in left breast. Patient is alive and well on Orasal and subQ mistletoe to date.

References

1. Pennington KL, et al. The Dynamic and Stress-Adaptive Signaling Hub of 14-3-3: Emerging Mechanisms of Regulation and Context-Dependent Protein–Protein Interactions. *Nature News*, 18 June 2018, https://www.nature.com/articles/s41388-018-0348-3.
2. Jonathan Collin <townsendpublisher1@yahoo.com>

Virginia Von Schaefer, MD, relies on more than 30 years of clinical experience in general and trauma surgery, endocrinology, and oncology to create strategies to solve her patients' complex medical problems. Her background in cell biology and biochemistry at Columbia University in New York City, established a special problem-solving mindset and framework that allows her to integrate "the best of both worlds" of conventional medical and surgical practice, along with an understanding of the fundamental biochemical/scientific basis for all current modalities. Continued study and shared knowledge with colleagues make it possible to evaluate and integrate the ever evolving, new advances for optimal patient care. Website: https://vvsmd.com/

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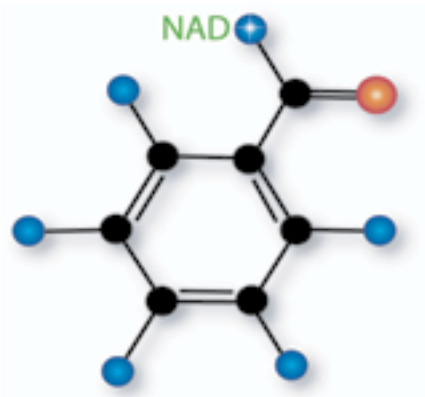

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The Science of Glycobiology

Salicinium changes the way the macrophage of the immune system recognizes diseased cells through immune modulation. The Nagalase enzyme produced by anaerobic cells shuts down the natural function of the immune system providing safety for these diseased cells.

The composite Salicinium molecule will only affect anaerobic cells destroying the enzymatic "cloak" which allows them to hide from the immune system's NK cells. Salicinium stops the production of Nagalase and lactate removing their protection while simultaneously stimulating the the innate immune macrophage to eliminate these diseased cells.

Circulating tumor cells are at the forefront of an ongoing or escalating malignant process. CTC testing has shown Salicinium affects these cells first therefore halting the spread of malignancy. Continued use of Salicinium will allow the immune system to steadily attack remaining malignant cells. The same testing also induces the death of cancer stem cells and Salicinium therapy, whether I.V. or oral, should be continued without interruption until testing shows no further indicators of malignancy.

- **In a study by R.G.C.C. of 967 patients Salicinium showed a 26.28% average apoptosis rate from a single dose with 82% sensitivity. A much higher cumulative apoptosis rate is recognized with ongoing treatment as the level of Salicinium builds within the tissues.**
- **Salicinium can be used alone or as an adjunct to other complementary therapies or as an integrative therapy to allopathic treatments.**
- **Salicinium is completely targeted - it will only enter anaerobic cells.**
- **Salicinium allows Gc-Maf to resume operation, greatly increasing Immunoglobulins**
- **Salicinium does not kill the malignant cells - the immune system does. Only the immune system can destroy anaerobic cells, Salicinium increases immune natural killer (NK) cells/Gc-Maf**

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Cancer Stem Cells

by Ralph W. Moss, PhD

Out of the innumerable articles written to commemorate the 50th anniversary of the National Cancer Act only a tiny minority mentioned one of the signal achievements of that effort: the discovery of cancer stem cells. But scientists from Harvard and Wayne State Universities got it right:

> The year 2021 marks the 50th anniversary of the National Cancer Act, signed by President Nixon, which declared a national "war on cancer." Powered by enormous financial support, this past half-century has witnessed remarkable progress in understanding the individual molecular mechanisms of cancer, primarily through the characterization of cancer genes and the phenotypes associated with their pathways.[1]

Key among these findings has been the identification of the markers of "stemness" in a special class of cancer cells known as "cancer stem cells" (CSCs). These are defined as "a subpopulation of tumor cells that can drive tumor initiation and can cause relapses."[2]

The existence of CSCs was strongly suspected in the 19th century by the likes of Rudolph Virchow, Julius F. Cohnheim, and John Beard, D.Sc. These European professors theorized that the ultimate origin of cancer could be found in primitive cells that were leftovers from the period of embryo formation. Modern scholars have written:

> More than 150 years ago, Rudolf Virchow and Julius Cohnheim proposed the intriguing hypothesis that cancer may develop from embryonic cell remnants that remain in the developing organs following embryogenesis. This hypothesis, known as the "embryonic rest hypothesis of cancer development," was popular in textbooks of pathology in the nineteenth and twentieth centuries.[3]

Even today, certain cancers are routinely recognized as of embryonal origin. This includes neuroblastomas, i.e., cancers that originate in neuroblast cells, usually of the adrenal gland, which are defined as "undifferentiated precursors of the central nervous system (CNS)."[4]

In all mammals, the maturation of neuroblasts is completed shortly after birth. In rare cases, however, neuroblasts fail to complete their development and become malignant." According to one dictionary, "neuroblastomas are tumors that can arise during the malignant degeneration of neuroblasts."[5]

Professor John Beard (1858-1924) of the University of Edinburgh, took this one step further. He proposed that all cancers were not just derived from "embryonal rests," as such remnants of earlier development were usually called but were identical to the trophoblastic cells of pregnancy. As we wrote in a special journal issue on Beard and Beard's legacy:

> Beard was the first to point to the parallels between cancer and the trophoblastic cells that envelop and nourish the embryo, characterizing cancer as 'irresponsible trophoblast.' He pointed out that the initiation of fetal pancreatic function coincided with a reduction in the invasiveness of trophoblast, which otherwise might progress to clinical cancer (ie, choriocarcinoma). Based on the above propositions, he recommended the therapeutic use of pancreatic enzymes in treating cancer and other diseases. This therapy created a worldwide controversy, and although rejected in his day, persists in the world of complementary and alternative medicine (CAM) today.[6]

I was thinking particularly of the work of Ernst T. Krebs, Jr., William B. Kelley, DDS, and Nicholas Gonzalez, MD, who wrote an entire book on the topic.[7] In conventional medicine, this theory is widely rejected today and only has a few adherents in the world of CAM. One logical flaw in the argument is that, were it true, all cancers would conspicuously produce the hormones associated with pregnancy. In fact, only a few of them do.

But it remains true that the first diagnostic tests for cancer, alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), and human chorionic gonadotropin (hCG), were all based on a recognition of some cancers' embryonic origin. These developments (flawed as they were) did keep alive the idea of a class of primitive cells lurking within a much larger population of ordinary tumor cells. These early thinkers paved the way for our current understanding of "cancer stem cells."

Indeed, Beard's thinking on the origin of cancer has been hailed as a forerunner of the present-day theory of cancer stem cells. "Cancer arises from displaced trophoblast of activated germinal cells," wrote Stewart Sell, MD, in his *Stem Cell Handbook*.[8] In this book, Beard's name followed that of the great Virchow and Cohnheim in anticipating today's CSC theory. This was the first time that Beard's name was linked to the concept of CSCs.

Cancer stem cells are now the subject of over 16,000 PubMed journal articles. The topic continues to fascinate an increasing number of researchers around the world. From a single article that first appeared in 1983, there are now almost 2,000 such articles per year, about five every day of the week.

This field has come a long way since 1997 when Prof. John Dick, Ph.D., and his group at the University of Toronto isolated a population of primitive stem cells in acute myeloid leukemia (AML). Today, there is "accumulating evidence" in the scientific literature that cancer stem cells are in fact the "driving force behind tumor initiation, progression, metastasis, drug resistance, and recurrence"[9]

Think about that! Scientists have discovered a group of unique cells that are responsible for just about everything that makes cancer fearful. Besides initiation, progression, metastasis, drug resistance, and recurrence, what exactly do we have to fear from this disease? Without the presence of CSCs, cancer might simply be a benign growth, a "space-occupying lesion" that could be ablated or permanently removed by robotic surgery.

Yet very few cancer patients ever hear about this breakthrough finding. That is because drug-oriented medical oncologists are waiting for approval of the first anti-CSC drug to be announced by the Food and Drug Administration (FDA). Meanwhile, there are phytochemicals (or nutraceuticals) that are already known to kill cancer stem cells. It is just a question of figuring out how to give these in the most effective way.

Cancer stem cells are the "driving force" behind tumor initiation, metastasis, drug resistance, and recurrence.

A key paper that points the way to a natural control of CSCs was the outstanding contribution of Dwight L. McKee, MD, and Cord Naujokat, MD, PhD, called "The Big Five."[10] McKee is a retired American medical oncologist, and Naujokat is a senior researcher at the Institute of Immunology, University of Heidelberg (Germany). They brought together a vast amount of research on the use of foods and food-derived factors on CSCs, especially resveratrol, soy isoflavones, sulforaphane, curcumin, and EGCG (green tea).

Another big step in this direction was taken by Australian researcher Myfanwy Webb, PhD, and the medical oncologist, Craig Kukard, MD. Their excellent 2020 article in *Integrative Cancer Therapies* reviewed the use of natural therapies for triple negative breast cancer (TNBC), "aimed at targeting cancer cell vulnerabilities."[11] The vulnerabilities in question are the markers of CSC. The substances found to counteract CSCs in TNBC turned out to be very similar to the "Big Five" in McKee and Naujokat's article. In particular, these identified seven substances that were relevant to the destruction of CSCs: curcumin, burdock, garlic, fisetin, Korean ginseng, sulforaphane and quercetin. But although there are about a dozen and

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Cancer Stem Cells

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a half articles on the natural treatment of CSCs, much work still needs to be done. In the future, hopefully, each individual's tumor cells will be studied for the presence of a dozen or so characteristic markers of CSCs, and then appropriate nutraceuticals will then be prescribed to counteract each of these. This is technologically possible at the present time.

However, although a scientific breakthrough is within our grasp, the political and economic barriers are more formidable. Such treatments inevitably run into what the former National Institutes of Health official, Wayne Jonas, MD, has called "the valley of death." This is the fact that natural treatments cannot deliver the financial returns that would justify the expense of clinical trials. It will take concerted public pressure to get the NIH and other non-profits to sponsor research into the individualized treatment of cancer stem cells with natural, non-toxic agents. The effort will be great, but the payoff in terms of improved outcomes could be equally enormous.

Dr. Moss is a graduate of New York University (BA, cum laude, Phi Beta Kappa, 1965) and Stanford University (MA, 1973, PhD, 1974, Classics). He is the former science writer and assistant director of public affairs at Memorial Sloan-Kettering Cancer Center in New York (1974-1977). Since leaving Sloan-Kettering in 1977, Moss has independently evaluated the claims of conventional and non-conventional cancer treatments all over the world.

He currently writes Moss Reports, detailed reports on the most common cancer diagnoses and provides informational and personalized consultations for cancer patients and their families. In 2019, he wrote "The Ultimate Guide to Cancer: DIY Research," to help lay people research their own cancers. This 50-page report is available free of charge at the mossreports.com website.

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Townsend Letter

ISSN 1940-5434

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This article is reprinted with the consent of the authors as a redacted summary of the following: León F. Villegas Vílchez, Julio Hidalgo Ascencios, and Thomas P. Dooley. GlucoMedix®, an extract of *Stevia rebaudiana* and *Uncaria tomentosa*, reduces hyperglycemia, hyperlipidemia, and hypertension in rat models without toxicity: a treatment for metabolic syndrome. *BMC Complementary Medicine and Therapies*. (2022) 22:62; https//doi.org/10.1186/s12906-022-03538-9

GlucoMedix® – An Extract of *Stevia rebaudiana* and *Uncaria tomentosa* Reduces Hyperglycemia, Hyperlipidemia, and Hypertension in Rat Models Without Toxicity

by León F. Villegas Vílchez,[1,2] Julio Hidalgo Ascencios,[2] and Thomas P. Dooley[3]

Abstract

Background: The objective of this *in vivo* study is to evaluate in five rat models the pharmacologic effects and toxicity of a commercial hydro-alcoholic extract, GlucoMedix®, derived from *Stevia rebaudiana* and the pentacyclic chemotype of *Uncaria tomentosa* (Willd.) DC, for use as a treatment for metabolic syndrome. The extract contains phytochemicals of *Stevia* (e.g., steviol glycosides) and *Uncaria* (e.g., pentacyclic oxindole alkaloids, but lacks tetracyclic oxindole alkaloids).

Methods: The pharmacologic assessments in three rat models include reductions in chemically induced hyperglycemia, hyperlipidemia (cholesterol and triglycerides), and hypertension, all of which are comorbidities of metabolic syndrome. Acute toxicity and 28-day subacute toxicity were assessed in rat models at doses higher than those used in the efficacy models.

Results: The acute oral toxicity was evaluated in Holtzman rats and the extract did not produce acute toxic effects or lethality, with the LD50 >5000 mg/kg (extract wet weight). Furthermore, subacute oral toxicity was evaluated in rats for 28 days at daily doses as high as 2000 mg/kg without toxicity or abnormal clinical chemistry or hematological effects. Daily oral doses of 250-1000 mg/kg were used to evaluate the treatment effects in hyperglycemic (alloxan-induced and glibenclamide-controlled), hyperlipidemic (cholesterol-induced and atorvastatin-controlled), and hypertensive (L-NAME-induced and enalapril-controlled) rat models. Alloxan-induced hyperglycemia was reduced in a dose-dependent manner within 28 days or less. Cholesterol-induced hyperlipidemic rats exhibited dose-dependent reductions in cholesterol and triglycerides at 21 days. Furthermore, GlucoMedix® produced a dose-dependent decrease in systolic and diastolic arterial blood pressure in L-NAME-induced hypertensive rats at 28 days.

Conclusions: The five *in vivo* rat models revealed that the all-natural phytotherapy GlucoMedix® is a safe and effective treatment for hyperglycemia, hyperlipidemia, and hypertension. This extract is expected to affect multiple comorbidities of metabolic syndrome, without any acute or subacute oral toxicity in humans. Although multiple prescription drugs are well known for the treatment of individual comorbidities of metabolic syndrome, no drug monotherapy concurrently treats all three comorbidities.

Results: Pharmacologic Dose Responses

In Figure 8, the dose responses of the various rat efficacy models are summarized. The treatment effects of GlucoMedix® are expressed as the percentage of the chemically induced maximum levels minus the uninduced baseline levels in each animal model. Herein, 100% represents no inhibition of the induced parameter, whereas 0% is total inhibition of the induced parameter (i.e., reduction to baseline). The glucose result is from 28 days of treatment; the cholesterol and triglycerides are from 21 days; and the blood pressures are from 28 days. It is unknown whether any further reductions in cholesterol and/or triglycerides would be achieved by an additional week of treatment (i.e., from 21 to 28 days).

Dose response curves are evident for each of the animal models tested, with the anti-hyperglycemic effect of GlucoMedix® being the most potent when comparing the three independent animal models. Note within the prior three sections ➤

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(above) the relative effectiveness of the highest dose of GlucoMedix® vs. the three pharmaceutical positive controls - Enalapril, Atorvastatin, and Glibenclamide. Even at the lowest oral dose of 250 mg/kg of the *Uncaria* plus *Stevia* extract, there is evidence of reductions in blood pressure, lipids, and glucose.

If Inhibitory Concentration 50% (IC_{50}) values are applied to GlucoMedix®, then the IC_{50} values for glucose, cholesterol, and triglycerides in these selected rat models are below 250 mg/kg, and for mean blood pressure it is approximately 500 mg/kg. Thus, to achieve a minimum of half-maximal inhibition in a genetic or diet-induced rat model of metabolic syndrome *per se* (i.e., manifesting multiple comorbid conditions) and for all of the endpoints assessed herein in individual rat models, then the recommended dose is 500 mg/kg. If total pharmacologic blockade is desired (and in this duration of treatment), then the Inhibitory Concentration 100% (IC_{100}) values in the selected rat models herein would be approximately 1,000 mg/kg for glucose, and greater than 1,000 mg/kg for cholesterol, triglycerides, and mean BP. Also, note that 1,000 mg/kg dosing is comparable to the clinical effect of the pharmaceutical positive controls. Furthermore, these IC_{50} values provide guidance toward allometrically scaled starting oral dosing in humans (see Discussion below).

Discussion

GlucoMedix® does not produce acute toxic effects in rats; the LD50 being greater than 5.0 g/Kg. Also, in 28-day subacute toxicity studies we did not observe mortality or signs of toxicity, and no significant weight loss was registered. Therefore, the NOAEL for the subacute toxicity study was 2,000 mg/kg. According to the dosage levels evaluated in the subacute and acute toxicity studies, the LOAEL (Lowest Observed Adverse Effect Level) was not found. The only statistically significant effects in the 28-day oral treatments were minor increases in hematocrit, hemoglobin, and red blood cells in males and hematocrit in females. Thus, GlucoMedix® could be considered with a wide margin of safety for oral use in humans.

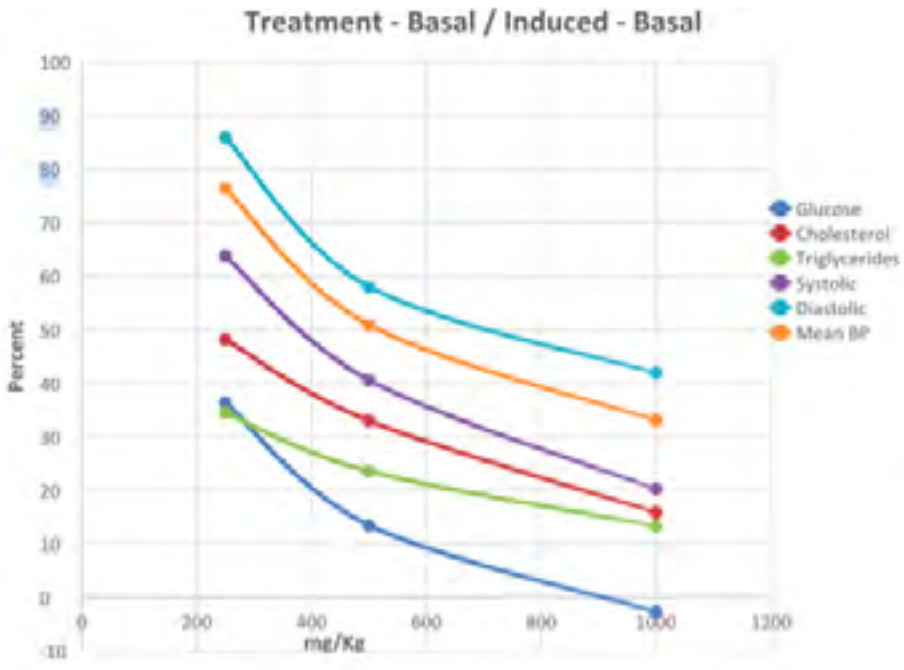
Regarding efficacy in three animal models, GlucoMedix® reduced the systolic and diastolic arterial pressure in hypertensive animals, which was induced by L-NAME, as evidenced with a 28-day treatment. In hyperglycemic and hyperlipidemic animals treated with GlucoMedix®, substantial and statistically significant beneficial effects were observed. All three rodent efficacy models manifested potent and dose dependent effects at 250-1000 mg/kg (extract wet weight), thus demonstrating pharmacologic benefits without any coincident adverse toxicities. The highest dose (1,000 mg/kg) was comparable to the pharmaceutical positive controls.

Various pharmacologic mechanisms of action (MOAs) of GlucoMedix® are plausible for reducing glucose, lipids, triglycerides, and blood pressure in the rat animal models.

Stevia and steviol glycosides might down-regulate the levels of glucose and lipids in blood, as well as arterial hypertension. *Stevia* phytochemicals or steviol glycosides were known in human clinical trials to affect type 2 diabetes.[1,2] There is evidence of a possible benefit regarding hypertension in humans.[3] However, another study of only 7 patients per group yielded a negative result for hypertension,[4] although statistically significant reductions in cholesterol, LDL, and glucose were observed.

The *Stevia*-derived ingredients were also effective in rat models in alloxan-induced hyperglycemia,[5-7] streptozotocin-induced hyperglycemia,[8] and cholesterol-induced hyperlipidemia.[9] Another rat study showed that stevioside and powdered *Stevia* leaves in high-carbohydrate and high-fat diets caused a significant reduction in blood glucose level after 4 weeks of treatment.[10] Our studies in three rat efficacy models are consistent with these prior findings, presuming that the steviol glycosides are contributing to the overall efficacy of GlucoMedix®.

Figure 8: Dose response for oral GlucoMedix® in rat models



GlucoMedix® (250, 500, 1,000 mg/kg) treatment effects, expressed as the percentage of the chemically induced maximum minus the uninduced baseline; glucose at 28 days; cholesterol and triglycerides at 21 days; systolic, diastolic, and mean BP at 28 days.

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Uncaria extracts have been found to reduce glucose levels in mice and rat animal models.[11,12] A hydro-alcoholic extract of *Uncaria* containing POAs (29.1 mg/g) in a streptozotocin-induced mouse model, showed a reduction in glycemic levels.[11] Likewise, rats treated with 75 and 150 mg/kg of *Uncaria tomentosa* dry extract showed a reduction in blood glucose.[12] One possible MOA for this glucose down-regulation is explained by alpha-glucosidase and alpha-amylase inhibitory activities within *Uncaria* extracts.[13,14] These enzymes catalyze the hydrolysis of complex polysaccharides, such as dietary starch and endogenous glycogen. This enzymatic antagonism of biodegradation of polysaccharide precursors might reduce blood glucose, and thus possibly contribute to the overall glycemic regulatory efficacy of GlucoMedix®.

Steviol glycosides and/or *Uncaria* phytochemicals might be affecting the endocrine and/or neuro-endocrine system, and in particular the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol levels might be a possible mediator under the influence of these bioactive compounds. Cortisol is known to play a key role in glucose utilization. Patients with metabolic syndrome exhibit elevated HPA axis properties leading to hypercortisolism.[15,16] Future studies of GlucoMedix® could assess levels of cortisol and insulin.

Another possible MOA is that the *Uncaria* POAs are affecting the immune system.[11,17-19] However, it should be noted that the subacute toxicology study at doses as high as 2000 mg/kg for four weeks did not reveal any significant alterations in white blood cell numbers or ratios. If the MOA is immunomodulatory, it is not being achieved by altering the number of white blood cells.

Regardless of the MOA, one significant factor to consider is that the three rodent efficacy models involved experimental induction agents (i.e., alloxan, L-NAME, and cholesterol) that result in parameters exceeding normal physiologic levels, whereas the acute and subacute toxicology models were not dependent on any induction events. In other words, the toxicity model was performed in a natural physiologic state. The 28-day toxicity studies further underscore that any efficacy benefit in hyper-normal physiological states (e.g., induced states or disease states) is not expected to result in any adverse outcome extending below baseline parameters in normal laboratory animals (or humans).

A beneficial aspect of these animal model efficacy and toxicity studies run in parallel is the establishment of a favorable therapeutic index. In other words, GlucoMedix® achieved the desired efficacy endpoints without any observable toxicity at or above the effective dose(s) and at coincident time points (i.e., at 3-4 weeks).

Toxicologic studies in rodents have demonstrated the safety of extracts and isolated compounds of *Uncaria tomentosa* and *Stevia rebaudiana.*[7,20,21] Our study shows that GlucoMedix® has an LD50 in rats greater than 5,000 mg/kg of body weight, and well-being parameters such as sleep, behavior pattern, motor activity, skin, coat, and appetite were normal. No weight loss was observed after two weeks of observation.

Metabolic syndrome is often associated with type 2 diabetes, but it can exist in patients lacking this comorbidity. In the US a diagnosis typically involves any three of five comorbidities, as per the NCEP-ATP III criteria. Although type 2 diabetes is common, it is not the essential factor driving the pathophysiology of metabolic syndrome in all patients.

Although some articles assert that alloxan induction is an experimental model for type 2 diabetes,[5,6] it should be noted that the alloxan-induced and glibenclamide-controlled rat model is more closely related to type 1 diabetes (insulin insufficiency), rather than type 2 diabetes (insulin resistance). This suggests that GlucoMedix® might be stimulating production of insulin from the remaining pancreatic beta cells following toxic damage to the tissue by alloxan. Thus, this animal model does not provide a precise correlate for type 2 diabetes within metabolic syndrome. Beyond the scope of the present experiment, two relevant rodent models for consideration for future confirmatory studies are C57BL6J male mice on high fat diet and Zucker Diabetic Fatty (ZDF) rats.[22,24]

GlucoMedix®

Stevia extract has long been used for the treatment of diabetes in South America.[25] Furthermore, stevioside is a potent sweetener with no calories. Thus, *Stevia*-derived products can achieve reductions in blood glucose in humans by two means: (a) as a substitute for dietary sugars, thus reducing ingested sugars; and (b) as a pharmacologic active ingredient affecting glucose homeostasis.

The GlucoMedix® extract of *Uncaria* and *Stevia* shows anti-hyperglycemic activity in alloxan-induced rats treated at doses of 250-1000 mg/Kg of body weight. GlucoMedix® might regulate the level of glucose by increasing insulin secretion and/or by a better utilization of glucose by peripheral tissues and muscles in diabetic rats.

One of the most common complications of diabetes mellitus is cardiovascular disease. Other studies have suggested that *Uncaria*, *Stevia*, and their metabolites promote cardiovascular health and reduce hypertension. Our results with GlucoMedix® show a decrease in cholesterol and triglyceride levels in hyperlipidemic rats at 21 days and a decrease in blood pressure induced by L-NAME in hypertensive rats at 28 days of treatment with doses of 250-1000 mg/Kg.

The 1,000 mg/kg daily dose (wet weight) is equivalent to administering 81.8 mg of steviol glycosides, 16.98 ug of isopteropodine, and 4.71 ug of pteropodine per kg of body weight in rats. This maximum tested dose of GlucoMedix® displayed the same or similar potency to the three pharmaceutical positive controls. However, comparison of dosing to other published rodent models treated with other extracts is somewhat problematic. For example, Ahmad and coworkers

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demonstrated anti-hyperlipidemic effects in cholesterol-induced rats using 200-500 parts per million of *Stevia* extract; presumably this represents 200-500 mg/kg dry weight of *Stevia* powder.[9] Thus, they tested 200-500 mg/kg vs. 29.2-116.7 mg/kg of *Stevia* powder within GlucoMedix® in the present study. As another example, Kujur and coworkers demonstrated anti-hyperglycemic effects in alloxan-induced rats using 50-100 mg/kg (wet weight) of *Stevia* extracts at 28 days; the dry weights are unknown.[7]

If the 250, 500, and 1,000 mg/Kg daily doses in rats (ca. 0.24 Kg) are extrapolated via allometric dosage conversion for oral administration in humans (65 Kg and 0.75 exponent), the corresponding allometric daily doses of GlucoMedix® required in an adult for "similar" pharmacologic effects would be 4, 8, and 16 g (wet weight).

Given that the extract mixture contains ca. 2.56 mg/100 ml of POAs, then these human allometric doses would contain only 0.10, 0.20, and 0.41 mg of POAs. Note that few active pharmaceutical ingredients (APIs) in the pharmacopeia are effective in the sub-milligram level in human adults. However, predicate examples do exist; an example is the phytochemical scopolamine that is effective at 0.1-0.5 mg in humans.[26,27] If the POAs are contributing to the efficacy endpoints, then they would by necessity be highly potent phytochemicals.

Allometric dosage conversion presumes similarities between the two species regarding pathophysiology, pharmacokinetics, and pharmaco-dynamics. A suggested human starting oral daily dose of GlucoMedix® that might be effective within 4 weeks at treating metabolic syndrome or its comorbidities is 4 g. Given that the IC_{50} values for glucose and lipids (cholesterol and triglycerides) were below 250 mg/kg in rats, then it is reasonable to speculate that adult doses lower than 4 g (and/or with longer duration of treatment) might also be effective in humans.

A physician-sponsored retrospective case series study has been reported of six humans afflicted by type 2 diabetes, which were treated with GlucoMedix® at daily doses of 4 or 6 g (28). The patients experienced reductions in hyperglycemia, and several of them coincidentally reduced or ceased treatments with prescription drugs or insulin. Thus, the suggested minimum allometric dose (4 g) based upon the rat efficacy model for hyperglycemia coincides with the minimum dosage used within the type 2 diabetes case series.

Furthermore, based upon the relative potencies in rats across the three indications summarized within Figure 8, the most potent effect was observed for hyperglycemia (IC_{50} <250 mg/kg), followed by hyperlipidemia (IC_{50} <250 mg/kg), and finally mean blood pressure (IC_{50} ~500 mg/kg). If this correlation also applies in humans, it suggests that treatment of hypertension might require higher daily dosing with GlucoMedix® than is required for glucose regulation.

Conclusions

Limitations of this work should be noted: (a) The pharmacologic effects might be due to *Stevia* alone, *Uncaria* alone, or the combination thereof; (b) The efficacy studies were based upon established chemical induction models, rather than genetic disease models that are predisposed to diabetes, hyperlipidemia, and hypertension. Future studies could also focus on alternative rodent models for hyperglycemia (and obesity) that mirror type 2 diabetes, such as C57BL6J male mice on high fat diet or Zucker Diabetic Fatty (ZDF) rats; and (c) The beneficial pharmacologic effects and lack of toxicity were assessed for up to 21 days (anti-hyperlipidemia) or 28 days (anti-hyperglycemia, anti-hypertension, and subacute toxicity).

A safe and effective natural product, such as GlucoMedix®, that can address multiple comorbidities of metabolic syndrome would be a welcome addition to the pharmacopeia and marketplace. We are unaware of any single US FDA-approved drug that can address all three conditions, although inexpensive monotherapies are available for treating hypertension (e.g., ACE inhibitors and beta blockers), hyperlipidemia (e.g., statins), and type II diabetes (e.g., metformin). A physician-sponsored case series of six type 2 diabetic patients suggests that this natural product at 1-1.5x of the suggested starting allometrically-scaled dose can address at least one of the three indications, namely hyperglycemia.[28] ◆

References are available online at www.townsendletter.com.

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Literature Review & Commentary

by Alan R. Gaby, MD
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Vitamin D for Palliative Care in Cancer Patients

Two hundred forty-four Swedish patients with advanced cancer and a serum 25-hydroxyvitamin D level below 20 ng/ml (median, 15.2 ng/ml) who were receiving home-based palliative care were randomly assigned to receive, in double-blind fashion, 4,000 IU per day of vitamin D or placebo for 12 weeks. One hundred fifty patients completed the trial. Most of the dropouts were due to death from cancer. Among patients who completed the trial, the increase in opioid use was significantly smaller in the vitamin D group than in the placebo group ($p = 0.03$). In addition, the mean severity of fatigue was significantly less in the vitamin D group than in the placebo group ($p < 0.01$).

Comment: Vitamin D deficiency is common in patients with advanced cancer. Likely contributing factors include poor appetite, decreased capacity to absorb dietary vitamin D, and lack of sunlight exposure. The results of the present study indicate that correction of vitamin D deficiency may improve fatigue and decrease the need for opioids in patients with advanced cancer who are receiving palliative care.

I once consulted with the wife of a patient who was receiving home hospice care for advanced cancer. Because of severe fatigue, he was in bed most of the time. He had not been out of the house for many months, and his diet contained little vitamin D. I recommended that he take 10,000 IU of vitamin D per day for one week, and then a lower dose for maintenance. Within 24 hours of taking the first dose, he was feeling so much better that he got up, got dressed, and took his wife out to dinner. Although he succumbed to his illness, vitamin D supplementation improved the quality of the final weeks of his life.

Helde Frankling M, et al. 'Palliative-D' - Vitamin D supplementation to palliative cancer patients: a double blind, randomized placebo-controlled multicenter trial. *Cancers*. 2021;13:3707.

CBD Oil As a Potential Treatment for Lung Cancer

A woman in her eighties was diagnosed in June 2018 by CT scan and lung biopsy with non-small cell lung carcinoma in the right middle lobe. She declined conventional therapy and chose to self-administer cannabidiol (CBD) oil at a dose of 0.5 ml, usually three times per day, occasionally twice a day. Serial imaging showed that her cancer decreased in size progressively from 41 mm to 10 mm over a period of 2.5 years.

Comment: Cannabinoids, which are chemically similar to our own body's endocannabinoids, can interact with signaling pathways to control the fate of cells, including cancer cells. Previous studies on the use of cannabinoids as a treatment for cancer have produced conflicting results. Based on the encouraging results in this case report, further studies on the use of CBD oil seem warranted.

Liew KL, et al. Lung cancer patient who had declined conventional cancer treatment: could the self-administration of 'CBD oil' be contributing to the observed tumour regression? *BMJ Case Rep*. 2021;14:e244195.

Vitamin C Improves Mental Vitality

In a cross-sectional study of 214 healthy young Korean adults (aged 20-39 years), there was a positive association between the serum vitamin C concentration and the ability to maintain attention ($p = 0.02$). Fifty-five percent of participants had an "inadequate" serum vitamin C level, which was defined as below 0.88 mg/dl. For comparison, the usual laboratory reference range for vitamin C is 0.6-2.0 mg/dl. Fifty individuals with "inadequate" vitamin C levels were randomly assigned to receive, in double-blind fashion, 500 mg of vitamin C twice a day or placebo for four weeks. Compared with placebo, vitamin C significantly increased attention ($p = 0.03$), engagement in work ($p = 0.03$), and cognitive function (as assessed by the Stroop color-word test; $p = 0.04$), and nonsignificantly improved fatigue ($p = 0.06$).

Comment: This study found that suboptimal vitamin C status is common among healthy young Korean adults, and that improving vitamin C status can improve work motivation, attention, and performance on cognitive tasks that require sustained attention. In a study of US adults (aged 20-59 years) participating in one of the National Health and Nutrition Examination Surveys, mean vitamin C intake was 85 mg per

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day among men and 67 mg per day among women.[1] The Recommended Dietary Allowance (RDA) for vitamin C is 90 mg per day for men and 75 mg per day for women. Thus, more than half of the adults in this study were consuming less than the RDA for vitamin C. Those individuals might experience benefits similar to those reported in the present study if they increased their vitamin C intake.

Sim M, et al. Vitamin C supplementation promotes mental vitality in healthy young adults: results from a cross-sectional analysis and a randomized, double-blind, placebo-controlled trial. *Eur J Nutr*. 2022;61:447-459.

Vitamin D Supplementation During Pregnancy Improves Children's Tooth Development

Six hundred twenty-three pregnant women participating in the Copenhagen Prospective Studies on Asthma in Childhood were randomly assigned to receive, in double-blind fashion, high-dose vitamin D (2,800 IU per day) or standard-dose vitamin D (400 IU per day), beginning at 24 weeks of gestation and continuing until one week postpartum. The mean serum 25-hydroxyvitamin D level at baseline was 30.7 ng/ml, which suggests that most of the women had adequate vitamin D status. A dental examination was performed at age 6 years in 496 children of the women in the study. An enamel defect was defined as having at least one molar affected by an opacity, enamel breakdown, and/or atypical restoration. The incidence of enamel defects in the permanent teeth was lower with high-dose vitamin D than with the standard dose (15.1% vs. 27.5%; odds ratio = 0.47; 95% confidence interval [CI], 0.27-0.81). Similar results were seen in the primary (baby) teeth (8.6% vs. 15.9%; odds ratio = 0.50; 95% CI, 0.28-0.87).

Comment: Defective enamel development affects up to 38% of schoolchildren. Impaired enamel formation can result in pain and rapid caries progression. Vitamin D plays a role in enamel development. In the present study, 2,800 IU per day of supplemental vitamin D was more effective than 400 IU per day for promoting satisfactory tooth development in the offspring of Danish women. This study was a post-hoc analysis of a previous study that found that the higher dose of vitamin D decreased the incidence of troublesome lung symptoms in this same group of children.[2]

Denmark is much farther north of the Equator than the northernmost parts of the United States. Therefore, Danish individuals receive less sunlight than those living in the US. Additional research is needed to determine whether the findings from this study apply to people living in the US.

Norrisgaard PE, et al. Association of high-dose vitamin D supplementation during pregnancy with the risk of enamel defects in offspring: a 6-year follow-up of a randomized clinical trial. *JAMA Pediatr*. 2019;173:924-930.

Omega-3 Fatty Acids and Heart Failure

In the Vitamin D and Omega 3 Trial (VITAL), 25,871 US adults (mean age, 67.1 years) were randomly assigned to receive, in double-blind fashion, 2,000 IU per day of vitamin D, 1,000 mg per day of omega-3 fatty acids, both treatments, or placebo for a median duration of 5.3 years. The present study, an ancillary study of VITAL, examined the effect of omega-3 fatty acids on the risk of hospitalization for heart failure (HF). The effect of omega-3 fatty acids was found to depend on whether the participants had type 2 diabetes. When omega-3 supplements were compared with placebo, the hazard ratio (HR) for first HF hospitalization was 0.69 (95% confidence interval [CI], 0.50-0.95) in participants with type 2 diabetes and 1.09 (95% CI, 0.88-1.34) in those without type 2 diabetes (p for interaction < 0.02). The presence of type 2 diabetes also modified the effect of omega-3 fatty acids on the risk of recurrent HF hospitalization (HR = 0.53; 95% CI, 0.41-0.69 in participants with type 2 diabetes; HR = 1.07; 95% CI, 0.89-1.28 in those without type 2 diabetes; p for interaction < 0.0001). In a secondary analysis, omega-3 supplementation reduced recurrent HF hospitalization (but not initial HF hospitalization) only in Black participants (p for interaction < 0.05).

Comment: While some previous studies found that omega-3 fatty acid supplementation prevented the development of HF, other studies found no beneficial effect. The results of the present study suggest that the effect of omega-3 fatty acids on risk of HF differs in different subsets of the population. Specifically, omega-3 fatty acids may help prevent HF in people with type 2 diabetes and in Black individuals, but not in others.

The literature on omega-3 fatty acids for the prevention and treatment of cardiovascular disease is voluminous, complex, contradictory, and confusing. Presumably, individuals with lower baseline omega-3 fatty acid intake, a higher level of systemic inflammation, or a hypercoagulable state would be more likely than others to benefit from omega-3 fatty acid supplementation. The present study suggests that Blacks and people with type 2 diabetes are also likely to benefit from omega-3 fatty acids.

Djousse L, et al. Diabetes mellitus, race, and effects of omega-3 fatty acids on incidence of heart failure hospitalization. *JACC Heart Fail*. 2022;10:227-234.

Interpreting 25-Hydroxyvitamin D Levels

The authors of this letter to the editor point out that there has been considerable controversy about how to interpret serum 25-hydroxyvitamin D (25[OH]D) levels. Because 25(OH)D is an acute phase reactant, the level declines in response to inflammation. Consequently, a low 25(OH)D level may not necessarily indicate vitamin D deficiency. The innate immune system responds to metabolic stress with chronic low-grade inflammation, as manifested by a small increase in the C-reactive protein (CRP) level. Minor CRP elevations are associated with many medical conditions and with various unhealthy lifestyles that lead to metabolic stress. Examples include diabetes, obesity, hypertension, atrial fibrillation, obstructive sleep apnea, excessive nutrient consumption, poor sleep, and unhealthy diets.

Low 25(OH)D levels are associated with numerous medical conditions that have an inflammatory component, including preeclampsia, autoimmune disorders, infectious diseases, cardiovascular disease, cancer, type 2 diabetes, subcutaneous and visceral adiposity and obesity, neurological disorders, and acute pancreatitis. These associations have generally been interpreted to indicate that vitamin D deficiency predisposes to or aggravates those conditions, rather than considering the possibility that the conditions themselves lead to a low 25(OH)

D level. About 30% of the general population has a minor CRP elevation, a fact that might explain why low 25(OH)D levels are so common. The authors concluded that 25(OH)D levels are unlikely to be a reliable measure of vitamin D status in people with one of the many conditions that are associated with systemic inflammation. Interpretation of a low 25(OH)D level may be aided by measuring the CRP level.

Comment: I have been making these same arguments about vitamin D testing for at least 15 years. It is encouraging to see that two other doctors have come to the same conclusion. Perhaps I was ahead of my time, or perhaps there are now two more doctors who don't know what they are talking about. I vote for the former.

Antonelli M, Kushner I. Low serum levels of 25-hydroxyvitamin D accompany severe COVID-19 because it is a negative acute phase reactant. *Am J Med Sci*. 2021;36:333-335.

Ginger for Symptoms of Hypothyroidism, or More Iranian Research Fraud?

Sixty hypothyroid Iranian patients with persistent hypothyroid symptoms despite having a normal TSH level while on levothyroxine therapy were randomly assigned to receive, in double-blind fashion, 500 mg of ginger powder twice a day or placebo for 30 days. Compared with placebo, ginger significantly improved hypothyroid symptoms, as assessed by the Thyroid Symptom Rating Questionnaire ($p < 0.001$). Compared with placebo, ginger also significantly improved mean scores for cold intolerance, constipation, dry skin, appetite, memory loss, and ability to concentrate, and also significantly decreased body weight and serum cholesterol levels.

Comment: Readers of the *Townsend Letter* know that I have concerns that many of the research studies from Iran appear to be fraudulent. There are several issues with the present study.

1. Questionable baseline data: In order to be included in the study, participants had to have a TSH level of 0.3-4.5 mIU/L. In Table 1, the mean TSH level in the ginger group was 3.62 ± 2.21 mIU/L. Assuming a Gaussian distribution of TSH values, with that mean and standard deviation, approximately 16% of the subjects in the ginger group (i.e., 4 or 5 subjects) would have had a TSH level of 5.83 or higher, which would have made them ineligible for the study. In order to be included in the study, participants also had to have a body mass index (BMI) of 19-35 kg/m^2. In Table 1, the mean BMI in the ginger group was 31.17 ± 5.28 kg/m^2. Assuming a Gaussian distribution of BMI values, with that mean and standard deviation, approximately 16% of the subjects in the ginger group (i.e., 4 or 5 subjects) would have had a BMI of 36.45 kg/m^2 or higher, which would have made them ineligible for the study.
2. Discrepancies regarding recruitment: The paper stated that the target sample size was 60 subjects. The Iranian Registry of Clinical Trials (IRCT) document that is associated with this paper stated that the target sample size was 120 subjects. The paper, but not the IRCT document, mentioned the use of multivitamins or the presence of vitamin D deficiency as exclusion criteria.
3. Discrepancies regarding dates: The IRCT document was registered on February 6, 2020. The document stated that recruitment was complete. However, the paper stated that the subjects were enrolled between August and November 2020.
4. Another possible issue: The 60 subjects enrolled in this study had all been referred to an endocrinology clinic, apparently because of persistent hypothyroid symptoms despite normalization of laboratory tests for thyroid function. One might reasonably assume that the purpose of such a referral would be to have the patient evaluated for other possible endocrine disorders that might be contributing to the symptoms. Patients who seek the care of a specialist are usually looking for symptom relief, not to be enrolled in a clinical trial in which they have a 50% chance of receiving a placebo and a 50% chance of receiving a treatment for which there is little or no prior evidence of efficacy. It is difficult to believe that many patients would waive their expected endocrine evaluation and instead agree to participate in this clinical trial. It is even more difficult to believe that 60 such individuals from a city of 134,000 people were enrolled in the study over a 4-month period.

Ashraf H, et al. Efficacy of ginger supplementation in relieving persistent hypothyroid symptoms in patients with controlled primary hypothyroidism: a pilot randomized, double-blind, placebo-controlled clinical trial. *Evid Based Complement Alternat Med*. 2022;2022:2022:5456855.

Interpreting Elevated Serum Vitamin B12 Levels

Fifty serum samples with very high levels of vitamin B12 (> 1476 pmol/L) were randomly selected to search for macro-B12 interference. Eighteen percent of the samples were found to contain macro-B12. Macro-B12 was detected with the use of a polyethylene glycol (PEG) precipitation procedure.

Comment: Elevated serum vitamin B12 levels have been seen in patients with hematologic disorders (promyelocytic leukemia, polycythemia vera, or hypereosinophilic syndrome) or liver disease. Macroforms of vitamin B12 (macro-B12) are sometimes present in serum. Such macroforms consist mainly of immunoglobulin-vitamin B12 complexes and are considered biologically inactive. Macro-B12 can interfere with the laboratory measurement of serum vitamin B12, resulting in falsely elevated levels. In the present study, nearly one-fifth of elevated vitamin B12 levels were an artifact caused by the presence of macro-B12. The authors of this study recommended that laboratories use the PEG precipitation procedure to screen for macro-B12 when the serum vitamin B12 level is elevated. Identification of this artifact would in some cases eliminate the need for unnecessary additional diagnostic tests.

Soleimani R, et al. Macro vitamin B12: an underestimated threat. *Clin Chem Lab Med*. 2020;58:408-415.

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On the Cover

Pancreatic Proenzymes and Primitive Cells

by Linda L. Isaacs, MD

For the past 30 years, I have offered an enzyme-based nutritional program to patients with cancer and other illnesses. It is both rewarding and challenging work. There are some days that vividly remind me why I have persevered through all these years.

In early 2022, I got a call from a former patient of my long-time colleague and friend, the late Nicholas Gonzalez, MD. This patient was diagnosed with squamous cell carcinoma of the lungs in late December 2009; the cancer had spread to his bones. The orthodox treatment available at the time had little to offer him. He heard through a friend of the program offered by Nick and me, and he became Nick's patient in January 2010. A year later, scans showed the tumors were gone. Nick published his case in 2014 as part of his article about the use of pancreatic enzymes in cancer.[1] When I spoke to the patient, he told me that there was no sign of the lung cancer that had been diagnosed more than a decade earlier.

Prior to Nick's death in 2015, the patient had agreed to an interview for a documentary, which was later televised. Another man and his wife saw that documentary, shortly after he was told that his colon cancer had returned; surgery and chemotherapy had not cured him. He contacted me and became my patient. Now, he has no sign of cancer on multiple follow-up scans. His oncologist is amazed. The details of his case are included in an article I wrote for *Alternative Therapies in Health and Medicine*.[2] The patient himself told his story in an interview in the *Price-Pottenger Journal of Health & Healing*, mentioning how grateful he is for the time he has had with his family, especially his son.[3]

When Nick's patient called, I was able to tell him that because he had diligently followed his treatment plan and then shared his story, another man was inspired to diligently follow the program I gave him. And a ten-year-old boy did not have to attend his father's funeral.

That is the kind of story that keeps me going. That is the kind of story that got me involved in the first place. When I was a third-year medical student, the intern for my internal medicine rotation was Nick Gonzalez. Even with the rigors of medical internship, he was continuing his investigation of the results of William Donald Kelley, the orthodontist and alternative cancer practitioner who had become notorious for his involvement in the treatment of Steve McQueen. Nick found multiple cases of patients who had done well in Kelley's files.

I still remember the impact some of those cases had on me when I heard about them for the first time. A man with prostate cancer in multiple bones, admitted to the hospital for pain relief, who went on the Kelley program and 10 years later was working part-time and playing the violin in a ragtime band. A woman with metastatic uterine cancer whose lung tumors resolved. A woman who had bilateral mastectomies before she was forty, and painful recurrence in the bone a few years later, who was alive and pain-free 17 years later (and who was still alive and well in 2016, 40 years after the recurrence). All of these cases and more are in Nick's monograph about Kelley, *One Man Alone*.[4] Nick and I both dedicated our professional lives to doing what we could to get this method properly investigated. Between the monograph about Kelley's results and our own efforts, we published more than 150 case reports describing patients with documented tumor regression, prolonged survival, or both.[1,2,4-9]

What is the method? It involves three components: dietary modification, nutritional supplements, and detoxification routines such as coffee enemas. All three components are important, but we believe the anti-cancer effect comes from large doses of pancreatic enzymes, taken away from meals.

The use of pancreatic enzymes for cancer goes back a century, beginning with the observations of the embryologist John Beard. Beard noted the similarity of the appearance and behavior of cancer to that of the precursor to the placenta, the trophoblast. The trophoblast invades the uterine wall, creates a blood supply for itself, and evades the maternal immune system, looking and acting like cancer does. But at a certain

point in development, the trophoblast matures, becoming less invasive. Beard reported that this happened around the same time that the fetus began producing pancreatic enzymes, months before birth. He postulated that pancreatic enzymes played a role in controlling the behavior of trophoblast cells, and that they could also play a role in controlling the behavior of cancer cells, as described in his 1911 book *The Enzyme Treatment of Cancer and Its Scientific Basis*.[10]

A 2022 review article of mine, published in *Integrative Cancer Therapies*, details the history of the clinical use of pancreatic enzymes against cancer in the decades after Beard published his theories.[11] In addition, the article discusses possible mechanisms of action on a cellular level. While for many years it was believed that pancreatic enzymes only have a role in digestion, in more recent years there has been an explosion of discoveries about the role of proteases (a class of enzymes that cleave proteins) in multiple aspects of physiology.[12] There are protease-activated receptors on the surfaces of many different types of cells, including cancer cells and trophoblast cells, where various proteolytic enzymes can affect the behavior of cells by clipping off surface receptors.[13,14]

There is reason to believe that the active agent against cancer is not the activated forms of the various proteolytic agents, but rather the proenzyme (inactive precursor) forms, based on research done in cell cultures.[15,16] The form of pancreas product that Nick and I used is minimally processed, and most of the enzymes it contains are in the precursor form.

While general theories about the action of pancreatic enzymes on cancer cells do exist, the exact mechanisms are not as detailed as some patients and practitioners desire. As an example, after a lecture, an attendee wanted to know what action pancreatic enzymes have on the p53 system and looked surprised and disappointed when I told him that as far as I know, no one has investigated this.

Kelley started using pancreatic enzymes for cancer based on a serendipitous discovery when he himself became ill, not based on an elaborate theory of their mechanism of action. Nick and I began using this treatment method based on patient histories in Kelley's files, not based on an elaborate mechanism of action. Our focus was on clinical results. For that reason, we preserved all the aspects of Kelley's methods, including coffee enemas, which are commonly regarded with derision in the orthodox medical world – through coffee enemas have a long history of use, as described in my review article on that subject.[17]

Beard's theories about cancer treatment were based on his observations about the fetus' manufacture of pancreatic enzymes around the time the trophoblast matured into the placenta. But Beard was not the first to notice that cancer looks and acts like embryonal tissue. In his 1914 book *The Cancer Problem*, Bainbridge, a surgeon based in New York City, discusses the concept of "embryonic rests," residual embryonic cells in adult tissues that give rise to cancer, proposed by Cohnheim in 1882.[18] Bainbridge dismissed the theory, though he did not elaborate on his reasons. Around the same time, Boveri suggested that cancer was caused by changes in a cell's nuclear material, recognized as the source of inherited information even though the exact nature of chromosomes had not been determined.[19] This gave rise to the Somatic Mutation Theory, the predominant theory about carcinogenesis in the medical world today, informing decisions about research goals and treatment methods in both the orthodox and alternative medical worlds.

The Somatic Mutation Theory states that cancer arises because of a mutation or collection of mutations in a mature somatic cell or in a stem cell, causing it to become a cell that proliferates and spreads. In the mindset based on the Somatic Mutation Theory, such mutated cells can only be treated by eradicating the defective cells, since nothing can fix such a mutation. Surgical removal, destruction by radiation, chemotherapy, or immunotherapy, or poisoning by affecting altered metabolic pathways are the only tools that can possibly work.

Pancreatic proenzyme treatment alone, without diet and detoxification, is usually not effective.

Alternate explanations of the development of cancer exist. The Tissue Organization Field Theory (TOFT), as expounded by Drs. Soto and Sonnenschein, states that chronic abnormal interactions between the stroma and cells in the tissues, such as in chronic inflammation, can affect cells to become more primitive in nature, "development gone awry" as the authors put it.[20] As cells become more primitive, their metabolism changes to become more similar to that of the early embryo, and they develop genetic instability. In this model, genetic mutations occur in cancer not as a cause, but as a consequence of the shift towards a more primitive phenotype. The authors compare the two models, Somatic Mutation and Tissue Organization Field, with their weaknesses and strengths, in a table that can be accessed at https://journals.plos.org/plosbiology/article/figure?id=10.1371/journal.pbio.3000670.t001. The most salient point in this table to me is this statement: "'Spontaneous cancer regression' is compatible with the TOFT. Tissue recombinants show that cancer cells (even of those carrying alleged "oncogenic" mutations) are 'normalized' when placed in homotypic "normal" tissues."

Beard's theory would suggest that pancreatic proenzymes control the aggressive behavior of the trophoblast, an early embryonic cell. If the Tissue Organization Field Theory is correct, then cancer consists of cells that have shifted towards more primitive behavior, and pancreatic proenzymes may normalize these cells and control their behavior. Some experimental support for this exists; Peran et al reported that a combination of proenzymes and amylase promoted cellular differentiation.[21]

TOFT also provides a theoretical underpinning for Nick's and my clinical observation that pancreatic proenzyme treatment alone, without diet and detoxification, is usually not effective. If cancer develops because of issues in the tissues such as chronic inflammation, a good quality diet can lessen that inflammation. Meanwhile, poor diets, continued toxin ➤

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exposure, or even negative emotional states could mean increased stressors in the tissues causing the production of more abnormal cells, overwhelming the proenzymes' ability to nudge those cells into better behavior.

I have written before in the *Townsend Letter* about the challenges that Nick and I faced as we attempted to conduct clinical research on the use of proteolytic enzymes in cancer.[22] Since those bleak times in the 1990s, more and more evidence has appeared in the medical literature about the role of proteases in physiology that would support their use. It is my hope that in the long run, Nick's efforts and mine will be vindicated.

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In her practice, she uses a nutritional approach for treating patients diagnosed with cancer and other serious degenerative illnesses. She and her colleague, the late Nicholas J. Gonzalez, MD, published articles about their work with cancer in the peer-reviewed journals *Nutrition* and *Cancer and Alternative Therapies in Health and Medicine*, and co-authored the book *The Trophoblast and the Origins of Cancer*. She has also published articles in *Integrative Cancer Therapies* and *Integrative Medicine: A Clinician's Journal*. Her website is www.drlindai.com.

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The Trophoblast Theory of Cancer

by Lawrence Wilson, MD

Introduction

This article presents basic information about the nature of cancer. The trophoblast theory of cancer is that cancer is caused by a normal tissue of the body, the *trophoblast*, that arises at the wrong time and place.

History of the theory. In 1902, John Beard, MD, a prominent embryologist, published a paper in a British medical journal, *The Lancet,* entitled "The Trophoblastic Theory Of Cancer" (Beard, J., 1902). The theory is quite simple and has never been disproven.

In fact, fairly recently it received strong confirmation by scientists at the University of Michigan (*Townsend Letter*, #240, 2003).

Dr. Beard showed that a normal tissue of the body, the **trophoblast**, exhibits characteristics identical to cancer. It is invasive, metastatic, forms new blood vessels (angiogenesis) and has the same specific markers and chemical composition as cancer cells.

The Origin of the Trophoblast

All human and animal bodies have a number of special cells called *totipotent* or *stem cells* that can take on different forms and different roles. Their activity depends upon the needs of the body and upon the biochemical environment of the body. One of the roles that these cells can take on is to become trophoblast.

The word *trophoblast* from Latin means "to nourish the baby." *Trophology* is another word for nutrition. A *blast* in medical terms is an immature organism or baby. The way the trophobast normally works is the following:

- A fertilized egg quickly develops a number of *totipotent* or *stem cells.*
- At this time, the fertilized egg is moving out of the Fallopian tube where fertilization often occurs. The egg is moving into the mother's uterus.
- When the fertilized egg reaches the uterus, the totipotent cells sense a need for nutrition. Also, the uterus has a more acid pH than the Fallopian tubes and there is a lot of estrogen present.
- This combination causes the totipotent cells to activate a genetic pathway that changes them into trophoblast.

Functions of the Trophoblast.

1. *Secreting human chorionic gonadotropin or HCG.* The trophoblast secretes a number of chemicals. An important one is HCG. This is the usual chemical used in pregnancy tests. It is also a test for cancer. (HCG is not really a hormone because it is not made by a gland.)
2. *The hooks.* The trophoblast cells develop tiny hooks that grab and hold onto the mother's uterine lining. This prevents the egg from falling out of the mother's uterus and being lost. This phase of pregnancy is called *implantation of the egg*.
3. *Lysis and invasion.* Next, the trophoblast secretes enzymes called lysozymes. These destroy the surface of the uterine lining around the egg. Then the trophoblast invades or burrows into the mother's uterine lining. It is able to digest normal uterine tissue in a special way so that it can use the nutrients and blood. The fertilized egg is a foreign body in the mother and needs nutrients.
4. *Angiogenesis.* As it grows, the trophoblast forms tiny tubules that become blood vessels. Through these vessels, it steals blood and nutrients from the mother and sends them to the developing baby. Later, the placenta helps with this job, but for the first 8-12 weeks of pregnancy, only the trophoblast nourishes the baby.
5. *Metastasis.* As it grows, the trophoblast *metastasizes* or spreads. It is able to invade normal tissue and convert its DNA to make more trophoblast-like tissue. This is a similar mechanism to the one that viruses use to replicate themselves in our bodies. However, trophoblast is not a virus. This mechanism of the trophoblast explains why each type of cancer in the body has a different 'look' to it. The cancer is part trophoblast, but mainly converted breast, lung, colon or other tissue.

What Goes Wrong to Cause Cancer?

Totipotent cells are found all over everyone's body at all times. The reason is that these cells can take over any function, if needed.

The problem occurs if the biochemistry of the body changes in certain ways to favor the production of trophoblast. When this occurs, trophoblast arises and, if not stopped, the person dies of cancer. Evidence of the theory follows:

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1. The pregnancy test. As mentioned above, the test for pregnancy, measuring human chorionic gonadotropin or HCG, is also a good test for the presence of cancer in the body.
2. Choreocarcinoma. Rarely, the trophoblast overgrows during pregnancy. This results in a very aggressive uterine cancer called *choreocarcinoma*.
3. Other. The trophoblast shares many chemical qualities with cancer cells, such as a sugar-based energy system.

What Activates the Trophoblast?

Scientists have studied the trophoblast. Transformation of totipotent cells into trophoblast outside of pregnancy occurs due to the following:

1. *An acidic tissue pH.* This is very common today and due mainly to a deficiency of alkaline reserve minerals such as proper forms of calcium, magnesium, sodium, potassium, zinc, selenium, chromium and manganese.
2. *Low pancreatic enzymes.* Pancreatic enzymes control the trophoblast. The levels are low in many people due to nutritional deficiencies.
3. *Other nutrient deficiencies,* especially low omega-3 fatty acids, low vitamin C, low vitamin A, and low iodine.
4. *Excessive amounts of toxic metals,* especially copper, cadmium, lead and nickel.
5. *Overuse of the sympathetic nervous system***.** This prevents adequate rest and rejuvenation of the body. It is very common today. One can measure this using hair mineral testing.
6. *Low available oxygen.* This can be due to shallow breathing, anemia or other problems.
7. *Toxic chemicals.* These poison the liver and other organs. They include medical drugs, toxic herbs, pesticides, aldehydes (from eating too much fermented food), and AGES (advanced glycation end products) from eating roasted and baked food. Most people are exposed to thousands of toxic chemicals.
8. *Autointoxication.* This is the production of toxic substances inside the body. One of the worst sources is root canal-filled teeth. These dead teeth all infect and discharge very poisonous toxins. Also, many people do not eat properly and do not digest food well. Instead, food putrefies and ferments, forming powerful toxins.
9. *Too much yeast in the body*. This can be due to the diet or is related to a damaged energy system in the body that forces the body to burn sugar for energy. Yeast produces many poisons including acetaldehyde and alcohol.
10. *Mental and emotional factors.* Negative emotions such as resentment, guilt, and loss of the will to live can contribute to trophoblast formation.

Reversal and Healing

A*ny therapy that causes totipotent cells to stop becoming trophoblast will help prevent and halt the growth of cancer.* By referring to the section above, one can see what this would include.

Therapies to 'turn off' the sympathetic nervous system. These are plenty of rest and sleep, and a nourishing diet high in alkaline reserve minerals. These are found mainly in properly *cooked*, not raw vegetables.

Raw vegetables supply many nutrients. However, humans cannot extract much mineral nutrition from raw vegetables because the minerals are locked in the tough vegetable fibers.

One can drink vegetable juices. However, they have another problem. They are very *yin* or cold in Chinese medical terms. This is quite harmful for those with cancer, so many practitioners today limit juices to 10-12 ounces daily of carrot juice.

Pancreatic enzymes to help digest food. This is very important. The pancreas is a parasympathetic organ, and the enzymes will control trophoblast growth.

Red heat lamp therapy. Shining three or four reddish infrared heat lamps on the body for 1.5 hours daily is excellent. This therapy nourishes the body and calms the sympathetic nervous system.

One can use what are called chicken brooder lamps. These are simple 250-watt reddish heat bulbs. They are inexpensive and sold at farm supply stores, some hardware stores, or on line.

One can build or buy a sauna powered by these lamps. The heat of the sauna also powerfully inhibits the sympathetic nervous system. Details to build or buy this type of sauna are at www.drlwilson.com or in the book, *Sauna Therapy* by Dr. Wilson.

Coffee enemas are excellent for colon and liver detoxification. This is the work of Drs. Max Gerson, MD, and William Donald Kelley, DDS. The colon and liver are among the most diseased organs in many people.

Deep breathing and good posture assist oxygenation. Other oxygen therapies such as drinking oxygenated water and others may also be helpful.

One can also buy an ozonator/ionizer air purifier. It will increase the oxygen level in your home or office.

Balancing body chemistry. One can use the method of Dr. Paul Eck to assess the stage of stress, the oxidation rate, and the ratios of the vital minerals. Balancing these ratios using food and supplements helps maintain a high level of adaptive energy in the body. This assists nutrition and detoxification.

Emotional and spiritual healing. One needs to forgive everyone for everything that has occurred in one's life in order to let go of resentments. Read uplifting books or other media and focus on the positive aspects of life.

Dr. Lawrence Wilson has worked as a nutrition consultant for over 40 years. He is also the author of four books. He has a large website with many articles about health and nutrition. For details, visit www.drlwilson.com. Dr. Wilson can be reached by email at https://drlwilson.vpweb.com.

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Intravenous Nutrient Therapy in Oncology – Selected Interventions

by Paul S. Anderson, NMD

Introduction

Due to space available for this article I will focus on basic nutrient interventions in the intravenous support of patients with cancer. This is definitely not done to minimize the contributions of other intravenous agents such as artesunate, DMSO, mistletoe, DCA, etc., and all the potential botanicals that are in use. I chose the following to focus on because they form, in my experience, the basis for a very broad set of offerings that can improve quality of life and outcomes in most patients with cancer.

High-Dose Intravenous Vitamin C (HDIVC)

The use of HDIVC was popularized largely by the work of Frederick Klenner, MD, who used HDIVC in hospital practice from the 1940s through his passing in 1984. Dr. Klenner published case reports from his practice during those years.[1-3] It is said he inspired Linus Pauling and Irwin Stone to expand the research on the benefits of vitamin C.[4]

HDIVC is a common therapy in integrative oncology. While lower doses of IV vitamin C are also used (and will be discussed separately) HDIVC has particular potential benefits I will outline here.

The mechanism of HDIVC falls in two broad categories: Becoming a "pro-drug" for hydrogen peroxide and also providing a host of nutrient and chemical manipulations that actually weaken cancer cells while strengthening normal non-cancerous cells.[5-7] The pro-drug for hydrogen peroxide part of the mechanism cannot be caused with oral vitamin C because not enough will absorb.[8,9]

HDIVC also has potent anti-inflammatory effects. Cancer is aggravated by inflammation,which can fuel abnormal cell division. Research has found that a series of IVC sessions can lower the blood inflammation marker C-reactive protein (CRP) by approximately 75 percent.[10]

Preliminary evidence also shows that IVC activates a gene that suppresses tumor formation,[11] and there is also an anti-angiogenic effect to HDIVC.[12]

Safety of HDIVC

The bottom line with respect to HDIVC is that in properly screened patients it is an extremely safe intervention. In a 2010 review of over 50,000 HDIVC infusions there were five reported serious adverse events in the literature.[13] In a review of the five cases mentioned I found that all could have been prevented with proper pre-HDIVC screening. The patient should be pre-screened prior to any HDIVC, and particular attention is paid to G6PD status, kidney function, electrolyte status, hemoglobinopathies, and other areas as clinically indicated.

Chemotherapy and HDIVC

A great deal of confusing information regarding the appropriate place and timing for the administration of HDIVC with other chemotherapeutic agents exists. I completed an up-to-date review of all available data in this arena.[14] A quote from a recent scientific paper shows the overall direction the data are pointing:

> Clinical investigation of pharmacologic ascorbate should be considered as an addition to existing cancer treatments. Its mechanism of action as a pro-drug for H2O2 generation is distinct from most currently used agents. For this reason, there is potential for synergy, or at least an additive effect, in combination with other drugs. Emerging data indicate that there are additive effects of ascorbate with other neoplastic agents.[15]

A review of available data in 2008 summarized multiple existing cancer therapies and their effect in combination with ascorbate and found all agents either not affected or enhanced by ascorbate. This review had one exception which was the drug bortezomib,[16] but later clinical data showed that even this agent had synergistic effect with HDIVC.[17]

A 2012 multicenter study involving 60 people newly diagnosed with cancer and receiving conventional cancer therapy were administered HDIVC twice weekly for four weeks. Significant relief was noted in quality-of-life scores that included fatigue, pain, insomnia, and constipation.[18] And a study of 39 terminal cancer patients not undergoing chemotherapy and radiation therapy and given IV C and oral vitamin C reported significantly lower scores of fatigue, pain, nausea/vomiting, and appetite loss. They also had higher scores for physical, emotional, and cognitive function.[19]

For background, the Bastyr Integrative Oncology Research Center (BIORC) study was funded by the National Institutes of Health (NIH)

and operated at the Bastyr University Research Center. I was the chief of IV services and operated the IV therapy clinic. My patient group consisted of Stage-4 cancer patients treated with HDIVC and many other IV therapies. We found the three-year survival rates of Stage IV colon, lung, and breast cancer patients and Stage III ovarian cancer patients receiving HDIVC from BIORC were dramatically better than national statistics (found in the National Cancer Institute's SEER program).[20,21]

More study needs to be done, but data presented between late 2011 and 2012 from the BIORC NIH-funded research also revealed only positive additive effects using HDIVC in combination with existing cancer treatments.[22] In a 2014 published review of the effects of intravenous vitamin C on cancer and quality of life the authors noted: "Several recent studies have indicated that intravenous (IV) vitamin C alleviates a number of cancer- and chemotherapy-related symptoms, such as fatigue, insomnia, loss of appetite, nausea, and pain. Improvements in physical, role, cognitive, emotional, and social functioning, as well as an improvement in overall health, were also observed."[23]

In summary, HDIVC in my experience (and borne out in the scientific study of it) is an incredibly helpful therapy for many patients with cancer as well as potentially assisting to prevent recurrences of prior cancers.

Low-Dose IV Vitamin C (LDIVC)

As mentioned, IV vitamin C has two different primary actions based on dose and the type of cell it interacts with. In regard to the dose, a "low dose" strategy is generally considered to be below the level needed to be an "oxidative" (HDIVC) therapy. Is a "low" dose (or dose range) known and is there any research showing lower doses can help?

In three scientific papers written on the dose threshold of LDIVC versus HDIVC none are completely in agreement (this is common in scientific papers) but generally speaking a low dose is considered between five and ten grams of IV vitamin C.[24-26]

Regarding scientific papers showing benefit with LDIVC, two[27,28] have been commonly cited and another (presented at a scientific meeting in the US) was a follow up to show safety in the US hospital setting.[29] All of these used low dose strategies and showed improved quality of life in patients with cancer.

Specialized Hydration with Nutrient Support

A landmark scientific paper regarding the nutritional status of cancer patients summarized the issue as follows: "Malnutrition is the most common secondary diagnosis in cancer patients. Even patients who are eating

Hydration IV therapy that includes nutrients reduces pain, rescues patients from chemotherapy side effects, and improves quality of life.

The question of "why would LDIVC be beneficial to quality of life in cancer" likely has multiple answers. In addition to the antioxidant support LDIVC offers, other benefits are published. One paper outlines LDIVC as having the ability to decrease gene mutations following oxidative stress (which is increased in cancer and by many cancer treatments).[30] Another paper shows LDIVC as augmenting natural killer cell function, which is incredibly important to remission and length of life in cancer patients.[31]

While the three QOL studies cited used a simple formula (of a base IV solution such as normal saline) and a small dose of vitamin C (five to ten grams) the use of LDIVC offers many other added potential benefits for broadening the therapeutic potential of the IV. As mentioned in the HDIVC section those high dose strategies require specific mineral additives and are best not combined with other additives such as many B-vitamins, glutathione etc. This restriction is to protect the oxidative properties of the HDIVC formula. Conversely, when using the LDIVC one can add other vitamins, minerals, and amino acids, and follow the LDIVC with glutathione as well. This allows for the full benefit in QOL and potentially other positive effects when used in patients with cancer. And while the LDIVC can be simply compounded in a bag of "Normal Saline," "Ringers Lactate" (NS or LR), I have typically compounded it in an isotonic osmolarity formula, mixing the LDIVC and basic nutrients.

can become malnourished because of specific biochemical and metabolic changes associated with cancer. These metabolic changes impair nutritional status and contribute to cancer-related malnutrition…"[32] The author goes on to cite studies showing that cancer-related weight loss, anorexia and nutrient depletion is much more widespread than originally believed.[33,34] The bottom line, illustrated by multiple studies, is that cancer patients are depleted and the use of IV nutrients can extend life and improve quality of life (QOL).[35-39]

So, how does this all relate to the use of "specialized hydration with nutrient support"? A method, coming from all the scientific papers mentioned above, emerged a number of years ago for us clinically in an effort to help cancer patients with improved QOL and decreased side effects from their cancer and cancer therapies. IV hydration in and of itself is quite simple. If the person has good cardiac and kidney function you can give them a hydrating IV solution (such as NS, LR, etc.) and you build their fluid volume. Our idea was to use the principles of hydration IV therapy while using nutrients instead of simply saline or a like fluid. The issue in the past was that most nutrient repletion solutions were actually dehydrating (which defeats the purpose of hydration) in exchange for nutrient repletion. This requires a little calculation, but over time I was able to construct hydrating solutions (in isotonic formulas) that had broad nutrients, including vitamins, minerals

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and amino acids. Using these formulas, the patient has the benefit of both hydration as well as nutrient repletion.

We have seen these formulas rescue people from severe side effects from chemotherapy, improve mental function, reduce pain, and improve QOL overall as well as at the end of life. In our clinical experience these specialized hydrating nutrient formulas are a critical part of IV therapy in patients who have cancer.

Radiation and Chemotherapy Side Effect Formulas

Below, I will share part of a human trial I implemented for patients with radiation burns after having therapeutic radiation for head and neck cancer. First it would be good to review why tissues are damaged giving rise to side effects (of radiation and chemotherapy) and what can be done about it. Neurological cells (and all others) are incredibly sensitive to mitochondrial damage, cell membrane damage and other effects. Many oncologic therapies have deleterious effects on the cell matrix and nerve function, leading to significant decreases in quality of life. Supplementation and augmentation of glutathione function can aid in the regeneration of all damaged body tissues. As mentioned, these effects are especially seen in nerve, digestive, joint, skin, and other critical tissues.

Augmenting Glutathione: The use of an augmented glutathione support therapy can help the more severely injured tissues heal. Glutathione function is tied to oxidative stress which leads (if unbalanced) to cell damage.[40] Glutathione status is depleted during chemotherapy.[41] Glutathione is depleted in and required as protectant for radiation therapy and exposure.[42,43] And finally glutathione has been shown to be cell protective in some chemotherapy exposures.[44,45] So the use of glutathione for repair after cancer therapy is an easy case to make.

This leads us to the clinical trial in patients with radiation damage after head and neck radiation therapy. The question came up in our research center "why not just provide glutathione IV alone and see what that does?" The answer was (and is) because in the body glutathione is not a "lone ranger" acting without support. Glutathione is like all antioxidants supported by cofactors, which assist it in returning to its useful "reduced" state. Otherwise, it gets used once and becomes a non-beneficial nutrient. So how was this issue solved for these patients with radiation damage and what did we learn?

The bottom line was (and is) that a well-rounded protocol needed to be employed, which not only supplied the glutathione but also the necessary cofactors for glutathione recycling as well as nerve repair. I started this therapy with these radiation-damaged patients and assessed their nerve damage every four weeks. The protocol was an IV session (with this combination therapy) twice a week for four to eight weeks then weekly for eight weeks then if needed twice monthly for two to three months. Most patients recovered 90% or more of their nerve and other damaged function. It is important to note that the time from injury (from radiation or chemotherapy) to use of the IV program was crucial. The more the delay the longer it took to have recovery.

Summary

In this article I have attempted to summarize basic nutritional interventions for intravenous use in patients who have cancer. I limited the discussion to low and high dose vitamin C, glutathione augmentation, and hydrating nutrient solutions. Although these are a small fraction of the intravenous options we potentially have, they do form the base of therapies that can help most patients with cancer.

Links to Protocols and Other Data Mentioned

A. Vitamin C, chemotherapy and radiation – data review. https://www.consultdranderson.com/wp-content/uploads/securepdfs/2020/12/6-Ascorbate-and-Oncologic-Therapies-2020.pdf
B. HDIVC electrolyte balanced formulas. https://www.consultdranderson.com/wp-content/uploads/securepdfs/2022/04/4-Ascorbate-and-Electrolytes-with-Formulas.pdf
C. Hydrating nutrient formulas. https://www.consultdranderson.com/wp-content/uploads/securepdfs/2022/04/9-Hydration-via-IV-Therapy.pdf
D. Radiation recovery / glutathione augmentation. https://www.consultdranderson.com/wp-content/uploads/securepdfs/2019/04/8a-GSH-Augmentation-and-Cell-Protection.pdf

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References are available online at www.townsendletter.com.

Paul S. Anderson, NMD, is a recognized educator and clinician in integrative and naturopathic medicine with a focus on complex infectious, chronic, and oncologic illness. He founded Advanced Medical Therapies in Seattle, Washington, a clinic focusing on cancer and chronic diseases and now focuses his time in collaboration with clinics and hospitals in the US and other countries. Former positions include multiple medical school posts, Professor of Pharmacology and Clinical Medicine at Bastyr University and Chief of IV Services for Bastyr Oncology Research Center.

He is co-author of several books, including *Outside the Box Cancer Therapies* with Dr. Mark Stengler, *Cancer…The Journey from Diagnosis to Empowerment* with Jack Canfield, and the IV textbook *A Scientific Reference for Intravenous Nutrient Therapy* with Drs Osborne and Carter. He is a frequent CME speaker and writer and has extended his educational outreach creating an online CE website "ConsultDrA.com" and Advanced Applications in Medical Practice (AAMP) conferences.

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Cancer Diagnostics: Tumor Markers, Cancer Genomics, Circulating Tumor Cells, and Circulating Tumor DNA

by Sean Devlin, DO

The statistical peril of developing cancer in one's lifetime is 40.1% in men and 38.7% in women according to the American Cancer Society. The risk of dying from that cancer: 21.34% in men and 18.33% in women.

Cancer is among the leading causes of death worldwide. In 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide. In 2020, an estimated 1,806,590 new cases of cancer were diagnosed in the United States and some 606,520 people will die from the disease. By 2040, new cancer cases per year are expected to grow to 29.5 million and the number of cancer-related deaths to 16.4 million.

Cancer is a complex illness that can affect any organ system in the body. A variety of factors contribute to the development and growth of cancer – from epigenetic influences like radiation, toxin exposure, obesity, and stress to a patient's genetic background. Combinations of these influences can create and promote cancer in the body. Several mechanisms provide for cancer's survival and growth in the human body. Some of these factors include evading cell death and senescence messaging, a limitless replication potential, the capacity for immune evasion, the ability to spread throughout the body, metabolic stress and genomic instability (see Figure 1).

Minimally invasive cancer surveillance, diagnostics and monitoring are critically important for patient care and have been evolving over the past decade. Many practitioners, from primary care physicians to surgeons and subspecialists, utilize organized approaches to evaluate and diagnose cancer patients.

In order to understand the road to a cancer diagnosis, let's start at the beginning. Practice styles may vary, however the pathway most clinicians and surgeons take in diagnosing and staging a patient with the suspicion for cancer includes the following:

Most physicians use the VINDICATE model to develop a differential diagnosis for a given patient's presentation. This template allows physicians to organize the case into distinct categories as they develop their assessment. The acronym VINDICATE stands for the following:

- V – Vascular
- I – Inflammatory
- N – Neoplastic/Cancerous Disease
- D – Degenerative / Deficiency Issue
- I – Idiopathic (Unknown), Intoxication (Drug induced)
- C – Congenital
- A – Autoimmune / Allergic
- T – Traumatic
- E – Endocrine

This differential diagnostic tool starts the clinician on their journey to discover what is the underlying cause of the patient's complaint. In the case of a cancer diagnosis, the clinician initiates a variety of tests and referrals to establish the cancer type, the stage of disease, and the patient's overall clinical situation. Although every case is different, the most logical approaches refine the diagnosis through taking a

Figure 1 'Hallmarks of Cancer'

complete history, performing a physical exam, obtaining a pathology specimen, and gathering appropriate lab work along with medical imaging. A thorough history includes information about physical signs and symptoms, which may be reflective of a mass effect. Common signs like pain and changes in bodily function can be associated with cancer. The history will also identify familial risk factors, like close relatives with cancer diagnoses, which guide clinicians in ordering certain genetic tests.

Some solid tumors, masses, or lesions are found directly upon exam (e.g.: physical exam or colonoscopy). Imaging of an asymptomatic patient may reveal a mass as well (e.g.: through an x-ray, ultrasound or mammography), or in a symptomatic patient (e.g.: abdominal pain, coughing up blood or neurological changes from the presence of a mass) where a CT/PET and/or an MRI is obtained. These scenarios, of course, can vary; but in general this is how most cancer diagnoses come about. Once a solid tumor mass is identified, a biopsy and/or tumor resection (partial or complete) can be performed to further the diagnostic process by examining the macro and microscopic nature of the tissue.

Normal cancer diagnostics include a wide range of pathology tools. Direct histological observation and staining measures can help define the type of cancer that someone is dealing with (see Figure 2). Once pathology is confirmed, the process of staging the cancer can begin. The purpose of staging is to gather prognostic information, which will include further lab work and anatomical imaging, and from there ultimately develop a therapeutic plan.

Advanced imaging technologies such as CT scans, PET scans, and MRI help stage the disease and guide therapeutic planning. Further imaging is used to monitor progression of the cancer and identify disease stability or regression.

Adjunctive lab testing can include measuring tumor markers. Common tumor markers, sometimes called cancer markers, are found in the blood, urine, or bodily tissues. Tumor markers are substances made by cancer cells or normal cells in response to cancer in the body. These markers vary in their value and should be used in concert with imaging and clinical findings to determine a patient's status. Other diagnostic and prognostic parameters include examining cancer cell receptors, gene mutations, and amplifications. Some of the most common cancer markers, receptors, and gene mutations include the following:

Markers and Cancer Type:

- CA15-3, CA27.29 seen in breast cancer
- CEA seen in colorectal cancer
- CA 19-9 seen in pancreatic cancer
- PSA, PAP seen in prostate cancer
- CA 125 seen in ovarian cancer
- Alpha Fetoprotein (AFP) seen in liver, testes, and ovarian cancers

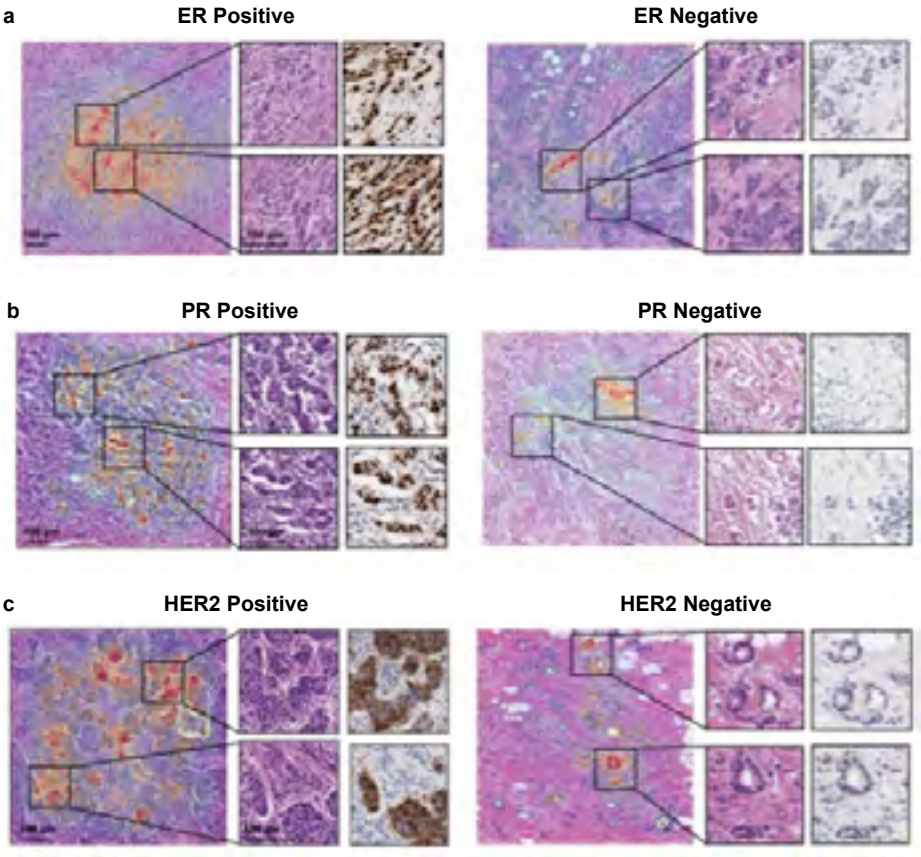
Cancer Cell Receptors and Gene Amplifications (see Figure 3):

- Progesterone receptor positive (PR+) seen in breast cancer
- Estrogen receptor positive (ER+) seen in breast and ovarian cancers
- Androgen receptor positive (AR+) seen in prostate cancer/other hormone sensitive cancers
- HER2/Neu gene amplification/ overexpression seen in breast, ovarian, pancreatic, and gastric cancers
- Programmed Death Ligand (PDL-1) seen in melanoma, GI cancers, lymphomas, and other cancers

Gene Mutations and Cancer Type:

- BRCA1/2 mutations seen in breast and ovarian cancer
- *KRAS* gene mutation seen in some colorectal and non-small cell lung cancer
- MYC gene expression seen in some leukemia and lymphoma
- RAS gene mutation seen in pancreatic, lung, and colorectal cancers
- TP53 gene mutation seen in breast cancer, bone and soft tissue sarcomas, brain tumors, and adrenocortical carcinomas
- EGFR gene mutation seen in non-small cell lung cancer

Figure 2 (Histology Slides) Example of Stained Breast Cancer Cells



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- BRAF gene mutations seen in melanoma, non-small cell lung cancer, and colorectal cancer
- BCR-ABL fusion gene seen in chronic myeloid leukemia, acute lymphoblastic leukemia, and acute myelogenous leukemia

Many tumor markers are proteins made by both normal cells and cancer cells, but they are made in higher amounts by cancer cells. Tumor markers include CA-125 (in ovarian cancer), estrogen receptor and progesterone receptor (in breast cancer), CEA (in colon cancer), PCA3 mRNA and PSA (in prostate cancer), EGFR and KRAS gene mutations (in non-small cell lung cancer).

A variety of tumor markers and characteristics, which are seen in and on tumors, may respond to therapies that may not be traditionally used per NCCN guideline treatments. Such markers include PD-L1, HER2/Neu protein, estrogen receptors, androgen receptors, BRCA1/BRCA2 mutations, KRAS mutations, and BRAF mutations.

Advances in cancer diagnostics have led to ever-evolving insights into this insidious disease. Beyond basic pathology and tumor markers, a variety of relatively new testing tools have opened more doors for cancer monitoring and guiding therapeutics.

Oncology is a rapidly evolving field and the direction cancer therapy is moving requires focus on an individual's tumor genetics. Personalized cancer medicine comes from studies of human genetics and the unique gene expression seen in tumors and individual cancer cells. By focusing on an individual's tumor genetics, practitioners can provide more individualized therapies and protocols in treating their patients in an effort to get better results with less potential for side effects.

Tumor genetic studies allow the promise of precision medicine to become a reality. Molecular profiling has become standard of care for many cancer types – and required for certain therapies. We must remember no two tumors are alike and they are created by an interplay between epigenetic factors, the immune system, the tumor microenvironment, and the patient's genetics. Complicating factors are circulating tumor cells and satellite lesions, and the fact that tumor heterogeneity varies within any given mass.

Comprehensive tumor profiling assesses DNA, RNA, and proteins. This provides the highest quality molecular blueprint to guide more precise and individualized treatment decisions, which are proven to extend overall survival.

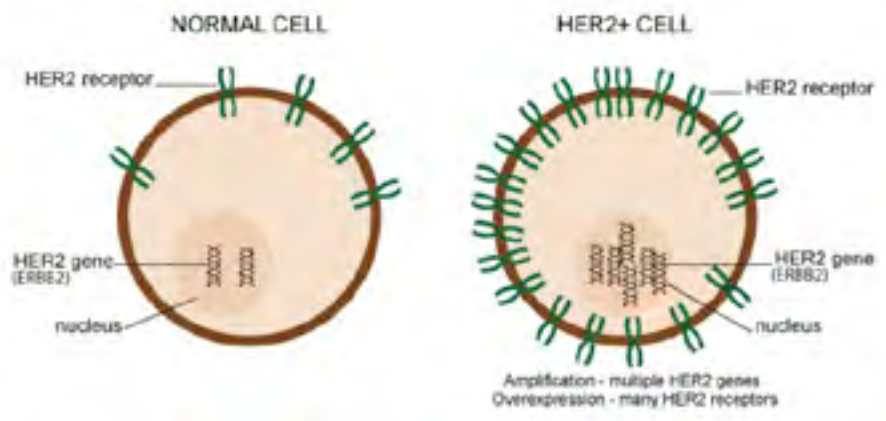
Types of tumor genetic and cancer cell analysis utilized include the following:

- *Immunohistochemistry (IHC)***:** detects the presence of specific protein markers which can assist with accurate tumor classification and diagnosis.
- Fluorescence in situ Hybridization (FISH): detects gene deletions, amplifications, translocations and fusions. Evaluating these genetic disturbances can provide improved prognostics and help guide therapies.
- *Next-Generation Sequencing (NGS)*: rapidly examines and detects DNA mutations, copy number variations and gene fusions across the genome. Clinical NGS involves analysis of raw genomic data and rapid clinical interpretations for consideration by the treating clinician. There are three general ways in which NGS can aid a clinician. The first is with diagnosis; tumor subtypes that only a few years ago were defined by morphologic criteria are now defined by genetic mutations. The second is finding an appropriate "targeted therapy," which can personalize the treatment. There are an increasing number of therapies which have indications for use based on DNA sequencing results. The third point at which clinicians stands to benefit is when a patient stops responding to a targeted therapy with known resistance mutations.
- *Sanger Sequencing*: examines strands of DNA to identify mutations by analyzing long contiguous sequencing reads
- *Pyro Sequencing (PyroSeq)*: detects and quantifies mutations, methylation, etc. through sequencing by synthesis
- *Fragment Analysis (FA/Frag. Analysis)*: detects changes in DNA or RNA to indicate the presence or absence of genetic markers

Beyond assessing tumor genetics there is a branch of diagnostic and prognostic testing which slowly grew over the past 20 years. This testing involves looking for and analyzing cancer cells and cancer cellular material that has broken away from the primary tumor (see Figure 4). These cells are referred to as circulating tumor cells and the cellular material in question is referred to as circulating tumor and/or cancer cell DNA.

Circulating tumor cells (CTCs) have long been assumed to be the substrate of cancer metastasis. In recent years, we have begun to leverage the potential of CTCs found in minimally invasive peripheral blood specimens to improve diagnostics, monitoring, and managing care for cancer patients. Over the past several years it has

Figure 3 'HER2 Expression in Normal Cell vs Cancer Cell'



been shown that individual patients who have a sustained and/or elevated circulating tumor cell level are at increased risk for disease progression and recurrence. A high CTC count has been also associated with poor prognosis in several cancers including breast, lung, and prostate cancer.

In fact, the overall survival and progression-free survival can be reflected by the number of circulating tumor cells present in a patient.

Liquid biopsies capture whole tumor cells in the blood. The whole cell can provide a lot of information by revealing the genome and transcriptome of the CTC and what downstream proteins could be targeted by anticancer agents.

These cells not only reveal the presence of a tumor; they also indicate that a cancer is progressing or spreading. Most clinicians and researchers agree circulating tumor cells are the seeds allowing a cancer to spread. This has been challenging to prove because circulating tumor cells are rare; they are heterogeneous and may look different from the collection of tumor cells they were shed from. However, their distinct cellular morphology, genetic characteristics and larger size make them easy to identify against other circulating cellular material. They have also been found in early-stage disease, leading some to believe the primary tumor may not have presented itself alone, but with other surrounding satellite tumors. These satellites may pose future risk of recurrence and/or new tumor growth.

The CTC count is usually low in non-metastatic cases, and the CTC detection cutoff has regularly been set at ≥ 1 CTC/7.5 mL of blood in most studies which validated this technology. Cells from solid tumors circulating in blood (CTCs) determine the risk of blood-borne metastases. It is therefore crucial to monitor the response of these cells in order to tailor therapies systematically.

Circulating tumor DNA (ctDNA) is found in the bloodstream and refers to DNA that comes from cancerous cells and tumors. Most DNA is found inside a cell's nucleus. As a tumor grows, cells die and are replaced by new ones. It is during these phases of rapid growth and death in which cancer cells shed DNA.

Researchers and clinician foresee a time when ctDNA and circulating tumor cells will be used in combination with other more traditional diagnostics to offer the best picture of what's happening with a cancer at any given time inside a patient (see Figure 5).

Tumor cell DNA acquires multiple genetic changes during tumor development leading to the tumor's heterogeneous state. Therefore, ctDNA may not be an exact match to the shedding tumor. The ctDNA is also not an exact match to the individual's DNA: finding DNA with genetic differences aids in tumor detection. Diagnosing the type of tumor using ctDNA may reduce the need for getting a sample of the tumor tissue (tumor biopsy) and certainly a better option if the biopsy procedure comes with great risk or simply isn't possible.

Analyzing the genome of tumor cells, ctDNA and DNA fragments can help doctors determine how effective a treatment may be. Some examples include the following:

- Monitoring treatment and seeing a decrease in the quantity of ctDNA may suggest the tumor is shrinking and treatment is successful.
- Monitoring periods with no symptoms (remission of cancer) in which lack of ctDNA in the bloodstream may indicate the cancer has not returned.

Cancer patients usually have a high level of Cell-Free (cfDNA) in their serum or plasma. Cell-free DNA refers to all non-encapsulated DNA in the bloodstream that is a result of cellular necrosis or apoptosis. This material can be from both normal tissue turnover along with that of cancer cells. Since tumor cells divide faster than normal cells, cfDNAs are seen in higher amounts in patients with cancer. Clinicians can tell the difference between the tumor DNA and normal cellular DNA when examining blood samples. One way to distinguish the two is that cfDNA are typically longer strands of DNA while ctDNA are generally shorter length fragments. Specifically, the ratio of total cfDNA to ctDNA is smaller in the cancer patient. A high level of known cancer mutations is found amongst the ctDNA of cancer patients. Gene mutations seen in TP53, EGFR, KRAS, PIK3CA, and BRAF genes were some of the most common. Temporal analysis also suggests that these mutations grew in number as patients received treatment for their cancer – demonstrating chemotherapy and targeted therapy most likely

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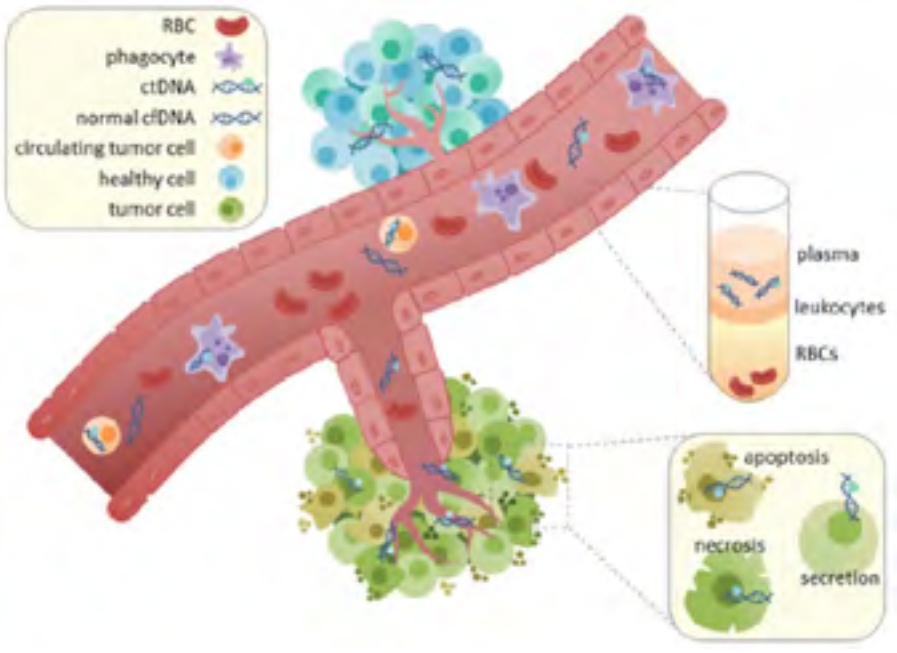
Figure 4 'Circulating Tumor Cells and Circulating Tumor Cell DNA'



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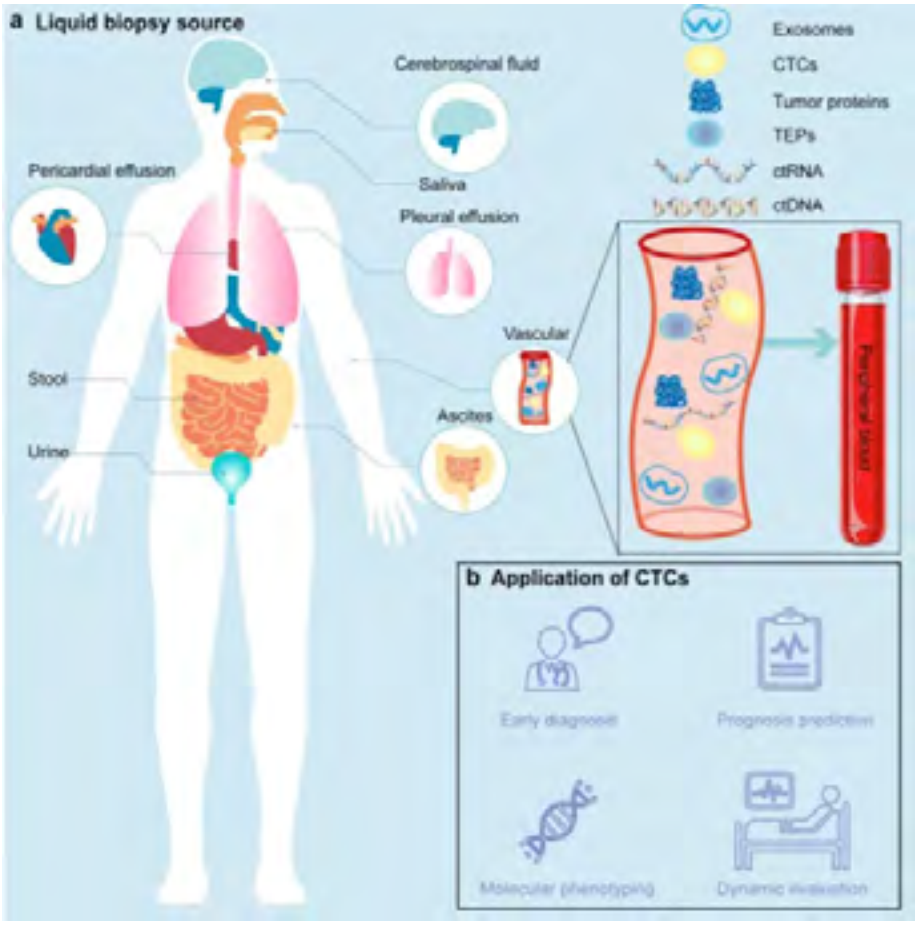
pressured the tumor cells to 'adapt or die'. The importance of patient monitoring is critical and can now rely on blood-based labs that assess disease progression and 'genomic pivots' the cancer is making to evade current treatments.

Future therapies may target circulating tumor cells as well as circulating cancer cell DNA and possibly use them to make personalized cancer vaccines. They will also be used to develop targeted immunotherapies, which have been specifically designed for the cancer patient.

Overall, the journey to a cancer diagnosis, staging, and disease monitoring requires many steps and involves a variety of specialists and technologies working synergistically over time. Our fundamental understanding of cancer has grown dramatically over the past 20 years, we understand it to be a multifaceted and complex illness. Each cancer diagnoses carries with it the opportunity for us to learn more, not only about the disease but also the patient and ultimately the unique interaction between the two. We have seen a vast number of diagnostic tests and precision genomic testing become available in the field of oncology and personalized medicine over the past 20 years. Today there are numerous companies worldwide who are utilizing and refining cutting edge diagnostics by harnessing the information held within the genome of the tumor, the individual circulating cancer cell, and the genetic material from both. By utilizing information about a given patient's cancer, at the microscopic and molecular level, we will be able to fine tune our diagnostic and prognostic capabilities for patients and offer more individualized therapeutics. By unlocking this information, we may find patients qualifying for clinical trials, novel targeted therapies, personalized immunotherapy, chemotherapy and repurposed medications which could prove lifesaving. Through advances in Artificial Intelligence programs, like Deep Learning technology, one will be able to forecast the likelihood of future mutations, make a more accurate overall prognosis for a given patient with cancer, and ultimately know real response rates to a variety of therapeutic agents and interventions.

Figure 5 'Liquid Biopsy to gather CTC's and ctDNA'



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Sean Devlin, DO, practices integrative oncology and functional medicine and is one the founders of the International Organization of Integrative Cancer Physicians (IOICP), which is a non-profit cancer research and educational foundation. Dr. Devlin is a board-certified and fellowship trained physician. Dr. Devlin holds a master's degree in biochemistry and has pursued doctoral studies in pharmacology with an emphasis on the evaluation of novel anti-neoplastic agents. Dr. Devlin has been honored to lecture nationally and internationally on a variety of medical topics and is regularly sought to provide his expert opinion through direct consultation, speaking engagements, and medical-legal review.

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Piperine as Adjunct in Complementary Oncology

by Davis W. Lamson, MS, ND

Tahoma Clinic (Tukwila, Washington)

Abstract

Piperine, isolated from black pepper, has a published record of many beneficial medical uses. Some fall into the area of complementary oncology. Yet in spite of defining publications, this agent seems largely ignored by that field. The present text is intended as a primer on piperine in complementary oncology, designed for the complementary practitioner and divided into subject categories to assist in better utilization of this agent.

Introduction

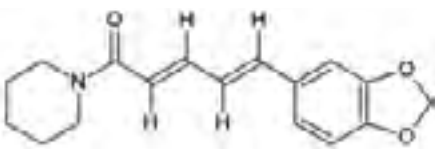
The appearance of a new natural agent for use in complementary oncology is rare. Piperine, isolated from black pepper, seems bypassed in this regard (Figure 1). Possibly the major awareness of piperine with respect to oncology occurred with the report in 1998 that it greatly increased the absorption of curcumin.[1] The mechanism seems general for increased absorption of almost any substance and has been demonstrated for several agents, with many in humans. Discussion is included below.

It is extracted from species of the Piper genus (e.g., black pepper).

A 2020 review and others earlier outline various biological effects of piperine, demonstrating a broadness of beneficial medicinal effects and well worth reading by the general physician.[2-5] Two previous reviews on piperine and cancer are available.[6,7] The present summary is limited to discussing attributes of piperine useful in oncology practice from a different view. It should be considered more of a primer developed to assist consideration of piperine use in complementary oncology rather than as an exhaustive survey. Information here is divided into the following categories.

- Safety of piperine
- Absorption and bioavailability of piperine
- Metabolism of piperine
- Piperine effect on P-glycoprotein and CYP3A4
- Potential incompatibility of piperine with high dose intravenous ascorbate
- Piperine and cancer stem cells
- Effect of piperine on radiotherapy
- Piperine and DNA
- Direct action of piperine on cancer
- Piperine as accessory to chemotherapy
- Piperine oral dosing

Figure 1: Piperine is 1-Piperoylpiperidine or (2*E*,4*E*)-5-(2*H*-1,3-Benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one.



Safety of Piperine

Piperine is included in the FDA GRAS list (Generally Recognized as Safe) for inclusion in food.[8] For a more quantitative estimate of safety, the results of a 1999 rat study are illustrative. Chemical toxicity is known to reduce glutathione and protein thiol groups, and cause cell injury. Piperine administered orally (5-20 mg/kg body weight) resulted in increased glutathione level, with no alteration of protein thiols. Glutathione reductase activity was not altered. The authors interpreted this as piperine having a protective role against cellular oxidation.

Using the usual conversion equation from rat to human, this corresponds for humans to 0.81 to 3.24 mg/kg or 40.5 mg to 162 mg of piperine for a 50 kg person.[10] That seems more than the average person might find comfortable on the stomach.

Absorption and Bioavailability of Piperine

Although piperine is lipophilic with low water solubility, it is rapidly absorbed across the small intestine boundary. It is suggested to alter membrane dynamics and permeability and induce proteins associated with cytoskeletal function thereby increasing small intestine absorptive surface. Piperine was shown to extend the length of rat intestine villi over a period of two hours, returning to usual by three hours.[11] (For that reason piperine is being studied at this clinic as a means of increasing nutritional absorption in persons with refractory celiac disease.)

There may be an additional factor regarding piperine enhancement of curcumin and possibly other molecules. A recent report states that curcumin and piperine interact to form a $\pi - \pi$ intermolecular complex, which enhances the bioavailability of curcumin by inhibition of glucuronidation of curcumin in the liver. Whether that result is due to piperine reduction of CYP3A4 was not discussed.[12]

Because of research on piperine as a general bioenhancer, it should be remembered that this may include any prescription drug. Thus, possible overdose of prescription medication needs to be kept in mind.

Metabolism of Piperine

Administration of piperine by gavage to rats at a dose of 30 mg (170 mg/kg) resulted in approximately 97% absorption. Three per cent of the dose was excreted as piperine in the feces and not detectable in urine. It was shown that piperine did not undergo any metabolic change during absorption.

Only traces of piperine (less than 0.15%) were detected in serum, kidney and spleen from 30 min to 24 h. The increased excretion of conjugated uronic acids, conjugated sulphates, and phenols indicated that scission of the methylenedioxy group of piperine, glucuronidation, and sulphation appear to be the major steps in the disposition of piperine in the rat.[13]

In a second study, oral administration of piperine (170 mg/kg) to rats examined metabolites in bile and urine. Four metabolites of piperine (piperonylic acid, piperonyl alcohol, piperonal and vanillic acid) were identified in the free form in 0-96-hour urine. Only piperic acid was detected in 0-6-hour bile.[14]

Piperine Effect on P-glycoprotein and CYP3A4

P-glycoprotein is a drug transporter that effluxes drugs from cells, including chemotherapeutic drugs, and is implicated in the development of resistance of cancer cells to chemotherapeutic drugs. The enzyme CYP3A4 contributes greatly to first-pass elimination of many drugs. Piperine inhibits both the drug transporter P-glycoprotein and the major drug-metabolizing enzyme CYP3A4. Results are from rodents, human cell studies and some human studies.[15-17]

Potential Incompatibility of Piperine with High Dose Intravenous Ascorbate

A number of publications report on the antioxidant effect of piperine. One reported that piperine scavenged hydrogen peroxide, superoxide, and hydroxyl radical generated by the copper-ascorbate system. It seems a reasonable assumption that oral piperine could greatly decrease the hydrogen peroxide-dependent oxidative effect of high dose ascorbic acid administered as cancer therapy on the same day.[18] There is *in vivo* demonstration of this effect when glutathione is included in high-dose intravenous ascorbate.[19]

Piperine and Cancer Stem Cells

Cancer stem cells (CSCs) are involved in recurrent hepatocellular carcinoma and there is a lack of effective treatment targeting these. CD44+ and CD133+ CSCs are greatly expressed in HepG2 cells. Piperine is known to be effective against metastasis and was found here to be active against CD44+/ CD133+ CSCs, causing cell cycle arrest at G1/G0 phase.

TGF-β activated epithelial-mesenchymal transition (EMT) has been involved in the invasion and metastasis of HepG2 cells in hepatocellular carcinoma. Piperine inhibited TGF-β, but was unable to restore the level of Vimentin (mesenchymal marker) and SNAIL (EMT-inducing transcription factor). This study was said to indicate that piperine could be an effective treatment strategy for recurrent hepatocarcinogenesis.[20]

To determine whether curcumin and piperine were able to modulate self-renewal of normal and malignant breast stem cells, the effects of these compounds were examined on mammosphere formation, on expression of the breast stem cell marker aldehyde dehydrogenase (ALDH), and on Wnt signaling. Curcumin and piperine each inhibited mammosphere formation, serial passaging and percent of ALDH+ cells, by 50% at 5 μM and completely at 10 μM concentration in normal and malignant breast cells. There was no toxicity to differentiated cells. Wnt signaling was inhibited by both curcumin and piperine by 50% at 5 μM and completely at 10μM.[21]

Effect of Piperine on Radiotherapy

Piperine was examined for radio-sensitizing the colorectal adenocarcinoma cell line HT-29. Pretreatment at 12.5 and 25 μg/mL concentrations was followed by exposed to γ-radiation (1.25 Gy). Combination treatment arrested cells at G2/M phase nearly 2.8-fold higher than radiation alone, inducing apoptosis through mitochondria-dependent pathway. Piperine was suggested for radio-sensitization in colon cancer.[22]

The expression of estrogen receptor beta (Erβ) was increased in the cells treated with piperine. Activation of ERβ, a nuclear hormone transcription factor promoting tumor suppression represents a novel clinical advance towards management and prevention of cancers. References are included on the benefit of ERβ in prostate, ovarian and lung cancer cells.[23-25]

Piperine enhances absorption of other molecules.

Piperine and DNA

Piperine showed specificity for G-quadruplex DNA over double stranded DNA, with highest affinity for G-quadruplex structure formed at the c-myc promoter region. In-vitro studies show that piperine causes apoptosis-mediated cell death that further emphasizes the potential of this natural product as a promising candidate for targeting G-quadruplex structure and act as a potent anti-cancer agent.[26]

Direct Action of Piperine on Cancer

Most of the citations of direct action of piperine on cancer are *in vitro* studies with few *in vivo*. Précis of effects on the four most common cancers are included. No reports on piperine with lymphoma or pancreatic cancer were found. The one report of piperine with leukemia cells is omitted as editors have found it of doubtful veracity.

Prostate cancer. Piperine inhibited proliferation of LNCaP, PC-3, 22RV1 and DU-145 prostate cancer cells in a dose dependent manner and induced apoptosis in hormone dependent LNCaP cells. An additional technique showed that apoptosis resulted in caspase activation in LNCaP and PC-3 cells. Piperine resulted in activation of caspase-3 and cleavage of PARP-1 proteins in LNCaP, PC-3 and DU-145 cells and disrupted androgen receptor expression in LNCaP cells. There was significant reduction of Prostate Specific Antigen (PSA) levels following piperine treatment in LNCaP cells.

NF-kB and STAT-3 transcription factors play a role in angiogenesis and invasion of prostate cancer cells. Treatment of LNCaP, PC-3 and DU-145 cells with piperine resulted in reduced expression of phosphorylated STAT-3 and NF-kB. Piperine also reduced cell migration of LNCaP and PC-3 cells and reduced the androgen-dependent and -independent

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tumor growth in a mouse model xeno-transplanted with prostate cancer cells. All this would seem a strong recommendation for a trial of piperine for human prostate cancer.[27]

Treatment with piperine blocked Voltage gated K^+ channels in both androgen sensitive (LNCaP) and insensitive (PC-3) prostate cancer cells and produced concentration-dependent induction of G1 phase cell cycle arrest and apoptosis.[28]

Piperine markedly repressed cell proliferation and migration, and induced apoptosis in metastatic DU145 prostate cancer cells. Piperine reduced the expression of Akt, MMP-9 and mTOR, suggesting they participate in regulating cell migration.[29]

The growth inhibitory effects of piperine on human prostate cancer was examined on DU145, PC-3 and LNCaP cells. Piperine gave dose-dependent inhibition of proliferation of these cell lines with cell cycle arrest at G0/G1. The level of $p21^{Cip1}$ and $p27^{Kip1}$ was increased dose-dependently by piperine in both LNCaP and DU145, but not in PC-3 cells, in line with more robust cell cycle arrest in the former two cell lines than the latter. Although piperine induced low levels of apoptosis, it promoted autophagy as evidenced by the increased level of LC3B-II and the formation of LC3B puncta in LNCaP and PC-3 cells.[30]

Breast cancer. The effect of piperine was investigated on the growth and motility of triple-negative breast cancer (TNBC) cells. Piperine inhibited the *in vitro* growth of TNBC cells, as well as hormone-dependent breast cancer cells, without affecting normal mammary epithelial cell growth. Piperine decreased the percentage of TNBC cells in the G2 phase of the cell cycle. In addition, G1- and G2-associated protein expression was decreased and $p21^{Waf1/Cip1}$ expression was increased in piperine-treated TNBC cells. Piperine inhibited survival-promoting Akt activation in TNBC cells and caused caspase-dependent apoptosis via the mitochondrial pathway. Combined treatment with piperine and γ radiation was more cytotoxic for TNBC cells than γ radiation alone. The *in vitro* migration of piperine-treated TNBC cells was impaired and expression of matrix metalloproteinase-2 and -9 mRNA was decreased, suggesting an antimetastatic effect by piperine. Intra-tumoral administration of piperine inhibited the growth of TNBC xenografts in immune-deficient mice.[31]

The mechanisms by which piperine exerts antitumor effects in HER2-overexpressing breast cancer cells was investigated. Piperine strongly inhibited proliferation and induced apoptosis through caspase-3 activation and PARP cleavage. HER2 gene expression was inhibited at the transcriptional level. Blockade of extracellular signal-regulated kinase (ERK)1/2 signaling significantly reduced sterol regulatory element-binding protein-1 and fatty acid synthase expression. Piperine strongly suppressed epidermal growth factor-induced MMP-9 expression through inhibition of Activator protein-1 and NF-kB activation by interfering with ERK1/2, p38 MAPK, and Akt signaling pathways resulting in reduced migration. Piperine pretreatment enhanced sensitization to paclitaxel killing in HER2-overexpressing breast cancer cells.[32]

Lung cancer. Mice with benzo(a) pyrene induced lung carcinogenesis were used to evaluate the effect of piperine on the mitochondrial tricarboxylic acid cycle and phase I and glutathione-metabolizing enzymes. Lung cancer bearing mice had a decrease in activities of mitochondrial enzymes with increased NADPH-cytochrome reductase, CYP450 and CYPb5 – along with lower activities of glutathione-metabolizing enzymes and G6PD. Piperine supplementation to tumor-induced animals lowered the phase-I enzymes with a rise in glutathione-metabolizing enzymes, which indicated an anti-tumor and anti-cancer effect along with a role in mitochondrial energy production.[33]

Piperine suppressed benzo(a)pyrene (B(a)p) induced lung cancer in mice. Altered levels of total protein and protein bound carbohydrate components were observed in serum, lung and liver tissues of tumor bearing mice. Dietary piperine (50 mg/kg body weight) to B(a)p animals decreased the total protein and protein bound carbohydrate levels of lung cancer bearing animals during initiation and post-initiation phases. Data suggest that piperine furnishes chemoprevention by modulating protein bound carbohydrate levels, which are indicators of tumorigenesis.[34]

Colon cancer. The effect of piperine was investigated on the growth of HRT-18 human rectal adenocarcinoma cells. Piperine inhibited metabolic activity and cell cycle progression of HRT-18 cells in a dose- and time-dependent fashion, suggesting a cytostatic and/or cytotoxic effect. HRT-18 cells died by apoptosis. The cells showed increased production of reactive oxygen species, indicating that cytotoxicity was mediated at least in part by reactive oxygen species.[35]

Piperine as Accessory to Chemotherapy

Piperine anticancer effects were examined against resistant human ovarian cancer cells, using the drug-sensitive ovarian cancer cell line W1 and its sublines resistant to paclitaxel (PAC) and topotecan (TOP). Piperine increases the cytotoxic effect of PAC and TOP in drug-resistant cells. An increase in receptor-type tyrosine-protein phosphatase kappa expression correlated with decreased phosphotyrosine level after piperine treatment and downregulation of P-glycoprotein and breast cancer resistant protein expression. There was a decrease in COL3A1 and TGFBI gene expression in investigated cell lines and increased COL3A1 expression in media from W1PR2 cells. Expression of Ki67 protein and cell proliferation rate decreased after piperine treatment. Piperine markedly inhibited W1TR cell migration. The authors stated that piperine can be considered a potential anticancer agent, increasing chemotherapy effectiveness in cancer patients.[36]

Docetaxel (DTX) is widely used for metastatic castration resistant prostate cancer, but efficacy is often compromised by drug resistance from low intracellular concentrations. Piperine (PIP) can enhance the bioavailability of other drugs via inhibition of CYPs and P-glycoprotein (P-gp) activities. Mice implanted with taxane-resistant human prostate cancer

Dr. Lamson has been a staff physician at Tahoma Clinic and received a naturopathic doctor degree from Bastyr University in 1982. His original training was as a research chemist and prior to practicing at Tahoma Clinic, he held positions in teaching and/or research at Iowa State University, Drexel University, and the University of Pennsylvania School of Medicine. He believes this initial training to be a major benefit in locating underlying causes of medical problems for his patients.

cells were administrated with saline as well as PIP and DTX separately and in combination. Compared with DTX alone, DTX-PIP combination significantly inhibited the tumor growth (114% vs. 217%) with corresponding higher intra-tumor DTX concentrations. DTX metabolism was much decreased from in mouse liver microsomes. DTX accumulation in MDCK-MDR1 cells was enhanced in the presence of PIP. PIP inhibited P-gp as well as CYP1B1 gene expression and induced a significant gene expression change relating to inflammatory response, angiogenesis, cell proliferation, or cell migration.[37]

Piperine and mitomycin-C (MMC) co-treatment resulted in a dose-dependent suppression of cell proliferation in cervical cancer cells resistant to MMC and in mice xenograft models. Decreasing of phosphorylated-signal transducer and activator of transcription (p-STAT3) was linked to the suppression of p65 by PP and MMC combination treatment. PP potentiated the effects of MMC on apoptosis induction, which was dependent on Bcl-2 inhibition. Pro-apoptotic proteins of Bax and Bid were up-regulated, accompanied with caspase cleavage. In mice xenograft models, the combined therapy inhibited tumor growth compared to the separate PP or MMC mono-therapy groups.[38]

Piperine Oral Dosing

From its origin as pepper extract, it seems best that piperine not be placed on an empty stomach. Trials at this clinic showed that 20 mg with a meal produced no obvious gastric irritation. The agent is mostly available as the product Bioperine in thin tablets of 10 mg. Step-wise escalation from 10 mg with a meal daily to 20 mg at meals two or three times daily was quite acceptable. If there were gastric difficulty at that level, it might be indicative of sub-optimal condition of the stomach lining and deserved separate attention.

Summary

The subjects covered above are not exhaustive but seem adequate to illustrate that piperine really is a neglected molecule for oncology use. There are few if any other agents that demonstrate enhanced absorption of other molecules, ability to concentrate agents in cancer cells, reduce invasion and metastasis by effect on cancer stem cells, enhance radiation and chemotherapy, interact with cancer cell DNA to cause apoptosis, and have a multiplicity of actions against cancer cells of many types – all with a great degree of safety.

Obviously, many more *in vivo* studies and eventually human ones are needed before mainstream oncology will give it a look. That's unlikely as there is no great profit to be made from a pepper extract. However, its very inexpensiveness and safety may foster investigation to find if tolerable doses can be effective in complementary oncology.

It is hoped that careful physicians will survey the existing literature on piperine and use its attributes for the benefit of their patients. ◆

References are available online at www.townsendletter.com.

Integrative Cancer Care

by Leigh Erin Connealy, MD

We want to dedicate this article to our courageous patients fighting their cancer battles with unwavering strength, positive attitudes, and endless determination daily. Although we have obtained approval to share the following stories, the patients' names have been changed out of respect for their privacy.

"Warren"

Warren is a pleasant 85-year-old gentleman coming up on ten years since his initial cancer diagnosis. In March of 2013, he noticed very slight irritation at the back of his throat. Warren was diagnosed with squamous cell carcinoma of the throat in August of 2013.

In October of that year, Warren had surgery to remove the cancer. He did not undergo any chemotherapy or radiation.

Leading up to treatment, he spent six weeks with a physician in his area utilizing immune-boosting therapies, including infusions of vitamins B, C, and D, along with ozone. He also received O2 blood treatments. Additionally, he stayed at Klinik Herzog in Germany for eight days before his operation. The patient believes this integrative approach helped slow or possibly stop tumor growth and aided in the successful removal.

Warren first came to the Cancer Center for Healing (the Center) in February of 2014 for continued integrative cancer care. This retired gentleman is happily married with two daughters. A life-long golfer, Warren says being out on the links each day is "his happy place." He also owns a vineyard and is a self-described avid wine taster. Warren reported being active, sleeping well, and taking American Nutraceuticals supplements during his first visit.

He was offered conventional medical treatment and integrative natural treatments and expressed his wishes to undergo natural and integrative therapies whenever possible. His previous success with integrative medicine and natural therapies set the stage for a favorable reception of our recommendations and compliance with our protocols at the Center.

After reviewing his diagnosis and medical history, Dr. Connealy ordered bloodwork, which revealed elevated ferritin, elevated monocytes, and elevated CRP (2.5 mg/L).

Dr. Connealy also ordered RGCC testing.* The Research Genetic Cancer Center (RGCC) offers a variety of blood tests that detect the presence and abundance of circulating tumor cells (CTCs) and cancer stem cells (CSCs). CTCs are problematic because they break off from the original tumor, move throughout the circulatory system, and search for new places to "nest." CSCs, located within a tumor, can self-renew and regrow even after conventional treatments such as chemotherapy.

One of the biggest downfalls of conventional cancer treatments is that these modalities alone can't eliminate CTCs and CSCs. And because CTCs and CSCs are responsible for 95 percent of all metastases and deaths from cancer, it is crucial these cells are eradicated along with the tumor.

That's where RGCC testing comes in. RGCC blood tests are the most accurate diagnostic tool for detecting CTCs. Dr. Conneally ordered tests explicitly looking for these circulating tumor cells that would also reveal which common chemotherapeutic, natural agents, and other drugs would work most effectively on Warren's cancer type.

Warren's initial CTC count in February 2016 was 7.1 cells/ml. For reference, most late-stage cancer patients (stage III or stage IV) have CTCs levels ranging from 5.0-10 cells/ml. Rarely we see numbers as high as 15 cells/ml. Patients are not considered cancer-free unless their CTC count is less than one, the ideal number being zero.

Imaging did not show any tumor burden, so Dr. Connealy recommended supportive oligonucleotide therapy (SOT). SOT Therapy combines a patient's own cancer cells with their immune-signaling cells. When SOT is administered intravenously, it interferes with cancer cells' ability to replicate and causes them to self-destruct via apoptosis. This treatment continues to seek out CTCs and destroy them 24/7 and can remain active 4.5-5 months after one infusion.

Warren received his first SOT treatment in April of 2014 and was advised to begin taking the supplement ImmPower and increase his intake of essential fatty acids (EFAs). He continued with chelation therapy and ozone therapy every two weeks at home. We prescribed regular phlebotomy to reduce his iron levels, which he later reported he did a handful of times with his physician locally.

Another therapy Warren regularly undergoes at home is infrared sauna. We endorse these treatments wholeheartedly as this therapy is known to support detoxification, boost the immune system, increase metabolism, and offer numerous other total-body benefits.

SOT therapy has been Warren's primary treatment at the Center. He's

received nine treatments since 2014, his most recent in April of this year.

Additional health concerns have cropped up over the years. In 2017, Warren mentioned his tongue was swollen, and he was having trouble swallowing. Dr. Connealy suggested an endoscopy and colonoscopy, which the patient declined to do. He has an enlarged prostate and sees a urologist locally for benign prostatic hyperplasia (BPH) and hematuria. Warren also has atrial fibrillation (Afib) and has had two unsuccessful cardioversions. He is under the care of a cardiologist near his home.

In his most recent visit this spring, Warren was feeling good overall. He reported some loss of muscle mass and noted that his activity level has decreased. He admitted to being a bit lazy and drinking a few glasses of wine daily, which led to a lengthy discussion regarding the importance of moving and exercising to maintain bone and muscle integrity.

He was advised to walk the golf course daily rather than ride in a cart. We also proposed adding in exercise while he watched his nightly TV shows to boost exercise compliance. Warren was instructed to incorporate bodyweight exercises such as wall push-ups and squats to build muscle and prevent bone loss. One suggestion was ten squats, or another set of exercises, during each commercial break.

Dr. Connealy recommended that Warren seek out IV Ozone treatment at home. This therapy involves removing a small amount of the patient's blood and infusing it with ozone. As the blood contacts the ozone, it turns into oxygen. This oxygen-rich mixture is then infused back into the patient's body, which increases oxygen delivery to cells, helps eradicate anaerobic cancer cells, and boosts the immune system overall. It is an excellent adjunct treatment to Warren's current protocol.

He was also advised to continue with his supplement regimen of lithium orotate, boluoke, tocotrienols, parent essential oils (PEOs), curcumin, Vitality C, and vitamin D. We also suggested adding magnesium for heart health and increasing vitamin C intake to give his immune system an additional boost, reduce inflammation, and favorably affect his CRP levels. Additionally, the patient has been following the RGCC supplement rotation (more on this below), which zeroes in on CTCs and rotates the most effective supplements for Warren's specific cancer type.

Warren has responded remarkably well to the SOT therapy and will continue with that along with his targeted nutritional supplement regimen. His CTCs continue to decline, and his most recent results from March of 2022 were 3.4 cells/ml. He will return in 4-6 months for a follow-up.

"Rose"

Rose is a 60-year-old female who originally saw us via remote consult in August 2017. Living on the East Coast, she was referred to the Center by her physician at home.

Rose was diagnosed with stage IV squamous cell carcinoma of the rectum in February of 2016 and informed there was a tumor. Prior to coming to the Center, she underwent two rounds of full-dose chemo on 3/7/16 and 3/8/16 and 28 sessions of radiation between 3/7/16 and 4/16/16. She also had a liver resection in May of 2016 laparoscopically, and the margins were clear.

During her initial consult, we discussed other preexisting health concerns/conditions. She had melanoma, which was removed in 1994 and found to be localized "in situ." In 1996, she had a case of viral meningitis. In addition to cancer, Rose was diagnosed with chronic Lyme in 2012, hospitalized for an ulcer earlier in 2017, and we discussed her ongoing breathing problems and asthma.

Rose also had a history of heavy drinking and smoking (10-19 cigarettes per day). Her father died suddenly from heart failure, her mother had recently passed, she ended a bad marriage in divorce, and she was in the process of building a house and moving with her new husband. Her life was filled with a great deal of sadness, emotional trauma, and stress. And it is crucial to note the role this chronic stress played in Rose's health when she was diagnosed with cancer.

Stress is toxic, and Dr. Connealy has linked chronic and ongoing stress and anxiety to nearly every one of the patients being treated for cancer at the Center. Rose was strongly encouraged to start meditating, use an infrared sauna regularly for detox, and undergo EVOX therapy.

EVOX therapy is a remarkable tool that "remaps the brain" and combats stress and anxiety.

EVOX therapy helps to reduce stress and anxiety using "Perception Reframing." When a person speaks, the energy in their voice corresponds to how they feel about specific topics. The EVOX records voice energy, plots it on a Perception Index graph, and determines which frequency signatures would work best to reduce a patient's unique stressors. These signatures are transferred to a hand cradle and transmitted to the patient as they listen to relaxing music and concentrate on the topic at hand. EVOX therapy is a remarkable tool that "remaps the brain" and combats stress and anxiety. We recommend EVOX to every new patient who comes to the Center.

Rose did seek out support from a counselor back home and reported feeling better after doing so. Faith and spirituality are now a big part of Rose's life, and she practices daily affirmations and prays daily as well. She has an excellent support system with her new husband and their five combined children.

For the last 15 years, Rose says she only drinks alcohol socially and has stopped smoking. She completely turned her habits around with lifestyle changes such as exercising daily, drinking plenty of water, and switching to a vegan diet.

Rose was already being treated with hormone replacement therapy (Armour Thyroid, progesterone, and estradiol)

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and taking beta-glucan, vitamin D, vitamin K, iodine, B vitamins, and plant-based digestive enzymes.

Because she lived across the county, we had her complete a Bioimmune Survey at a location near her. Also called a bio-meridian test, the Bioimmune Survey measures the meridian pathways in the body. Using acupuncture points, this diagnostic tool determines how energy is flowing throughout the body. It can reveal inflammation, show deficiency, damage, and degeneration of specific organs, and even clue us into how far along a patient is in the cancer development process. This vital tool helps us fine-tune a patient's cancer treatment protocol.

We also prescribed RGCC testing to determine CTC levels and which natural supplements would most effectively treat her cancer type. In September 2017, Rose's CTC count was 7.3 cells/ml.

Dr. Connealy recommended the RGCC nutritional supplement protocol*, supplements to increase pancreatic enzymes, a NutraEval kit to test for nutritional deficiencies, and a nagalase kit, which tests for the presence of this enzyme secreted by cancer cells. Her blood draws for the NutraEval and nagalase were done by her primary care physician at home on the East Coast. Bravo suppositories to lower nagalase levels were recommended when Rose's levels were found to be elevated.

In April 2019, an ultrasound revealed a solid mass in Rose's left breast. She was recommended a mammogram and told to have a biopsy, but she initially refused. Later a biopsy was performed, revealing an enlarged, noncancerous fibroid.

New findings discussed during a consult in March of 2020 included *Candida,* heavy metals, and virus. Lab results showed an elevated CRP level (indicative of inflammation), and Rose was told the *Candida* protocol could help lower her CRP.

We continued to order regular blood work and additional RGCC testing to determine which supplements would work best to fight Rose's specific cancer cells. During this timeframe, her CTC count continued to decrease.

Between 2017 and 2019, MRIs of the liver showed her liver lobe grew and was slightly larger in 2017 and 2018 and then decreased in size in 2019. Initially thought to be metastasis, there are no additional concerns with the latest scans and bloodwork.

Rose's primary treatments have been the Bioimmune Protocol** and the RGCC supplement protocol. Like Warren and many of our other patients, Rose has successfully undergone three SOT IV treatments (May 2018, October 2018, and November 2021) with plans to complete her fourth SOT this summer.

As of August 2020, an MRI revealed no anal mass and no metastatic disease in the pelvis or abdomen. Anal fibrosis was noted in the scan. Rose's CTCs continued to decrease.

Rose's most recent Bioimmune Survey did reveal *Candida* and heavy metals present. Dr. Connealy recommended an anti-*Candida* protocol and a 21-day cleanse. Rose is mostly compliant and sticks with the RCGG CTC rotation as prescribed.

Current medication recommendations include an increased dose of naltrexone; starting griseofulvin for *Candida*; continuing the next round of the RGCC supplement rotation and the Bioimmune Protocol supplements; staying on estradiol, Armour thyroid, and progesterone; and continuing topical testosterone. Rose was also strongly advised to complete a liver flush at least once a year and continue with regular exercise to support bone health and ward off osteoporosis. Her latest CTC levels were 4.4 cells/ml.

In addition to consistent imaging and detailed blood work every six months and regular tele-visits and zoom follow-ups with her doctors at the Center, Rose will continue to see her primary care physician, an OBGYN, and a cancer specialist locally on the East Coast.

As is the case with Warren, collaborating with patients' oncologists and the team of medical professionals that are local to them allows us to work together and provide the best possible care and the most hopeful outcomes.

Rose is a work in progress who is continually making efforts to better her health. Her latest scans and tests show this dedication to a healthier, more balanced lifestyle. Her story is a testament to the fact that it is never too late to take steps toward better choices and, ultimately, a better quality of life.

Leigh Erin Connealy, MD, is the medical director of the Cancer Center For Healing and the Center For New Medicine in Irvine, California. Dr. Connealy's multidisciplinary treatment protocols, team of healthcare professionals, and holistic approach to health and healing have made the Centers the largest integrative/functional medicine clinic in North America, visited by more than 64,000 patients from all over the world. Author of *The Cancer Revolution* and *Be Perfectly Healthy* and a sought-after speaker who has appeared on numerous TV and radio shows, webinars, and podcasts, Dr. Connealy has been named one of the Top Functional & Integrative Doctors in the U.S.

*The RCGG Supplement Protocol uses a blood test to determine which nutritional supplements will best target the CTCs for an individual's type of cancer. These supplements are rotated and changed regularly, with patients taking two different supplements each month and then rotating those out for two new supplements each month until they make it through the whole cycle and start the protocol again. This practice allows optimal nutrient absorption and minimizes resistance to these natural substances. Examples of common supplements used in the rotation include (but are not limited to) curcumin, paw-paw, organic cordyceps, CoQ10, and quercetin.

**The Bioimmune Protocol consists of several Chinese and Tibetan herb blends and other well-known nutraceuticals such as high-dose vitamin C, noni, nattokinase, ecomer and other natural therapies to help boost the immune system.

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Letters to the Editor

Clarification: "From 'Dis-Ease' to Better Health: A Model for Recovering from Chronic Lyme Disease, Mold Illness, and Related Conditions"

In the "Letter from the Publisher" in the July 2022 *Townsend Letter*, the publisher made the statement: "Forsgren's model would argue against immediate treatment with antibiotics unless they are absolutely indicated."

I would like to clarify that this statement is not entirely consistent with my belief or a perspective shared in the article itself.

What was shared is that there are many foundational steps that I would explore before incorporating antimicrobials. This, however, was not intended to be a statement against pharmaceutical antibiotics as part of Step 9 in some cases.

In cases of acute exposure, antibiotics are often an appropriate tool that may prevent years of struggle if the acute exposure turns into chronic Lyme disease. This is a scenario where I would personally consider both antibiotics and natural tools.

In cases of chronic Lyme disease, which was the focus of the article, a broad toolbox is necessary. Thus, while I may not personally consider antibiotics as the top tool in the toolbox, there are cases where these may be supportive and beneficial.

When I originally was diagnosed in 2005, the commonly used tools were antibiotics. I was on daily antibiotics for over three years at that time. While I did make some improvement, these were not the entire solution to my problem as many of the other areas outlined in the article required further exploration.

If I were starting over, I would approach my recovery differently; using the steps outlined in the article. I no longer think that long-term antibiotics are a primary tool given the many options we now have available. That said, shorter, more targeted use of antibiotics may benefit some patients.

In Better Health,
Scott Forsgren, FDN-P, HHP

On Book Reviews

I just finished reading the *The Real Anthony Fauci* book by Robert F. Kennedy, Jr. Thanks for the book review and comments on this indispensable manuscript every natural health library should have.

I found it was an incredible work of meticulous research with numerous citations and data to show the connections between Dr. Fauci, Mr. Gates and Big Pharma's lies. He showed us how the government and corporate greed trump public health and safety. It was a great resource for anyone interested in their health or the health of the public. His subtitle should have been: Follow the Truth vs. Follow the Money.

Thanks for noting the dental health book *Chew on This...* by Dr. Grube and Anita Vasuez Tibau. It is good to see you include some holistic dental books that connect the oral conditions, problems and treatments to chronic diseases of the rest of the body.

Books like these are needed to teach practitioners that common dental treatments and conditions can have a significant effect on patients' whole body health and vitality.

Blessings,
Rev. Dr. Stephen A. Lawrence
@revdrsalauthor

CALENDAR

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

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

AUGUST 20: NATUROPATHIC WOMEN'S HEALTH SEMINAR in in Scottsdale, Arizona. CEs available. CONTACT: https://naturopathicwomenshealth.com/

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

SEPTEMBER 8-10: THE PEDIATRIC BRAIN AND RESILIENCE SUMMIT in Rancho Palos Verdes, California. CONTACT: https://www.a4m.com/pediatric-brain-health-summit-2022.html

SEPTEMBER 8-10: A4M/MMI ADVANCED CARDIOVASCULAR HEALTH (Module XVI-A) in Rancho Palos Verdes, Calfornia. CONTACT: https://www.a4m.com/module-xvi-a-2022.html

SEPTEMBER 10: PSYCHIATRY REDEFINED presents FUNCTIONAL MEDICINE FOR PSYCHIATRY – A Patient-Centered Approach to Mental Health Care online. CONTACT: https://www.psychiatryredefined.org/functional-medicine-for-psychiatry-conference-2022/

SEPTEMBER 15-17: NATIONAL RESTORATIVE MEDICINE in Sedona, Arizona and online. CONTACT: https://restorativemedicine.org/conferences/2022-national-conference/

SEPTEMBER 16-18: ENDOCRINE BALANCE AND BIO-IDENTICAL HORMONE RESTORATION in Boston, Massachusetts. CONTACT: https://www.a4m.com/bhrt-symposium-a4m-september-2022.html

SEPTEMBER 16-18: A4M/MMI PEPTIDE THERAPY CERTIFICATION in Boston, Massachusetts. CONTACT: https://www.a4m.com/peptides-certification-module-i-2022.html

SEPTEMBER 16-18: A4M/MMI FRONTIERS IN NEUROLOGY AND BRAIN HEALTH (Module 111) in Boston, Massachusetts. CONTACT: https://www.a4m.com/module-iii-a4m-september-2022.html

SEPTEMBER 16-18: A4M/MMI CLINICAL STRATEGIES TO OPTIMIZE METABOLIC RESILIENCY, IMMUNOCOMPETENCE, AND BIOTRANSFORMATION (Module VII) in Boston, Massachusetts. CONTACT: https://www.a4m.com/module-vii-a4m-september-2022.html

SEPTEMBER 22-23: INTERNATIONAL CONFERENCE ON APITHERAPY AND HONEY BEE PRODUCTS in Vancouver, Canada. CONTACT: https://waset.org/apitherapy-and-honey-bee-products-conference-in-september-2022-in-vancouver

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

OCTOBER 8-9: ASSOCIATION FOR THE ADVANCEMENT OF RESTORATIVE MEDICINE PEPTIDE/STEM CELL INTENSIVE online. CONTACT: https://restorativemedicine.org/conferences/2022-peptide-course/

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

OCTOBER 15-16: NEURAL THERAPY TO ELIMINATE PAIN TRAINING COURSE with Bryan Rade, ND, in Halifax, Nova Scotia. Learn a minimally invasive therapy to address pain. Space limited. CONTACT: www.eastcoastnaturopathic.com

OCTOBER 27-29: A4M/MMI IV/CHELATION THERAPY in Charleston, South Carolina. CONTACT: https://www.a4m.com/iv-chelation-therapy-symposium-a4m-october-2022.html

OCTOBER 27-29: A4M/MMI PELLET THERAPY in Charleston, South Carolina. CONTACT: https://www.a4m.com/pellet-therapy-a4m-october-2022.html

OCTOBER 27-29: A4M/MMI LONGEVITY MEDICINE AND BIO-HACKING: OPTIMIZING LIFESPAN in Charleston, South Carolina. CONTACT: https://www.a4m.com/module-viii-a4m-october-2022.html

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

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

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

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

NOVEMBER 5-6: OREGON ASSOCATION OF NATUROPATHIC PHYSICIANS ANNUAL CONFERENCE in Portland, Oregon. CONTACT: https://www.oanp.org/page/AnnualConference

NOVEMBER 12-13: HEARTQUEST GLOBAL INTERACTIVE CONFERENCE on the Renaissance of New Healing Solutions in Scottsdale, Arizona. CONTACT: https://www.heartquestglobalsolutions.com/nov-2022-conference

DECEMBER 9-10: INTERNATIONAL CONFERENCE ON PREVENTIVE AND INTEGRATIVE MEDICINE in New York City, New York. CONTACT: https://waset.org/preventive-medicine-and-integrative-medicine-conference-in-december-2022-in-new-york

DECEMBER 9-11: A4M presents LONGEVITY FEST 2022 in Las Vegas, Nevada. CONTACT: https://www.a4m.com/longevity-fest-2022.html

DECEMBER 9-11: A4M/MMI PEPTIDE THERAPY CERTIFICATION in Las Vegas, Nevada. CONTACT: https://www.a4m.com/peptides-ii-a4m-december-2022.html

DECEMBER 9-11: A4M/MMI ADVANCED ENDOCRINOLOGY: THE HORMONAL SYMPHONY (Module 1) in Las Vegas, Nevada. CONTACT: https://www.a4m.com/module-i-a4m-december-2022.html

DECEMBER 9-11: A4M/MMI TRIADS: A SYSTEMS BIOLOGY APPROACH (Module V) in Las Vegas, Nevada. CONTACT: https://www.a4m.com/module-i-a4m-december-2022.html

JANUARY 28-29, 2023: INTERNATIONAL CONFERENCE ON TRADITIONAL MEDICINE AND HERBS in New York City, New York. CONTACT: https://waset.org/traditional-medicine-and-herbs-conference-in-january-2023-in-new-york

APRIL 22-23: INTERNATIONAL CONFERENCE ON INTEGRATIVE MEDICINE AND NUTRITION in New York City, New York. CONTACT: https://waset.org/integrative-medicine-and-nutrition-conference-in-april-2023-in-new-york

JUNE 2-4: SASKATCHEWAN ASSOCIATION OF NATUROPATHIC DOCTORS HEALING SKIES CONFERENCE in Saskatoon, Saskatchewan, Canada. CONTACT: http://www.sasknds.com/healing-skies-conference.html

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Using the Rice Bran Arabinoxylan Compound

review by Burt Berkson, MD, MS, PhD
bberkson@nmsu.edu

Cancer Treatment Breakthrough by Professor Serge Jurasunas
Holodigm Publications; available at Amazon.com
ISBN-13: 978-0975851616; c. 2021; $29.90 (US)

Though I have personally known Professor Serge Jurasunas for less than a year, I have been familiar with his medical work for some time from reading the *Townsend Letter*. Professor Serge is a natural medicine trailblazer of the highest order, with over 55 years of experience. He has journeyed into previously unexplored territories and has developed innovative protocols for the treatment of cancer and other maladies. His book, *Cancer Treatment Breakthrough,* is an informative and instructive journey through the understanding of natural cancer therapies. By reading it, doctors will learn many valuable lessons developed by a master of natural medicine.

Conventional medical therapy for cancer involves surgery, chemotherapy, radiation, immunotherapy, and other interventions that are only effective some of the time and may have dreadful adverse side effects. Professor Serge describes natural effective treatment options that are devoid of these injurious reactions.

The book opens with a serious discussion on immuno-oncology, describing the innate and the adaptive immune systems. Professor Serge goes on to depict cancer as an epidemic disease. He writes that there is no magic bullet for treating cancer and that there is a need for therapies without toxicity of chemotherapy. From there he outlines the cell cycle and asks the question, "Can the immune system fight cancer?" In addition, he defines oxidative stress and by what means one can mitigate its harmful effects. Subsequently, the book discusses the p53 mechanism and how it modulates the key regulators of the immune signaling pathways.

The book presents an extensive study on how the natural killer (NK) cells function and explains the way they kill cancer cells using the mechanism of apoptosis through the secretion of perforin and enzymes and the indirect mechanism using cells of the acquired immune system.

Professor Serge explains that cancer is also a disease of the microenvironment, and he describes how a hostile microenvironment may inhibit immune system defenses and aid tumor cell growth. We learn from the book that in a hostile microenvironment, immunosuppressive cells inhibit NK cells and this may encourage cancer cells to thrive.

The second part of the book is about complementary means of diagnosis and is very detailed as it goes on to describe how to teach the immune system to combat cancer.

Professor Serge presents an extensive study on the mechanism of action and the attributes of rice bran arabinoxylan as an immune stimulation agent and a cancer fighter. For 28 years Professor Serge Jurasunas has used rice bran arabinoxylan as a biological response modifier stimulating NK cells to kill cancer.

Rice bran arabinoxylan compound (RBAC) is a shitake mushroom mycelial enzymatic breakdown product of a particular rice bran liberating its medicinal properties. It was developed by Daiwa Japan and has no known toxicity. Besides its effectiveness in stimulating natural killer cell activity, this agent is also very effective medicine for an ailing digestive tract. The book describes how RBAC increases the body's defensive mechanisms alone and even while a patient is receiving chemotherapy and or radiation.

The book is full of helpful illustrations demonstrating in various ways how the immune system functions and how various agents help a person heal from cancer. Professor Serge Jurasunas describes examples of case histories showing tumor size decrease when he is using RBAC alone. In other cases, he describes a more dramatic decrease in tumor size using chemotherapy plus RBAC. It is not surprising that integrative doctors and some conventional oncologists from many parts of the world are using RBAC for their cancer patients.

In 1964, Professor Serge studied under Dr. Bernard Jensen at Hidden Valley Ranch. After this, Professor Serge went on to become a pioneer in nutrition, with diet and food recommendations becoming the basis of his cancer treatment. A chapter of the book focuses on these recommendations.

Professor Serge's book is an educative assemblage on alternative cancer therapies. His chapters on immunology and arabinoxylan were particularly informative to me and I enjoyed reading and learning from his numerous successful case histories describing patients who had recovered from serious malignant disease.

The medical establishment finds little or no profit in most alternative cancer protocols and does not respect a treatment option unless it has gone through many years and hundreds of millions of dollars of clinical studies to prove their idea of "evidence-based medicine." They almost completely ignore interesting and important case studies and series demonstrating successful therapies. Someone once wrote in *The Lancet*, "If everything must be 'evidence-based,' where do the new ideas come from?"

I think that all broad-minded physicians who seek a thorough lesson on how to treat cancer patients alternatively should read this remarkable book and learn from Professor Serge.

Burt Berkson, MD, MS, PhD, is the author of *The Alpha Lipoic Acid Breakthrough* and co-author *of Syndrome X,* and *User's Guide to B-Complex Vitamins.*

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The Natural Killer Cell in Anticancer Therapy – An Important Role for Natural Compounds

by Professor Serge Jurasunas, MD(Hom), ND

Author of *Cancer Treatment Breakthrough – Immuno-Oncology Using Rice Bran Arabinoxylan Compound*

Abstract

Patients, but also doctors, are usually not well informed about the role played by a specific immune cell, known as the natural killer (NK) cell, and its relation to cancer. An NK cell can kill cancer cells directly without needing an antigen and, therefore, can kill more quickly. Considerable research into how NK cells function has been done over the past 20 years in order to improve cancer treatment, especially for high-risk patients.[1]

Natural killer (NK) cells are central components of innate immunity and play a pivotal role in responding to tumors with perforin and granzymes (cytotoxic granules). NK cells use either the intrinsic apoptotic mechanism or, independently of perforin, through TRAIL, an apoptotic protein that interacts with the receptor of the target cell. Under stimuli, natural killer (NK) cells also produce several cytokines, including IL12, IL10, IFN-γ , TNF, that in turn activate other immune cells (such as T-cells, macrophages), the maturation of dendritic cells, as well as the inhibition of angiogenesis.

In this article, we describe the mechanism and evidence of the NK cell as an immunomodulator with other anti-cancer properties. NK cells have a major role to play in cancer prevention and treatment and in viral infections as well. NK cells can be seen as a new, efficient, safe immunotherapy for malignant disease. A number of natural compounds, including mushrooms, rice bran arabinoxylan, and curcumin, enhance the efficacy of NK cells in controlling cancer.

Introduction

In 1975 Rolf Keissling and his Swedish colleagues discovered a type of T-cell that kills many types of tumor cells. Keissling named this effector cell "natural killer (NK) cell" because of its being able to kill directly and quickly a target cell without the need of an initial sensitization. It was proven that many types of cancer cells express high levels of ligands for NK cell receptors, which leads to their recognition and killing by NK cells[2]; and it is known that natural killer cells enhance immune surveillance[3] and play an important role in both the adaptive and innate immune responses.

NK cells have been well established as innate cytotoxic effector cells in the lysis of target cells. Until recently conventional medicine has largely rejected the use of complementary and alternative medicine (CAM) agents because of lack of biological evidence. Over past years, however, several natural agents, working as biological response modifiers, have shown strong evidence for enhancing natural killer (NK) cell cytotoxicity and up-regulating NK cell numbers and activity.

Cancer – A Disease of the Immune System and Microenvironment

In addition to the malignant cell itself, which has been the central attraction in today's oncology, cancer today is also viewed as a disease of the immune system and microenvironment as explained in my book, *Cancer Treatment Breakthrough – Immuno-Oncology Using Rice Bran Arabinoxylan Coumpound*. Today, oncology has finally given more consideration to the immune system as a weapon to treat cancer. According to Kevin Harrington of London's Royal Marsden NHS Hospital, formerly Professor of Biological Cancer Therapies at the Mayo Clinic, the immune system is at the core of the puzzle of how we can treat cancer more effectively; immunotherapy has become the 4th pillar of oncology.[4]

For the past few years, immunotherapy has been used as a complementary therapy or as a replacement for chemo-radiation. Immunotherapy uses mononuclear antibodies to target checkpoint regulators PD-1 and PD-L1; however, this treatment has side effects and is not always efficient. A new line of evidence has shown that the p53 tumor suppressor gene may play a role in tumor immunology and that the modulation of the programmed cell death ligand, PD-L1, along with a loss of p53 activates tumor progression.[5]

Natural killer cells may be one new safe and effective direction to adopt in order to prevent or better treat cancer.[6] Science is quickly moving with new evidence about the role that natural killer cells can play. My clinical work is also giving me a new opportunity to observe how we can better treat cancer by harnessing NK cells by using natural compounds.[7]

What Are Natural Killer Cells and Their Role in Cancer

Natural killer cells are one of our body's most powerful defenses against cancer and are even considered the first line of defense against new invaders and cancer cells. It has been shown

continued on page 58 ➤

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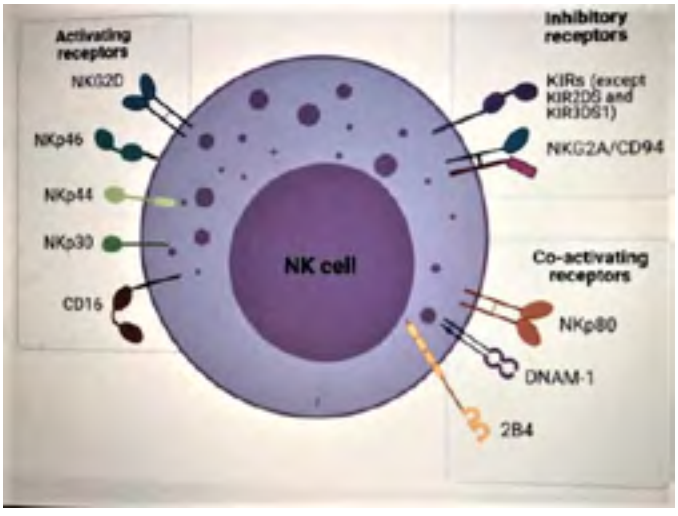
Natural Killer Cells

➤ *continued from page 56*

that NK cells can control both local tumor growth and metastasis due to their ability to exert direct cytotoxicity and to secrete immunostimulatory cytokines like IFN-γ. The active role of NK cells is not restricted to the killing of cancer cells; they also play a key role in affecting other immune cells such as T-cells, DC, and macrophages.

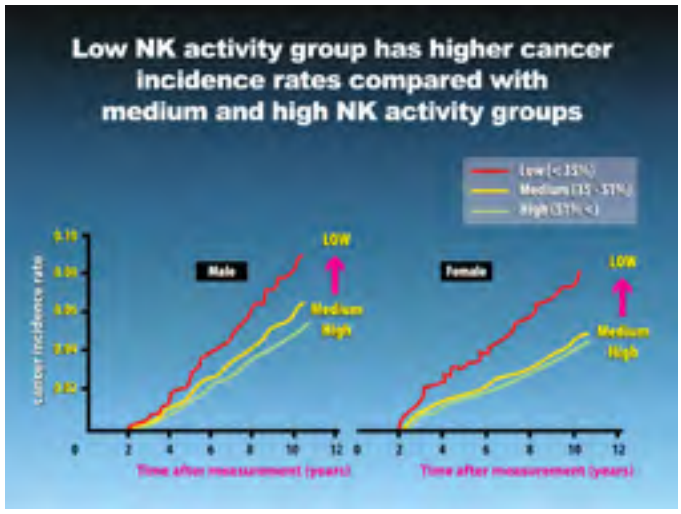
Natural killer cells are a type of cytotoxic lymphocyte critical to the innate immune system but also bridging the innate and adaptive immune system. They are large granular lymphocytes (LGL) and constitute a third kind of cell, differentiated from the common lymphoid progenitor-generating B and T lymphocytes. NK cells are known to differentiate and mature in the bone marrow but also in the lymph nodes, spleen, tonsils, and thymus as well, where they enter into the circulation and patrol from a resting state. They rapidly respond to virally infected cells, acting at around 3 days post-infection,[8] and respond to tumor formation. NK cells express two types of surface receptors, activating and inhibitory receptors (see Figure 1).[9-10] The balance between the signals mediated in these receptors determines the outcome of NK cell activation or inhibition.

Figure 1: NK Cell - Activating and Inhibiting Receptors



Recent studies on NK cell receptors have indicated the possible receptors responsible for tumor recognition and thus provide new support for the hypothesis of NK cell-mediated tumor surveillance. NK cells can directly recognize transformed cancer cells and kill them faster through lysis. However, NK cells – through inhibitory receptors that predominate over the activating signals – can recognize healthy cells and not destroy them; healthy cells express on their surface the MHC class I molecules (Major Histocompatibility Complex), which act as ligands for inhibitory receptors.[11] MHC class 1 is deficient in most tumor and infected cells, leaving them vulnerable to NK cell killing. NK cells can eliminate target cells that do not express a sufficiently large number of MHC molecules. It has been proven that many types of tumor cells express high levels of ligand that lead to their recognition and destruction by NK cells.[12]

Figure 2: NK Cell Activity Level Comparison



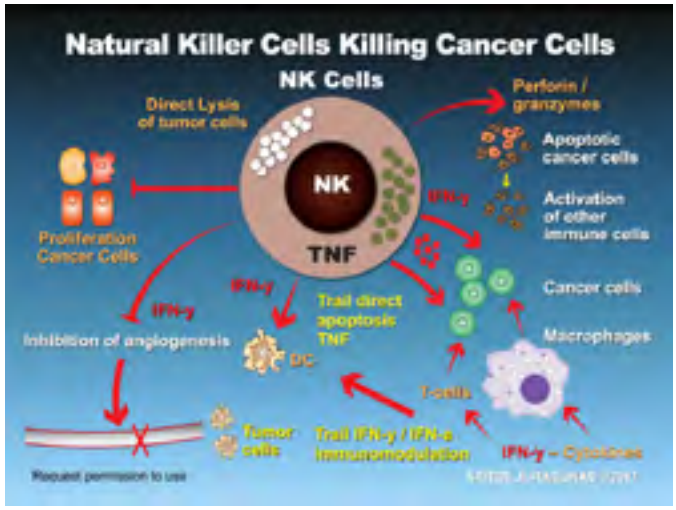
NK Cell Cytotoxicity

We know NK cells that patrol in a resting state become active in response to immuno-regulatory proteins called cytokines that interact with NK cell receptors. NK cells are regulated and activated by various cytokines such as IL1, IL2, IL15, IL18, IL21, and type 1 IFNs. In the case of tumor cells, active NK cells switch their inhibitory receptors to activating receptors in order to bind to cancer cells. Cytokines such as IL15, IL12, IL10, and IL18 enhance NK cell cytotoxicity against tumor target cells; and the production of IFN-γ by NK cells and can be seen as a new cancer immunotherapy.[13]

Enhanced NK cell function resulting in increased anti-tumor activity has been reported after IL15 administration to tumor-bearing mice.[14] Additionally, IL15 – either as a single agent or in combination with several antitumor drugs – was shown to increase the survival of mice that bear NK cell-sensitive tumors.[15] Mice injected with IL15 showed an expanded NK cell population. IL15 stood out to be the most promising cytokine to be used for NK cell activation. IL15 plays an important role in the maturation and survival and homeostatic expansion of NK cells.[16]

A phase I clinical trial using an infusion of IL15 into the metastatic malignant patient showed proliferation and expansion

Figure 3: How NK Cells Kill Cancer Cells



of NK cells along with other anti-tumor immune cells, such as CD8+ T cells and gamma delta T cells.[17] Evidence showed that IL15 could be used in future clinical trials *in vivo* or *in vitro* to enhance NK cell anti-tumor effects. However, IL10 is also a potent inducer of NK cell proliferation, cytotoxic function, and IFN-γ production in combination with IL18.

NK Cells Produce Cytokines

After activation, a natural killer cell produces cytokines and up-regulates effectors or adhesion molecules like perforin, granzymes, FAS ligand (FASL) and TRAIL (tumor necrosis factor-related apoptosis-inducing ligand). Cytokines produced by NK cells, in turn, activate other immune cells like B lymphocytes, T lymphocytes, and macrophages, and accelerate dendritic cells maturation.[18]

IFN-γ secreted by NK cells is one of the most potent cytokines and plays a crucial role in anti-viral, anti-bacterial, and anti-tumor activity. IFN-γ participates in cancer elimination by inhibiting cellular proliferation, including inhibition of angiogenesis,[19] preventing the formation of blood vessels that the tumor needs to supply nutrients and oxygen for growth and expansion. IL12 secreted by NK cells also inhibit angiogenesis.[20] Both IFN-γ and TNF-α can cause direct tumor necrosis by inflicting tumor-associated capillary injury, but they also generate an adaptive immune response by activating other immune cells. IFN-γ can also play a key role in the stimulation of dendritic cells (DC), increasing the destruction of cancer cells because DC also function as direct cytotoxic effectors against a tumor.[21]

NK Cell Direct-Killing Mechanism

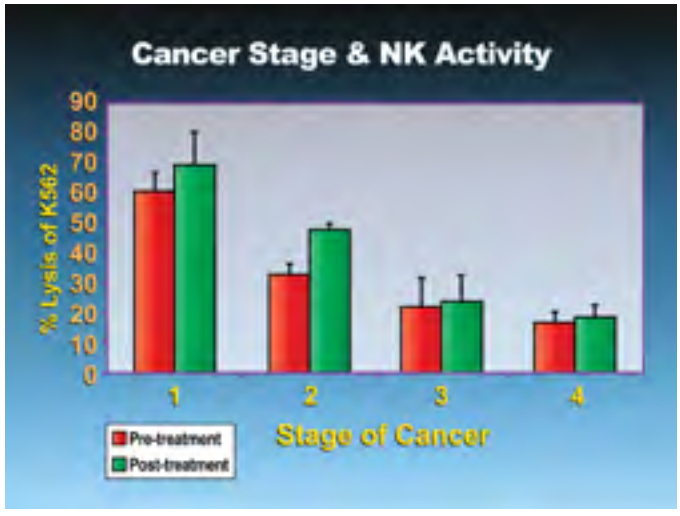
NK cells become active in response to cytokines which first interact with inhibitory or activating receptors on NK cells and make a direct and rapid attack on cancer cells by releasing cytotoxic granules from their cytoplasm.[22] NK cells attach themselves to the membrane of cancer cells receptors by first injecting cytolytic granules containing perforin,[23] which is a membrane-disrupting protein that perforates the target phospholipid membrane forming pores that create an aqueous channel and permit the entry of other cytotoxic proteases called granzymes leading to DNA disintegration and apoptosis of the cancer cells.[24,25] This channel implicates an intrinsic apoptosis pathway through the p53 tumor suppressor gene, mitochondria, and the binding of Bax that penetrate the mitochondria and lead to the release of cytochrome C. Cytochrome C combines with apoptotic protease activating factor APAF-1 and procaspase 9, leading to the formation of caspase 9 and to the subsequent activation of the caspase cascade, including caspase 3 that induces the death of the target cell.[26,27] However, overexpressed BcL2 and downregulated Bax can suppress the intrinsic pathway, and overexpressed survivin can inhibit caspase 3 and caspase 7 activity, thus blocking the apoptosis of cancer cells.[28]

Survivin, an inhibitor of apoptosis, is highly expressed in breast cancer and other cancers and contributes to chemoresistance as well as stimulating angiogenesis and tumor growth.[28] I have published several articles in *Townsend Letter* concerning p53 gene expression and survivin, especially the one called "The Molecular Basis of Prostate Cancer and Targeting Therapies," where I describe the activity of survivin in this type of cancer and how it can be targeted.[29] The reader can see some examples in my book that includes a chapter about p53, the Guardian of Our Immunity; there is a link between the p53 tumor suppressor gene and immune checkpoint PD-1 and PD-L2.

NK cells can use another alternative channel independent of the p53 tumor suppressor gene and perforin\granzymes to induce apoptosis via Fas Ligand (CD95) and TRAIL. TRAIL is a multifunctional transmembrane protein functioning as a death ligand normally expressed on the surface of natural killer cells and T-cells, macrophages, and dendritic cells. It plays a role in both T cells and NK cells to induce apoptosis and is being investigated as a new target for cancer therapy.[30] TRAIL receptors activate apoptosis through cell-surface death receptors DR5 and DR4 that lead to the recruitment of the adaptor protein FADD, which activates intracellular apoptotic pathway by recruitment of caspases 8 and 10, which then cleave to the effector caspase 3 and, in turn, triggers apoptosis through the disintegration of the cell. TRAIL appears to be a second option that provides a rapid efficient route to apoptosis.[31]

But at the moment, the most investigated road to apoptosis by natural killer cells is through the secretion of perforin and granzymes, which also seems the fastest channel. An activated NK cell can kill a cancer cell in five minutes and repeat the process up to 27 times before dying. Circulating cancer cells are more easily destroyed by NK cells than those in a solid tumor, but it all depends on the concentration of immune cells and NK cells within the tumor. It has been shown that cancer patients have decreased cytotoxic NK cells activity compared to a healthy person (see Figure 2).[32,33] Normally with activated NK cells, the majority of cancer cells that enter into the circulation are eliminated within the first 24 hours, thereby providing evidence of the central role played by NK cells in the control of metastasis.[34] However, cancer patients have low levels of basal NK cell activity, such as 30%-50%, compared to a healthy person for several reasons; these include low levels of NK cells in the peripheral blood, tumor decreased production of perforin and granzymes,[35] reduced expression of activation receptors, defective production of cytokines, and loss of ability to adhere to target cells. NK cell activity also declines ➤

Figure 4: Cancer Stage and NK Cell Activity (See ref. 37). 18 patients with breast cancer (invasive ductal carcinoma): Stage 1 (n=2), Stage 2 (n=4); Stage 3 (n=5); Stage 4 (n=7).



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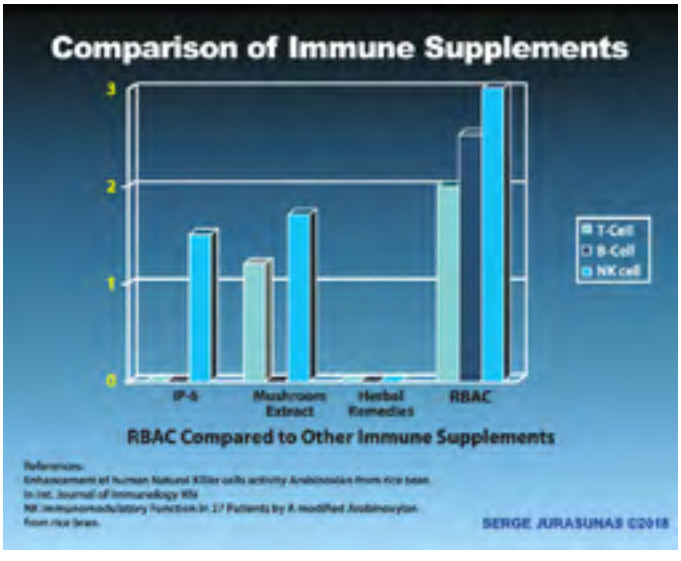
with aging, producing less perforin and granzyme,which increases cancer risk and infection. Studies on animals done in the past have shown evidence that low NK cell activity results in increased tumor cell survival in the bloodstream and metastasis in secondary organs such as the lung.[36] Some authors showed that a higher density of NK cells is an indicator of a good prognosis in breast cancer. An evaluation of natural killer cell activity in patients with different stages of breast cancer patients, pre and post surgery was identified.[37]

The activity of the natural killer cells in various stages of cancer, pre and post surgery was different and consequently there is a significant correlation between disease stage and NK cell activity, where NK activity gradually decreases with the increase in cancer stage. (See Figure 4). Thus the main goal in breast cancer therapy is to increase NK cells, especially in stage III and IV. It also correlates with higher free radical activity in metastatic breast cancer compared with tumors with no metastasis.[38,39]

A variety of stressors can suppress NK cell function due to excessive free radical activity from physical or psychological stress, depression, trauma, anxiety, nutritional deficiency, heavy metal toxicity, etc. Psychological stress has a profound impact on NK cell activity. Surgical procedures also can induce significant immunosuppression, particularly profound suppression of NK cells affecting both cytotoxicity activity and cytokine production, thereby increasing the risk of metastasis. Many patients die from recurrence because of minimal residual diseases and micrometastasis present at the time of surgery.[40,41] Chemotherapy can trigger excessive toxic free radical activity, inhibit immune activity, and contribute to the malignant progression of tumor cells, enhancing their metastatic potential. The more you undergo chemotherapy, the more you increase the level of oxidative stress, inflammation that activates COX2 and NF-KB that in turn stimulate angiogenesis, inhibit apoptosis the immune response, and induce resistance to chemotherapy regimens.[40,41] As explained previously, the inhibitor of apoptosis, survivin, which is overexpressed in most breast cancers, is downregulated by oxidative stress – thus the correlation between free radical activity and survivin with the progression of the disease.[42]

If you follow your patients during a course of chemotherapy for a primary tumor or even after recurrence and a new chemotherapy regimen, you notice that it may exhibit a very strong persistent condition of oxidative stress that needs to be reduced since permanent oxidative stress is associated with metastasis condition. Of course, this depends on each patient and the type and stage of cancer. (See my book for an example of oxidative stress and stage of disease; also p 155-159 with a case of breast cancer). NK cells affected by ROS undergo ionic changes that cause them to lose their ability to adhere to target cells both *in vitro* and *in vivo*. Cumulative experience demonstrates the connection between oxidative stress, depressive disorders, and a higher risk of tumor growth, disease recurrence, and a higher risk of mortality, especially in breast cancer patients. This is probably due to decreased NK cells activity and mutation of p53 protein. Several factors may cause mutation of the p53 gene such as oxidative stress, tobacco, pesticides, or bacteria. These can all induce mutation in the p53 gene.

Figure 6: Immune Supplement Comparison

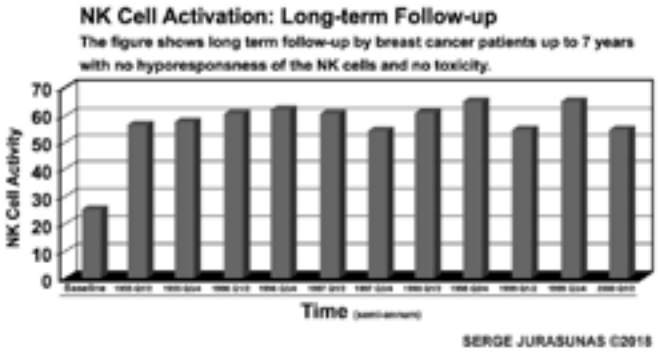


NK Cells Are Modulated by the Tumor Microenvironment

In recent years, the tumor microenvironment (TME) has received increasing attention due to its crucial roles in tumor immune suppression, distant metastasis, local resistance, and targeted therapy response.[43,44] Today we just realize that the TME is as important as the tumor itself. Multiple factors determine whether tumor cells will be eliminated by the immune system or escape because of defective immune cells or immunosuppression.

Tumor growth occurs more easily in a hostile environment. In fact, growing evidence has shown that tumors cannot develop in a healthy environment. In early tumor growth, there is a reciprocal relationship developed between cancer cells and the components of the TME that support tumor growth, cell survival, local invasion, and metastatic dissemination. The composition of the TME varies between tumor types and stage of the disease, but hallmark features include cancer cells, fibroblasts, endothelial cells, immune cells, blood vessels, epithelial cells, myeloid-derived suppressor cells, stromal cells, and the extracellular matrix (ECM). TGF-B cytokines produced by tumor cells in the TME is highly immunosuppressive; they can shut off the normal immune system and increase the resistance of cancer cells by suppressing the immune response of NK cells. Tumor cells can also adopt another important strategy for immune evasion by recruiting T regulatory (Treg) cells in the microenvironment with immunosuppressive effect.[45] Liyanage and colleagues (2002) showed that Treg cells

Figure 7: Long-term Survival

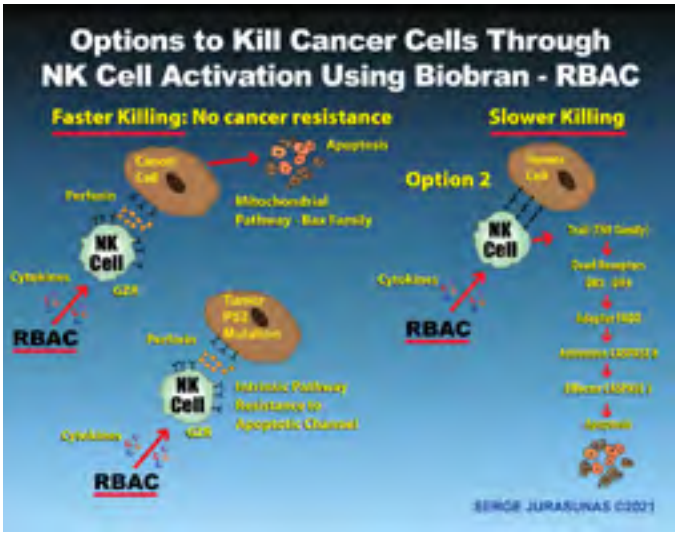


are increased in the peripheral blood and greatly increased in the TME in humans with breast cancer carcinoma, which as a consequence suppresses the NK cell cytotoxicity. TGF-B not only suppresses immune cells but also apoptosis and contributes to activating angiogenesis and is highly associated with breast cancer metastasis invasion to the bone and lung.[46,47] As a direct effect, TGF-B limits NK cell cytotoxicity and IFN-γ production, downregulating the expression of NKP30 and NKG2D and its ligand, MICA in cancer patients.[48]

Excessive free radical activity (reactive oxygen species) in the TME promotes inflammation and in turn activates COX2 and NF-KB that also suppress the immune response and apoptosis. Chronic inflammation is a well-accepted hallmark of cancer that provides a favorable microenvironment for tumor initiation, progression, and metastasis.[49] This is why, as previously explained, it is important to do some testing about the stage of inflammation of the patient, especially during a course of chemotherapy. Another abnormal condition is hypoxia and an acidic microenvironment that obliges the tumor to produce growth factors such as VEGF in order to get an oxygen supply and nutrients. Hypoxia can also have a bad effect on NK cell receptors NKp46, NKp30 with less secretion of perforin and granzymes.[50]

Of course, tumors become infiltrated with diverse innate and adaptive immune cells; the killing of cancer cells is dependent on the quality and quantity of infiltrated immune cells such as T cells, NK cells, etc. Some tumors, known as cold tumors, do not respond to immune attacks because they are surrounded by immunosuppressive cells, such as myeloid-derived suppressor cells (MDSC), and keep T-cells from trying to move into the tumor and killing it. NK cell function also is impaired so cold tumors usually do not respond to immunotherapy.[51] Some bad cancers such as pancreatic cancer and glioblastoma, the most devastating malignant form of primary brain tumors, are typically cold tumors and therefore do not respond to immunotherapies or poorly to chemotherapy. Additionally, human studies in glioblastoma have demonstrated that TGF-B is overexpressed.[52] Both apoptosis and immune response is suppressed, thus cancer cells can grow faster and escape from chemo/radiation apoptotic pathway killing. WT p53 regulates TGF-B while mutant p53 is known to distort TGF-B signaling, which paradoxically displays both tumor-suppressive and pro-oncogenic functions.[53] I have published several articles in the *Townsend Letter* about the function of p53 gene expression and mutant p53 in human cancers that support tumor growth and are linked to a poorer prognosis.[54]

Figure 8: Options to Kill Cancer Cells



The Role of the p53 Gene in the Tumor Microenvironment

In the tumor microenvironment (TME) p53 tumor suppressor gene plays a crucial role; it recently emerged as an important regulator of the antitumor immune response at a different level. However, it has been shown that p53 can modulate immune cells in several ways. It has been clear now that the p53 status of the cancer cells has a profound impact on the TME.[55,56] For instance, it is now accepted that p53 dysfunction in various compartments of TME leads to immunosuppression and immune evasion. While WT p53 (wild type p53) regulates inflammation in the TME through signal transduction, p53 dysfunction/mutated p53 enhances the production of inflammatory cytokines such IL-6 and IL12 from macrophages and activates NF-κB that in turn promotes immunosuppression and evasion of the tumor. Activated or reactivated p53 function reverses the immunosuppression and enhances anti-tumor immunity.[57]

We understand now that loss of p53 function in cancer cells modifies the immune environment since it results in profound changes in cytokine and chemokine secretion with important effects on the immune environment. The p53 gene as a transcription factor may modulate PD-1 and PD-L1 checkpoint inhibitor receptor expression through pattern recognition receptors, cytokine production, and expression of MHC.[58] Thus activation of the p53 may also modulate the various types of immune cells in the TME, including the inhibition of the immunosuppressive Treg cells.[59] The loss of p53 function, which occurs in the majority of advanced tumors, can impair immune surveillance of tumors by decreasing the efficiency of NK cells. WT p53 boosts the recruitment of NK cells within the tumor and potentially the activation rate of the NK cells that reach the tumor. WT p53 tumor suppressor gene or reactivation of the p53 gene

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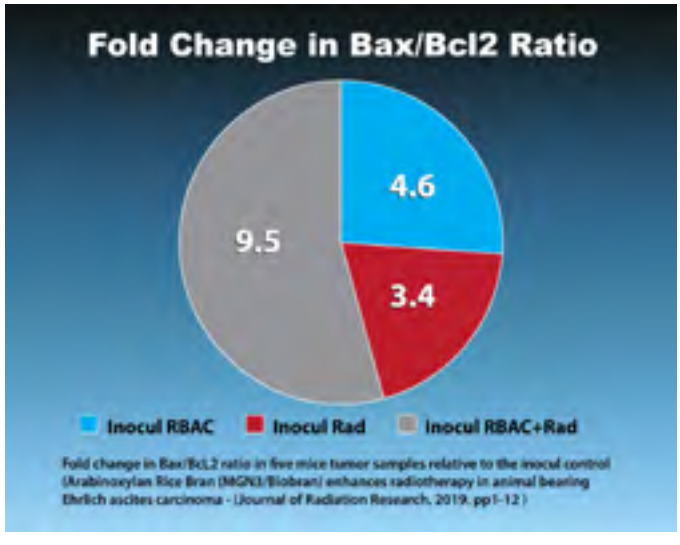
Figure 9: Shows How RBAC Improves the Bax/BcL2 Ratio Together with Radiation



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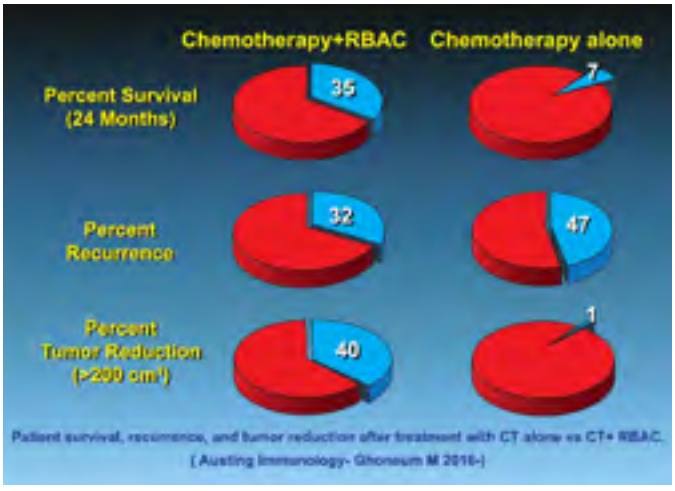
can activate an anticancer response via direct transcriptional regulation of the NK cell ligands and ULBP1 and ULBP2, which connect to activating receptors expressed at the surface of NK, leading to the enhanced killing of tumor cells.[60] Additionally it has been observed, *in* vitro and *in* vivo, a strong induction of various important chemokines and cytokines as well as NK cell-activating IL11, IL12, and IL15 from p53. The success of killing cancer cells in a tumor is mainly dependent on the apoptosis pathway through the p53 tumor suppressor gene and on the quantity and quality of immune cells within the tumor.

At the tumor bed, NK cells may control tumor growth by interacting directly with tumor cells through interaction with other immune cells.[61] However, loss or mutation of p53 in cancer affects, as earlier mentioned, the recruitment and activity of NK cells, cytotoxic T cells within the tumor, and killing of cancer cells. Several tumor biopsy specimens from several solid tumors have revealed little NK cell infiltration into the tumors. It has been shown that a high density of NK cells infiltrated in the tumor has been linked with a good prognosis in multiple solid tumors. However, there are cases of tumors that appear to be refractory to NK cell-mediated killing because of a presence in the immunosuppressive microenvironment, such as the activity of Treg cells. Tregs can be abundantly present in primary breast tumors and metastasis. Several studies have reported that high Treg infiltration in primary tumors and sentinel lymph nodes is associated with the occurrence of lymph node metastasis. Tregs occupy a central role in breast cancer initiation and progression and provide critical support to metastasis formation.[62,63] Depletion of Treg cells markedly inhibits tumor growth. Any natural substances that can shut off or prevent the development of Treg cells in breast cancer could enhance immunity and assist in tumor killing.[63] Today, p53 has become an attractive topic of interest in the literature of cancer biology. Targeting p53 in the TME represents an immunologically desirable strategy for reversing immunosuppression and enhancing antitumor immunity.[64]

Figure 10: Comparison of Chemo Alone Chemo + RBAC



Enhancing NK Cells to Target Tumor Cells

Several recent articles published in various countries have shown that reactivating the immune system to treat cancer using natural compounds is now attracting oncologists.[65] Why? While conventional immunotherapies have shown some benefits in some types of cancer, others such ovarian cancers, for instance, still have high recurrence and mortality.[66] For this reason self-reactivating immune cells with natural compounds may offer a better anticancer response.

For several decades I have been using some natural compounds that have shown efficacy in improving the condition of my patients, such as reduction of tumor size and tumor markers, improving anemia, and a better quality of life. More recently in a case of pancreatic cancer with multiple lesions in the liver and a CA 19-9 at 12134, the CA 19-9 measure dramatically decreased to 2466 after one month of treatment. Many types of supplements available online are just for commercial business but not with therapeutic value.

Several natural compounds have been proposed as a novel therapy that may improve cancer treatment and patient survival, and it is true if using RBAC as I describe in my book. Several compounds have shown efficacy in enhancing immune activity, especially NK cells, but also in activating apoptosis, decreasing inflammation, regulating genes, and slowing down or inhibiting tumor growth.These compounds include a variety of mushrooms such maitake, reishi, and agaricus, that contain beta-glucans that increase T-cell proliferation, macrophages, dendritic cells, and NK cell activity.[67] These mushrooms have also the capacity to modulate a number of cytokines, such as NF-κB and TGF-B1, and angiogenesis.[68] Phytochemicals, including resveratrol, curcumin, genistein, quercetin, and apigenin, are known to activate the p53 tumor suppressor gene and target other genes such Bax, survivin, BcL2, and activate caspases effectors.

Curcumin, which I fully describe in my book may be one of the most important anti-cancer compounds with efficiency in regulating immune cell activity, including NK cells and dendritic cells besides acting as a strong antioxidant and inhibiting NF-κB activity. Now my book is based on the clinical application of rice bran arabinoxylan compound (RBAC) that I have used for the past 28 years because it has shown superiority over many other natural biological response modifiers (BRMs).

RBAC has demonstrated a strong efficacy to enhance NK cell activity by increasing the secretion of perforin, granzyme, and adhesion to the target cells.[69] RBAC is also a potent activator of dendritic cell maturation and function, and thus not only does it increase the anti-cancer effect but can be used as a support of dendritic cell vaccination. The basis for this mechanism of anticancer effects of RBAC is founded in its ability to act as a potent biological response modifier; it has already been identified as a potent cancer immunotherapy. As explained in the article, IL12, IL15 stand out to be the most promising cytokines to be used as activators of NK cells. Taken orally, RBAC increases the production of IL12, IL15, and IL18, which in turn augments and increases NK cell activity and enhances immune cells to secrete IL15, IL12, IFN-γ that activate other immune cells and inhibit angiogenesis.[70] In a study, breast cancer patients had a decrease in NK cell activity and decreased level of IFN-γ; NK cell activity was 175% lower and TNF-α activity was 100% higher.[71] We can understand the important role that RBAC can play in the treatment of breast cancer, in fact as a complementary therapy in conventional

cancer.[72] Not only does RBAC enhance NK cells and other immune cells but also inhibits Treg cells with immunosuppressive effects.

RBAC works in synergy with curcumin to inhibit Treg cells and to increase apoptosis thus augmenting the killing of cancer cells.[73] One case of breast cancer recurrence with multiple metastases that got worse during chemotherapy was almost eliminated when I prescribe RBAC conjointly with liposomal curcumin (page 163). Using RBAC together with curcumin even increased the inhibition of Treg cells. One of the advantages of RBAC is that it keeps the same efficacy even after taking it for several years. RBAC does not exhibit hyporesponsiveness. Oral administration of RBAC for seven years by cancer patients resulted in enhanced NK cell activity, which was maintained at a high level over the seven-year period with no toxicity.[74]

However repeated administration with other BRMs resulted in depression of NK cells activity over this period of time.[75] In my practice I have used RBAC with different types of cancer patients for a period of up to seven years, such as with several cases of multiple myeloma, resulting in stabilization of the disease. You can see in my book the story of a young boy with a Ewing Sarcoma that has been taking RBAC for now, a period of six years. It kept the remaining spinal tissue tumor dormant, which in my opinion validates this compound. Treatment with RBAC causes a remarkable increase in NK cell activity in various cancers after a period of one and two weeks: breast cancer 154-332%; prostate 174-385% (this is why RBAC is so efficient in prostate cancer); multiple myeloma 100-537%. Not only does RBAC enhance NK cell activity but it also works as a cytokine therapy to inhibit and decrease tumor growth, with chemotherapy and without chemotherapy.

I gave an example of RBAC without chemotherapy in my book. A whole book is necessary to describe the effects of RBAC as an antioxidant defense as it increases apoptosis by decreasing BcL2, thus improving the ratio BAX/BcL2, which in turn increases the killing of cancer cells. RBAC plus radiotherapy further increased upregulation of p53 and Bax expression by 284% and 244.1% respectively, and BcL2 expression was suppressed by 95.4%.[76] So RBAC is working in synergy with radiotherapy and chemotherapy (see Figures 9 and 10) and should be used as a support for cancer patients and also to minimize or avoid metastasis or disease recurrence, especially in breast cancer with metastasis to bone, lung, brain, which is very common.

Conclusion

We can improve the quality of life of the patient, avoid metastasis condition, minimize adverse effects, increase patient lifespan, as has been demonstrated with RBAC in various studies.[77] We can also improve the efficacy of conventional therapy by using a leading BRM such as RBAC which in fact, is used by thousands of doctors all over the world.

In my book, I give details of a study done at the Mayo Clinic in Jacksonville, Florida, by a group of medical doctors using RBAC on lung cancer and also the results of several studies done with RBAC at the University of Miami. The real revolution is the way to enhance NK cell activity without toxicity by using RBAC – which is not the case with the new CAR T cells that can be effective against some types of cancers but can also cause serious or even life-threatening side effects, not to mention the very expensive cost. Natural compounds could be what oncology has been searching for: a new, simple, efficient immunotherapy that targets multiple avenues without toxicity.

RBAC is available as MGN3 or Biobran in Europe and was sold in the past in the US as MGN-3 and is now available as BRM4.

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References and Figure 5 are available online at www.townsendletter.com.

Serge Jurasunas is an internationally well-known practitioner and researcher in complementary oncology and molecular medicine besides being a naturopath and a fervent believer in nutrition and detox since 1967. Serge Jurasunas, Professor of Naturopathic Oncology, has devoted over five decades to treating all kinds of diseases and cancer of all types and grades, developing innovative therapies and being a pioneer in several approaches. He is the author of over 150 papers and eight books in three different languages. For the past 15 years, he has devoted much time to the study of the p53 tumor suppressor gene with clinical application. Professor Serge Jurasunas is a frequent contributor to *Townsend Letter* and maintains a private part-time practice only for cancer patients but also with outside patients from several countries via E-mail and Skype.

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Niacin and Cancer – How Vitamin B3 Protects and Even Helps Repair Your DNA

by W. Todd Penberthy, PhD, Andrew W. Saul, and Robert G. Smith, PhD

Orthomolecular Medicine News Service

Although an individual's DNA sequences cannot be changed, the expression of genes can be modified by diet, including supplementation with high-dose niacin to boost NAD levels.

Cells that have had DNA damage are frequently transformed into cancer cells due to mutation. When our tumor suppressor genes are mutated, they can no longer function, and cells can grow without regulation and become cancerous. In a healthy situation, when a cell has DNA damage, poly-ADP ribose (PAR) is added to the DNA, and the cell will stop dividing. If the DNA can be repaired, the cell may continue dividing normally. If the damage is too much, then the cell will die by apoptosis. If the DNA damage is too extreme and acute, then the cell will die by the uncontrollable and messy process of necrosis, which will then adversely affect neighboring cells, likely causing greater collateral damage to them. When the PAR polymer is formed, NAD can become depleted, and cell death occurs because cells cannot live more than a minute or two without NAD.

Niacin, PAR and Sirtuins

Poly-ADP ribose (PAR) is a polymer that is made starting from NAD, which is made from vitamin B3 (niacin, niacinamide).[1] PAR is produced especially in response to any damage to DNA as with radiation oncology treatments, UV sunlight, many chemotherapeutics, and other DNA-damaging environmental toxins. When the DNA damage is extreme, unless there is adequate vitamin B3 (niacin or niacinamide), NAD can become so depleted that cells die by apoptosis (programmed cell death) or with more extreme damage by necrosis. PARP1 is the enzyme responsible for this enzymatic activity and inhibitors of PARP1 will prevent this as well, thus keeping the cell alive, but at great cost.

The two primary niacin/niacinamide concentration-responsive pathways are defined by poly-ADP-ribose polymerase-1 and the sirtuins.

While PARP1 is more studied in the context of DNA damage repair, genome stability, and cancer research, the other major NAD epigenetics pathway involves the sirtuins, of which there are seven genes in humans. These genes are most known for their roles in lifespan across the animal kingdom, even in yeast. Generally, there has been a tremendous amount of research focused on identifying small molecule activators of sirtuins for many types of therapeutics as well as longevity focused supplements, where resveratrol, pterostilbenes, and polyphenols in general are the most well-known molecules.

Sirtuins work on DNA by removing a 2-carbon molecule (deacetylation), from the higher order structure of DNA wrapped around histone solenoid-like structures on chromosomes. This activity resembles that which is seen in caloric restriction, the only method shown to increase lifespan in all animal models. Sirtuins use NAD as their substrate for their activity, and sirtuin activity is increased simply by keeping NAD levels up—which can be accomplished by adequate doses of niacin.

Here's where niacin/niacinamide comes in. Vitamin B3 is the essential molecular precursor to nicotinamide adenine dinucleotide (NAD). All roads in longevity research consistently point to the importance of NAD in controlling lifespan, the most bioenergetically demanding processes (muscle and nerve), and susceptibility to all disease, including cancer.

NAD is made starting from niacin/niacinamide. The NAD precursors are niacin (or chemically, nicotinic acid), niacinamide (nicotinamide), nicotinamide riboside, or nicotinamide mononucleotide. These are all commercially available as supplements, with niacin or niacinamide as the cheapest, oldest, and most studied forms.

Niacin or niacinamide was the first form of vitamin B3 to be discovered. These have been fortified in flour since the 1940s eradication of the pellagra epidemics that were endemic during the first decades of the 20th century United States.

NAD

In basic biology courses we learn about the central role that NAD plays in bioenergetics, where NAD is shorthand for nicotinamide (or niacinamide) adenine dinucleotide. Its reduced form, NADH, is used to create the voltage gradient for mitochondria that generate energy for cells, ultimately producing 3ATPs per NADH with conversion to NAD+.

However, molecular genetics research also reveals that NAD is required for the function of over 400 genes, which is far more than any other vitamin.[2,3] Moreover, NAD is involved in most of the 55 human cytochrome P450 drug-metabolizing enzymes. This family of phase 1 detoxification enzymes is widely known for its role in drug metabolism, but also functions normally in detoxification of

environmental chemicals as well as the metabolism of steroids, prostaglandins, and some other vitamins. Research on NAD is ongoing and complex. Here we focus on NAD-related cellular transformation leading to the development of clinical cancer.

Niacin, Cancer, DNA, and Chemotherapy

The involvement of niacin in preventing cancer and chemotherapeutic side effects is not commonly recognized, but decades of research has established that niacin deficiency is common in cancer patients and cancer patients require larger amounts of niacin to correct deficiency.[4] Generally, studies indicate that NAD functions as a preservative protecting cellular DNA from mutation and also preventing mutated cancer cells from surviving. Niacin deficiency promotes cancer by decreasing genomic stability, increasing the chances both for mutation and survival of mutated cancer cells.

Studies indicate that niacin deficiency delays DNA repair, promotes accumulation of DNA strand breaks, chromosomal translocations, telomere erosion typical of aging, and promotes cancer. Rat model studies indicate that most of these aspects of genomic instability are all minimized by the recommended levels of niacin.[5] Niacin deficiency also increases levels of the tumor suppressor p53.[6] Studies in mice indicate that mild niacin deficiency can cause an increased incidence of ultraviolet-B induced skin cancer.[7]

Kirkland concluded after decades of niacin deficiency cancer research, "With exposure to stressors, like chemotherapy or excess sunlight, supraphysiological [large] doses of niacin may be beneficial."[4]

Studies have found that essentially all cancer patients are niacin deficient at first diagnosis, and almost half are still deficient after supplementation with RDA levels of niacin.[5] This strongly supports supplementation with a high-dose NAD precursor (e.g. niacinamide 3x 500mg/d). Adequate dosing is likely to be beneficial for the health of all cancer patients.

Niacin and Chemotherapies

Most cancer chemotherapies work by damaging the DNA of the rapidly dividing cells. Like most cancer chemotherapeutics, studies in rats have shown that niacin deficiency on its own causes anemia,[7] and it also increases the severity of mutagen-induced anemia and the development of cancer.

Chemotherapeutics targeting the NAD biosynthetic enzyme NAMT (NAMPTi) are currently in clinical trials.[8,9] All NAMPTi clinical trials to date have shown dose-limiting toxicity presentations resembling severe niacin deficiency, or pellagra. Pellagra killed over 100,000 people in the southern United States 1900-1920, and prompted the discovery of niacin.[9] Moreover, no NAMPTi trial has demonstrated a reduction in tumor burden. Thus, the results of NAMPTi clinical trials do not support the idea of NAMPT targeting as a beneficial approach to treating cancer.

The amino acid glutamine plays an interesting role in cancer as there are glutamine-dependent tumors, and glutamine is required in the final step of biosynthesis to NAD starting from niacin or tryptophan, but not from niacinamide.

Thus, niacinamide or niacin supplementation is critically important for cancer patients. The beneficial effect of adequate niacin supplementation has been proven by studies showing that niacin supplementation can protect a cancer patient's bone marrow cells from the side effects of genotoxic chemotherapy drugs.

The role of NAD in the bioenergetics of cancer is huge. Cancer cells perform glycolysis at exceptionally high rates, demanding and taking glucose at the expense of healthy cells. There are distinct advantages and differences in the NAD precursor pathways as related to cancer. Niacinamide would appear to be most preferred with respect to bioenergetic perspective of cancer. This is planned to be briefly presented in a future OMNS release, but a summary and consistent practical takeaway suggestion that takes this into conclusion is included below.

Summary

Supplementation with vitamin B3 (niacin), the precursor to NAD, can lower the risk of cancer. NAD deficiencies are observed in nearly all cancer patients, likely due to the energy-draining component of suffering from hyper-proliferative cells. Chemotherapeutics commonly cause additional NAD deficiencies. There have been concerted efforts and considerations of targeting the NAD biosynthetic pathways as a novel patentable approach to the development of chemotherapeutics, but the results to date are in no way encouraging or exceptional, where dose-limiting toxicities resemble that of the deadly NAD deficiency disease pellagra.

Many decades of research focused on using NAD precursors to favorably alter epigenetics via PARP1 and now sirtuin pathways indicate that supraphysiological doses of niacin will preserve the integrity of the genome, prevent mutation, and help prevent the rogue survival and proliferation of transformed cancer cells. In short, niacin prevents cancer and metastasis.

NAD research is both complex and likely highly rewarding, and we still have much to learn regarding which NAD precursors are the best for addressing cancer. Nonetheless, studies strongly support high-dose NAD precursor supplementation. That means taking niacin, starting with low dosages, 100-200 mg niacin, to get accustomed to the flush, and working up to 500 mg three times a day (1,500 mg total). During treatment for cancer, however, niacinamide may be the preferred form since it is not dependent on glutamine for the synthesis of NAD and glutamine restriction is helpful in treatment of cancer. The authors recommend this measure as potentially highly beneficial to saving the health of all cancer patients. Summary:

1. NAD deficiency is associated with greater risk for mutagenesis with cancer, and this is likely best avoided using daily niacin, e.g. starting with 3x100-200 mg/d to get to the know the flush and then working up to 3x500-1,000 mg/d.
2. For cancer patients, chemotherapy commonly causes NAD deficiency, which is best rescued with niacinamide; e.g. 3x500 mg/d.
3. Dietary relevance, glutamine restriction with niacinamide; glucose restriction and ketogenic diet is recommended.[10,11]

For more information: http://orthomolecular.org/subscribe.html and also the OMNS archive link http://orthomolecular.org/resources/omns/index.shtml.

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References are available online at www.townsendletter.com.

High Dose Vitamin C for Cancer – The Struggle with "Non-Evidence-Based" Medical Practice

by Dr. Raymond CF Yuen

Orthomolecular Medicine News Service

While serving as a consultant for a cancer support group, I was often asked how diet, nutrition or supplements can help cancer patients. Eventually, I searched and found that many vitamins and micronutrients are clinically helpful in improving quality of life and prolonging patient survival. I began to explore the use of non-toxic medicines or nutrients to help prevent and reverse cancer, and one of the star products I found was vitamin C. I applied high dose intravenous vitamin C (HDIVC) combined with other micronutrients and supplements to help patients. Amazingly, but not surprisingly, many of them improved. To spread the word to the medical world, I published a report on some case histories.[1] The report drew some attention and many criticisms about the vitamin C treatment. What puzzled me was that the opposing views were mainly from medical professionals. They criticized the HDIVC treatment as non-evidence-based and unlawful. I rechecked the medical literature and clinical research on vitamin C and noted that the controversy had been there since Captain James Lind used citrus fruits to treat his sailors, and more recently, Linus Pauling and Cameron used HDIVC in their cancer trials.[2]

Although HDIVC as a cancer treatment therapy has not been well documented, it is well supported and recognized as a supportive or adjunct cancer treatment.[3-7] HDIVC has proven effective in reducing complications from chemotherapy[8] and radiotherapy.[9] It also enhances the killing of cancer cells,[10,11] which improves patients' quality of life and survival.[8,12] Recent findings have documented that HDIVC enhances immunotherapy and reduces its adverse side effects.[13,14]

The more I researched vitamin C and its clinical application, the more I realized it is a panacea for medicine.[15] How could a trained physician miss out on this potential cure for most inflammatory diseases, including cancer, cardiovascular disease, and infectious diseases such as Covid-19?

I am convinced HDIVC only appears to be a controversial treatment for those unaware of recent research on essential nutrients -- and who have a potential conflict of interest.[2,16] Despite my struggle to convince the medical establishment of its clinical utility, HDIVC is crucial for cancer treatment.[1,17,18] I hope my work on vitamin C research will help clarify some of the medical myths about HDIVC therapy and its clinical application in cancer immunotherapy.[2,3,19] Knowledge about vitamin C saves lives.

Malaysia, Indonesia, and Singapore are relatively strict about the use of alternative medicine such as HDIVC for cancer and other chronic diseases. HDIVC is classified as non-evidence-based medical practice, and doctors utilizing it are threatened with being censored and penalized. Yet, somehow, many physicians and specialists quietly provide HDIVC for their patients and relatives or even for their politicians. In contrast, countries like the Philippines, Taiwan, and Thailand are quite open to HDIVC, and every year draws more medical tourists. Hong Kong is more flexible in alternative medical treatment, and some clinics there offer HDIVC as supportive care for cancer with special permission granted by the medical authority. I hope recent research will produce more clinical data to "certify" that HDIVC is beneficial for treating cancer.

However, time is running out for some cancer patients. An immediate application of HDIVC could be life-saving for them. Even though the medical establishment does not accept the efficacy of HDIVC, given its safety profile and potential benefits in cancer treatment, HDIVC may be given on the grounds of compassionate use. Even for the advanced stages of cancer, HDIVC has proven effective in reducing inflammation and improving quality of life.[20,21]

In the ten years that I have been administering HDIVC for cancer patients, I have always found it effective in improving patients' quality of life and survival. I have seen stage 4 cancer patients who were given a poor prognosis survive longer than their oncologists' prediction or expectation. I have documented a stage 4 ovarian cancer patient who survived more than five years.[17] Now for over eight years, she is still asymptomatic, cancer-free, and has a good quality of life.

Recent research has shown that while chemotherapy kills cancer, it also tends to enhance the spread of cancer throughout the body,[22] and most cancer patients given chemotherapy eventually develop side effects or other organ failures.[22] Another common phenomenon is the off-label use of chemotherapeutic drugs for cancer patients, which according to one study often accounts for more than half of adult cancer treatments.[23] In another study, 33% to 65% of end-stage cancer patients were more likely to be given such off-label drugs. Eaton et al. reported that 82% of end-stage breast cancer patients take off-label chemotherapy.[24] The US National Cancer Institute has stated that the actual figure of off-label cancer drugs might be even higher than reported.[25]

This off-label chemotherapy is non-evidence-based and often has significantly higher side effects and reduces patients' quality of life. We have proposed the off-label use of HDIVC for cancer[26] because it is much safer with good patient outcomes. HDIVC is more body-friendly and can even enhance immune functions to help neutralize cancer.[19] For these very desperate cancer patients, treatments that are not focused solely on killing cancer cells may be preferred. HDIVC treatment may control the tumor growth while improving quality of life and lengthening survival periods.[7,16]

Notably, high dose vitamin C has been used for the last five decades either as supportive care or as an anti-cancer treatment[27] with anecdotal successes coupled with very good safety profiles.[18,28] Nevertheless, so far, it has failed to achieve any regulatory approval. Fortunately, the various vitamin C mechanisms that control cancers are now much better documented, and there are currently many ongoing clinical trials.[11,29,30] With the currently better known high dose vitamin C pharmaco-kinetics and anti-cancer mechanisms,[31-33] it is recommended that all cancer patients should be considered on compassionate grounds to receive high dose vitamin C as supportive treatment or as an adjunct anti-cancer therapy.[7,11]

Regulations apart, for a desperate patient without realistic treatment modalities, the patient's therapeutic response should be our guiding principle – rather than continuing to adhere to strict treatment guidelines. This is especially true in the treatment of advanced cancers, for such cancers may involve a multiplicity of organs, and the involvement of each organ may also differ. Thus, the treatment of choice should be more precise and personalized.

High dose intravenous vitamin C reduces inflammation and improves quality of life and survival.

In contrast to the official rulings alluded to above, high dose vitamin C may be considered as an innovative cancer treatment that fulfills most of these requirements:

1. There is clinical plausibility[34,35]
2. There is biological plausibility[5,11,32]
3. There is proven clinical effectiveness[36]
4. It is affordable to most desperate cancer patients[5,18]
5. It may enhance the effects of regimens[14,37,38] (therapy-related)
6. It may repair the damage, e.g., vocal cord recovery[39] (disease-related)
7. It may eradicate cancer stem cells.[4,10,40,41]

Recent well-documented research shows that high dose vitamin C therapy has several biological mechanisms of action on cancer cells.[6,11,35] This is undoubtedly the rationale for its strong history of clinical success in treating cancers.[42] However, the clinical efficacy remains controversial since the gold standard for an investigational drug would be to conduct randomized controlled trials—which is difficult without patent benefits for vitamin C. Apparently, with limited funding, one has to work much harder on vitamin C research. Reassuringly, there is growing evidence supporting the anti-cancer effects of high dose vitamin C, especially as recent research suggests that vitamin C is well tolerated and has minimal side effects.[29,43] Recently, there have been a few ongoing randomized and non-randomized clinical trials of high dose vitamin C on cancer.[29,30,44] As of 2018, the cancer researchers at the Holden Comprehensive Cancer Centre of the University of Iowa have received a five-year grant of $9.7 million from the US National Cancer Institute for high dose vitamin C cancer research.[44] Undoubtedly, more and more high dose vitamin C clinical research activities are to be undertaken soon. One of the reasons is, although cancer treatment resistance is closely related to cancer stem cells, vitamin C may be able to eradicate these stubborn cancer stem cells.[10,40,41,45] Meanwhile, with the safety profile and clinical effectiveness of vitamin C, it would be advisable to commence high dose vitamin C on compassionate grounds for desperate cancer patients.[12,46,47]

At this period of severe economic depression, COVID-19 pandemic, HDIVC is attractive as it not only has a good safety profile but is also eminently affordable. Moreover, as no exceedingly expensive, very time-consuming drug development efforts are required, HDIVC would seem more crucial than controversial.

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References are available online at www.townsendletter.com.

A New Way of Looking at the Underlying Cause of Cancer

by Robert A. Eslinger, DO, HMD

It is no secret that since President Nixon "declared war on cancer" we have not come very far. To be sure we understand the workings of the cancer cells themselves and in some cases have helped people live slightly longer lives once they are diagnosed with the disease…but!

The big BUT is have we learned how to really extend people's lives, improved the quality of those lives, and in the end eliminate the disease?

The answer is a resounding…not so much!

There was a study published in 2017 in *JAMA Oncology* that showed of 62 new oncology drugs approved between 2003 and 2013, only 43 percent offered a survival benefit of three months or longer, 11 percent offered a survival benefit of less than three months, 15 percent had an unknown survival benefit, and 30 percent offered no survival benefit at all![1]

There is proof now that cancer is not fundamentally a disease caused by genetic abnormalities. What underlies and drives the genetic changes does not lie in the cell nucleus. The cause of these is a fundamental shift in the metabolism (the cytoplasm) of the cell that causes the genetic changes.[2]

In fact, the concept that the DNA is masterminding the life of the cell (and all life for that matter) is wrong! The DNA is the map not the brain.

Today the field of "epigenetics" is growing rapidly. What it basically says is that the environment (the composition of the cytoplasm) in the cell is what triggers which genes get "turned on" and which get turned "off."

It used to be that most of our DNA was considered "junk" DNA. Essentially what that meant was we didn't know what it does. We know now that we all have a huge number of genes that are just kept inactive until the epigenetics dictates their activation.

So, the big question is what controls the epigenetics? We will get to that.

The most important organelle (tiny organs inside each of our cells) to comprehend when trying to understand the origin of cancer is not the nucleus, but the mitochondria.

The mitochondria are the energy furnaces that produce the energy that our body uses to perform all its functions from the nutrients that we consume in our diets and the air we breathe.

Usually there are thousands of mitochondria inside each of our cells.

Normally the two main nutrients they consume are sugar and oxygen. They are combined and burned chemically to produce all the energy we need.

This is why we breath and eat. The energy producing reaction inside the mitochondria is called "oxidative phosphorylation"; this will generate ATP (adenosine triphosphate), which is the fuel that all our cells run on.

It is called aerobic metabolism and it is how we all get through every single day. By this process our mitochondria can produce 36 molecules of ATP for every molecule of sugar burned.

Our blood carries the oxygen and nutrients to all these cells and carries the waste products from these reactions away from the cells and to the lungs, kidneys, bowel or lymphatic fluid for disposal.

Now we do not have a direct blood vessel into each and every cell. The vessels get smaller and smaller until they reach the smallest ones called the capillaries. From here the oxygen and nutrients diffuse out through the vessel walls and through the interstitial spaces dissolved in the lymphatic fluid.

The waste products and carbon dioxide then diffuse back into the capillaries to be carried away.

If all goes well, we maintain a state of health, and everything works the way it is supposed to.

This is where the importance of normal cytoplasm comes into play. It is said that our bodies contain somewhere between 70-80 percent water, but our cells do not just contain plain water. They have many compounds dissolved in it that change its composition into what has only recently come to be known as the"fourth phase of water"[3] or structured water.

Everyone understands that water exists in our world in the three forms of steam (gas), liquid and solid (ice). What most people don't understand is that there is a fourth phase that water can take. The best way to understand this phase is to think of it as an orderly lineup of all the water molecules and their electrical charges.

It turns out that all the water inside every one of our cells exists as a gel. This is the true form of the cytoplasm, and it consists of "structured water." The composition of this gel is what determines its function.

What I mean by that is the normal composition of our cells consists of the electrolytes sodium and potassium among many other compounds. For a cell to be healthy, it must have mostly potassium inside and mostly sodium outside the cell membrane. This "sodium/potassium gradient" is determined by the composition of the gel and the amount of ATP produced by the mitochondria.

One extremely important function of this gradient is that it creates a "halo"

of an electric charge around each cell to leave space so the oxygen and nutrients can diffuse through to reach all the cells and they can discharge all their wastes and carbon dioxide back into the capillaries.

If this gradient is not properly maintained the space between the cells can begin to shrink to the point where the cells start to clump together, and this diffusion of products cannot take place properly. Then the cells further away from the capillaries will not be able to get enough oxygen or nutrients.

Every one of our cells has a backup system to produce ATP if it is not able to obtain enough oxygen. Nobel Laureate Otto Warburg, MD, PhD, claimed in his research in the 1920s that if a cell has a drop of more than 30% in its oxygen supply it will switch over to its backup energy production, which consists of a process called glycolysis or anaerobic metabolism.

That is burning sugar without using oxygen. A way of producing energy that is 18 times less efficient than aerobic metabolism. The very hallmark of cancer!

This change into abnormal metabolism can then shift the epigenetics of the cell in such a way as to activate any dormant oncogenes (cancer triggering genes-if they are present) that could then go on to perpetuate the abnormal metabolism and begin to grow a tumor.

The most important research that has been done recently in this area has been performed by Dr. Thomas Seyfried. He has done his work at Boston College and has established that cancer is, first and foremost, a metabolic disease, not an abnormal genetic disease arising in the nucleus.[2]

Some relatively new information is revealing several very interesting results.

Those of you who have heard of Gerson therapy probably did not know that it was an early attempt to restore the normal sodium/potassium gradient across the cell membranes through dietary means. Most people also don't know that his diet was not totally vegetarian or even vegan. He recommended smoothies with raw liver in them!

He did have a certain degree of success in curing some cancer cases.

Digitalis is a drug that has been known about and utilized to treat a number of heart conditions for many years. Originally it was developed from an extract of the foxglove plant.

More current research (2009 in *American Journal of the Medical Sciences)* has shown that it can also block cell proliferation triggering apoptosis (cell death) in different malignant cell lines.

For a cell to be healthy, it must have mostly potassium inside and mostly sodium outside the cell membrane.

A 2006 article in *Breast Cancer Research and Treatment* stated "ouabain and related digitalis preparations possess potent anti-breast cancer activity" and called it "a new paradigm for development of anti-breast cancer drugs."

The underlying theme of this research is that these cardiac glycosides at appropriate doses have a strong effect on restoring the healthy sodium/potassium distribution across the cell membrane. This will begin to return the electrical charge (the "halo") between the cells back to normal.

Another simple way to promote the restoration of the cell spacing back towards normal is the regular consumption of structured water.

This is where the fourth phase of water comes in to play.

"Normal" or "Regular" water consists of a liquid made up of molecules of water (a polar molecule with a positively and a negatively charged end) bonding with each other in a very random pattern. This makes it harder for it to penetrate through the cell membrane.

Victor Schauberger was an amateur engineer in the late 19th and early 20th century in Austria who figured out that much of the power in vortexes (whirlpools) comes from their ability to line up the molecules in such a way that they create structured water.

This structure is made using principles of "Magnetohydrodynamics." It is applied to the water using a simple inexpensive apparatus that creates a vortex and uses a magnetic field. It changes the structure of the water so that it has a much easier time penetrating the cell membrane and helping restore the proper sodium/potassium gradient.

This allows for greater cellular communication, intracellular water movement, enzyme function, cleansing of the cells, efficient transport of nutrients into (and waste products out of) the cells, greater stabilization, superior energy flow, electrical communication between cells and many other metabolic reactions.

I am not saying this information offers anywhere near a magical solution to a very dreadful disease. It does however offer some ideas about new areas of research that need to be explored in greater detail.

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Robert A. Eslinger, DO, HMD, has been practicing medicine for 45 years. After completing his education and training in 1978, he joined the US Public Health Service. He was stationed, as the medical director, in a clinic located on an Indian reservation 70 miles from the nearest hospital in Neah Bay, Washington. After about two months, he started noticing that much of what he was taught in his conventional medical training just wasn't working or at least it wasn't working as well as he wanted it to. Then he met and started training with one of the local tribal medicine women and learning about herbs, supplements, homeopathy, and nutrition. In 2002 he passed his boards to receive the HMD (Homeopathic Medical Doctor) in the state of Nevada. He is currently licensed to practice medicine in Idaho, California and Nevada and certified in family practice by the American College of Osteopathic Family Practitioners. A Fellow of the American Association of Integrative Medicine and a founding member of the International Organization of Integrative Cancer Physicians. he is now the owner/medical director of Reno Integrative Medical Center in Reno, Nevada.

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After Cancer Treatment

by Amy Rothenberg, ND

This article is an excerpt from Introduction to *You Finished Treatment, Now What? A Field Guide for Cancer Survivors* by Amy Rothenberg, ND.

You'd think the last day of chemo or the final radiation treatment would be a time to rejoice and celebrate. But for many cancer patients, the last day of treatment is soon followed by a sense of dread and despair. The fighting stance and the rallying cries end. The outpouring of support slows. It's on to "life as usual," which is not easy if you don't feel well and medical "active surveillance" seems served up with a hefty portion of stress and anxiety.

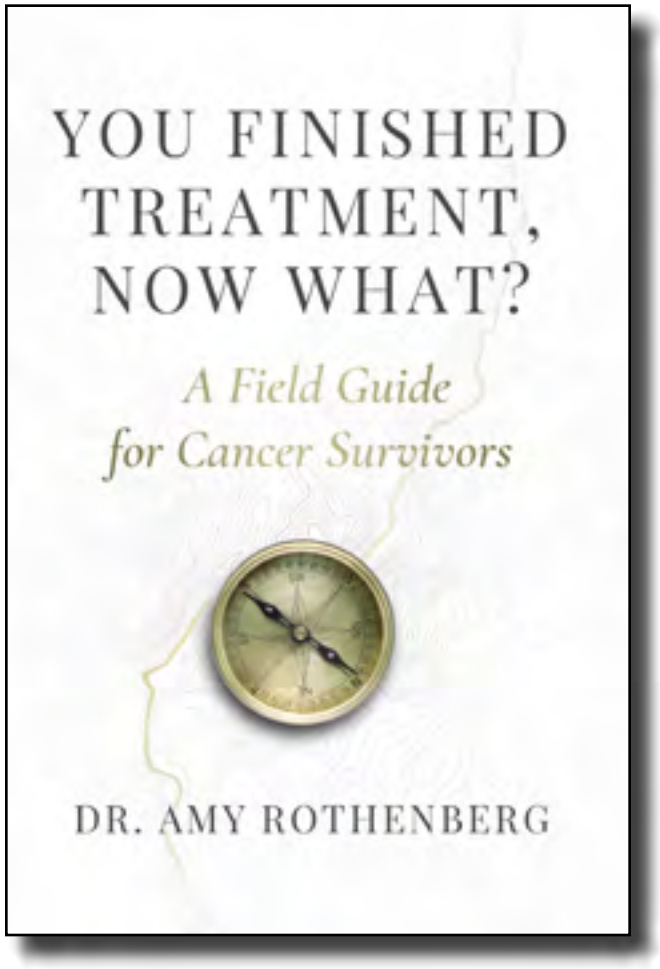
I know this terrain intimately, as a cancer survivor/thriver and as a licensed naturopathic doctor. I was living a healthy lifestyle and blessed with pristine health when diagnosed with breast and then ovarian cancer in 2014. I wrote extensively on the topic of using natural medicine *during* my own cancer treatment. It was certainly eye-opening to be in the patient chair after so many years as a doctor.

I had the great fortune of receiving state-of-the-art conventional treatment at a world-renowned teaching hospital. I was in excellent hands with some of the smartest people I have ever met. I also had guidance and encouragement from brilliant colleagues in the naturopathic profession who specialize in integrative oncology and who were enormously generous and caring, for which I am eternally grateful. My goals for naturopathic approaches were several: enhance efficacy of my conventional care, prevent side effects, address side effects that arose, and to glean general support throughout my time of treatment….

After cancer treatment, I have committed to many of the approaches described in this book and continue to take my health, and my ability to impact my health, seriously. I kicked up my already healthy relationship with exercise, I further tidied up my diet, I let go of certain commitments and people in my life that caused undue stress. I added specific anti-cancer supplements to my daily intake, and so much more.

I continue to work with my naturopathic physician colleagues as well as my oncologists. We create a treatment plan that dovetails with the details of my medical story and also takes into account my temperament and my capacity to do the work that is part of getting well and staying healthy. I continue, years out, with approaches that encourage physical vitality, spiritual peace, mental clarity, and emotional balance, while doing all I can to reduce my risk of recurrence.

Should my cancer ever return, which I deeply hope it does not, I will always feel I did as much as I possibly could, to protect the life I hold so dear. Creating a plan, committing to it, and modifying as needed, is empowering. I aim to model much of the content of this book for my patients, understanding first-hand what it means to be disciplined without becoming rigid, what it takes to make changes without disrupting my family life, how to make small sacrifices, while also prioritizing pleasure and fun in day-to-day moments of my life.



My perspective is further defined by cancer patients and survivors I've treated in my practice over the last 36 years. I offer evidence-based information alongside a cheerleading nature. I emphasize lifestyle medicine: how you eat, exercise, reduce stress, decrease exposure to environmental toxins, and more. I employ a full toolbox of natural medicines to help address specific health challenges. I remind patients it's possible to shift modifiable risk factors that may have led you to be more susceptible to developing cancer in the first place….

I work collaboratively with patients' skilled conventional medical providers. And as proof of natural and lifestyle

medicine emerges, I see more and more interest in, and respect for such approaches, from medical colleagues. An integrative approach is always ideal, taking the best from all parts of medicine. No two patient stories are the same, but some elements ring true: we all need information, creative problem-solving, and compassion as we navigate post-treatment life.

And the need is ever-expanding. The number of survivors is growing as treatment for all kinds of cancer improves. By the 2040s, the US will be home to more than 26 million cancer survivors. In addition, there will be many other people living productive lives *with* cancer, while taking medications ➤

Natural Medicine Approaches to Peripheral Neuropathy

A well-known side effect of certain chemotherapeutic agents is neuropathic pain and peripheral neuropathy, which is nerve pain and nerve damage in the extremities. There is growing evidence that certain natural substances, given *during* the time of chemotherapy, can help to prevent or mitigate neuropathy, and I hope these will become standard of care. The recommended natural substances for prevention of neuropathy differ based on which chemotherapy is taken, as the mechanism of action causing the nerve damage is different with each chemotherapy drug. And, of course, recommendations are only for substances that will not interfere with the efficacy of the chemotherapy. Some people use cold pack treatments to keep the chemo from getting to the extremities, which has also been shown to decrease neuropathy, but it's not easy to do and some will not tolerate the cold.

Peripheral neuropathy can manifest as numbness, burning, tingling, altered or lowered sensation, a reduction in strength, as well as pain, anywhere in the extremities. This can impact fine motor coordination, gait, the capacity to do daily activities, and quality of life.

For those with lingering neuropathy, numerous approaches can potentially reduce symptoms. The most researched approaches are acupuncture, exercise, topical applications, dietary changes, and nutritional supplements. In addition, stress plays a role in exacerbating peripheral neuropathy.

Acupuncture, which also shows evidence to help with mood, lymphedema, and sleep, has been examined for its role in addressing neuropathy. Though not every study shows help, many studies do, and acupuncture's low cost and nil side effect profile make it worth considering.

Exercise helps with both balance and strength and may also help with numbness, tingling, and altered temperature sensations. See the chapter *Exercise Your New Best Friend* for more about getting moving. Physical therapy can also be useful; whatever you learn and practice with a physical therapist, be sure to thoroughly understand the exercises so you can continue to do them on your own. Consistent yoga practice also shows promise for helping reduce mild to moderate peripheral neuropathy.

Some of my patients with neuropathy have benefited from topical agents. Menthol in a 1% preparation can be applied twice a day to the affected area. Similarly, capsaicin, prescribed by your physician as a patch, sold under the brand name *Qutenza* (no affiliation), may be tried. It does have side effects for some people, including rash, itching, nausea, and elevated blood pressure, so please use under careful supervision.

With regard to diet, again an anti-inflammatory focus is best: whole grains, lean meat and poultry, fish, vegetables, fruit, nuts, and healthy oils, such as olive, avocado, and coconut oils. Remember that poultry and fish are high in vitamin B12, essential for healthy nerves. Eat to create the least amount of systemic inflammation, which in turn may help with peripheral neuropathy.

The nutritional supplements that hold the most promise for peripheral neuropathy include acetyl L-carnitine, vitamin E, alpha lipoic acid, vitamin D (for those who are tested deficient in vitamin D), and omega-3 fatty acids. Glutamine may also show efficacy when put to further clinical trials. In addition, be sure you are getting enough B vitamins by taking a B-complex supplement because B vitamins are central to healthy nervous system function.

Botanical medicines are studied for their effect on peripheral neuropathy, and many herbs show promise – from curcumin (*Curcumin longa*) to cannabinoid products. Further clinical trials are needed to confirm efficacy, but if you have completed treatment and are not concerned about interfering with chemotherapy, many botanical medicines work to decrease inflammation, promote circulation, and calm the nerves. See the chapter on *Botanical Medicine* for more information.


Dr. Rothenberg at her last chemotherapy appointment, 2014

Attending to the big stressors in your life and your stress response is also shown to be helpful with peripheral neuropathy because chronic stress exacerbates neuropathic pain. Breathing exercises, mindfulness meditation, positive imagery, and a gratitude practice can all help decrease the intensity and severity of peripheral neuropathy as well as support a better quality of life. See the chapter on the *Head Game* for more details.

For many people, it's a combination of approaches that works best. If you are no longer taking chemotherapy and can bring in more strategies, it often takes trial and error to find the best combination for effective treatment. By advocating for yourself and continuing to engage with your providers and asking for help, you will hopefully find help for this challenging, long-term effect of cancer care.

You Finished Treatment, Now What? A Field Guide for Cancer Survivors by Amy Rothenberg, ND. Koehler Books (2022). Hardcover, softcover, ebook, and audiobook available at https://dramyrothenberg.com, on Amazon, and wherever books are sold.

Book Excerpt: *You Finished Treatment, Now What?*

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and using other approaches that help keep them alive. Improvements in the world of oncology are made all the time, and many of us are recipients of those advances.

Nonetheless, there is a time I call "mopping up," where we work to reverse collateral damage from cancer treatment. Many survivors struggle with their health after cancer treatment. Natural, integrative medical approaches are helpful *and* can be applied in a way that does not interfere with ongoing medications, or put you at further risk of cancer. Research shows that cancer survivors often report physical and psychological challenges well after cancer care has ended and that their needs often go unmet….

Common side effects include low blood counts, lymphedema, "chemo brain," skin issues, weight loss, weight gain, peripheral neuropathy, digestive disturbances, anxiety, depression, insomnia, and fatigue. That said, in my decades of practice, I've seen cancer survivors with symptoms on nearly every system of the body, including far-reaching cognitive and ongoing emotional issues.

Of course, some survivors may have had these concerns *before* being diagnosed and treated for cancer. But for others, these symptoms are entirely new and most unwelcome – like another bad chapter layered over an already overwhelming ordeal of a cancer diagnosis and treatment. You may have had no symptoms or only mild symptoms at the time of diagnosis. Perhaps you had a few risk factors and previously enjoyed good health. Being diagnosed with cancer may have been especially shocking. Then, as symptoms arose from conventional treatments, which by design, can be harsh in order to get the job done, it may have felt like a further blow. This book can help you right the ship, to unwind from some of the trauma and impact of life-saving conventional care….

I write this book to fill the gap of information and offer guidance for survivors, to help you rebuild and restore, and to support the innate resilience of the human body and spirit. And for people living with cancer, in and out of treatment, many for years to come, you'll also find actionable ideas. Perhaps you have a genetic propensity to cancer or have another illness, the treatment for which puts you at risk for cancer – study these guidelines. Family members and caregivers may benefit from reading these pages. And I write these chapters for medical providers, in hopes that more of you will offer, or at least endorse such recommendations, or refer you to a practitioner who has pertinent expertise.

Some offerings are general, others more pointed toward specific complaints. I share information and experience to encourage you to be proactive about your health instead of waiting around for cancer to develop or return. I am also interested in helping you address the psycho-emotional element of your story, because for most everyone, psychological symptoms impact the way we move through life, in sickness *and* in health. Emotions influence the physical body in predictable and important-to-understand ways….

You do not need to take up every suggestion written in this book, even if research and clinical experience from each section show promise or results. No one can do everything that could potentially be cancer-preventive. There is simply not enough time in the day. Some patients drive themselves – and their loved ones – a bit weary trying to do all that is possible, at great expenditure of time, resources, and energy. Remember, your body reflects the habitual, not the occasional. Certain approaches will have more appeal than others depending on your personality, temperament, time, resources, support, and other factors.

Be kind and gentle with yourself, it's another essential component of healing. I prefer when my patients make slow, gradual, more permanent changes, instead of trying to change everything all at once. If you already live a healthy lifestyle, you may find some ways to amplify your efforts, or you may discover ways to fine-tune with natural medicines aimed to address particular residual complaints.

Before you embark on creating a plan for yourself, consider working with a licensed naturopathic doctor or other medical provider well-versed in this material, as part of your medical dream team. As with all good medicine, specific treatment plans need to be individualized to the patient. If you came to me or to a colleague, we'd want to know what type of cancer you had, where it was, what approaches were taken, and which – if any – side-effects you experienced. We'd want to know about ongoing or residual health issues from treatment. From there we'd map out a strategy and a plan.

In addition to using the information in these pages, please keep up your ongoing medical oversight, including patient visits, laboratory analysis, and pertinent scanning. This remains essential, as early discovery of either new cancers or metastatic illness is always best. A number of organizations regularly update recommendations for follow-up care, based on types of cancers. I support this kind of surveillance entirely.

I write this book about being a doctor, being a patient, getting sick, getting better, and staying healthy, and how it is possible – to one degree or another – for you and so many other cancer survivors. I am dedicated to helping you improve your capacity for regaining and maintaining your health, and for best possible health outcomes. Natural medicine cannot help every person or every complaint, but I feel sad when I hear patients say, "*Well, I'm lucky to be alive, I can live with this*." Let's face it: we're all lucky to be alive. *And* quality of life matters, as well. I want to help, without giving false hope.

I wish you the clarity of mind to take up appropriate approaches, the discipline needed to stay the course, and resilience to handle setbacks or challenges. Knowledge about your body, biochemistry, and physiology can help inform your decision-making related to both lifestyle and treatment approaches. Knowledge is power. Take this information and make it your own.

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The Lobay Viewpoint

by Douglas Lobay, BSc, ND
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Mr. Smiley and the Bioresonance Machine

Mr. Smiley was tall, slender, bespectacled gentleman with a twist of grey hair parted to one side and small, round, tea-shade glasses. He was probably close to 70 years old, and he wore an aged pale corduroy suit. His facial features were somewhat gaunt and hollow, but he had a friendly smile. He looked bookish like an accountant or librarian. He had an easygoing, honest, and soft spoken personality. He had moved from Manitoba to my small former hometown on the 49th parallel in southwestern British Columbia. He and his wife were retired. He had some digestive issues. He heard that I practiced naturopathic medicine and made an appointment to see me. He was easy to talk to and I immediately liked him.

He was interested in natural medicine and liked reading. He wanted some information. I did some testing and gave him some dietary advice. I didn't see him again until a few years later. He said he purchased a MORA Bioresonance machine from a German Biological Medicine Company for a rather large sum of money. He was experimenting with the machine to see how it improved health. He brought the machine in to show me. It looked high tech with a bright green digital display, some dials and knobs, wires and two hand-held cylinders. It made some interesting oscilloscope patterns and low to high pitched sounds when it was turned on. We tried the machine on several of my long-term patients. I wasn't really sure what it did or if it helped anybody.

Several years went by and Mr. Smiley came to see me. He said he was suffering from terminal pancreatic cancer. I tried to give him some dietary and nutritional supplementation advice that I thought might help him some. He said he was tired of taking supplements. He said he tried his MORA machine and it didn't seem to be helping him. He wanted to gift me his bioresonance machine before he passed. At least he thought I would know what to do with it. I thanked him and he left.

I was first introduced to the theory and practice of bioresonance medicine when I was a high school student contemplating what career path to take in life. I had my first encounter with a naturopathic physician when travelling with my family on a shopping trip to the Okanagan city of Kelowna. He was a large and somewhat stout man who seemed smart and knew what he was doing. He had multiple rooms set up with small green boxes called VEGA machines. The patient would hold a round, metallic cylinder in one hand connected to the machine and the doctor would press on the corner of the finger with a small, metallic pen-like stylus. He would introduce vials in a metallic honeycomb on the machine and watch and hear as the needle on the machine was deflected upward or downward. The doctor might test multiple vials of different substances. He would then make conclusions on what was wrong with the patient, what food allergy or sensitivity they might have or what they might be deficient in. It looked interesting; the doctor was professional, and he appeared to be busy.

After I graduated from naturopathic school in 1991 I purchased a used VEGA machine from this same doctor and started to use it in my practice. I tried to review the fundamentals of electric theory. I completed my electrical pre-apprenticeship training and have a rudimentary knowledge and understanding of electricity. I understand the basics about electrons, protons, and charges. I also understand about current, or flow of electricity, measured in amperage, voltage or electric pressure and resistance to flow measured in ohms. At a simplistic level the VEGA machine, or at least the one I had, is a simple galvanometer that measures the flow of current or electricity. Some parts of the human skin conduct electricity better than other areas. A metal cylinder is held in one hand to complete the circuit and a small, pen-like stylus measures the electric current in the other hand. Resistance is measured and graded by how far the needle deflects downward. Some patients have grown to expect that I use the VEGA machine when they see me to help diagnose their issues. As the years go by, I have become much more receptive of the idea that medicine is as much a science as it is an art. ➤

Lobay Viewpoint

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As the Y2K hysteria grew at the end of last century I had the good fortune to respond to a help wanted ad in our local newspaper looking for a chelation doctor to help out at a local clinic. I met Vic. He was an ostrich farmer from a small town in the North Okanagan. He had made the fortuitous, incredibly risky but remunerative venture of renting a jetliner and importing ostriches into North America from Africa at a time when nobody else was. Vic essentially took over an intravenous chelation clinic from a respected medical doctor who was ready to retire. Dr. Neal originally tried to sell the clinic, but no one was interested in buying it. The doctor was going to close the clinic and move to Mexico. In stepped Vic. Dr. Neal basically gave him the clinic and patients lock, stock and barrel to see if he could keep it afloat. Vic hired another doctor from another town to help keep the clinic going, but it didn't work out. I responded to the ad, had the proper credentials and stepped into a busy, established chelation practice. The experience was fruitful and gratifying.

The old and seemingly wise doctor had a large, industrial space-like machine called RIFE sitting in the corner of his office. It looked like an oscilloscope with dials and had a black plastic case with metal baffles and a long, tall glass cathode that protruded out of the top. There was a small, handheld terminal with wires attached to the machine that allowed you to select different programs and settings. When the machine was turned on and adjusted just right the cathode would light up a brilliant purple color, an incessant, almost irritating whir of the machine and cooling fan would occur. A specific frequency between 1 to 10,000 hertz was selected on the terminal and entered. In theory the machine would emit that same frequency to treat a specific health condition or disease for as long as the machine was turned on. You could change and select a different frequency at any time and you could even input, multiple frequencies at the same time. There was a manual that had all the different frequencies and what they were potentially good for. For instance, a specific frequency might be used to treat strep throat. Another frequency for general immune stimulation. And so forth.

I kept the RIFE machine and used it for some patients while they were getting intravenous chelation therapy like the old doctor had did. I experimented with different frequencies. I didn't charge for the treatments. Some long-term patients used to expect it with their treatments and wanted to sit close to the machine while it was on. Some patients liked it, some didn't. Some said

they felt better afterward and it helped them. Some said they had a mild headache afterward and couldn't think as clear. I couldn't say for sure if it really helped anything. All I knew was that it interfered with our cordless phone when it was on and you stood too close to it. It did something. After about ten years the machine conked out and died. I tried to contact the company that made it, but it no longer existed.

A quasi-experimental design evaluated 311 patients for allergic symptom improvement over one year with recurrent treatment by bioresonance therapy. There was a significant improvement in symptoms. However, the study was observational and subjective and was not randomized, blinded or placebo controlled.[1]

The activity level of antioxidant enzymes, including catalase, glutathione and SOD or superoxide dismutase, were measured in blood lymphocytes of patients with rheumatoid arthritis before and during bioresonance therapy. Antioxidant activity of glutathione and SOD improved while catalase showed no improvement.[2]

Bioresonance testing and therapy made no improvement in 32 children with chronic atopic dermatitis aged between 1.5 to 16.8 years old monitored over 1.5 year period. There was no difference in skin symptoms or biological markers with those treated compared to those not treated with bioresonance therapies. And the therapies provided no significant improvement when added to conventional therapies.[3]

A randomized, double-blind placebo-controlled study of 20 patients with non-organic gastrointestinal complaints was performed using bioresonance therapy. According to the physician and patients' subjective responses, there was a significant improvement in symptoms reported.[4]

Seventy-five patients with confirmed osteoarthritis of the knee joint received either standard pharmacological and physiotherapy alone or with the addition of bioresonance therapy. Those patients that received standard therapy along with bioresonance therapy showed statistically more improvement that lasted longer compared to regular therapy. Bioresonance therapy was well tolerated and showed no side effects.[5]

A study evaluated 140 patients with clinical depression and offered one of three therapies: pharmacological therapy, pharmacological therapy plus bioresonance therapy and bioresonance therapy alone. The study showed that bioresonance therapy offered a significant improvement in recovery from depression with or without pharmacological therapy.[6]

A double-blind placebo-controlled study evaluated 190 patients who smoked into one of two groups. There was a significant reduction in the group treated with bioresonance therapy compared to placebo at one week, one month, and one year following treatment.[7]

VEGA electrodermal testing is limited and misaligned as to what it actually represents. Measuring electric resistance to a potential allergen does not constitute a true allergic reaction by biological standards. A true allergy is an immunological reaction involving different white blood cells and antibody levels. At best a VEGA reaction represents a "sensitivity."[8]

A small randomized double-blind study of 30 volunteers were evaluated by VEGA electrodermal testing for known existing positive allergies. The VEGA results could not accurately distinguish those with previous positive allergies with those who didn't.[9]

Some studies show that ALS or amyotrophic lateral sclerosis may be caused by retroviruses. There is no evidence that using a RIFE machine or any of the frequencies recommended produces any improvement.[10]

My experience with bioresonance machines in clinical practice has been limited to specific MORA, VEGA and RIFE machines that I have been exposed to. The people that introduced me to the machines have been just as unique and varied as the machines themselves. I have experimented with the machines over my years in clinical practice as a naturopathic physician. I cannot reliably say that the machines work or don't work. I cannot say for sure if the machines are beneficial or they just fail to live up to their hype. The left side of my brain tells me that they are unproven and unscientific. The science behind the machines is still largely dodgy and sketchy. A quick search of medical databases like PubMed reveals only a small handful of scientific studies. The studies are generally small and lower quality. Some studies are negative and yet some are positive and show some statistical benefits. Obviously, more high-quality studies, reviews and meta-analyses would be preferred before a final conclusion can be made. Being in naturopathic medicine has been a blessing and a curse of sorts. It has afforded me the opportunity to say "what if " and "just maybe." And just maybe there is more to this story….

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Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, MSW
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Using the Homeopathic Miasms to Make Sense of Our Crazy World

Finding the Right Remedy for You: Kingdom, Family, Miasm

The sheer number of homeopathic remedies is mind-boggling: over 8000 and growing! Just think: *any* substance in nature can be prepared and prescribed as a homeopathic medicine! Compare this to the number of antibiotics, antifungals, or corticosteroids. This specificity, corresponding to the uniqueness of each patient, is astounding. When a patient clearly fits a remedy, it is still exciting after almost forty years in practice because I feel reasonably certain that the remedy will have a profound effect on the patient as a whole.

The challenge is to find that one remedy for the individual. I have written often of the kingdoms (mineral, animal, and plant), as a way to narrow the range of possible remedies in order to find the *simillium* (the one best remedy, or ideal match). There are a variety of schema that help the homeopath find that remedy. The one I continue to find most helpful is the *Sensation Method* of Dr. Rajan Sankaran, but I greatly respect other teachers, especially Jeremy Sherr, Massimo Mangialavori, Jan Scholten, and Michal Yakir. An invaluable complement to the classification of kingdoms is the concept of miasms. I have written occasionally about miasms but never in the context of understanding what is going on in our world. Samuel Hahnemann, the illustrious physician who founded homeopathy, observed that, even if the correct remedy relieved a patient's symptoms, the tendency, in some cases, was to become ill again. Why did this occur and how could it be addressed?

That is how Hahnemann's concept of *miasms* came to be. A miasm, literally, is swamp air... an unhealthy vapor or atmosphere. In other words: a predisposition to a particular disease which interferes with treatment and healing. Hahnemann introduced three main miasms: *psora*, *sycosis*, and *syphilis*. This concept was originally introduced by Hahnemann in his book, *The Chronic Diseases*, published in 1928. Originally, it was postulated that 85% of disease was due to psora (literally "the itch). The remaining 15% were said to be either syphilitic or sycotic.

During my study at *Bastyr University* (then called *John Bastyr College of Naturopathic Medicine*), I never really knew much about how to apply the miasms. Bob and I once sat in with Dr. Proceso Sánchez Ortega, famous for his studies of miasms, in Mexico City. His method was to list every symptom in the case and then to add them up to see which miasm was predominant. It wasn't until 1993, when I studied with Dr. Rajan Sankaran in Mumbai that I began to grasp how to actually apply the concept of miasms clinically. Since that time, I have found them to be immensely helpful in finding patients' remedies and understanding their dynamics.

In brief, the following are the miasms, and a brief explanation of each. I have referred to them often in articles and teaching but never actually written about using them to understand our world situation. The two sources, out of countless, that I use here are Rajan Sankaran's and *Schema* and *Miasms of the New Millennium* by Nancy Herrick and Roger Morrison (quite a *magnum opus* on the subject). In brief, from the least serious and entrenched, to the most.

1. *Acute* (Rabies) miasm (introduced by Hahnemann)
2. *Typhoid* miasm (Sankaran)
3. *Malarial* miasm (Sankaran)
4. *Ringworm* miasm (Sankaran)
5. *Psoric* miasm (Hahnemann)
6. *Sycotic* miasm (Hahnemann)
7. *Cancer* miasm (Foubister)
8. *Tubercular* miasm (Vithoulkas)
9. *Leprosy* miasm (Vakil)
10. *Syphilitic* miasm (Hahnemann)

Why was it necessary to introduce more miasms? Because they were archaic and not very helpful clinically much of the time; in fact, they were often ignored, and the remedy based exclusively on *materia medica*. So, Dr. Sankaran and his colleagues organized nearly 250 remedies to specific miasms. We are talking about 250 remedies, initially, out of a pool, now, of over 8000. But that work opened a door for me, and for many other homeopaths, to integrating miasms into our clinical prescribing. I have since found this to be invaluable in selecting remedies for many patients, especially adults.

Again, the reason for miasms, when originally introduced by Dr. Hahnemann, was to address deep, persistent, underlying predispositions, which, despite the prescription of a homeopathic remedy that matched the individual's symptoms well, the person would become ill again. The tendency remained.

A Basic Description of These Miasms

Acute: Think first of acute illnesses, especially serious or life-threatening ones such as scarlet fever or pneumonia. We are talking about being on the edge of life or death. Such a condition is often sudden and unexpected. I remember when my husband, Bob, had scheduled a 50th birthday party just after we returned from teaching in Boulder. He awoke that Saturday morning feeling exhausted, not himself. We canceled the event, though one unfortunate friend didn't get the message and showed up at the door, only to be given the news that Bob might be contagious. I woke Sunday morning very early to find bright red blood in the bathroom sink. We raced off island to an ER, to be told by the on-staff doc that he had severe bacterial pneumonia and would likely not have lasted even another five hours! But the acute miasm applies not only to those suffering such a life-or-death acute illness, but also individuals who feel as if they are. It might be a fight or flight state, mania, or a severe phobia in which one feels one's very existence is under threat.

Typhoid: Few of us have suffered from typhoid unless we happened to travel to Africa, Asia, Eastern Europe, or Latin America. In fact, I remember it being one of the few travel vaccinations that we received prior to travel to the Amazon. Typhoid is characterized by a high fever along with being bedridden from violent diarrhea. The situation is not as immediately life-threatening as the acute miasm, yet the situation is still urgent and death, though not imminent, is certainly possible. The feeling of the individual is: I will do anything to get through this crisis and, once I do, I can rest. Pathologies belonging to the typhoid miasm are colitis, Crohn's disease, and states of collapse.

Malarial: In the malarial miasm, the patient suffers but there is no imminent threat to one's life. One can think of malaria where the symptoms, such as fever, may recur every 72 hours. The suffering is characterized by intermittent attack leaving one feeling weak, vulnerable, and dependent. The individual feels unfortunate, harassed, stuck, and generally miserable. Other pathologies belonging to the malarial miasm include recurring hemorrhoids, migraines, asthma, or rheumatic pain.

Ringworm: Ringworm and other fungal conditions are not life-threatening, but they are extremely annoying and may require a constant effort to keep them at bay. The feeling of the patient is to try, try, and try again to find a solution. Think of nail fungus, where individuals are forever trying to find something that works, resorting to one medication after another. Or patients with whatever condition who go from one practitioner to the next or one treatment after another, never giving up hope that a cure or relief will be found.

Psoric: The feeling is one of struggle against an external problem but with a feeling of optimism. In the Sankaran system, this category is not nearly as common as the other miasms.

Sycotic If you think of gonorrhea, which is the primary condition in this miasm, the feeling is one of shame, embarrassment, and covering up. There is a feeling of chronicity; that the problem cannot be overcome but, instead, must be accepted. Genital herpes is a perfect example, where one may suffer recurrences lifelong and runs the perpetual risk of passing the condition on to one's sexual partner. The desire to hid may be literal, such as hiding the eruption or disfigurement, or a feeling of inferiority or shame on a more inward level. Besides STDs, asthma, eczema, and cancer can belong to this miasm.

Cancer: I dedicated an article to the cancer miasm years ago, referring to "the stain of perfectionism." The individual feels (s)he must do everything perfectly, thoroughly, flawlessly in order to maintain control. One feels pushed to, and beyond, one's limit to keep one's health, family, life under control. Mistakes and chaos are intolerable. Pathologies include cancer and neurological disorders, including multiple sclerosis.

Tubercular: This miasm invokes the feeling of "run for your life," or "burning the candle at both ends." So much to do, so many places to go, so many people to meet... and so little time. There is a tremendous feeling of frantic hurry. Most common are respiratory conditions, classically TB, arthritis with deformation, and a psychiatric feeling of being persecuted.

Leprosy: Individuals belonging to this miasm will use words such as "shunned" or "reviled." They feel loathed by others, resulting in self-hatred and disgust. Think of a terribly disfiguring skin condition or mannerism. The individual may feel depressed to the point of harboring suicidal thoughts, and self-mutilation and suicidal ideation are common.

Syphilitic: This is the final miasm in the progression, and the most desperate. Prior to antibiotics, syphilis carried a death sentence, resulting in physical or mental destruction. Pathologies involve destruction of the bones, heart, and nervous system, leading ultimately to death. Violent thoughts, suicidal ideation, and destructiveness, such as through addictions, including alcoholism, are common.

How to Use Miasms in Thinking About Our World Today

As synchronicity would have it, I had signed up to attend a virtual homeopathic webinar by some of my favorite Canadian colleagues, Sunil Anand and Roland Guenther, on "Collective Catastrophes and Transgenerational Trauma." They presented,

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deeply and articulately, some of the same points I wanted to cover here, including the application of miasms to treating patients suffering from our societal maladies. Many of us, worldwide, are trying to make sense of what often seems to be chaos bordering on insanity. As with individual patients, once we identify the miasm, along with the kingdom (usually animal, plant, or mineral), then we can narrow the likely remedies considerably. Here are some examples of a few of the miasmatic themes that I see at play during this time. I present them in hopes of diminishing, at least a bit, what I find to be global confusion, bewilderment, divisiveness, separation, and despair.

Acute Miasm: "*Any moment could be my last. I am just trying to survive.*"

Hunger. Over 800 million adults and children worldwide go hungry – not only in Sierra Leone, Haiti, Liberia, Democratic Republic of Congo, Yemen, Somalia. Ninety years ago, Joseph Stalin's Soviet regime inflicted a devastating famine on Ukraine, killing nearly four million people. It was known as genocide by hunger, the *Holodomor.* This appears to be happening yet again. The USDA estimates that over 38 million people, including 12 million children, in the US are food insecure.

Homelessness. Globally over 1.5 billion people live in inadequate housing condition, and it is on the rise. Here in Seattle, one only needs to drive to the downtown REI, after passing the myriad of tents under the nearby bridge, or visit Ravenna Park, Pioneer Square, or the University District. All of these, in the past, were safe, charming, lovely. And this tragic circumstance is in the stomping grounds of Amazon, Microsoft, and Starbuck's. Our charming town of Langley on Whidbey Island in Washington has such a severe housing crisis that providers of basic services can no longer afford to live here.

Suicide. Even in our small town of Langley, Washington, two beloved members of the community took their own lives within the past year and a half. Not to mention many more in profound despair due to the isolation of the pandemic, being trapped in homes or apartments during lockdowns, feeling far from those near and dear, or having no one.

Ongoing panic and terror associated with Covid. Be it an ongoing terror of contagion, of running the risk of catching Covid by association with friends, family, community, or the panic of being forced to be vaccinated.

Threat of injury or murder. As hunger and scarcity rise, so do theft, murder, and uncertainty about safety, possessions. livelihood. In Ukraine we are talking about not knowing when the next bomb or sniper will destroy one's home, family, life – whether one's home will still be standing and safe the next hour or day. The reality of living moment to moment, not knowing whether one will see the male relatives left behind. Of grabbing a pet crate or carrying a dog or cat in one's arms, and of setting out on a journey to another country, leaving behind life as one knew it. In the US, of not knowing when your children might be the victims of another school or mall mass murder. When Bob and I wrote *Rage Free Kids*, just after the Columbine school shooting, we had no idea it would be only the beginning of countless, senseless mass shootings, the most recent, in Buffalo, just last week. Think about sending your kids to school, going to work or to worship yourself, or being pulled over by a law enforcement agent: for many parents this alone invokes the acute miasm.

Typhoid Miasm. *"I will do whatever is needed to get through the crisis. Then I can rest."*

Health Care Workers During the Pandemic and in War-Torn Settings. Think of the ER and ICU workers at the height of the Covid pandemic. The photos we all saw of beyond-exhausted medical care teams catching some sleep on a bench, on the floor. Bruised faces from hours after hour of masking and protective gear. The medical personnel who faced screaming by family members who were not satisfied with their care.

Postal Service Workers. One of my long-time patients has worked for USPS for nearly forty years. Previously, she loved her job. It involved lots of walking, she finished by 3PM each day, and she counted her blessings to be paid well and have a secure retirement. Then came Amazon deliveries through the postal service. Now, at 3PM, having delivered all the mail in her truck, she had to deliver another truckload of Amazon packages, and worked feverishly until 7PM. She was the fourth postal employee in her post office to turn in her resignation over a short period of time. The postal clerk, beside herself, could only reply, "Oh, no, not you, too!" Pushing, pushing, pushing, in hopes of a rest that doesn't come. We live in town of 1000 residents on Whidbey Island, and the same is true. The beleaguered postal workers are there seven days a week, rain or shine, on the verge of exhaustion, hold back tears or rage.

Other Service Workers. Our community is very ecological, treasuring its recycling centers. Having returned recently from six months in Chile, where recycling is hit and miss, to say the least, I was quite happy to be back to a place where folks eagerly line up to dump their recyclables. I happened to ask the attendant what it had been like for her during the height of the pandemic. She looked as if she would break into tears and shared how she had been spat on, sworn at, and sprayed with vinegar by locals who were terrified that they might catch the virus from her. She was still hanging in there, out of desperation no doubt.

Syphilitic Miasm. The syphilitic miasm is about end-stage destruction, decay, despair, devastation, violence, murder, and death. The mere image of victims' noses falling off, a deformity resulting from the destruction of the bony framework, makes one shudder. Think of anarchy, suicide bombers, nuclear war. Having babies in bomb shelters or missiles being fired on a maternity hospital. The moment-to-moment life-threatening work conditions of journalists in war zones internationally, such as the Palestinian, Shireen Abu Akleh, as she shouted for aid to save the life of a colleague. The utter, senseless destruction of humans, animals, habitats for the sake of resources, power grabs, and pure selfishness. The breakdown and wanton desecration of bodies, families, homes, hospitals.

War is nothing new in our lifetimes. As much as we might hope that the genocide and mass destruction of WW2 might

have taught us "never again," that is far from what has happened.

Ukraine. The world is now riveted on the current battle for Ukraine which is only too real and immediate thanks to the social media and the intimate, up-to-the-moment world wide web. Vladimir Putin, for one, seems to be the epitome of the syphilitic miasm: poisoning or imprisoning enemies, sending 19-year-old Russian soldiers to die in a foreign land for no apparent reason except for power. I recently learned a bit about the chilling history of Putin's family. During the Siege of Leningrad, Putin's brother died of diphtheria and his parents only later learned where he, along with half a million other victims of the siege were buried. Putin himself shared the story of his mother's remarkable salvation. Returning from the hospital, Putin's father saw corpses being carried out on stretchers to be buried in a mass grave. He recognized his wife, Putin's mother, injured but alive, on her way to being buried in a mass grave. Striking out with his crutches, he made them carry her back to their apartment. There he nursed her back to health, only to give birth, sometime later, to their son, Vladimir. Previous to that time, five of his six brothers had perished in battle, as well as some of his mother's relatives. This is the ongoing generational terrain of the syphilitic miasm.

The Destruction of Sea and Land Habitat Worldwide. The Amazon rain forest is a prime example of this unconscionable selfish land rape. We had the good fortune to visit the indigenous Huaorani tribe of Ecuador some years ago. They were the victims of extraction and logging by Royal Dutch Shell, then Texaco. The deforestation, illegal hunting, and collection of animals and their parts for food, Chinese medicine, and pet trade have pushed many species to the brink of extinction. This is the same message of the recent films *Seaspiracy* and *Becoming Cousteau*.

Deaths Due to Covid Worldwide. The number of reported deaths worldwide are 522 million, of which over 6 million have been reported in the US, 43 million in India, and 31 million in Brazil. I have no desire to engage in a discussion of accuracy of reporting, but rather to point out the enormous destruction/loss of life during this time, not to mention of livelihood.

Decay and Despair on Individuals, Families, Social Systems During the Pandemic. Regardless of personal beliefs about CV diagnosis, mass vaccinations, lockdowns, the effect on the social fabric worldwide has been devastating, individually, culturally, societally.

How to Use This Information

Miasms are a fascinating, practical concept in homeopathy to understand patients, societies, processes, and to narrow the field of the eight thousand-plus homeopathic remedies now available. We have Dr. Samuel Hahnemann to thank for adding this dimension to homeopathic philosophy and practice during his lifetime and to Rajan Sankaran and others, mentioned above, to elaborate on, expand, and categorize remedies in this way. I hope that this material can provide yet another useful framework for homeopaths and others to make sense of what often seems to be a senseless world.

Postscript

Just a day or two after finishing this article, appalled by the senseless murders at Uvalde and Buffalo, on top of the murderous war in Ukraine, I was struck yet again by the syphilitic abyss of our current world situation. I received a Clinician Alert, at the same time, from the Snohomish, Washington Health District informing me that syphilis transmission is on the rise.

> Syphilis transmission was nearly eliminated in Washington State in the miid-1990s following population-level behavioral changes elicited by the response to the human immunodeficiency virus.... Rates of syphilis among cisgender women and among heterosexual men in Washington State have been rising since 2015, even more so during 2010-2021.... The 2021 rate of total syphilis among cisgender women in Washington was nearly double that observed in 2020 and more than 8 times higher than in 2012.... A record 51 cases of congenital syphilis were reported in 2021 (versus 3 cases in 2019 and 10 in 2020).

A coincidence? I don't think so.

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Curmudgeon's Corner

by Jacob Schor, ND, FABNO
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Complete Freund Adjuvant

A new study from Aude Fahrer and her Australian colleagues deserves our attention, not so much that the suggested treatment must be adopted immediately but because we may wish to in the future and even if we don't others will. This study reports on a series of trials conducted using a suspension of dead mycobacteria emulsified with mineral oil, which was injected directly into cancer tumors. A simple technique that costs next to nothing nevertheless seems to work.[1]

This current report is the follow up to a March 2012 essay Fahrer wrote that was published in *Immunology and Cell Biology*.[2] Reading that paper is necessary to understand these current results. Fahrer proposed treating cancer with a combination of older pragmatic strategies that seemed to work. Recent advances in the understanding how dendritic cells function and how they trigger or silence T-cell responses led her to reconsider these therapies as now they can be explained. Her ideas drew directly from William Coley's century-old attempts to fight cancer using bacterial toxins. Instead of Coley's toxins, she proposed using the mixture of dead bacteria known as Complete Freund's Adjuvant and injecting it directly into tumors rather than giving it by IV.

Cytotoxic T-cells can kill cancer cells directly. But as Fahrer explained, in order to do this, "…they must be primed (that is, initially activated and expanded) by dendritic cells. The function of dendritic cells is to continuously sample the proteins in a tissue (for example, those from cancerous cells or from infectious microbes) and then carry these proteins back to lymph nodes where they can be shown to T cells. Activated dendritic cells can prime T cells specific for the proteins they display. Once activated and expanded, cytotoxic T cells then return to the tissues to kill any other cell (in this case, cancer cells or infected cells), displaying the same protein…." In dendritic cells, the default setting is to turn off immune responses rather than to prime them. Most of the proteins that dendritic cells move to the lymph nodes and present to T cells come from normal cells and it would be a problem if the dendritic cells were activated. Nonactivated dendritic cells turn off T cells preventing autoimmune disease against such normal proteins. The Toll-like receptors on the dendritic cells recognize microbial products like cell membrane materials or bacterial DNA or viral nucleic acids and see them as danger signals.[3] Microbes or their remnants will activate dendritic cells getting them to prime an immune response.

Jules Freund first described his immune stimulating microbial cocktail in 1956, which was eventually named after him, Complete Freund's Adjuvant (CFA).[4] Immunologists have used this compound as a method to trigger immune responses in animal experiments for the half century since. CFA consists of heat-killed mycobacterium bacteria (usually *M. tuberculosis*) emulsified in mineral oil. Accustomed as we are to using high-tech nano-emulsions, it is refreshing to read that these emulsions are made just prior to injection by repeatedly drawing the mixture in and out of the dispensing vial into the syringe until the mixture thickens as it becomes emulsified. The injection creates a localized deposit of dead bacteria that slowly releases over a period of weeks to months. Immune cells are activated and drawn to the injection site in the tumor.

In her 2012 paper, Fahrer suggested that Complete Freund Adjuvant be emulsified with saline and then injected directly into tumors in order to activate the dendritic cells. These dendritic cells will have already sampled tumor proteins and priming them with the adjuvant would get them to present the tumor proteins to T cells and Fahrer predicted that this would trigger a potent anti-cancer T-cell response.

There is a parallel strategy already being used in cancer treatment known as 'personalized dendritic cell vaccines.' A patient's dendritic cells are isolated and grown in vitro, loaded with cancer proteins, activated and then reinjected. This is a labor intensive and expensive procedure. "It takes about one to three months to make that personal vaccine. And it is expensive – it is probably going to cost about $100,000 for each person to make that vaccine...."[5]

In contrast activating dendritic cells *in situ* as Fahrer proposed is simple and cheap, about $20 for the ingredients and a single injection. We've talked for years about how spontaneous (think Saint Peregrine) infections or induced infections (think Coley's toxins) can lead to tumor regression.[6] Fahrer reminded her readers that "… our much 'cleaner' modern society, with aseptic surgery, and with the widespread use of antibiotics to treat bacterial infections – while evidently leading to a dramatic

decrease in serious disease and death from bacterial diseases – has also led to a dramatic reduction in the rate of spontaneous cancer remissions."

Fahrer's proposed technique reminds us of protocols used by William Coley who initially injected a mixture of heat-killed *Streptococcus pyogenes* and *Serratia marcescens* into tumors. Coley's success rates in treating cancer were so good, they are still hard to believe. Five-year survival rates for patients treated with Coley's toxin were 43% for inoperable cancers (including carcinomas, melanomas and sarcomas) and 61% for operable cancers.[7] The five-year survival rate for inoperable sarcomas was 52%, with 21% of patients remaining disease free for at least 20 years.[8] Keep in mind that Coley's procedure was intensive. Coley's patients received daily injections or every other day for months on end. He initially injected the toxins directly into tumors in 1898, but by 1915 had shifted to intramuscular, and then intravenous injections.[9]

Fahrer proposed using CFA instead of Coley's toxin. As mentioned, CFA is made from heat-killed mycobacteria. We are familiar with BCG as a cancer treatment, which is made from live *Bacille Calmette-Guerin*, another *Mycobacterium bovis* strain. For BCG to have an anticancer effect, it either needs intimate contact between the BCG and the tumor cells or the tumor and the BCG have to drain into the same regional lymph node drainage. Fahrer assumes that if live BCG is safe to use, dead CFA will be safer.

Another advantage of CFA over BCG is that the oil emulsion continues to act for weeks and often requires only a single injection; a single dose of CFA injected into a tumor should work as well as repeated doses of Coley's toxins.

In August 2021, Fahrer's group summarized their ongoing research in the *Journal for Immunotherapy of Cancer*. They have now tested CFA injections against three types of cancer in mice (breast, colorectal and mastocytoma), dogs (mastocytoma), and horses (melanoma).

Mice were injected with cell lines of rapidly growing cancers to produce tumors. CFA injections were helpful for the mice against mastocytoma and breast cancer but did not have a statistically significant effect against colorectal cancer. Mice given mastocytoma who were treated lived significantly longer than the control mice, 14 days vs. 10 days. Mice injected with breast cancer also survived significantly longer, 20 days vs. 17.5 days. In the colorectal cancer, the survival difference between CFA and placebo did not achieve significance, 14 vs. 13 days. Six of the 186 treated mice, about 3%, with mastocytoma had complete tumor regression and survived for up to two years without recurrence.

These mice studies were followed by a clinical trial treating naturally occurring mastocytoma in dogs. This cancer is common in dogs who will have a median survival of less than four months. Of 14 dogs treated with a single CFA injection, three showed complete regression of their tumors and two other dogs lived substantially longer than predicted.

A third animal trial involved gray horses. These horses are genetically highly susceptible to developing melanoma and more than 70% will get it. Eleven horses with melanoma were treated with CFA injections. Three of the horses showed clinical responses that included remission and reduction in mass size.

Fahrer and colleagues report that intratumor CFA injections have been tried on about a dozen human patients in cancer clinics in Switzerland and Australia after prior treatments had failed. Several of these patients experienced seemingly favorable responses; the most notable was a patient with metastatic renal cell cancer. Images of his retreating tumors are included in the current report.

All of the models used in these experiments have an inherent weakness. Fahrer clearly states that it takes a minimum of two to four weeks for the immune system to mount a significant response after CFA injections. The experimental animals, as well as the humans, in these trials, had such advanced terminal cancers that there was inadequate time to see an immune response take effect. Consider that the control mice with mastocytoma only survived ten days. Histology samples showed early signs of systemic immune responses against the cancer and these were positively associated with tumor regression.

It would make sense to consider CFA injections as a first line or early therapy rather than a last-ditch attempt after all other therapies have failed as was the case in the human subjects included. Multiple failed prior treatments likely left the immune response to adjuvant stimulation hampered. For CFA to work well, we would want a robust and healthy immune system. For example, with breast cancer, we might want to initiate CFA therapy immediately after an initial biopsy comes back positive.

CFA injections are probably outside the scope of most naturopathic doctors, though I admit to not being a legal expert on such matters. The human research is premature to encourage use. This probably won't stop some patients or their providers from wanting to try this, even as a last-ditch attempt.

Fahrer's proposed use of CFA is attractive in part because it is so congruent with naturopathic principles of treatment. The technique stimulates the inherent healing properties of the body, triggering the body's immune system to act by employing a natural agent.

To use Fahrer's words, this "could be a game changer. If this works well, it will be a new treatment option with far fewer side effects, which will be available for cancer patients…." She goes on, describing CFA's potential as a, "a game-changing low-cost and non-toxic treatment could offer people battling cancer a new alternative to chemotherapy."[10] "The best things about this new treatment is that it requires few doses, is simple to administer, and has low side effects," but the real advantage and also its problem is cost.

As mentioned, the entire course of CFA treatment could cost as little as $20. In comparison, Keytruda (pembrolizumab), the popular immunotherapy drug, sells for about $10,000 per dose and is given at three- or six-week intervals for up to two years.

To paraphrase Willie Sutton, "go where the money is." There is money to be made with the status quo and no profit in this new therapy, even if proven highly effective.

Yet not everyone in the world can afford modern cancer treatment. An estimated 1.3 billion people in the world live in severe poverty, defined as less than $2/day.[11]

Years may be spent debating whether a $20 shot is more or less efficacious than $100,000 personalized treatments that might work better, but the poor of the world have no choice and CFA could become a common treatment based only on low cost and simplicity of administration. This alone is reason why we should be aware of Fahrer's technique and her ongoing research.

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Sleep: A to ZZZs

by Catherine Darley, ND
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Providing Shift Workers Sleep and Preventive Health

As 24/7 operations become further embedded in our culture, this lifestyle becomes more accepted and unquestioned by business decision makers. The individuals who work all night are most affected, and some of them are our patients. Shift workers have distinct health risks that require additional monitoring, plus some shift workers develop shift work disorder. We will start with discussion of those additional health risks, including cancer, and then discuss how to help shift workers get the sleep they need.

About 20% of Americans do shift work. Although there are several definitions, the most useful relate the work schedule to the individual, with the definition of shift work as "work or commute to work that interferes with the person's natural sleep hours." With this definition, the schedule that would be shift work for one person is not shift work for another. As people age their circadian rhythm tends to shift earlier,[1] so what was not shift work for a younger person may become shift work as they age. Morning types are less able to tolerate shift work. Those shift workers who don't develop a disorder have a delayed melatonin pattern, while those who develop shift work disorder have a melatonin pattern similar to people on a day schedule.[2]

Shift workers have increased health risks in many domains, including cardiovascular disease, reproduction, digestive complaints, and cancer, among others. Periodontal disease odds increase by more than twice.[3] Depression risk increases by 42%.[4] In night shift workers thyroid stimulating hormone (TSH) is found to be increased, although the data on thyroid disease rates is inconclusive.[5] Age related macular degeneration is found to be increased in male shift workers, though not in women.[6] Night shift workers have greater odds of developing type 2 diabetes, and their risk increases with more night shifts worked per month.[7] The risk of developing cardiovascular disease is 17% more in night workers versus day workers, and the risk increases 7% every five years.[8] Asthma risk is also increased, as is having reduced lung function.[9] Shift workers are also prone to increased accidents and errors on the job.

Cancer is one of the concerning risks of shift work. There are multiple types of cancer associated with night shift work, notably breast and esophageal cancer, and melanoma. Basal cell carcinoma and liver cancer risk decreases, and the data on prostate cancer is mixed.[10-12]

The pathophysiology of the shift work–cancer relationship is still being elucidated. In 2019 the International Agency for Research on Cancer stated that "night shift is a probable carcinogen (Group 2A)."[13] A key piece is likely the reduction in melatonin found in shift workers. Along with its role in circadian rhythms, melatonin has many actions throughout the body, including as an antioxidant, anti-inflammatory, immune modulating, hormone regulation, and is anti-proliferative in *in vitro* studies.[14] In estrogen positive breast cancer, melatonin can alter the concentration of estrogen receptors.[15] All this gives melatonin a protective role for our cells. Other changes with shift work that could promote cancer are changes to the telomere length, hormone timing and total production, and insulin receptor substrates.[16-18]

Shift work disorder (ICD G47.26) is a type of circadian rhythm sleep-wake disorder.[19] It can be diagnosed when these criteria are met: a) a complaint of poor sleep and/or excessive

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sleepiness with a reduction in total sleep, b) present for three months or more and concordant with shift work, c) sleep diary or actigraphy shows a disrupted sleep pattern, and d) not better explained by another sleep, medical or mental disorder, poor sleep hygiene, or substance. Not every person who does shift work will necessarily have shift work disorder.

A key problem for shift workers' sleep and alertness is that their core body temperature minimum usually remains at the normal time for humans, which is in the night, about 3 hours before natural waking. When core body temperature is at its minimum, we are the most sleepy, perform the worse, and have the least motivation. This makes it difficult to work well during the night as well as difficult to sleep soundly during the day.

A strategy developed in 2012 by Smith and Eastman[20] has worked well in my office. With this strategy, the core body temperature minimum is shifted into the daytime sleep period, which improves both daytime sleep and nocturnal alertness. There are several steps (see graphic). First, determine with a patient a core block of three to four hours that they will always sleep, regardless of whether it is a workday or a free day. For instance, a nurse working 7 pm to 7 am may decide her core sleep block will be 8 am to noon every day of the week. The second step is to schedule adequate sleep around that core block. Our nurse can plan to sleep 8 am to 4 pm on workdays, and 4 am to noon on free days. The next component is to intentionally design light and dark exposure so as to promote melatonin production during sleep, and nocturnal alertness. Pulses of bright light for 15 minutes every hour or two during the night will increase alertness. Then create dark by wearing blue-light blocking goggles from the time the shift worker clocks out (before they leave the building), until they are in their darkened bedroom ready to sleep. In the two hours after waking get 20 to 30 minutes of bright light, preferably outdoors, to signal the beginning of their day.

Additionally, shift workers can use melatonin in two different ways to promote sleep. On free days, when they wish to sleep at 4 am, use low dose 0.3 mg of melatonin six hours beforehand to shift their body clock earlier. With this low dose the patient should not feel acutely sleepy. However, do have them take it the first few nights when they are safely at home and can observe whether they do get sleepy. If so, discontinue or maintain only on days that they are home and not at risk of accidents. The second way for shift workers to use melatonin is a 3 mg dose at bedtime on workdays. In our example, the patient would take 3 mg at 8 am.

Some shift workers have parenting or other responsibilities during the day that interfere with sleep. In these cases, help create as reliable a sleep schedule as possible. If necessary, extend sleep on free days, although with the knowledge that insufficient sleep for a night impairs performance. The melatonin phase response curve can be used to determine the right timing of melatonin in these cases.[21]

Optimize the bedroom for daytime sleep by making it very dark, so dark your patient can't see their hand when held at arm's distance. Light blocking shades can be used on the

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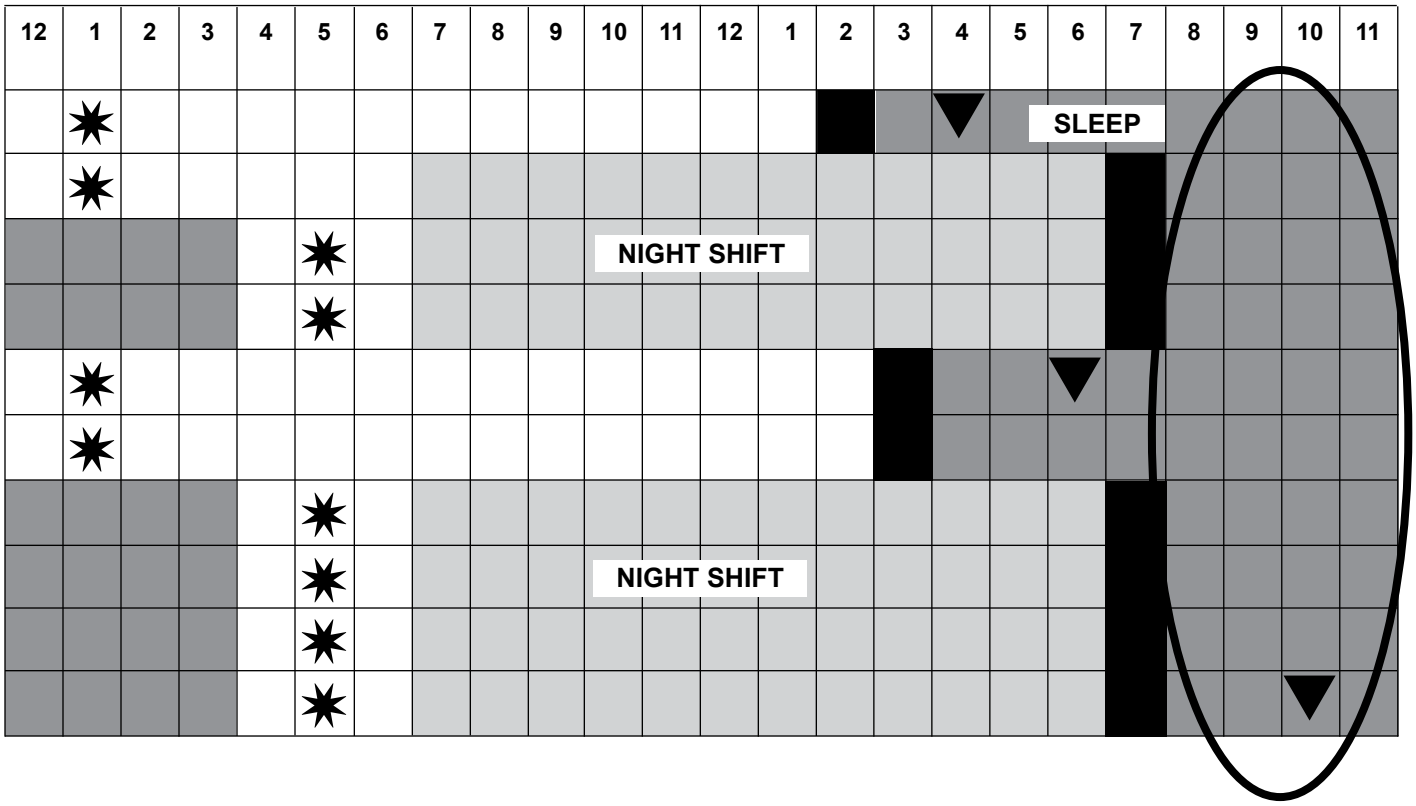
Healthy Shift-worker Sleep Pattern

Smith MR and Eastman CI. *Nature and Science of Sleep* 2012;4:111-132



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window, with an additional curtain over it that Velcros to the outer edge of the window frame. To block sounds from the home or neighborhood a white noise machine or fan can be helpful, as can earplugs. Pediatric-sized earplugs or customized silicone earplugs can be more comfortable. The temperature of the bedroom should be cool, cooler than 65 degrees if possible. Keeping cool enough for daytime sleep can be tricky, there are also cooling fabrics and mattress toppers available. The bedroom door should be shut, both to prevent interruptions and for fire safety.

The strategic use of caffeine for alertness may be useful. Taking it in the first half of the shift so that it is in effect during the lull in alertness, but yet is waning by the end of the night shift, can increase subjective alertness. Modafinil (200 mg) and Armodafinil (150 mg) are both FDA approved to improve nocturnal alertness for shift workers.[22] Note that although they improved alertness, objectively measured sleepiness was still pronounced. The most common side effect of these medications is headache, followed by anxiety, dizziness, and nausea.

People are social creatures. It can be emotionally difficult to need to sleep while others are awake, and to be awake when the world is asleep. To improve success with this plan it is helpful to first brainstorm with your patient activities they can happily do in those late hours when the rest of the household is asleep. Some activities could be exercise, online or in person shopping, studying or reading, paperwork, watching movies, housework. Then also discuss what they want to be sure to prioritize on the days that they are up at noon – outdoor recreation, seeing friends and family, and appointments that can only be done during business hours. Another challenge to shift workers' sleep is a family dynamic that often develops in which the family feel they don't get enough attention from the shift worker, while the shift worker doesn't feel that their sleep time is respected. Having a facilitated conversation that sets reliable times that the shift worker will be available for family and distinct sleep hours that will be respected can often improve the family dynamic. Planning ways to overcome these barriers in advance will make the plan much more successful.

So, for our shift workers, address both their immediate sleep needs and long-term increased health risks. Use the above strategy to move their core body temperature minimum into the daytime sleep period, which will improve both sleep and nocturnal alertness on the job. Then continue to monitor and prioritize preventive care for those increased health risks in terms of cardiovascular, reproductive, mental health, and cancer.

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Women's Health Update

by Tori Hudson, ND
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The Potential Role of Vaginal Microbiota and the Contraction of and Persistence of Humanpapilloma Virus (HPV)

Sexually transmitted infections (STIs) are among the most frequent infectious diseases throughout the world and are defined as infectious organisms that are transmitted between sex partners. According to the Centers for Disease Control (CDC), about 19 million cases are reported each year with more than 20 different STIs.[1] HPV is one of the most frequent causes of STIs in women worldwide with more than 200 different HPV genotypes that are generally classified into high and low risk groups, which is based on their potential risk of causing cancer. About 99% of all cervical malignancies are one or more of the following HPV high risk types (16,18,31,35,39,45,51,52,56, 58,59). High risk types also play a role in other cancers, including anal, oropharyngeal, vulvar, vaginal and penile.

HPV is easily transmitted from one person to another via skin and mucus membranes and while relatively common, the majority are subclinical and temporary due to suppression and clearance by an immunocompetent immune system. Cervical cytology and HPV tests are widely used for cervical cancer screening in countries that have easy access for people, and thus early detection is considered a key aspect of cervical cancer protection in particular.

The human microbiome is the sum of microorganisms that may reside in various parts of the human body, their genetic information and how they interact with the environment of the host. While we now have a significant amount of data mapping of microbiota in several sites of the human body, especially the gut, there is emerging evidence that the vaginal microbiota may play a key role in HPV carcinogenesis[2] and is related to protection against dysbiosis as well as HPV infection.[3,4]

In healthy reproductive-aged women, vaginal pH is primarily determined by lactic acid producing bacteria primarily lactobacillus species. If lactobacilli do not dominate the vaginal microbiota, a woman's anti-bacterial defensive mechanisms are compromised.[5] Alterations in vaginal microbiota and respective changes in vaginal pH are associated with bacterial vaginosis, *Chlamydia trachomatis*, trichomoniasis, and urinary tract infections. Five major community state types (CST) in the vagina have been described.[6] These researchers studied the vaginal microbiota of 396 asymptomatic women and characterized the species in five groups based on their genes. In a healthy vaginal environment, CST I, II, III, V are dominated *by Lactobacillus crispatus* (*L. crispatus*), *L. gasseri*, *L. iners*, and *L. jensenii*, respectively. CST IV is characterized by depletion of lactobacilli and increased diversity of anaerobic bacteria such as Atopodium.[6]

An extensive systematic review was published in 2020 of studies reporting data on the association of microbiota and HPV.[7] Of the 78 articles retrieved from PubMed and 291 from Scopus, 16 studies were eligible for inclusion in the review. These 16 studies included a total of 1,204 patients. The detected microbiotas in these studies included several types of microorganisms: *L. iners,* which is classified as CST III was found in 13 studies (72.2%); *L. crispatus* a CST I classification was found in eight studies (44.44%) and CSTIV-B which represents anaerobic microbiomes combined with a reduction in Lactobacillus was found in five studies (27.7%); Megasphaera, *G. vaginalis*, and *L. jensenii*, which is classified as CSTV were found in four studies (22.22%); Sneathia, *L. gasseri*, classified as CST II as well as CST IV-A represents Peptoniphilus, Anaerococcus, Corynebacterium, Finegoldia, and Prevotella was found in two studies (12.5%) and in one study each (6.25%), dialister, *L. formicalis*, Fusobacterium, *L. gallinarum*, and *L. salivarus* (which was found only in South African women).

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So what does all of this mean regarding vaginal microbiota association with HPV and cervical intraepithelial neoplasia (CIN). In one of the studies in the review, women with HPV had a higher diversity and a lower proportion of Lactobacillus with a specific lower prevalence of *L. iners* and *L. crispatus*. Other common organisms among HPV positive women were *L. gasseri* and *Gardnerella vaginalis*. In another of the studies, women who were eventually diagnosed with CIN also had a high diversity of microbiota and were usually colonized by Sneathia; and in women with invasive cervical cancer, Fusobacterium was the most common type of organism. In another of the studies included in the review, there was an abundance of Lactobacillus and *L. reuteri* specifically in women with CIN II. Contrast that with HPV negative women who had *L. crispatus*/CSTI and *L. gasseri*/CSTII as the most common species. L*. crispatus* appears to be related to decreased prevalence of oncogenic HPV types, and high-risk HPV infections appear to have a decreased population of Lactobacillus and an increased abundance of anaerobes, particularly Prevotella and Leptotrichia.

HPV remission is another area of interest. In one report CST III was the classification group with the fastest remission, while CST IV-B was the one with the slowest, with CSTIV-B being a risk factor for HPV persistence. Remember from earlier in this article, in a healthy vaginal environment, CST III is dominated by *L. iners* and CST IV is characterized by depletion of lactobacilli and increased diversity of anaerobic bacteria such as Atopodium. CST IV-A represents Peptoniphilus, Anaerococcus, Corynebacterium, Finegoldia and Prevotella.

Women who are HPV negative who later become HPV positive may have a higher CSTIV-A microbiota than those with CST I. *L. crispatus* has another standout feature in that it was found to be a protective factor against HIV, high-risk HPV and Herpes Simplex type 2 with a high abundance in uninfected women.

Ethnicity is another factor that strongly affects the vaginal microbiota. In this review, Afro-Caribbean women have a fourfold higher risk of suffering from a vaginal dysbiosis or high microbiota diversity which indicates that CST IV is the most common type of microbiota in comparison with European/ Caucasian and African women. Even though this was the case, the prevalence of HPV and the rate of more severe dysplasia was not proportionately higher, which is surprising.

In summary, among all the microbiota, it's Fusobacteria, including Sneathia, as possible microbiological markers correlated with HPV although the relationship between HPV infection and the coexistence with other types of vaginal microbiota is either protective or predisposing to HPV. The evolution of HPV infection is in direct correlation with the dominant vaginal species or genus. *L. gasseri*, *L. jensenii*, and *L. crispatus* seem to be protective while Sneathia, *Anaerococcus tetradius*, Peptostreptococus, Fusobacterium, *Gardnerella vaginalis*, and *L. iners* in combination with a low amount of the other types of Lactobacillus, lead to elevated rates of HPV infection, greater disease severity, and lower rates of HPV remission. Other factors such as nicotine use, lack of barrier contraception, and low vaginal estrogen can also lead to elevated rates of HPV infection. The low vaginal estrogen connection is again related to the vaginal microbiome and the subsequent lower amounts of lactic acid-producing lactobacilli in the postmenopausal state.

Perhaps the greatest limitation of this study and how to put it to clinical use is that we don't use the tools of DNA tests, sequencing and polymerase chain reaction amplification of genes, gram stains, microbiological cultures and vaginal pH in our usual assessment and management of HPV. For persistent HPV infections and/or higher grade lesions with recurrences, in particular, we could incorporate at least some of these tests in addition to HPV DNA testing, the most easily being vaginal pH, gram stains, and microbiological cultures. There are vaginal microbiome tests on the market, even some for home use. One is called EVVY. Molecular methods of next generation sequencing are being used to characterize the vaginal microbiota and even a single vaginal swab sample, a nucleic acid amplification test (NAAT) can detect small amounts of microbial DNA and assess overall diversity and the vaginal microbiome.

When it comes to intervention with probiotics and HPV, we are at the early edge of understanding interventions, but particular species as well as nutraceutical proteins such as lactoferrin deserve attention. For the moment, our creative thinking in connecting dots and clinical judgement on protocols is in play, perhaps gleaning from some of the research on vaginal probiotics and bacterial vaginosis in terms of dosing regimens. For starters, I'm going to look towards vaginal *L. crispatus*, *L. jensenii*, and *L. gasseri,* along with testing for bacterial vaginosis and the use of vaginal estrogen in postmenopausal women with persistent and/or recurrent HPV/CIN.

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by 8.9% and all-cause mortality was nonsignificantly lower by 20% in the supplement group, compared with the placebo group. The incidence of ischemic heart disease was the same in each group. When the data for men and women were analyzed separately, marked differences were seen. Among men, the incidence of cancer was significantly lower by 31%, and all-cause mortality was significantly lower by 37% in the supplement group, compared with the placebo group. Among women, the incidence of these outcomes was nonsignificantly higher by 3-4% in the supplement group than in the placebo group.

It is noteworthy that the supplement used in this trial contained zinc but not copper. Zinc interferes with copper absorption, and long-term use of even modest doses of zinc can decrease body stores of copper.[4] Animal studies have demonstrated that copper deficiency can cause cardiovascular disease.[5] Therefore, the outcome for cardiovascular disease and possibly for all-cause mortality as reported in this study may have been better if the supplement had included copper.

In the second trial, 14,641 U.S. male physicians were randomly assigned to receive, in double-blind fashion, a daily multivitamin (Centrum Silver) or placebo for a mean of 11.2 years.[6] Compared with placebo, total mortality was nonsignificantly lower by 6% and the incidence of major cardiovascular events was nonsignificantly higher by 1% in the supplement group, compared with the placebo group.

At the time this study was conducted, Centrum Silver contained (in addition to vitamins and minerals) FD&C Blue 2 Aluminum Lake, FD&C Red 40 Aluminum Lake, FD&C Yellow 6 Aluminum Lake, polyethylene glycol, polyvinyl alcohol, sodium aluminum silicate, sodium benzoate, talc, titanium dioxide, crospovidone, and butylated hydroxytoluene. It would be reasonable to speculate that long-term daily ingestion of these chemicals could be harmful. Therefore, any potential benefit of the vitamins and minerals in Centrum Silver might have been negated by one or more of these other chemicals. In addition, until the year 2008, the zinc present in Centrum Silver was balanced with copper in the form of cupric oxide (personal communication, Pfizer Consumer Healthcare, December 7, 2012). According to animal research, cupric oxide cannot be absorbed.[7] Thus, for about 70% of the time this study was conducted, the zinc in the product was not properly balanced with copper. As noted above, zinc-induced copper deficiency could have increased the risk of cardiovascular disease and possibly increased all-cause mortality, potentially negating a beneficial effect of other components of the product.

In the third trial, 21,442 US adults were randomly assigned to receive, in double-blind fashion, Centrum Silver or placebo for a mean of 3.6 years.[8] All-cause mortality was nonsignificantly lower by 7%, the incidence of cardiovascular disease was nonsignificantly lower by 2%, and the incidence of cancer was nonsignificantly lower by 3% in the supplement group, compared with the placebo group. By the time this study was conducted, the cupric oxide in Centrum Silver had been replaced by an absorbable form of copper. However, the product still contained a wide range of potentially toxic chemicals.

Thus, each of the three large trials cited by the Task Force showed a reduction in mortality ranging from 6% to 20%. One of these studies found a large and statistically significant decrease in both cancer and all-cause mortality in men, but not in women. This profound difference in outcomes between the sexes is a fertile area for additional research. None of the products used in these studies could be considered optimal. All of the trials might have produced better results if the supplements had been better formulated and had been free of potentially toxic extraneous chemicals.

The Task Force is correct in their assertion that there is no definitive proof that multivitamins prevent cardiovascular disease or cancer or decrease mortality among the general population. However, I believe they erred by failing to note that there was some evidence of benefit in these studies.

Nutritional supplements have demonstrated value for a wide range of health conditions including fatigue, anxiety, depression, insomnia, poor stress tolerance, arthritis, migraines, kidney stones, premenstrual syndrome, heart failure, osteoporosis, acne, respiratory infections, diabetes, age-related macular degeneration, and many others. Regardless of whether or not they can prevent two specific diseases or help you live longer, there is overwhelming evidence that nutritional supplements, when used properly, are not a waste of money.

Alan R. Gaby, MD

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They're Telling Us That Nutritional Supplements Are a Waste of Money

On June 21-22, 2022, headlines were all over the news claiming that taking vitamins and other supplements is a waste of money. From *WebMD*: "Vitamins, Supplements a Waste of Money for Most, Task Force Says." From *CNN Health*: "Are you wasting your money on supplements? Most likely, experts say." From *New Scientist*: "Vitamins and dietary supplements are a waste of money for most people." From the *News Ticker* on CBS Boston: "Experts say vitamin supplements are likely a waste of money."

It is curious that these headlines were nearly identical, considering that the US Preventive Services Task Force (USPTF) to which the media reports were referring did not actually state that taking supplements is a waste of money. What the Task Force did state was, "The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of supplementation with multivitamins for the prevention of cardiovascular disease or cancer. Evidence is lacking and the balance of benefits and harms cannot be determined."[1,2] The Task Force also acknowledged that their report had a number of limitations. First, since the USPSTF focused on cardiovascular disease and cancer and secondarily on all-cause mortality, it did not exclude the possibility that there are other benefits of some supplements. Second, since the review was focused on healthy populations without known nutritional deficiencies, it did not cover therapeutic use of supplements in persons with physical symptoms, medical conditions, or nutritional deficiencies. Third, there may be other dosages, formulations, or supplement combinations that could be beneficial.

The fact that so many media outlets came up with an almost identical misleading headline makes one think that reporters were just lazily (and without any analysis of their own) repeating a statement from a press release. In the body of their reports the media did, for the most part, present a more accurate account of what the USPSTF actually had said. However, as is often the case, the headline is what people focus on and remember. Who might have put out such a misleading headline? One obvious candidate would be a representative of the pharmaceutical industry, an industry that loves to make nutritional supplements look bad. A colleague of mine once overheard a pharmaceutical rep bragging about how easy it was to put out a press release bashing nutritional supplements.

Analysis of the USPSTF Report

But let's put aside the issue of misleading media headlines and take a closer look at some of what was in the USPSTF report. The Task Force's conclusions regarding multivitamin use and risk of death, cardiovascular disease, and cancer were based on a review of nine randomized clinical trials (RCTs). Among the nine RCTs were three large trials that looked specifically at death, cardiovascular disease, and cancer and were rated as good-quality studies. Those three RCTs comprised most of the evidence upon which the USPSTF report was based.

In the first of those three trials, 13,017 French men and women (aged 35-60 years) were randomly assigned to receive, in double-blind fashion, a daily nutritional supplement or placebo for a median of 7.5 years.[3] The supplement provided daily 120 mg of vitamin C, 30 mg of vitamin E, 6 mg of beta-carotene, 100 µg of selenium, and 20 mg of zinc. In the group as a whole, the incidence of cancer was nonsignificantly lower

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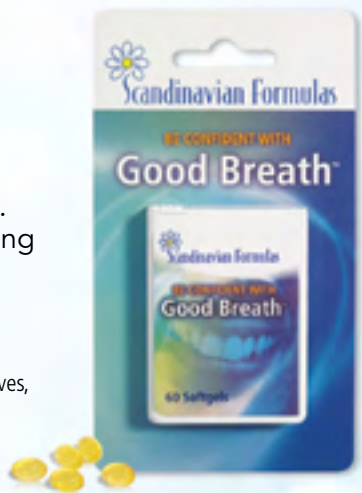

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